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**Modulators of LXR**

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(56) Related Art
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(54) Title: MODULATORS OF LXR

(57) Abstract: Coumpounds, compositions and methods for modulating the activity of nuclear receptors are provided. In particular, heterocyclic compounds are provided for modulating the activity of nuclear receptors, including liver X receptor (LXR) and orphan nuclear receptors. In certain embodiments, the compounds are N-substituted pyridones.

# MODULATORS OF LXR

## RELATED APPLICATIONS

Benefit of priority is claimed herein to U.S. provisional patent application No. 60/342,707, filed December 21, 2001, to Bayne *et al.*, entitled "MODULATORS OF LXR". For U.S. national stage purposes and where appropriate, the disclosure of the above-referenced application is incorporated by reference herein in its entirety.

## FIELD OF THE INVENTION

Compounds, compositions and methods for modulating the activity of liver X receptors (LXRs) are provided. In particular, pyridone derivatives are provided for modulating the activity of LXRs.

## BACKGROUND OF THE INVENTION

### Nuclear Receptors

Nuclear receptors are a superfamily of regulatory proteins that are structurally and functionally related and are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones (see, *e.g.*, Evans (1988) *Science 240*:889-895). These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in response to ligands for the receptors.

Nuclear receptors can be classified based on their DNA binding properties (see, *e.g.*, Evans, *supra* and Glass (1994) *Endocr. Rev. 15*:391-407). For example, one class of nuclear receptors includes the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors which bind as homodimers to hormone response elements (HREs) organized as inverted repeats (see, *e.g.*, Glass, *supra*). A second class of receptors, including those activated by retinoic acid, thyroid hormone, vitamin $D_3$, fatty acids/peroxisome proliferators (*i.e.*, peroxisome proliferator activated receptors or PPARs) and ecdysone, bind to HREs as heterodimers with a common partner, the retinoid X receptors

(*i.e.*, RXRs, also known as the 9-*cis* retinoic acid receptors; see, *e.g.*, Levin *et al.* (1992) *Nature 355*:359-361 and Heyman *et al.* (1992) *Cell 68*:397-406).

RXRs are unique among the nuclear receptors in that they bind DNA as a homodimer and are required as a heterodimeric partner for a number of additional nuclear receptors to bind DNA (see, *e.g.*, Mangelsdorf *et al.* (1995) *Cell 83*:841-850). The latter receptors, termed the class II nuclear receptor subfamily, include many which are established or implicated as important regulators of gene expression. There are three RXR genes (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), coding for RXR$\alpha$, -$\beta$, and -$\gamma$, all of which are able to heterodimerize with any of the class II receptors, although there appear to be preferences for distinct RXR subtypes by partner receptors *in vivo* (see, *e.g.*, Chiba *et al.* (1997) *Mol. Cell. Biol. 17*:3013-3020). In the adult liver, RXR$\alpha$ is the most abundant of the three RXRs (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), suggesting that it might have a prominent role in hepatic functions that involve regulation by class II nuclear receptors. See also, Wan *et al.* (2000) *Mol. Cell. Biol. 20*:4436-4444.

**Orphan Nuclear Receptors**

Included in the nuclear receptor superfamily of regulatory proteins are nuclear receptors for whom the ligand is known and those which lack known ligands. Nuclear receptors falling in the latter category are referred to as orphan nuclear receptors. The search for activators for orphan receptors has led to the discovery of previously unknown signaling pathways (see, *e.g.*, Levin *et al.*, (1992), *supra* and Heyman *et al.*, (1992), *supra*). For example, it has been reported that bile acids, which are involved in physiological processes such as cholesterol catabolism, are ligands for farnesoid X receptor (FXR).

Since it is known that products of intermediary metabolism act as transcriptional regulators in bacteria and yeast, such molecules may serve similar functions in higher organisms (see, *e.g.*, Tomkins (1975) *Science 189*:760-763 and O'Malley (1989) *Endocrinology 125*:1119-1120). For example, one biosynthetic pathway in higher eukaryotes is the mevalonate pathway, which leads to the synthesis of cholesterol, bile acids, porphyrin, dolichol, ubiquinone, carotenoids, retinoids, vitamin D, steroid hormones and farnesylated proteins.

**LXR$\alpha$ and LXR$\beta$**

LXR$\alpha$ is found predominantly in the liver, with lower levels found in kidney, intestine, spleen and adrenal tissue (see, *e.g.*, Willy, *et al.* (1995) *Gene Dev. 9(9)*:1033-1045). LXR$\beta$ is ubiquitous in mammals and was found in nearly all tissues examined. LXRs are activated by certain naturally occurring, oxidized derivatives of cholesterol (see, *e.g.*, Lehmann, *et al.* (1997) *J. Biol. Chem. 272(6)*:3137-3140). LXR$\alpha$ is activated by oxycholesterol and promotes cholesterol metabolism (Peet *et al.* (1998) *Cell 93*:693-704). Thus, LXRs appear to play a role in, *e.g.*, cholesterol metabolism (see, *e.g.*, Janowski, *et al.* (1996) *Nature 383*:728-731).

**Nuclear Receptors and Disease**

Nuclear receptor activity has been implicated in a variety of diseases and disorders, including, but not limited to, hypercholesterolemia (see, *e.g.*, International Patent Application Publication No. WO 00/57915), osteoporosis and vitamin deficiency (see, *e.g.*, U.S. Patent No. 6,316,5103), hyperlipoproteinemia (see, *e.g.*, International Patent Application Publication No. WO 01/60818), hypertriglyceridemia, lipodystrophy, hyperglycemia and diabetes mellitus (see, *e.g.*, International Patent Application Publication No. WO 01/82917), atherosclerosis and gallstones (see, *e.g.*, International Patent

Application Publication No. WO 00/37077), disorders of the skin and mucous membranes (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. WO 98/32444), acne (see, *e.g.*, International Patent Application Publication No. WO 00/49992), and cancer, Parkinson's disease and Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334). Activity of nuclear receptors, including LXRs, FXR and PPAR, and orphan nuclear receptors, has been implicated in physiological processes including, but not limited to, bile acid biosynthesis, cholesterol metabolism or catabolism, and modulation of cholesterol 7$\alpha$-hydroxylase gene (CYP7A1) transcription (see, *e.g.*, Chiang *et al.* (2000) *J. Biol. Chem. 275*:10918-10924), HDL metabolism (see, *e.g.*, Urizar *et al.* (2000) *J. Biol. Chem. 275*:39313-39317 and International Patent Application Publication No. WO 01/03705), and increased cholesterol efflux and increased expression of ATP binding cassette transporter protein (ABC1) (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Thus, there is a need for compounds, compositions and methods of modulating the activity of nuclear receptors, including LXRs, FXR, PPAR and orphan nuclear receptors. Such compounds are useful in the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders in which nuclear receptor activity is implicated.

**SUMMARY OF THE INVENTION**

Compounds for use in compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating liver X receptors (LXR$\alpha$ and LXR$\beta$), FXR, PPAR and/or orphan nuclear receptors are provided. In certain embodiments, the compounds are N-substituted pyridone compounds. In one embodiment, the compounds provided

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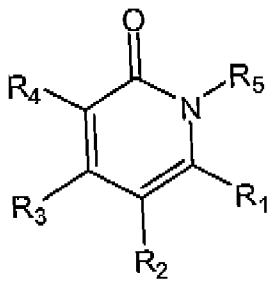
herein are agonists of LXR. In another embodiment, the compounds provided herein are antagonists of LXR. Agonists that exhibit low efficacy are, in certain embodiments, antagonists.

A first aspect of the invention provides for a compound having formula I:




or a pharmaceutically acceptable derivative thereof, wherein

$R^1$ is selected from substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

$R^2$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl;

$R^3$ and $R^4$ are selected from (i) or (ii) as follows:

(i) $R^3$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylaminocarbonyl or $C(J)OR^{30}$; and $R^4$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, azide, $C(J)R^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, $CH_2OR^{31}$, $CR^{30}=CR^{31}R^{32}$, $NO_2$, $NR^{31}R^{32}$;

(ii) $R^3$ and $R^4$, together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring, with the proviso that the heterocyclic ring has one oxo substituent;

$R^5$ is substituted or unsubstituted aralkyl or substituted or unsubstituted heteroaralkyl, wherein $R^5$ is optionally substituted with one or more groups selected from alkyl, haloalkyl, halohydroxyalkyl, alkoxy, alkoxyalkoxyalkyl, alkoxyalkyl, aryl, halo, alkoxycarbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, alkylcarbonyl, arylcarbonyl, alkylalkelenedioxy and dialkylalkelenedioxy;

$R^{30}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

$R^{31}$ and $R^{32}$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or $R^{31}$ and $R^{32}$ together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

J is O, S or $NR^{40}$;

$R^{35}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

$R^{40}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl, and heteroaralkynyl moieties of $R^1$, $R^2$, and $R^3$, are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from $Q^1$, where $Q^1$ is halo, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, azide, hydroxy, oxo, thia, nitrile, nitro formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyldiaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, heterocyclyloxy, alkoxyalkyl, alkoxyalkoxyalkyl, alkylheteroaryloxy, alkylcycloalkoxy, cycloalkyloxy, heterocyclyloxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocyclyloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, arylureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, haloalkylarylamino, arylamino, diarylamino, alkylarylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino, haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylenedioxyalkyl, dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyl,

alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two $Q^1$ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (i.e., $-O-(CH_2)_z-O-$), thioalkylenoxy (i.e., $-S-(CH_2)_z-O-$) or alkylenedithioxy(i.e., $-S-(CH_2)_z-S-$) where z is 1 or 2; and

each $Q^1$ is independently unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from $Q^2$, where $Q^2$ is halo, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, azide, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, arylcarbonylalkyl,a minocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio.

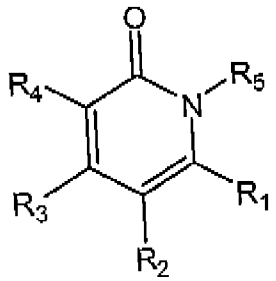
A second aspect of the invention provides for a pharmaceutical composition comprising a compound according to the first aspect of the invention or a pharmaceutically acceptable derivative thereof in a pharmaceutically acceptable carrier.

A third aspect of the invention provides for the use of a compound according to the first aspect of the invention or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for treatment of a disease or disorder selected from hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

A fourth aspect of the invention provides for the use of a compound according to the first aspect of the invention or a pharmaceutically acceptable derivative thereof for reducing cholesterol levels in a subject in need thereof.

A fifth aspect of the invention provides for a method of treating a disease or disorder selected from hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders, comprising administering to a subject in need thereof an effective amount of a compound of the first aspect o the invention or a pharmaceutically acceptable derivative thereof, or a composition according to the second aspect of the invention.

Disclosed herein the compounds for use in the compositions and methods provided herein have formula I:




where, $R^1$ is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

$R^2$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl;

$R^3$ and $R^4$ are selected from (i), (ii), (iii) or (iv) as follows:

(i) $R^3$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $C(J)OR^{30}$ or

$C(J)NR^{31}R^{32}$; and $R^4$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, pseudohalide, $C(J)R^{30}$, $C(J)OR^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, $CH_2OR^{31}$, $CR^{30}=CR^{31}R^{32}$, $NO_2$ or $NR^{31}R^{32}$;

(ii) $R^3$ and $R^4$, together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring;

(iii) $R^3$ and $R^4$, together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring with the proviso that the nitrogen atom in the heterocyclic ring is not substituted with a phenyl ring; or

(iv) $R^3$ and $R^4$, together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring with the proviso that the heterocyclic ring does not have more than one oxo substitutent;

$R^5$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;

$R^6$ and $R^7$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted

alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or $NR^8$;

$R^8$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;

$R^9$ and $R^{10}$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

$R^{30}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

$R^{31}$ and $R^{32}$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, $C(J)R^{35}$; or $R^{31}$ and $R^{32}$, together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

J is O, S or $NR^{40}$;

$R^{35}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

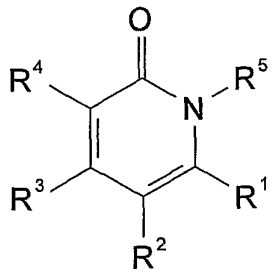
$R^{40}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of $R^1$, $R^2$, $R^3$, $R^5$, $R^6$, $R^7$, $R^8$, $R^9$ and $R^{10}$ are unsubstituted or substituted with one or more substituents, in one embodiment, one to three or four substituents, each independently selected from $Q^1$, where $Q^1$ is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl,

arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyldiaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkaoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, heterocycloxy, alkoxyalkyl, alkoxyalkoxyalkyl, alkylheteroaryloxy, alkylcycloalkoxy, cycloalkyloxy, heterocyclyloxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, arylureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, haloalkylarylamino, arylamino, diarylamino, alkylarylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino, haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylenedioxyalkyl, dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two $Q^1$ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-$(CH_2)_z$-O-), thioalkylenoxy (*i.e.*, -S-$(CH_2)_z$-O-)or alkylenedithioxy (*i.e.*, -S-$(CH_2)_z$-S-) where z is 1 or 2; and each $Q^1$ is independently unsubstituted or substituted with one or more substituents, in one embodiment, one to three or four substituents,

each independently selected from $Q^2$, where $Q^2$ is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino, hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, arylcarbonylalkyl, aminocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula I:



where $R^1$ is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocyclylalkyl; $R^2$ is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl; $R^3$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted

heteroaryl; $R^4$ is halide, pseudohalide, $C(J)R^{30}$, $C(J)OR^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, $CH_2OR^{31}$, $CR^{30}=CR^{31}R^{32}$, $NO_2$ or $NR^{31}R^{32}$; and $R^5$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted aralkenyl, substituted or unsubstituted aralkynyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaralkenyl, substituted or unsubstituted heteroaralkynyl, $-N=CR^6R^7$ or $-NR^9R^{10}$;

where $R^6$ and $R^7$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each independently 1, 2 or 3, and X is O, S or $NR^8$;

$R^8$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted heteroarylcarbonyl;

$R^9$ and $R^{10}$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

$R^{30}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

$R^{31}$ and $R^{32}$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$;

J is O, S or $NR^{40}$;

$R^{35}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

$R^{40}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl and heteroaralkynyl moieties of $R^1$, $R^2$, $R^3$, $R^5$, $R^6$, $R^7$, $R^8$, $R^9$ and $R^{10}$ are unsubstituted or substituted with one or more substituents, in one embodiment, one to three or four substituents,

each independently selected from $Q^1$, where $Q^1$ is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, ureido, alkylureido, arylureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two $Q^1$ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-$(CH_2)_z$-O-), thioalkylenoxy (*i.e.*, -S-$(CH_2)_z$-O-)or alkylenedithioxy (*i.e.*, -S-$(CH_2)_z$-S-) where z is 1 or 2; and

the aryl and heteroaryl groups of $Q^1$ are unsubstituted or substituted with one or more substituents, in one embodiment, one to three or four substituents, each independently selected from $Q^2$, where $Q^2$ is alkyl, halo, pseudohalo, alkoxy, aryloxy or alkylenedioxy.

In certain embodiments, $R^2$ is hydrogen, or is substituted or unsubstituted alkyl. In other embodiments, $R^2$ is hydrogen.

In another embodiment, $R^3$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl. In another embodiment, $R^3$ is substituted or unsubstituted alkyl. In another embodiment, $R^3$ is haloalkyl. In other embodiments, $R^3$ is lower haloalkyl. In another embodiment, $R^3$ is lower perfluoroalkyl. In another embodiment, $R^3$ is trifluoromethyl or pentafluoroethyl. In another embodiment, $R^3$ is trifluoromethyl.

In other embodiments, $R^4$ is pseudohalide. In another embodiment, $R^4$ is cyano.

In another embodiment, $R^6$ and $R^7$ are selected with the proviso that (i) they are not both methyl; and (ii) they do not together form pentylene (*i.e.*, $-(CH_2)_5-$).

The groups $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$, $Q^1$ and $Q^2$ are selected such that the resulting compound has nuclear receptor modulation activity, such as in at least one assay described herein, including LXR or orphan nuclear receptor modulation activity, such as LXR antagonist or agonist activity. In certain embodiments, the compounds provided herein have an $IC_{50}$ and/or $EC_{50}$ of less than about 100 $\mu$M in a LXR$\alpha$ or LXR$\beta$ binding or co-transfection assay. The LXR$\alpha$ or LXR$\beta$ $IC_{50}$ and/or $EC_{50}$ values for the compounds provided herein are, in certain embodiments, less than about 50 $\mu$M, 25 $\mu$M, 10 $\mu$M, 1 $\mu$M, 100 nM, 10 nM or 1 nM in binding or co-transfection assays. In certain of these embodiments, the compounds provided herein are LXR agonists.

In other of these embodiments, the compounds provided herein are LXR antagonists. In other embodiments, the compounds provided herein exhibit a % efficacy relative to standard (N-(3-((4-fluorophenyl)-(naphthalene-2-sulfonyl)amino)propyl)-2,2-dimethylpropionamide) of greater than about 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140% or more in a co-transfection assay.

Also of interest are any pharmaceutically-acceptable derivatives, including salts, esters, enol ethers, enol esters, solvates, hydrates and prodrugs of the compounds described herein. Pharmaceutically-acceptable salts, include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc, aluminum, and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

Pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof, that deliver amounts effective for the treatment, prevention, or amelioration of one or more symptoms of

diseases or disorders that are modulated or otherwise affected by nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, or in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated, are also provided. The effective amounts and concentrations are effective for ameliorating any of the symptoms of any of the diseases or disorders.

Methods for treatment, prevention, or amelioration of one or more symptoms of diseases or disorders mediated by or in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated, are provided. Such methods include methods of treatment, prevention and amelioration of one or more symptoms of hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, or cardiovascular disorders, using one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof.

Methods of modulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors, using the compounds and compositions provided herein are also provided. The compounds and compositions provided herein are active in assays, such as the assays provided herein, that measure the activity of nuclear receptors, including LXR and/or orphan nuclear receptors. These methods include inhibiting and up-regulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors.

Methods of reducing cholesterol levels in a subject in need thereof by administration of one or more compounds or compositions provided herein are also provided.

Methods of modulating cholesterol metabolism using the compounds and compositions provided herein are provided.

Methods of treating, preventing, or ameliorating one or more symptoms of diseases or disorders which are affected by cholesterol, triglyceride, or bile acid levels by administration of one or more of the compounds and compositions provided herein are also provided.

Methods of raising the plasma level of high density lipoprotein (HDL) by adminstration of one or more compounds and compositions provided herein are also provided.

In practicing the methods, effective amounts of the compounds or compositions containing therapeutically effective concentrations of the compounds, which are formulated for systemic delivery, including parenteral, oral, or intravenous delivery, or for local or topical application, for the treatment of nuclear receptor, including LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated, including, but not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, or cardiovascular disorders, are administered to an individual exhibiting the symptoms of these diseases or disorders. The

amounts are effective to ameliorate or eliminate one or more symptoms of the diseases or disorders.

Articles of manufacture containing packaging material, a compound or composition, or pharmaceutically acceptable derivative thereof, provided herein, which is effective for modulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated, are provided.

**BRIEF DESCRIPTION OF DRAWINGS**

Figure 1 provides in vitro data for the compounds whose synthesis is described in the Examples. Data is provided for LXR$\alpha$ and LXR$\beta$ receptors. Average $EC_{50}$ ("EC50_AVG") for LXR agonism is provided as follows: I = 0.0001-0.01 $\mu$M, II = 0.01-0.1 $\mu$M, III = 0.1-1.0 $\mu$M, IV = 1.0-10.0 $\mu$M and NC = Not Calculated. Average percent efficacy ("EFF_AVG") for LXR agonism relative to control (N-(3-((4-fluoro-phen-yl)-(naphthalene-2-sulfonyl)-amino)propyl)-2,2-dimethylpropionamide) is provided as follows: A = 0-50%, B = 50-100%, C = 100-150%, D > 150% and NC = Not Calculated. Average Ki is provided as follows: A1 = 0.0001-0.1 $\mu$M, B1 = 0.1-1 $\mu$M, C1 = 1-2 $\mu$M, D1 = >2 $\mu$M.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

### A. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, a nuclear receptor is a member of a superfamily of regulatory proteins that are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones. These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in repsonse to a ligand therefor. Nuclear receptors may be classified based on their DNA binding properties. For example, the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors bind as homodimers to hormone response elements (HREs) organized as inverted repeats. Another example are receptors, including those activated by retinoic acid, thyroid hormone, vitamin $D_3$, fatty acids/peroxisome proliferators and ecdysone, that bind to HREs as heterodimers with a common partner, the retinoid X receptor (RXR). Among the latter receptors is LXR.

As used herein, an orphan nuclear receptor is a nuclear receptor for which the natural ligand is unknown.

As used herein, liver X receptor or LXR refers to a nuclear receptor implicated in cholesterol biosynthesis. As used herein, the term LXR refers to both LXR$\alpha$ and LXR$\beta$, two forms of the protein found in mammals. Liver X receptor-$\alpha$ or LXR$\alpha$ refers to the receptor described in U.S. Patent Nos. 5,571,696, 5,696,233 and 5,710,004, and Willy *et al.*

(1995) *Gene Dev. 9(9)*:1033-1045. Liver X receptor-$\beta$ or LXR$\beta$ refers to the receptor described in Peet *et al.* (1998) *Curr. Opin. Genet. Dev. 8(5)*:571-575; Song *et al.* (1995) *Ann. N.Y. Acad. Sci. 761*:38-49; Alberti *et al.* (2000) *Gene 243(1-2)*:93-103; and references cited therein; and in U.S. Patent Nos. 5,571,696, 5,696,233 and 5,710,004.

Diabetes mellitus, commonly called diabetes, refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose, referred to as hyperglycemia. See, e.g., LeRoith, D. et al., (eds.), DIABETES MELLITUS (Lippincott-Raven Publishers, Philadelphia, Pa. U.S.A. 1996). According to the American Diabetes Association, diabetes mellitus is estimated to affect approximately 6% of the world population. Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for macrovascular and macrovascular diseases, including nephropathy, neuropathy, retinopathy, hypertension, cerebrovascular disease and coronary heart disease. Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

There are two major forms of diabetes: type 1 diabetes (formerly referred to as insulin-dependent diabetes or IDEM); and type 2 diabetes (formerly referred to as noninsulin dependent diabetes or NIDDM).

Type 2 diabetes is a disease characterized by insulin resistance accompanied by relative, rather than absolute, insulin deficiency. Type 2 diabetes can range from predominant insulin resistance with relative insulin deficiency to predominant insulin deficiency with some insulin resistance. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistant individuals, the body secretes abnormally high amounts of insulin to compensate for this defect. When inadequate amounts of

insulin are present to compensate for insulin resistance and adequate control of glucose, a state of impaired glucose tolerance develops. In a significant number of individuals, insulin secretion declines further and the plasma glucose level rises, resulting in the clinical state of diabetes. Type 2 diabetes can be due to a profound resistance to insulin stimulating regulatory effects on glucose and lipid metabolism in the main insulin-sensitive tissues: muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. In Type 2 diabetes, free fatty acid levels are often elevated in obese and some non-obese patients and lipid oxidation is increased.

Premature development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases are characteristic features of patients with diabetes. Hyperlipidemia is an important precipitating factor for these diseases. Hyperlipidemia is a condition generally characterized by an abnormal increase in serum lipids in the bloodstream and is an important risk factor in developing atherosclerosis and heart disease. For a review of disorders of lipid metabolism, see, e.g., Wilson, J. et al., (ed.), Disorders of Lipid Metabolism, Chapter 23, Textbook of Endocrinology, 9th Edition, (W. B. Sanders Company, Philadelphia, Pa. U.S.A. 1998). Hyperlipidemia is usually classified as primary or secondary hyperlipidemia. Primary hyperlipidemia is generally caused by genetic defects, while secondary hyperlipidemia is generally caused by other factors, such as various disease states, drugs, and dietary factors. Alternatively, hyperlipidemia can result from both a combination of primary and secondary causes of hyperlipidemia. Elevated cholesterol levels are associated with a number of disease states, including coronary

artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma.

Dyslipidemia, or abnormal levels of lipoproteins in blood plasma, is a frequent occurrence among diabetics, and has been shown to be one of the main contributors to the increased incidence of coronary events and deaths among diabetic subjects (see, e.g., Joslin, E. Ann. Chim. Med. (1927) 5: 1061-1079). Epidemiological studies since then have confirmed the association and have shown a several-fold increase in coronary deaths among diabetic subjects when compared with nondiabetic subjects (see, e.g., Garcia, M. J. et al., Diabetes (1974) 23: 105-11 (1974); and Laakso, M. and Lehto, S., Diabetes Reviews (1997) 5(4): 294-315). Several lipoprotein abnormalities have been described among diabetic subjects (Howard B., et al., Arteriosclerosis (1978) 30: 153-162).

The term "insulin resistance" can be defined generally as a disorder of glucose metabolism. More specifically, insulin resistance can be defined as the diminished ability of insulin to exert its biological action across a broad range of concentrations producing less than the expected biologic effect. (see, e.g., Reaven, G. M., J. Basic & Clin. Phys. & Pharm. (1998) 9: 387-406 and Flier, J. Ann Rev. Med. (1983) 34:145-60). Insulin resistant persons have a diminished ability to properly metabolize glucose and respond poorly, if at all, to insulin therapy. Manifestations of insulin resistance include insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. Insulin resistance can cause or contribute to polycystic ovarian syndrome, Impaired Glucose Tolerance (IGT), gestational diabetes, hypertension, obesity, atherosclerosis and a variety of other disorders. Eventually, the insulin resistant individuals can

progress to a point where a diabetic state is reached. The association of insulin resistance with glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, high blood pressure, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plasminogen activator inhibitor-1), has been referred to as "Syndrome X" (see, e.g., Reaven, G. M., Physiol. Rev. (1995) 75: 473-486).

The term "diabetes mellitus" or "diabetes" means a disease or condition that is generally characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels in the body. The result of these defects is elevated blood glucose, referred to as "hyperglycemia." Type 2 diabetes often occurs in the face of normal, or even elevated, levels of insulin and can result from the inability of tissues to respond appropriately to insulin. Most type 2 diabetic patients are insulin resistant and have a relative deficiency of insulin, in that insulin secretion can not compensate for the resistance of peripheral tissues to respond to insulin. In addition, many type 2 diabetics are obese. Other types of disorders of glucose homeostasis include Impaired Glucose Tolerance, which is a metabolic stage intermediate between normal glucose homeostasis and diabetes, and Gestational Diabetes Mellitus, which is glucose intolerance in pregnancy in women with no previous history of type 1 or type 2 diabetes.

The term "complication" of diabetes includes, but is not limited to, microvascular complications and macrovascular complications. Microvascular complications are those complications which generally result in small blood vessel damage. These complications include, e.g., retinopathy (the impairment or loss of vision due to blood vessel damage in the eyes); neuropathy (nerve damage and foot problems due to blood

vessel damage to the nervous system); and nephropathy (kidney disease due to blood vessel damage in the kidneys). macrovascular complications are those complications which generally result from large blood vessel damage. These complications include, e.g., cardiovascular disease and peripheral vascular disease. Cardiovascular disease refers to diseases of blood vessels of the heart. See. e.g., Kaplan, R. M., et al., "Cardiovascular diseases" in HEALTH AND HUMAN BEHAVIOR, pp. 206-242 (McGraw-Hill, New York 1993). Cardiovascular disease is generally one of several forms, including, e.g., hypertension (also referred to as high blood pressure), coronary heart disease, stroke, and rheumatic heart disease. Peripheral vascular disease refers to diseases of any of the blood vessels outside of the heart. It is often a narrowing of the blood vessels that carry blood to leg and arm muscles.

The term "hyperlipidemia" refers to the presence of an abnormally elevated level of lipids in the blood. Hyperlipidemia can appear in at least three forms: (1) hypercholesterolemia, i.e., an elevated cholesterol level; (2) hypertriglyceridemia, i.e., an elevated triglyceride level; and (3) combined hyperlipidemia, i.e., a combination of hypercholesterolemia and hypertriglyceridemia.

The term "dyslipidemia" refers to abnormal levels of lipoproteins in blood plasma including both depressed and/or elevated levels of lipoproteins (e.g., elevated levels of LDL, VLDL and depressed levels of HDL).

Exemplary Primary Hyperlipidemia include, but are not limited to, the following: (1) Familial Hyperchylomicronemia, a rare genetic disorder which causes a deficiency in an enzyme, LP lipase, that breaks down fat molecules. The LP lipase deficiency can cause the accumulation of large quantities of fat or lipoproteins in the blood;

(2) Familial Hypercholesterolemia, a relatively common genetic disorder caused where the underlying defect is a series of mutations in the LDL receptor gene that result in malfunctioning LDL receptors and/or absence of the LDL receptors. This brings about ineffective clearance of LDL by the LDL receptors resulting in elevated LDL and total cholesterol levels in the plasma;

(3) Familial Combined Hyperlipidemia, also known as multiple lipoprotein-type hyperlipidemia; an inherited disorder where patients and their affected first-degree relatives can at various times manifest high cholesterol and high triglycerides. Levels of HDL cholesterol are often moderately decreased;

(4) Familial Defective Apolipoprotein B-100 is a relatively common autosomal dominant genetic abnormality. The defect is caused by a single nucleotide mutation that produces a substitution of glutamine for arginine which can cause reduced affinity of LDL particles for the LDL receptor. Consequently, this can cause high plasma LDL and total cholesterol levels;

(5) Familial Dysbetaliproteinemia, also referred to as Type III Hyperlipoproteinemia, is an uncommon inherited disorder resulting in moderate to severe elevations of serum TG and cholesterol levels with abnormal apolipoprotein E function. HDL levels are usually normal; and

(6) Familial Hypertriglyceridemia, is a common inherited disorder in which the concentration of plasma VLDL is elevated. This can cause mild to moderately elevated triglyceride levels (and usually not cholesterol levels) and can often be associated with low plasma HDL levels.

Risk factors in exemplary Secondary Hyperlipidemia include, but are not limited to, the following: (1) disease risk factors, such as a history of type 1 diabetes, type 2 diabetes, Cushing's syndrome,

hypothyroidism and certain types of renal failure; (2) drug risk factors, which include, birth control pills; hormones, such as estrogen, and corticosteroids; certain diuretics; and various β-blockers; (3) dietary risk factors include dietary fat intake per total calories greater than 40%; saturated fat intake per total calories greater than 10%; cholesterol intake greater than 300 mg per day; habitual and excessive alcohol use; and obesity; and (4) non-genetic dyslipidemias.

The terms "obese" and "obesity" refers to, according to the World Health Organization, a Body Mass Index (BMI) greater than 27.8 $kg/m^2$ for men and 27.3 $kg/m^2$ for women (BMI equals weight (kg)/height ($m^2$). Obesity is linked to a variety of medical conditions including diabetes and hyperlipidemia. Obesity is also a known risk factor for the development of type 2 diabetes (See, e.g., Barrett-Conner, E., Epidemol. Rev. (1989) 11: 172-181; and Knowler, et al., Am. J Clin. Nutr. (1991) 53:1543-1551).

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acetals, ketals, hemiacetals, hemiketals, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethyl-benzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not

limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula C=C(OR) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl or heterocyclyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula C=C(OC(O)R) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl or heterocyclyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

As used herein, treatment means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating a nuclear receptor, including LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor

activity, including LXR and/or orphan nuclear receptor activity, is implicated.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

The term "modulate" refers to the treating, prevention, suppression, enhancement or induction of a function or condition. For example, the compounds claimed herein, can modulate hyperlipidemia by lowering cholesterol in a human, thereby suppressing hyperlipidemia.

As used herein, the $IC_{50}$ refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as modulation of LXR activity, in an assay that measures such response.

As used herein, $EC_{50}$ refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

The term "cholesterol" refers to a steroid alcohol that is an essential component of cell membranes and myelin sheaths and, as used herein, incorporates its common usage. Cholesterol also serves as a precursor for steroid hormones and bile acids.

The term "triglyceride(s)" ("TGs"), as used herein, incorporates its common usage. TGs consist of three fatty acid molecules esterified to a glycerol molecule and serve to store fatty acids which are used by muscle cells for energy production or are taken up and stored in adipose tissue.

As used herein, a prodrug is a compound that, upon *in vivo* administration, is metabolized by one more steps or processes or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, *e.g.*, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. The compounds provided herein include all possible isomers, as well as, their racemic and optically pure forms. Optically active (+) and (-), (r)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. In the case of amino acid residues, such residues may be of either the L- or D-form. The configuration for naturally occurring amino acid residues is

generally L. When not specified the residue is the L form. As used herein, the term "amino acid" refers to $\alpha$-amino acids which are racemic, or of either the D- or L-configuration. The designation "d" preceding an amino acid designation (*e.g.*, dAla, dSer, dVal, etc.) refers to the D-isomer of the amino acid. The designation "dl" preceding an amino acid designation (*e.g.*, dlPip) refers to a mixture of the L- and D-isomers of the amino acid. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization *in vivo*. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form.

As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

As used herein, the nomenclature alkyl, alkoxy, carbonyl, *etc.* is used as is generally understood by those of skill in this art.

As used herein, alkyl, alkenyl and alkynyl carbon chains, if not specified, contain from 1 to 20 carbons, or 1 to 16 carbons, and are straight or branched. Alkenyl carbon chains of from 2 to 20 carbons, in

certain embodiments, contain 1 to 8 double bonds, and the alkenyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 double bonds. Alkynyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 triple bonds, and the alkynyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 triple bonds. Exemplary alkyl, alkenyl and alkynyl groups herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-penytyl and isohexyl. As used herein, lower alkyl, lower alkenyl, and lower alkynyl refer to carbon chains having less than about 6 carbons. As used herein, "alk(en)(yn)yl" refers to an alkyl group containing at least one double bond and at least one triple bond.

As used herein, "cycloalkyl" refers to a saturated mono- or multi-cyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments of 3 to 6 carbon atoms; cycloalkenyl and cycloalkynyl refer to mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond. Cycloalkenyl and cycloalkynyl groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenyl groups, in further embodiments, containing 4 to 7 carbon atoms and cycloalkynyl groups, in further embodiments, containing 8 to 10 carbon atoms. The ring systems of the cycloalkyl, cycloalkenyl and cycloalkynyl groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)yl" refers to a cycloalkyl group containing at least one double bond and at least one triple bond.

As used herein, "substituted alkyl," "substituted alkenyl," "substituted alkynyl," "substituted cycloalkyl," "substituted cyclo-alkenyl," and "substitued cycloalkynyl" refer to alkyl, alkenyl, alkynyl,

cycloalkyl, cycloalkenyl and cycloalkynyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three substituents.

As used herein, "aryl" refers to aromatic monocyclic or multicyclic groups containing from 6 to 19 carbon atoms. Aryl groups include, but are not limited to groups such as fluorenyl, substituted fluorenyl, phenyl, substituted phenyl, naphthyl and substituted naphthyl.

As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 15 members where one or more, in one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrrolidinyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, N-methylpyrrolyl, quinolinyl and isoquinolinyl.

As used herein, a "heteroarylium" group is a heteroaryl group that is positively charged on one or more of the heteroatoms.

As used herein, "heterocyclyl" refers to a monocyclic or multicyclic non-aromatic ring system, in one embodiment of 3 to 10 members, in another embodiment of 4 to 7 members, in a further embodiment of 5 to 6 members, where one or more, in certain embodiments, 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "substituted aryl," "substituted heteroaryl" and "substituted heterocyclyl" refer to aryl, heteroaryl and heterocyclyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three substituents.

As used herein, "aralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl group.

As used herein, "heteroaralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by a heteroaryl group.

As used herein, "halo", "halogen" or "halide" refers to F, Cl, Br or I.

As used herein, pseudohalides or pseudohalo groups are groups that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides. Pseudohalides include, but are not limited to, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, and azide.

As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl, trifluoromethyl and 1-chloro-2-fluoroethyl.

As used herein, "haloalkoxy" refers to RO- in which R is a haloalkyl group.

As used herein, "sulfinyl" or "thionyl" refers to -S(O)-. As used herein, "sulfonyl" or "sulfuryl" refers to $-S(O)_2-$. As used herein, "sulfo" refers to $-S(O)_2O-$.

As used herein, "carboxy" refers to a divalent radical, -C(O)O-.

As used herein, "aminocarbonyl" refers to $-C(O)NH_2$.

As used herein, "alkylaminocarbonyl" refers to -C(O)NHR in which R is alkyl, including lower alkyl. As used herein, "dialkylaminocarbonyl" refers to -C(O)NR′R in which R′ and R are independently alkyl, including lower alkyl; "carboxamide" refers to groups of formula -NR′COR in which R′ and R are independently alkyl, including lower alkyl.

As used herein, "diarylaminocarbonyl" refers to -C(O)NRR' in which R and R' are independently selected from aryl, including lower aryl, such as phenyl.

As used herein, "arylalkylaminocarbonyl" refers to -C(O)NRR' in which one of R and R' is aryl, including lower aryl, such as phenyl, and the other of R and R' is alkyl, including lower alkyl.

As used herein, "arylaminocarbonyl" refers to -C(O)NHR in which R is aryl, including lower aryl, such as phenyl.

As used herein, "hydroxycarbonyl" refers to -COOH.

As used herein, "alkoxycarbonyl" refers to -C(O)OR in which R is alkyl, including lower alkyl.

As used herein, "aryloxycarbonyl" refers to -C(O)OR in which R is aryl, including lower aryl, such as phenyl.

As used herein, "alkoxy" and "alkylthio" refer to RO- and RS-, in which R is alkyl, including lower alkyl.

As used herein, "aryloxy" and "arylthio" refer to RO- and RS-, in which R is aryl, including lower aryl, such as phenyl.

As used herein, "alkylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 1 to about 20 carbon atoms, in another embodiment having from 1 to 12 carbons. In a further embodiment alkylene includes lower alkylene. There may be optionally inserted along the alkylene group one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkylene groups include, but are not limited to, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-(CH_2)_3-$), methylenedioxy ($-O-CH_2-O-$) and ethylenedioxy ($-O-(CH_2)_2-O-$). The term "lower alkylene" refers to alkylene groups having 1 to 6 carbons. In

certain embodiments, alkylene groups are lower alkylene, including alkylene of 1 to 3 carbon atoms.

As used herein, "azaalkylene" refers to $-(CRR)_n-NR-(CRR)_m-$, where n and m are each independently an integer from 0 to 4. As used herein, "oxaalkylene" refers to $-(CRR)_n-O-(CRR)_m-$, where n and m are each independently an integer from 0 to 4. As used herein, "thiaalkylene" refers to $-(CRR)_n-S-(CRR)_m-$, where n and m are each independently an integer from 0 to 4.

As used herein, "alkenylene" refers to a straight, branched or cyclic, in one embodiment straight or branched, divalent aliphatic hydrocarbon group, in certain embodiments having from 2 to about 20 carbon atoms and at least one double bond, in other embodiments 1 to 12 carbons. In further embodiments, alkenylene groups include lower alkenylene. There may be optionally inserted along the alkenylene group one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkenylene groups include, but are not limited to, $-CH=CH-CH=CH-$ and $-CH=CH-CH_2-$. The term "lower alkenylene" refers to alkenylene groups having 2 to 6 carbons. In certain embodiments, alkenylene groups are lower alkenylene, including alkenylene of 3 to 4 carbon atoms. As used herein, "1,3-diaza-1,3-butadienylene" refers to $-N=CH-N=CH-$. As used herein, "1,2-diaza-1,3-butadienylene" refers to $-N=N-CH=CH-$. As used herein, "2,3-diaza-1,3-butadienylene" refers to $-CH=N-N=CH-$.

As used herein, "azaalkenylene" refers to $-NR-(CR=CR)_n-$, where n is 1 or 2; and also refers to $-CR=CR-NR-CR=CR-$. As used herein, "oxaalkenylene" refers to $-O-(CR=CR)_n-$, where n is 1 or 2; and also refers to $-CR=CR-O-CR=CR-$. As used herein, "thiaalkenylene" refers to $-S-(CR=CR)_n-$, where n is 1 or 2; and also refers to $-CR=CR-S-CR=CR-$.

As used herein, "alkynylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 2 to about 20 carbon atoms and at least one triple bond, in another embodiment 1 to 12 carbons. In a further embodiment, alkynylene includes lower alkynylene. There may be optionally inserted along the alkynylene group one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkynylene groups include, but are not limited to, $-C\equiv C-C\equiv C-$, $-C\equiv C-$ and $-C\equiv C-CH_2-$. The term "lower alkynylene" refers to alkynylene groups having 2 to 6 carbons. In certain embodiments, alkynylene groups are lower alkynylene, including alkynylene of 3 to 4 carbon atoms.

As used herein, "alk(en)(yn)ylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 2 to about 20 carbon atoms and at least one triple bond, and at least one double bond; in another embodiment 1 to 12 carbons. In further embodiments, alk(en)(yn)ylene includes lower alk(en)(yn)ylene. There may be optionally inserted along the alkynylene group one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alk(en)(yn)ylene groups include, but are not limited to, $-C=C-(CH_2)_n-C\equiv C-$, where n is 1 or 2. The term "lower alk(en)(yn)ylene" refers to alk(en)(yn)ylene groups having up to 6 carbons. In certain embodiments, alk(en)(yn)ylene groups have about 4 carbon atoms.

As used herein, "cycloalkylene" refers to a divalent saturated mono- or multicyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments 3 to 6 carbon atoms; cycloalkenylene and cycloalkynylene refer to divalent mono- or multicyclic ring

systems that respectively include at least one double bond and at least one triple bond. Cycloalkenylene and cycloalkynylene groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenylene groups in certain embodiments containing 4 to 7 carbon atoms and cycloalkynylene groups in certain embodiments containing 8 to 10 carbon atoms. The ring systems of the cycloalkylene, cycloalkenylene and cycloalkynylene groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)ylene" refers to a cycloalkylene group containing at least one double bond and at least one triple bond.

As used herein, "substituted alkylene," "substituted alkenylene," "substituted alkynylene," "substituted cycloalkylene," "substituted cycloalkenylene," and "substitued cycloalkynylene" refer to alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene and cycloalkynylene groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three substituents.

As used herein, "arylene" refers to a monocyclic or polycyclic, in certain embodiments monocyclic, divalent aromatic group, in one embodiment having from 5 to about 20 carbon atoms and at least one aromatic ring, in another embodiment 5 to 12 carbons. In further embodiments, arylene includes lower arylene. Arylene groups include, but are not limited to, 1,2-, 1,3- and 1,4-phenylene. The term "lower arylene" refers to arylene groups having 5 or 6 carbons.

As used herein, "heteroarylene" refers to a divalent monocyclic or multicyclic aromatic ring system, in one embodiment of about 5 to about 15 members where one or more, in certain embodiments 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "heterocyclylene" refers to a divalent monocyclic or multicyclic non-aromatic ring system, in certain embodiments of 3 to 10 members, in one embodiment 4 to 7 members, in another embodiment 5 to 6 members, where one or more, including 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "substituted arylene," "substituted heteroarylene" and "substituted heterocyclylene" refer to arylene, heteroarylene and heterocyclylene groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three substituents.

As used herein, "alkylidene" refers to a divalent group, such as =CR'R", which is attached to one atom of another group, forming a double bond. Alkylidene groups include, but are not limited to, methylidene ($=CH_2$) and ethylidene ($=CHCH_3$). As used herein, "arylalkylidene" refers to an alkylidene group in which either R' or R" is an aryl group. "Cycloalkylidene" groups are those where R' and R" are linked to form a carbocyclic ring. "Heterocyclylidene" groups are those where at least one of R' and R" contain a heteroatom in the chain, and R' and R" are linked to form a heterocyclic ring.

As used herein, "amido" refers to the divalent group -C(O)NH-. "Thioamido" refers to the divalent group -C(S)NH-. "Oxyamido" refers to the divalent group -OC(O)NH-. "Thiaamido" refers to the divalent group -SC(O)NH-. "Dithiaamido" refers to the divalent group -SC(S)NH-. "Ureido" refers to the divalent group -HNC(O)NH-. "Thioureido" refers to the divalent group -HNC(S)NH-.

As used herein, "semicarbazide" refers to -NHC(O)NHNH-. "Carbazate" refers to the divalent group -OC(O)NHNH-. "Isothiocarbazate" refers to the divalent group -SC(O)NHNH-. "Thiocarbazate" refers to the divalent group -OC(S)NHNH-.

"Sulfonylhydrazide" refers to the group $-SO_2NHNH-$. "Hydrazide" refers to the divalent group -C(O)NHNH-. "Azo" refers to the divalent group -N=N-. "Hydrazinyl" refers to the divalent group -NH-NH-.

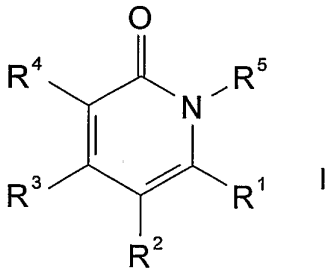
Where the number of any given substituent is not specified (*e.g.*, "haloalkyl"), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens. As another example, "$C_{1-3}$alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three carbons.

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem. 11*:942-944).

**B. Heterocyclic Modulators of Nuclear Receptors**

Compounds for use in compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating liver X receptors (LXR$\alpha$ and LXR$\beta$), either selectively or in combination, and/or orphan nuclear receptors are provided.

In one embodiment, the compounds have formula I:

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where, $R^2$ is substituted or unsubstituted alkyl or hydrogen, where the substituents are selected from one or more $Q^1$; and $R^1$, $R^3$, $R^4$ and $R^5$ are

selected above. In another embodiment, $R^2$ is lower alkyl or hydrogen. In another embodiment, $R^2$ is hydrogen.

In another embodiment, $R^1$ is selected from substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl and substituted or unsubstituted heterocyclyl, where the substituents are selected from one or more $Q^1$.

In another embodiment, $R^1$ is substituted or unsubstituted aryl, where the substituents are selected from one or more $Q^1$.

In another embodiment, $R^1$ is substituted or unsubstituted heteroaryl, where the substituents are selected from one or more $Q^1$.

In another embodiment, $R^1$ is substituted or unsubstituted heterocyclyl, where the substituents are selected from one or more $Q^1$.

In other embodiments, $R^1$ is substituted or unsubstituted methyl, substituted or unsubstituted cyclohexyl, substituted or unsubstituted cyclopentenyl, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted naphthyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted indanyl, substituted or unsubstituted benzofuryl, substituted or unsubstituted thianaphthyl or substituted or unsubstituted indolyl, where the substituents are selected from one or more $Q^1$.

In other embodiments, $R^1$ is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted furyl,

substituted or unsubstituted thienyl, or substituted or unsubstituted pyrrolyl, where the substituents are selected from one or more $Q^1$.

In another embodiment, $R^1$ is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted thienyl, where the substituents are selected from one or more $Q^1$.

In other embodiments, $R^1$ is substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted benzofuryl, substituted or unsubstituted thianaphthyl or substituted or unsubstituted indolyl, where the substituents are selected from one or more $Q^1$.

In another embodiment, $R^1$ is substituted or unsubstituted phenyl.

In another embodiment, $R^1$ is substituted or unsubstituted thienyl.

In certain embodiments, $R^1$ is unsubstituted or substituted with one or more $Q^1$, in one embodiment, one to three or five substituents, in another embodiment, one or two substituents, each independently selected from $Q^1$, where $Q^1$ is halo, pseudohalo, nitro, hydroxy, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, haloalkyl, alkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkylaralkyl, alkylarylcarbonyl, heterocyclylcarbonyl, alkoxycarbonyl, alkoxycarbonylaryloxy, aryloxycarbonyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, alkylaryloxy, alkylaryloxyalkyl, alkyldiaryloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, alkylheteroaryloxy, cycloalkyloxy, heterocyclylalkoxy, heterocyclyloxy, haloaryloxy, alkylcarbonylaryloxy, arylamino, alkylarylamino, aralkylamino, alkylcarbonylamino, alkylaminocarbonyl,

haloalkylcarbonylamino and arylthio; and each $Q^1$ is unsubstituted or further substituted with $Q^2$, which is hydrogen, alkyl, aryl, alkoxy, hydroxycarbonyl, alkoxycarbonyl, pseudohalide, halo, aryloxy, aralkoxy, haloalkyl, alkylthio, alkylamino, dialkylamino or hydroxy.

In another embodiment, $R^1$ is substituted with $Q^1$, which is selected from alkoxycarbonylaryloxy, aryloxy, alkylaryloxy, alkylaryloxyalkyl, alkyldiaryloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, alkylheteroaryloxy, cycloalkyloxy, heterocyclylalkoxy, heterocyclyloxy, heteroaryloxy, haloaryloxy, alkoxycarbonylheterocycloxy, alkylcarbonylaryloxy, dialkylaminoaryloxy, alkoxyaryloxy, cyanoaryloxy, aryloxyaryloxy, dialkylaryloxy, haloalkylaryloxy, alkylthioaryloxy, alkylarylamino, hydroxyaryloxy, arylamino, alkylamino, aralkylamino and arylthio.

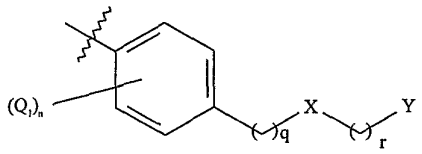
In another embodiment, $R^1$ is substituted with $Q^1$, which is selected from alkyl, alkoxy, halo, pseudohalo, haloalkyl, nitro, hydroxy, alkoxy, aralkoxy, heterocyclylalkoxy, alkylcarbonylamino and alkylamino-carbonylamino.

In another embodiment, $R^1$ is substituted with $Q^1$, which is selected from methyl, ethyl, trifluoromethyl, nitro, hydroxy, n-butyloxy, 3-(2-piperidinyl)ethoxy, methylcarbonylamino, ethylaminocarbonylamino, chloro, bromo, benzylamino, methylphenoxymethyl, trifluoromethylcarbonylamino, methoxycarbonyl, phenoxy, cyano, n-butoxy, benzoxy, 1-piperidinyl, methoxy, hydroxycarbonyl, tert-butoxycarbonylpiperazinylcarbonyl, hydroxymethyl, 1-piperidinylcarbonyl, phenyl, methylphenyl, dimethylamino, methylcarbonylamino, methoxyphenoxy, methylphenoxy, piperidinylmethyl, biphenoxy, benzoxycarbonyl, piperazinylcarbonyl, benzyl, phenylthio, chlorophenoxy, methylbenzyl, hydroxymethylphenoxy, ethoxycarbonylphenoxy, tertbutylmethylphenoxy, tertbutylbiphenoxy, ethylphenoxy,

isopropylphenoxy, tertbutylphenoxy, N,N-dimethylphenoxy, N,N-phenylmethylamino, 3-methylphenyl-1-amino, trifluoromethylphenoxy, ethylphenoxy, methylcarbonylphenoxy, tetrahydropyranyloxy, tetrahydronaphthoxy, hydroxycarbonylphenoxy, 1,3-hexafluoro-2-hydroxypropylphenylamino, benzoxyphenoxy, cyclohexyloxy, alkylindanyloxy, methoxycarbonylphenoxy, isopropylphenoxy, tert-butylphenoxy, N,N-dimethylaminophenoxy, methoxyphenoxy, methoxycarbonylphenoxy, cyanophenoxy, fluorophenoxy, benzoxyphenoxy, trifluoromethylphenoxy, bromophenoxy, 3,5-ditrifluoromethylphenoxy, methylthiophenoxy, indolyl, tert-butoxycarbonyl-piperidinyloxy, hydroxyphenoxy, pyrimidinoxy and pyrazinoxy.

In another embodiment, $R^1$ is substituted with $Q^1$, which is selected from methyl, methoxy, chloro, ethyl, trifluoromethyl, nitro, hydroxy, n-butoxy, 3-(2-piperidinyl)ethoxy, methylcarbonylamino or ethylaminocarbonylamino.

In another embodiment, $R^1$ has formula IA:



where, n is an integer from 0 to 4, in one embodiment, from 0 to 2, in another embodiment, 0 or 1; q and r are each independently selected from 0 to 5, in one embodiment 0 to 3, in another embodiment 0 or 1; X is O, S or NR', where R' is alkyl, aryl or hydrogen; Y is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted cycloalkyl,

where the substituents, when present are selected from one or more $Q^1$ as above. In another embodiment, $Q^1$ is selected from halo, hydroxy, alkyl, alkoxy, alkoxycarbonyl, haloalkyl, alkylcarbonyl, hydroxycarbonyl, hydroxyhaloalkyl, aryl, aralkoxy and heteroaryl. In another embodiment, X is O. In another embodiment X is S. In another embodiment, X is NR'. In another embodiment, R' is lower alkyl or hydrogen. In another embodiment, R' is hydrogen. In another embodiment, Y is substituted or unsubstituted aryl. In another embodiment, Y is substituted or unsubstituted heteroaryl. In another embodiment, Y is substituted or unsubstituted phenyl.

In another embodiment, $R^1$ is methyl, cyclohexyl, 1-cyclopentenyl, 5-indanyl, phenyl, 1-naphthyl, 2-naphthyl, 3-methylphenyl, 2-chlorophenyl, 4-chlorophenyl, 3-ethylphenyl, 3-trifluoromethylphenyl, 3-nitrophenyl, 3-hydroxyphenyl, 3-n-butoxyphenyl, 3-benzyloxyphenyl, 3-(2-piperidinyl)ethoxyphenyl, 3-methylcarbonylaminophenyl, 3-ethylaminocarbonylaminophenyl, 2-methylphenyl, 2-methoxyphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 3-benzylaminophenyl, 3-(3-methyl)phenoxymethylphenyl, benzyl, 3-trifluoromethylcarbonylaminophenyl, 3,5-dimethylphenyl, 2-chloro-3-methylphenyl, phenylethyl, 4-butoxyphenyl, 4-methoxycarbonylphenyl, 4-phenoxyphenyl, 4-cyanophenyl, 4-benzoxyphenyl, 4-(1-piperidinyl)phenyl, 4-hydroxycarbonylphenyl, 4-(4-tert-butoxycarbonylpiperazin-1-ylcarbonyl)phenyl, 4-hydroxymethylphenyl, 4-(1-piperidinylcarbonyl)phenyl, 4-dimethylaminophenyl, 4-methylcarbonylaminophenyl, 4-nitrophenyl, 6-(1,2,3,4-tetrahydro)naphthyl, 4-(4-methoxyphenoxy)phenyl, 4-(2-methylphenoxy)phenyl, 4-(3-methylphenoxy)phenyl, 4-(4-methylphenoxy)phenyl, 4-(3-methoxyphenoxy)phenyl, 4-(1-piperidinylmethyl)phenyl, 4-(4-biphenoxy)phenyl, 3-(1-benzoxycarbonyl)-

piperidinyl, 4-(1-piperazinylcarbonyl)phenyl, 5-(2-methyl-2,3-dihydro)benzofuryl, 4-benzylphenyl, 4-phenylthiophenyl, 4-(4-chlorophenoxy)-2-chlorophenyl, 4-(3-biphenoxy)phenyl, 4-(1-benzoxycarbonyl)-piperidinyl, 4-piperidinyl, 4-(1-(3-methylbenzyl))-piperidinyl, 4-(3-methyl-4-hydroxyphen-1-oxy)phenyl, 4-(2-methyl-4-hydroxyphenoxy)phenyl, 4-(4-ethoxycarbonylphenoxy)phenyl, 4-(2-methyl-4-tertbutylphenoxy)phenyl, 4-(2-phenyl-4-tertbutylphenoxy)phenyl, 4-(3-ethylphenoxy)phenyl, 4-(3-isopropylphenoxy)phenyl, 4-(3-tertbutylphenoxy)phenyl, 4-(3,5-dimethylphenoxy)phenyl, 4-phenoxy-2-methylphenyl, 4-(2-methylphenoxy)-2-methylphenyl, 4-(2-methylphenoxy)-3-methylphenyl, 4-N-methyl-N-phenylaminophenyl, 4-(3-trifluoromethylphenoxy)phenyl, 4-(4-ethylphenoxy)phenyl, 4-(4-isopropylphenoxy)phenyl, 4-(4-tertbutylphenoxy)phenyl, 4-(3-methylcarbonylphenoxy)phenyl, 4-(3,4-dimethylphenoxy)phenyl, 4-(2-tetrahydropyranyloxy)phenyl, 4-(2-tetrahydropyranyloxy)-3-methylphenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 4-(4-methylphenoxy)-3-methylphenyl, 4-(2-ethylphenoxy)phenyl, 4-(2-isopropylphenoxy)phenyl, 4-(5,6,7,8-tetrahydronaphthyloxy)phenyl, 4-(3-hydroxycarbonylphenoxy)phenyl, 2-methyl-4-hydroxyphenyl, 4-phenoxy-2-hydroxyphenyl, 3-phenoxyphenyl, 4-(4-(1,3-hexafluoro-2-hydroxypropyl)phenylamino)phenyl, 4-(2,3,4-trimethylphenoxy)phenyl, 4-(4-benzyloxyphenoxy)phenyl, 4-(3-(methyl-3-indanyloxy)phenyl, 4-(2-methyl-5-benzothiazoloxy)phenyl, 4-cyclohexyloxyphenyl, 4-(3-methoxycarbonylphenoxy)phenyl, 4-(3-isopropylphenoxy)-3-methylphenyl, 4-tert-butyl-phenoxy-3-methylphenyl, 4-N,N-dimethylaminophenoxy-3-methylphenyl, 4-methoxy-phenoxy-3-methylphenyl, 3-methoxy-phenoxy-3-methylphenyl, 4-(3-methoxycarbonyl-phenoxy)-3-methylphenyl, 4-(3-cyanophenoxy)-3-methylphenyl, 4-(4-fluorophenoxy)-3-methylphenyl, 4-(4-benzoxy-

phenoxy)-3-methylphenyl, 4-(3-benzoxy-phenoxy)-3-methylphenyl, 4-(2,5-dimethylphenoxy)-3-methylphenyl, 4-(2-chlorophenoxy)-3-methylphenyl, 4-(3-chlorophenoxy)-3-methylphenyl, 4-(2-trifluoromethylphenoxy)-3-methylphenyl, 4-(3-trifluoromethylphenoxy)-2-methylphenyl, 4-(3-bromophenoxy)-phenyl, 4-(4-bromophenoxy)-phenyl, 4-(3-benzyloxy-phenoxy)-phenyl, 4-(3-cyanophenoxy)-phenyl, 4-(4-cyanophenoxy)phenyl, 4-(2,4-dimethylphenoxy)-phenyl, 4-(3,5-trifluoromethylphenoxy)phenyl, 4-(4-methylthio-phenoxy)-phenyl, 4-(4-N,N-dimethylamino-phenoxy)-phenyl, 5-indolyloxyphenyl, 4-(1-tert-butoxycarbonyl-piperidin-4-oxy)-phenyl, 4-(4-hydroxyphenoxy)-phenyl, 4-(2-pyrimidinoxy)-phenyl, 4-(2-pyrazinoxy)-phenyl, 2-thienyl, 2-(5-chloro)thienyl, 2-(5-bromo)thienyl, 2-(5-phenyl)thienyl, 3-thianaphthyl, 3-methyl-2-thianaphthyl, 2-(5-(3-methylphenyl))-thienyl, 3-pyridinyl, 2-pyrazinyl, 4-(1-phenyl-5-methyl)pyrazolyl, 2-(1-methyl)pyrrolyl, 3-(1-methyl)indolyl, 3-(1-benzyloxycarbonyl)-piperidinyl, 4-(1-benzyloxyarbonyl)-piperidinyl, 4-piperidinyl, 4-(1-(3-methylbenzyl)-piperidinyl, 2-furyl, 2-(5-methyl)-furyl, 3-(2,5-dimethyl)-furyl, benzofuryl, 3-(2,4-dimethyl)-furyl, 2-thiazolyl or 5-(2,4-dimethyl)thiazolyl.

In another embodiment, $R^1$ is phenyl, 1-naphthyl, 2-naphthyl, 3-methylphenyl, 3-methoxyphenyl, 2-chlorophenyl, 3-ethylphenyl, 3-trifluoromethylphenyl, 3-nitrophenyl, 3-hydroxyphenyl, 3-n-butoxyphenyl, 3-benzyloxyphenyl, 3-(2-piperidinyl)ethoxyphenyl, 3-methylcarbonyl-aminophenyl, 3-ethylaminocarbonylaminophenyl, 2-methylphenyl, 2-methoxyphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-chlorophenyl or 4-chlorophenyl.

In another embodiment, $R^1$ is 3-(3-methyl)phenoxymethylphenyl, 4-phenoxyphenyl, 4-benzoxyphenyl, 4-(4-methoxyphenoxy)phenyl, 4-(2-methylphenoxy)phenyl, 4-(3-methylphenoxy)phenyl, 4-(4-methylphenoxy)phenyl, 4-(3-methoxyphenoxy)phenyl, 4-(4-

biphenoxy)phenyl, 4-(4-chlorophenoxy)-2-chlorophenyl, 4-(3-biphenoxy)phenyl, 4-(3-methyl-4-hydroxyphenoxy)phenyl, 4-(2-methyl-4-hydroxyphenoxy)phenyl, 4-(4-ethoxycarbonylphenoxy)phenyl, 4-(2-methyl-4-tertbutylphenoxy)phenyl, 4-(2-phenyl-4-tertbutylphenoxy)phenyl, 4-(3-ethylphenoxy)phenyl, 4-(3-isopropylphenoxy)phenyl, 4-(3-tertbutylphenoxy)phenyl, 4-(3,5-dimethylphenoxy)phenyl, 4-phenoxy-2-methylphenyl, 4-(2-methylphenoxy)-2-methylphenyl, 4-(2-methylphenoxy)-3-methylphenyl, 4-(3-trifluoromethylphenoxy)phenyl, 4-(4-ethylphenoxy)phenyl, 4-(4-isopropylphenoxy)phenyl, 4-(4-tertbutylphenoxy)phenyl, 4-(3-methylcarbonylphenoxy)phenyl, 4-(3,4-dimethylphenoxy)phenyl, 4-(4-methylphenoxy)-3-methylphenyl, 4-(2-ethylphenoxy)phenyl, 4-(2-isopropylphenoxy)phenyl, 4-(5,6,7,8-tetrahydronaphthyloxy)phenyl, 4-(3-hydroxycarbonylphenoxy)phenyl, 2-methyl-4-hydroxyphenyl, 4-phenoxy-2-hydroxyphenyl, 3-phenoxyphenyl, 4-(2,3,4-trimethylphenoxy)phenyl, 4-(4-benzyloxyphenoxy)phenyl, 4-(3-methoxycarbonylphenoxy)phenyl, 4-(3-isopropylphenoxy)-3-methylphenyl, 4-tert-butyl-phenoxy-3-methylphenyl, 4-N,N-dimethylaminophenoxy-3-methylphenyl, 4-methoxy-phenoxy-3-methylphenyl, 3-methoxy-phenoxy-3-methylphenyl, 4-(3-methoxycarbonyl-phenoxy)-3-methylphenyl, 4-(3-cyanophenoxy)-3-methylphenyl, 4-(4-fluorophenoxy)-3-methylphenyl, 4-(4-benzoxy-phenoxy)-3-methylphenyl, 4-(3-benzoxy-phenoxy)-3-methylphenyl, 4-(2,5-dimethylphenoxy)-3-methylphenyl, 4-(2-chlorophenoxy)-3-methylphenyl, 4-(3-chlorophenoxy)-3-methylphenyl, 4-(2-trifluoromethylphenoxy)-3-methylphenyl, 4-(3-trifluoromethylphenoxy)-2-methylphenyl, 4-(3-bromophenoxy)-phenyl, 4-(4-bromophenoxy)-phenyl, 4-(3-benzyloxy-phenoxy)-phenyl, 4-(3-cyanophenoxy)-phenyl, 4-(4-cyanophenoxy)phenyl, 4-(2,4-dimethylphenoxy)-phenyl, 4-(3,5-

trifluoromethylphenoxy)phenyl, 4-(4-methylthio-phenoxy)-phenyl or 4-(4-N,N-dimethylamino-phenoxy)-phenyl.

In another embodiment, $R^1$ is 4-N-methyl-N-phenylaminophenyl, 4-(4-(1,3-hexafluoro-2-hydroxypropyl)phenyl-1-amino)phenyl or 4-phenylthiophenyl.

In another embodiment, $R^1$ is 2-thienyl, 2-(5-chloro)thienyl, 2-(5-bromo)thienyl, 2-(5-phenyl)thienyl, 3-thianaphthyl, 3-methyl-2-thianaphthyl or 2-(5-(3-methylphenyl))-thienyl. In another embodiment, $R^1$ is thienyl. In another embodiment, $R^1$ is 2-thienyl.

In another embodiment, $R^1$ is 3-pyridinyl, 2-pyrazinyl, 4-(1-phenyl-5-methyl)pyrazolyl, 2-(1-methyl)pyrrolyl, 3-(1-methyl)indolyl, 3-(1-benzyloxycarbonyl)-piperidinyl, 4-(1-benzyloxycarbonyl)-piperidinyl, 4-piperidinyl or 4-(1-(3-methylbenzyl)-piperidinyl.

In another embodiment, $R^1$ is 2-furyl, 2-(5-methyl)-furyl, 3-(2,5-dimethyl)-furyl, benzofuryl or 3-(2,4-dimethyl)-furyl.

In another embodiment, $R^1$ is 2-thiazolyl or 5-(2,4-dimethyl)thiazolyl.

In another embodiment, $R^3$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted aryl, substituted or unsubstituted alkoxycarbonyl or substituted or unsubstituted alkylaminocarbonyl, where the substituents are selected from one or more $Q^1$. In another embodiment, $R^3$ is substituted or unsubstituted alkyl or substituted or unsubstituted aryl. In another embodiment, $R^3$ is substituted or unsubstituted alkoxycarbonyl. In another embodiment, $R^3$ is substituted or unsubstituted alkyl. In another embodiment, $R^3$ is haloalkyl. In certain embodiments, $R^3$ is substituted with $Q^1$, which is halo, pseudohalo, alkyl, alkoxy, alkoxycarbonyl or aryloxycarbonyl. In another embodiments, $R^3$ is substituted with $Q^1$,

which is halo. In further embodiments, $R^3$ is substituted with $Q^1$, which is fluoro, chloro, phenyl, methyl, methoxy or methylamino.

In further embodiments, $R^3$ is substituted or unsubstituted methyl, or substituted or unsubstituted phenyl. In another embodiments, $R^3$ is methyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, chlorodifluoromethyl, 1-(1-methoxy-1-fluoro)ethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethoxymethyl, methoxycarbonylmethyl or phenyl. In another embodiment, $R^3$ is trifluoromethyl, methyl, methoxycarbonylmethyl or phenyl.

In another embodiment, $R^4$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkynyl, pseudohalide, hydroxycarbonyl, $CH_2NR^{31}R^{32}$ or $NO_2$; where the substituents are each independently selected from one or more $Q^1$. In another embodiment, $R^4$ is pseudohalide. In another embodiment, $R^4$ is substituted or unsubstituted methyl, substituted or unsubstituted acetyl. In another embodiment, $R^4$ is substituted or unsubstituted acetyl, where the substitutent is trialkylsilyl. In further embodiments, $R^4$ is substituted with $Q^1$, which is trialkylsilyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkoxycarbonylamino, dialkylamino, alkylamino or amino.

In another embodiment, $R^4$ is alkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl or aryloxycarbonylaminoalkyl. In another embodiment, $R^4$ is hydrogen, cyano, nitro, hydroxycarbonyl, trimethylsilylacetyl, acetyl, methylcarbonylaminomethyl, ethylcarbonylaminomethyl, n-propylcarbonylaminomethyl, isopropylcarbonylaminomethyl, n-octylcarbonylaminomethyl, phenylcarbonylaminomethyl, benzylcarbonylaminomethyl, phenylethylcarbonylaminomethyl,

ethoxycabonylaminomethyl dimethylaminomethyl or aminomethyl. In another embodiment, $R^4$ is cyano.

In certain embodiments, $R^3$ and $R^4$, together with the atoms to which they are attached, form substituted or unsubstituted heterocyclic ring. In certain embodiments, $R^3$ and $R^4$, together with the atoms to which they are attached, form substituted or unsubstituted heterocyclic ring, with the proviso that the nitrogen atom in the heterocyclic ring is not substituted with a phenyl group. In certain embodiments, $R^3$ and $R^4$, together with the atoms to which they are attached, form substituted or unsubstituted heterocyclic ring, with the proviso that the heterocyclic ring does not have more than one oxo substitutent. In another embodiment, $R^3$ and $R^4$ together with the atoms to which they are attached form 2-oxotetrahydropyridine or 2-oxo-3-pyrroline.

In another embodiment, $R^5$ is substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaralkyl, $-N=CR^6R^7$ or $-NR^9R^{10}$. In another embodiment, $R^5$ is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, $-N=CR^6R^7$ or $-NR^9R^{10}$. In another embodiment, $R^5$ is substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, $-N=CR^6R^7$ or $-NR^9R^{10}$. In further embodiments, $R^5$ is substituted or unsubstituted aralkyl, or $-N=CR^6R^7$. In another embodiment, $R^5$ is substituted or unsubstituted aralkyl. In another embodiment, $R^5$ is substituted or unsubstituted heterocyclylalkyl. In another embodiment, $R^5$ is substituted or unsubstituted heteroaralkyl. In another embodiment, $R^5$ is $-N=CR^6R^7$. In another embodiment, $R^5$ is substituted or unsubstituted heterocyclyl.

In another embodiment, $R^5$ is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted phenyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted benzyl, substituted or unsubstituted 2-phenethyl, substituted or unsubstituted 1-phenethyl, substituted or unsubstituted 3-phenylpropyl, substituted or unsubstituted 1,2,3,4-tetrahydro-1-naphthyl, substituted or unsubstituted 3-pyridylmethyl, substituted or unsubstituted 4-pyridylmethyl, substituted or unsubstituted 2-pyrazinyl, substituted or unsubstituted thiazolylmethyl, substituted or unsubstituted oxazolylmethyl.

In another embodiment, $R^5$ is substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted 2-phenethyl, substituted or unsubstituted 1-phenethyl, substituted or unsubstituted 3-phenylpropyl, substituted or unsubstituted 1,2,3,4-tetrahydro-1-naphthyl, substituted or unsubstituted 3-pyridylmethyl, substituted or unsubstituted 4-pyridylmethyl, $-N=CR^6R^7$ or $-NR^9R^{10}$.

In another embodiment, $R^5$ is substituted or unsubstituted piperidinyl, substituted or unsubstituted 3-pyridylmethyl, substituted or unsubstituted 4-pyridylmethyl, substituted or unsubstituted 2-pyrazinyl, substituted or unsubstituted thiazolylmethyl, or substituted or unsubstituted oxazolylmethyl.

In another embodiment, $R^5$ is substituted or unsubstituted benzyl.

In certain embodiments, $R^5$ is unsubstituted or substituted with one or more, in one embodiment, one, two or three $Q^1$ groups, where $Q^1$ is alkyl, haloalkyl, halohydroxyalkyl, alkoxy, alkoxyalkoxyalkyl, alkoxyalkyl, aryl, halo, alkoxycarbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, alkylcarbonyl, arylcarbonyl, alkylalkelenedioxy or dialkylalkelenedioxy. In other embodiments, $R^5$ is unsubstituted or substituted with one or more

$Q^1$ groups, where $Q^1$ is alkyl, haloalkyl, alkoxy, aryl, halo, alkoxycarbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy, alkylcarbonyl or arylcarbonyl.

In other embodiments, $R^5$ is unsubstituted or substituted with one or more, in one embodiment one, two or three, $Q^1$ groups, where $Q^1$ is methyl, isopropyl, trifluoromethyl, methoxy, fluoro, bromo, methoxycarbonyl, chloro, methylthio, phenoxy, trifluoromethoxy, 3-pyridyl, 4-pyridyl, 2-pyridyl, ethyl, n-propyl, cyclohexyl, n-propyloxymethyl, n-pentyloxymethyl, n-octyloxymethyl, ethoxymethyl, n-butoxymethyl, n-hexyloxymethyl, n-octyloxymethyl, tert-butyl, ethoxycarbonyl, methylcarbonyl, hydroxy, phenyl, benzyl, n-butyl, ethoxy, phenylcarbonyl, 2-(2-methyl)-methylenedioxy, 1-piperidinyl, 5-(2,2-dimethyl)-methylenedioxy, methoxymethoxymethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, 1-piperidinylmethyl or 1,3-trifluoro-2-hydroxypropyl.

In another embodiment, $Q^1$ is methyl, trifluoromethyl, methoxy, fluoro, bromo, methoxycarbonyl, chloro, methylthio, phenoxy, trifluoromethoxy, 3-pyridyl, 4-pyridyl, 2-pyridyl, ethyl, tert-butyl, ethoxycarbonyl, methylcarbonyl, hydroxy, phenyl, benzyl, n-butyl, ethoxy or phenylcarbonyl.

In another embodiment, $R^5$ is 2,4-dimethylbenzyl, 4-isopropylbenzyl, 4-tert-butylbenzyl, 2,4,5-trifluorobenzyl, 1-naphthylmethyl, 4-(2-(2-methyl)-1,3-dioxymethylene)benzyl, 4-methylbenzyl, 4-ethylbenzyl, 1-piperidinyl, 4-methylcarbonylbenzyl, 5-(2,2-dimethyl)-1,3-dioxymethelenemethyl, 1,2-dihydroxypropanyl, benzyl, 4-(2-methyl)-thiazolylmethyl, 4-(2-phenyl)thiazolylmethyl, 3-methoxymethoxymethylbenzyl, 3-hydroxymethylbenzyl, 4-hydroxymethylbenzyl, 4-hydroxyethylbenzyl, 4-methoxymethylbenzyl, 4-(1-piperidinylmethyl)benzyl, 3-biphenyl, 4-biphenyl, 4-(1,3-trifluoro-2-

hydroxypropyl)phenyl, 4-(2-ethyl)thiazolylmethyl, 4-(2-isopropyl)thiazolylmethyl, 4-(2-propyl)thiazolylmethyl, 4-(2-benzyl)thiazolylmethyl, 4-(2-methyl)oxazolylmethyl, 4-(2-ethyl)oxazolylmethyl, 4-(2-propyl)oxazolylmethyl, 4-(2-phenyl)oxazolylmethyl, 4-(2-benzyl)oxazolylmethyl, 4-(2-cyclohexyl)oxazolylmethyl, 4-n-propyloxymethylbenzyl, 2-(5-methyl)pyrazinylmethyl, 4-n-pentyloxymethylbenzyl, 4-n-octyloxymethylbenzyl, 3-ethoxymethylbenzyl, 3-n-butoxymethylbenzyl, 3-n-hexyloxymethylbenzyl, 3-n-octyloxymethylbenzyl, 2-methylbenzyl, 4-methylbenzyl, 3-methylbenzyl, phenylethyl, 4-(2,5-dimethyl)thiazolylmethyl, 4-(2-isopropyl-5-methyl)thiazolylmethyl, 4-(2-ethyl-5-methyl)thiazolylmethyl, 4-(2-methyl-5-ethyl)thiazolylmethyl, 4-(2,5-diethyl)thiazolylmethyl, phenyl, 2-phenylethyl, 3-phenylpropyl, benzyl, 3-methylbenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-phenylbenzyl, 1-phenylethyl, 1,2,3,4-tetrahydro-1-naphthyl, 2-fluorobenzyl, 4-fluorobenzyl, 2,4-difluorobenzyl, 4-bromobenzyl, 4-methoxycarbonylbenzyl, 2-chlorobenzyl, 4-chorobenzyl, 4-methylthiobenzyl, 4-phenoxybenzyl, 4-trifluoromethoxybenzyl, 3-pyridylmethyl or 4-pyridylmethyl.

In another embodiment, $R^5$ is 4-(2-(2-methyl)-1,3-dioxymethylene)benzyl, 1-piperidinyl, 5-(2,2-dimethyl)-1,3-dioxymethelenemethyl, 4-(2-methyl)-thiazolylmethyl, 4-(2-phenyl)thiazolylmethyl, 4-(1-piperidinylmethyl)benzyl, 4-(2-ethyl)thiazolylmethyl, 4-(2-isopropyl)thiazolylmethyl, 4-(2-propyl)thiazolylmethyl, 4-(2-benzyl)thiazolylmethyl, 4-(2-methyl)oxazolylmethyl, 4-(2-ethyl)oxazolylmethyl, 4-(2-propyl)oxazolylmethyl, 4-(2-phenyl)oxazolylmethyl, 4-(2-benzyl)oxazolylmethyl, 4-(2-cyclohexyl)oxazolylmethyl, 2-(5-

methyl)pyrazinylmethyl, 4-(2,5-dimethyl)thiazolylmethyl, 4-(2-isopropyl-5-methyl)thiazolylmethyl, 4-(2-ethyl-5-methyl)thiazolylmethyl, 4-(2-methyl-5-ethyl)thiazolylmethyl, 4-(2,5-diethyl)thiazolylmethyl, 3-pyridylmethyl or 4-pyridylmethyl.

In another embodiment, $R^5$ is phenyl, 2-phenylethyl, 3-phenylpropyl, benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-phenylbenzyl, 1-phenylethyl, 2,4-dimethylbenzyl, 2-fluorobenzyl, 4-fluorobenzyl, 2,4-difluorobenzyl, 4-bromobenzyl, 4-methoxycarbonylbenzyl, 2-chlorobenzyl, 4-chorobenzyl, 4-methylthiobenzyl, 4-phenoxybenzyl, 4-trifluoromethoxybenzyl, 3-pyridylmethyl, or 4-pyridylmethyl.

In another embodiment, $R^5$ is $-N=CR^6R^7$ where $R^6$ and $R^7$ are each independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl; or together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each 2, and X is O or $NR^8$; where $R^8$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkylcarbonyl, or substituted or unsubstituted arylcarbonyl.

In other embodiments, $R^6$ and $R^7$ are each independently hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted n-propyl, substituted or unsubstituted i-propyl, substituted or unsubstituted i-butyl, substituted or unsubstituted tert-butyl, substituted or unsubstituted phenyl, substituted or unsubstituted s-butyl, substituted or unsubstituted 3-pentyl, or substituted or unsubstituted naphthyl; where the substituents are selected from one or more $Q^1$. In another embodiment, $R^6$ and $R^7$ are unsubstituted or substituted with one or more, in one embodiment one or two, $Q^1$ groups, where $Q^1$ is hydroxy, halo, alkyl or alkoxy. In another

embodiment, $R^6$ and $R^7$ are unsubstituted or substituted with one or more, in one embodiment one or two, $Q^1$ groups, where $Q^1$ is hydroxy, chloro, bromo, methyl or methoxy.

In other embodiments, $R^6$ and $R^7$ are each independently hydrogen, methyl, phenyl, ethyl, isopropyl, n-propyl, s-butyl, 3-pentyl, isobutyl, t-butyl, 2-naphthyl, 2-hydroxyphenyl, 2-hydroxy-5-chlorophenyl, 4-bromophenyl, 2-hydroxy-4-bromophenyl, 2-methylphenyl or 4-methoxyphenyl. In other embodiments, $R^6$ and $R^7$ are each independently hydrogen, methyl, ethyl, isopropyl, n-propyl, s-butyl, 3-pentyl, isobutyl or t-butyl.

In another embodiment, $R^6$ and $R^7$ together form substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, or $-(CH_2)_xX(CH_2)_y-$ where x and y are each 2, and X is O or $NR^8$, where the substituents are selected from one or more $Q^1$. In other embodiments, $R^6$ and $R^7$ together form substituted or unsubstituted butylene, substituted or unsubstituted pentylene, substituted or unsubstituted hexylene, or substituted or unsubstituted pentenylene, where the substituents are selected from one or more $Q^1$. In other embodiments, $R^6$ and $R^7$ are unsubstituted or substituted with one or more, in one embodiment one or two, substituents selected from $Q^1$, which is alkyl, alkoxycarbonyl, aryl, aralkyl, halo, alkoxy and alkylthio. In other embodiments, $R^6$ and $R^7$ are unsubstituted or substituted with one or more, in one embodiment one or two, substituents selected from $Q^1$, which is methyl, ethyl, tert-butyl, ethoxycarbonyl, ethyl, phenyl, benzyl, n-butyl, chloro, methoxy, ethoxy, methylthio and methoxycarbonyl.

In another embodiment, $R^6$ and $R^7$ together form $-(CH_2)_xX(CH_2)_y-$ where x and y are each 2, and X is O or $NR^8$, where $R^8$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkylcarbonyl, or substituted or unsubstituted arylcarbonyl, and the substituents are

selected from one or more $Q^1$. In other embodiments, $R^8$ is alkyl, alkylcarbonyl or arylcarbonyl. In another embodiment, $R^8$ is methyl, methylcarbonyl or phenylcarbonyl.

In other embodiments, $R^6$ and $R^7$ together form pentylene, 2,2,4,4-tetramethylpentylene, 3,3-dimethyl-1-pentenylene, 2-methyl-1-pentenylene, 3-methylpentylene, 3-ethylpentylene, 3-tert-butylpentylene, 1-methylpentylene, 2-methylpentylene, hexylene, butylene, 1-methylbutylene, 2-methylbutylene, 1,3-ethylenebutylene, 3-ethoxycarbonylpentylene, 1-ethylpentylene, 1-phenylpentylene, 1-benzylpentylene, 1-n-butylpentylene, 1,1-dimethylpentylene, 1-chloropentylene, 1-methoxypentylene, 1-ethoxypentylene, 1-methylthiopentylene or 1-methoxycarbonylpentylene.

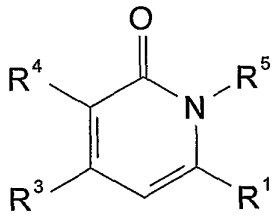
In another embodiment, $R^5$ is $-NR^9R^{10}$, where $R^9$ and $R^{10}$ are each independently hydrogen, or substituted or unsubstituted aryl. In another embodiment, $R^9$ and $R^{10}$ are each independently hydrogen, or substituted or unsubstituted phenyl. In another embodiment, $R^9$ and $R^{10}$ are each independently hydrogen or phenyl.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula I, where $R^1$ is substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heteroaralkyl; $R^2$ is hydrogen, or substituted or unsubstituted alkyl; $R^3$ is haloalkyl; $R^4$ is cyano; and $R^5$ is substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heterocyclyl, or $-N=CR^6R^7$; where $R^6$ and $R^7$ are each independently hydrogen or substituted or unsubstituted alkyl;

where the alkyl, heterocyclyl, aryl, heteroaryl, aralkyl and heteroaralkyl moieties of $R^1$, $R^2$, $R^3$, $R^5$, $R^6$ and $R^7$ are unsubstituted or substituted with one or more substituents, in one embodiment one to

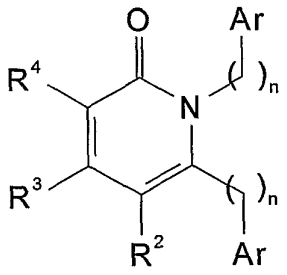
three or four substituents, each independently selected from $Q^1$, as defined above.

In another embodiment, the compounds for use in the compositions and methods have formula II:



where $R^1$, $R^3$, $R^4$ and $R^5$ are selected as above.

In another embodiment, the compounds for use in the compositions and methods have formula III:

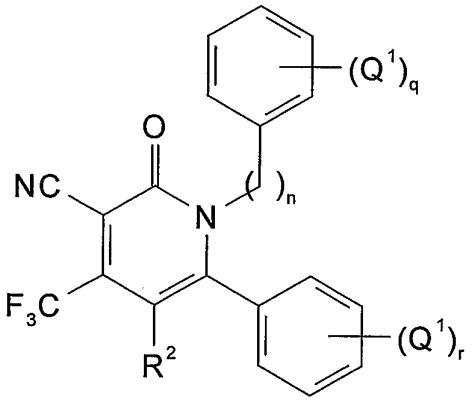


where $R^2$, $R^3$ and $R^4$ are selected as above; each Ar is independently substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl; substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, where there are 0 to 5 substituents, in one embodiment 0, 1, 2 or 3 substituents, each independently selected from $Q^1$; and each n is independently an integer from 0 to 6, in one embodiment 0 to 3, in another embodiment 0 or 1.

In another embodiment, the compounds are of formula III where $R^2$ is hydrogen. In another embodiment, the compounds have formula III where $R^3$ is haloalkyl. In another embodiment, the compounds have

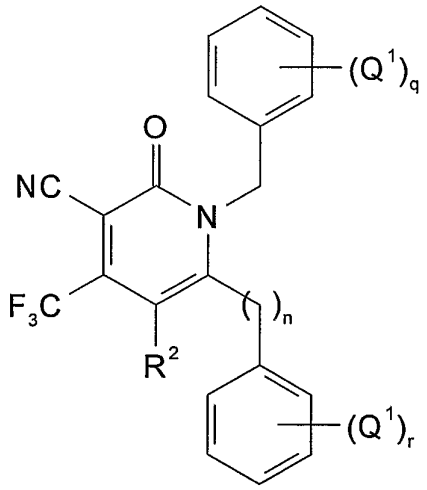
formula III where $R^3$ is perfluoroalkyl. In another embodiment, the compounds have formula III where $R^3$ is trifluoromethyl or pentafluoroethyl. In another embodiment, the compounds have formula III where $R^3$ is trifluoromethyl. In another embodiment, the compounds have formula III where $R^4$ is cyano. In another embodiment, the compounds have formula III where Ar is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl. In another embodiment, the compounds have formula III where Ar is N-pyrrolidinyl.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula IV:



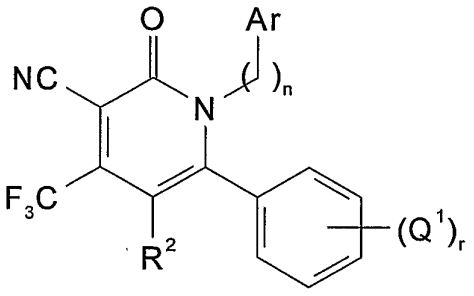

where $R^2$, $Q^1$ and n are selected as above; and q and r are each independently an integer from 0 to 5, or from 0 to 3, or 0 or 1.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula V:



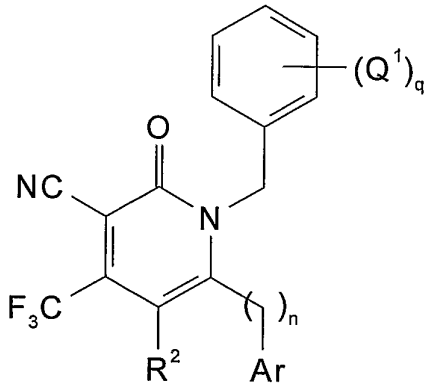
where $R^2$, $Q^1$, q, r and n are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula VI:



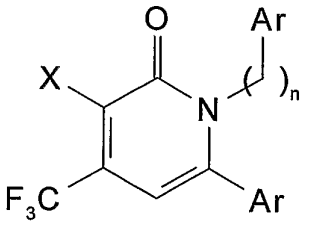
where Ar, $R^2$, $Q^1$, r and n are selected as above. In another embodiment, the compounds have formula VI where Ar is substituted or unsubstituted heteroaryl.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula VII:



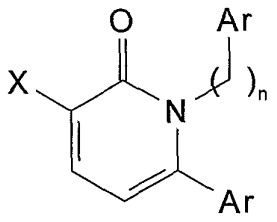
where Ar, $R^2$, $Q^1$, q and n are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula VIII:



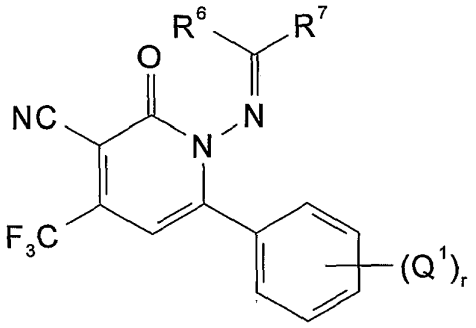
where each Ar is independently selected as above; n is selected as above; and X is cyano, nitro or $NR^{31}R^{32}$, where $R^{31}$ and $R^{32}$ are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula IX:



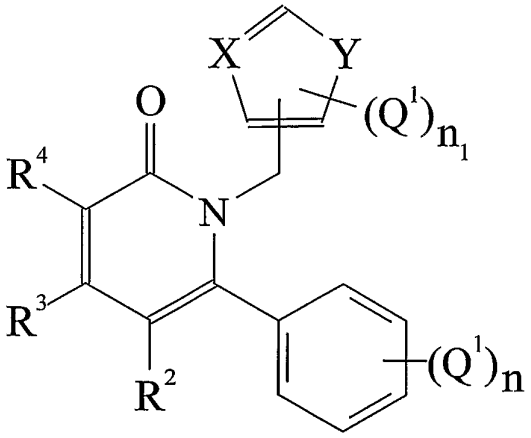
where each Ar is independently selected as above; n is selected as above; and X is bromo, CHO, $COOR^{30}$ or $CONR^{31}R^{32}$, where $R^{30}$, $R^{31}$ and $R^{32}$ are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula X:



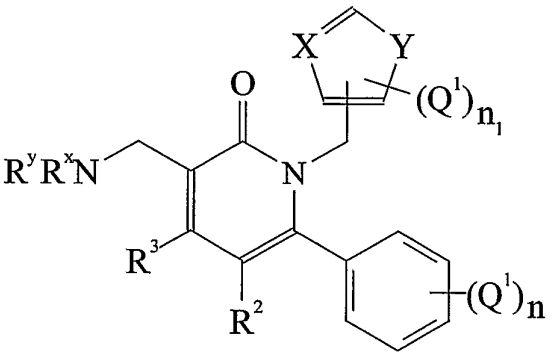
where $Q^1$, r, $R^6$ and $R^7$ are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XI:



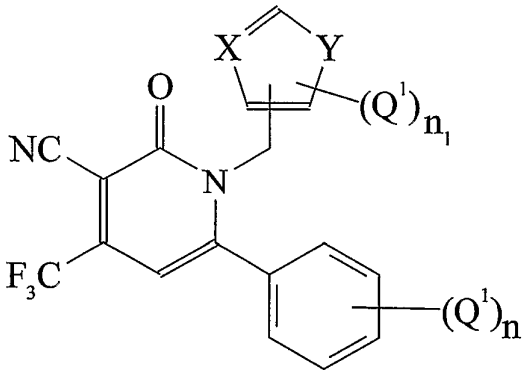
wherein n is an integer from 0 to 5; $n_1$ is an integer from 0 to 2; Y is selected from O, S and NR', where R' is hydrogen, alkyl or aryl; X is N; $Q^1$, $R^2$, $R^3$ and $R^4$ are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XII:



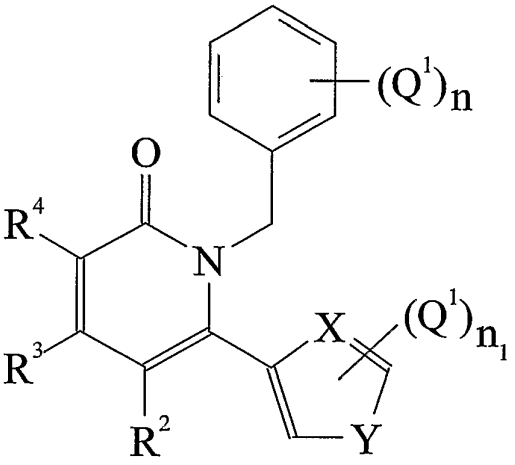
wherein n is an integer from 0 to 5; $n_1$ is an integer from 0 to 2; Y is selected from O, S and NR', where R' is hydrogen, alkyl or aryl; X is N; $R^x$ and $R^y$ are each independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylcarbonyl, aralkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl and aralkoxycarbonyl; $Q^1$, $R^2$, $R^3$ and $R^4$ are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XIII:



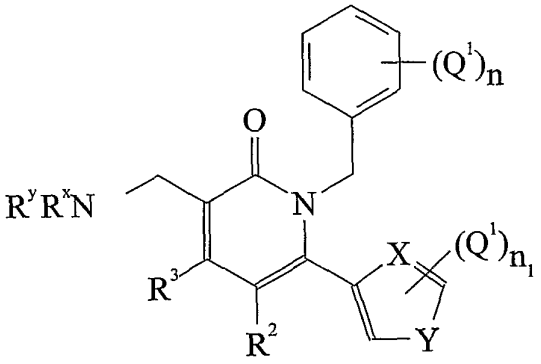
wherein the variables are as defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XIV:



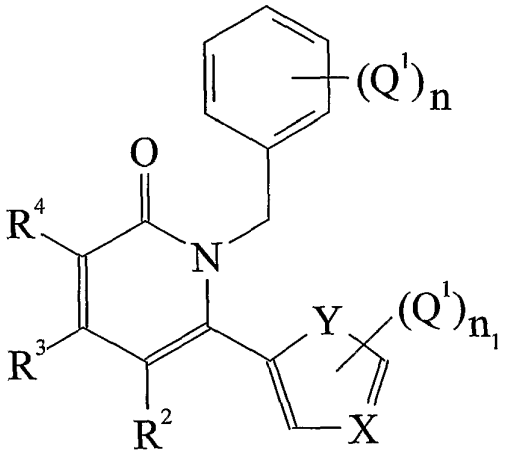
wherein the variables are defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XV:



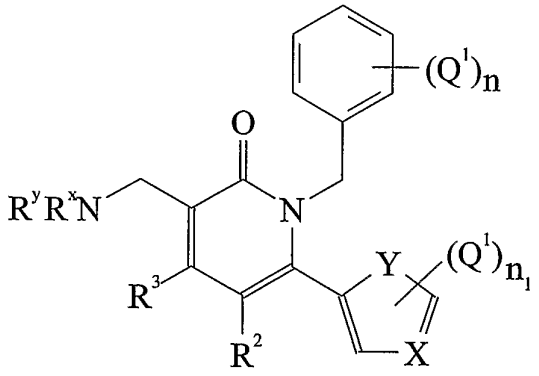
wherein the variables are as defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XVI:



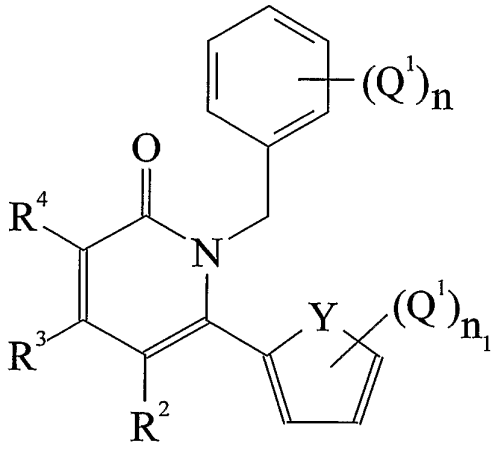
wherein the variables are as defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XVI1:



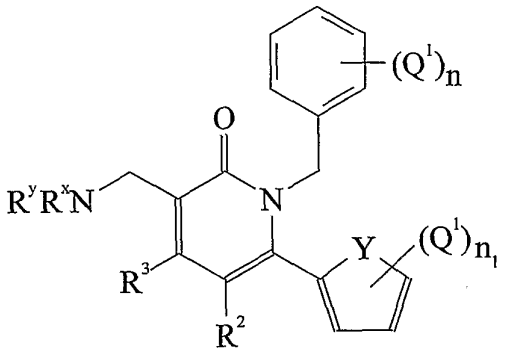
wherein the variables are as defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XVII:



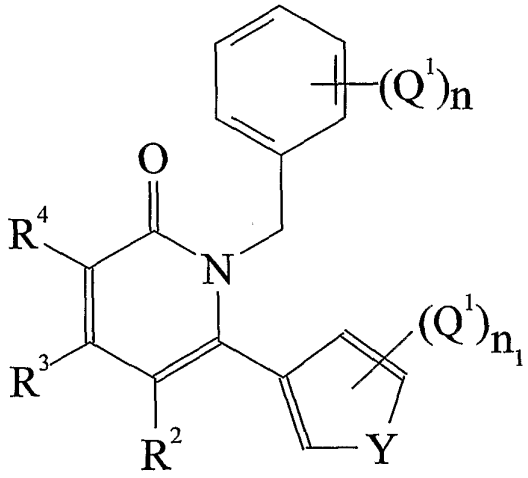
wherein the variables are as defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XVIII:



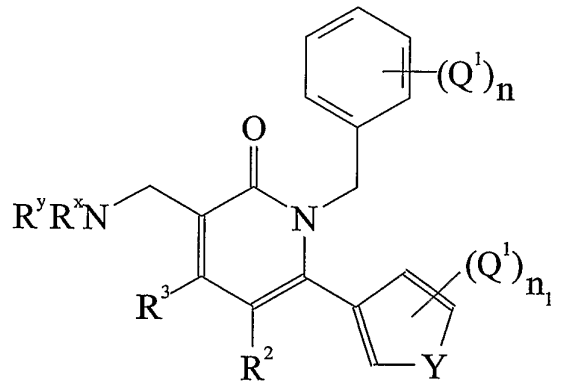
wherein the variables are as defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XIX:



wherein the variables are as defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formula XX:



wherein the variables are as defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein are selected from Figure 1.

In another embodiment, the compounds for use in the compositions and methods provided herein are selected from:

1-Cyclohexylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Isopropylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

2-Oxo-6-phenyl-1-(3,3,5,5-tetramethyl-cyclohexylideneamino)-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(4,4-Dimethyl-cyclohex-2-enylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (isomer 1);

1-(4,4-Dimethyl-cyclohex-2-enylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (isomer 2);

1-(3-Methyl-cyclohex-2-enylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

2-Oxo-6-phenyl-1-(1-phenyl-ethylideneamino)-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(Benzylidene-amino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(1-Ethyl-propylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(4-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(4-Ethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(4-tert-Butyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Cycloheptylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Cyclopentylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Methyl-cyclopentylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(3-Methyl-cyclopentylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(Bicyclo[2.2.1]hept-2-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(Adamantan-2-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(1-Methyl-piperidin-4-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-ylimino)-cyclohexanecarboxylic acid ethyl ester;

2-Oxo-6-phenyl-1-(tetrahydro-pyran-4-ylideneamino)-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Amino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Amino-2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile;

1-sec-Butylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(1,2-Dimethyl-propylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(1-Methyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Butylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Isobutylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Methyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Ethyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(3-Methyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2,2-Dimethyl-propylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(1-Acetyl-piperidin-4-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-[(Naphthalen-2-ylmethylene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-[(2-Hydroxy-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-[(2-Hydroxy-5-chloro-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-[(4-Bromo-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-[(2-Hydroxy-4-bromo-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-[(2-Methyl-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-[(4-Methoxy-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Cyclohexylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Cyclohexylideneamino-2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Methyl-cyclohexylideneamino)-2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile;

1-(1,2-Dimethyl-propylideneamino)-2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile;

1-Cyclohexylideneamino-2-oxo-6-*o*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-*o*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(1,2-Dimethyl-propylideneamino)-2-oxo-6-*o*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Cyclohexylideneamino-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Cyclohexylideneamino-6-(2-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Methyl-cyclohexylideneamino)-6-(2-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(1,2-Dimethyl-propylideneamino)--6-(2-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(1,2-Dimethyl-propylideneamino)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Cyclohexylideneamino-2-oxo-6-*p*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-*p*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(1,2-Dimethyl-propylideneamino)-2-oxo-6-*p*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Cyclohexylideneamino-6-(3-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Methyl-cyclohexylideneamino)-6-(3-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(1,2-Dimethyl-propylideneamino)-6-(3-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Ethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

2-Oxo-6-phenyl-1-(2-phenyl-cyclohexylideneamino)-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Benzyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2,2-Dimethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Chloro-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Methoxy-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Ethoxy-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Methlythio-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

2-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-ylimino)-cyclohexanecarboxylic acid methyl ester;

(3R)-1-(3-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

2-Oxo-6-phenyl-1-phenylamino-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

2-Oxo-1-phenylamino-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-Cyclohexylideneamino-6-(4-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(2-Methyl-cyclohexylideneamino)-6-(4-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

1-(1,2-Dimethyl-propylideneamino)-6-(4-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile;

6-(2-Chloro-phenyl)-1-cyclohexylideneamino-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(2-Chloro-phenyl)-1-(1,2-dimethyl-propylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(3-Chloro-phenyl)-1-cyclohexylideneamino-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(3-Chloro-phenyl)-1-(2-methyl-cyclohexylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(3-Chloro-phenyl)-1-(1,2-dimethyl-propylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(4-Chloro-phenyl)-1-cyclohexylideneamino-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(4-Chloro-phenyl)-1-(2-methyl-cyclohexylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(4-Chloro-phenyl)-1-(1,2-dimethyl-propylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(2-Chloro-phenyl)-1-(2-methyl-cyclohexylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(3-Methoxy-phenyl)-1-(2-methyl-cyclohexylideneamino)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Cyclohexylideneamino-6-(3-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(1,2-Dimethyl-propylideneamino)-6-(3-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-phenyl-4-trifluoromethyl-3',4',5',6'-tetrahydro-2H,2'H-[1,1']bipyridinyl-3-carbonitrile;

2-Oxo-6-phenyl-1-pyrrolidin-1-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-yl)-3-phenyl-urea;

2-Oxo-6-m-tolyl-4-trifluoromethyl-3',4',5',6'-tetrahydro-2H,2'H-[1,1']bipyridinyl-3-carbonitrile;

2-Oxo-1-pyrrolidin-1-yl-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Amino-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Cyclohexylideneamino-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Cyclopentylideneamino-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-1-(1-phenyl-ethylideneamino)-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(1-Benzoyl-piperidin-4-ylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(Benzylidene-amino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Methyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Ethyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-tert-Butyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Methyl-cyclopentylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3-Methyl-cyclopentylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-naphthalen-2-yl-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3-Methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-1-phenethyl-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-1-phenethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-4-methyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Methyl-benzyl)-4-methyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3-Methyl-benzyl)-4-methyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Methyl-benzyl)-4-methyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;

4-Methyl-2-oxo-1-phenethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-phenyl-1-(3-phenyl-propyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-phenyl-4-trifluoromethyl-1-(2-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-phenyl-4-trifluoromethyl-1-(3-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-phenyl-4-trifluoromethyl-1-(4-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Biphenyl-4-ylmethyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(2-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-1-(3-phenyl-propyl)-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(3-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(4-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Biphenyl-4-ylmethyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-(3-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-(2-chloro-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-(3-ethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-(3-trifluoromethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-(3-nitro-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-(3-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-1,6-diphenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

(1R)-2-Oxo-6-phenyl-1-(1-phenyl-ethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

(1S)-2-Oxo-6-phenyl-1-(1-phenyl-ethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-phenyl-1-(1,2,3,4-tetrahydro-naphthalen-1-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-(3-butoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-(3-benzyloxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-2-oxo-6-[3-(2-piperidin-1-yl-ethoxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

N-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-acetamide;

1-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-3-ethyl-urea;

1-(2,4-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester;

1-(2-Chloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Chloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Methylthio-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-1-(4-phenoxy-benzyl)-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

4-(3-Cyano-2-oxo-6-*m*-tolyl-4-trifluoromethyl-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester;

1-(2-Chloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Chloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Methylthio-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-1-(4-phenoxy-benzyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

(1-Benzyl-3-cyano-2-oxo-6-phenyl-1,2-dihydro-pyridin-4-yl)-acetic acid methyl ester;

2-Oxo-6-phenyl-1-(4-trifluoromethoxy-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-phenyl-1-pyridin-3-ylmethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-phenyl-1-pyridin-4-ylmethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Nitro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-*m*-tolyl-1-(4-trifluoromethoxy-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-1-pyridin-3-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-1-pyridin-4-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Nitro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Morpholin-4-yl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-urea;

1-Benzyl-2-oxo-6-(3-phenethyloxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-2-oxo-6-[3-(2,2,2-trifluoro-ethoxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-[3-(3-methyl-butoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxy]-acetic acid methyl ester;

4-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxy]-butyric acid methyl ester;

1-Benzyl-6-[3-(3-hydroxy-propoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-5-methyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-2-oxo-4,6-diphenyl-1,2-dihydro-pyridine-3-carbonitrile;

4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-ylmethyl)-benzoic acid;

Ethyl-carbamic acid 3-(1-benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl ester;

Butyl-carbamic acid 3-(1-benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl ester;

1-Benzyl-6-[3-(2-methyl-benzyloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-[3-(3-methyl-benzyloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Benzyl-6-[3-(4-methyl-benzyloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

4-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxymethyl]-benzoic acid methyl ester;

3-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxymethyl]-benzoic acid methyl ester;

[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxy]-acetic acid;

4-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxy]-butyric acid;

N-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-butyramide;

Cyclohexanecarboxylic acid [3-(1-benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-amide;

N-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-benzamide;

[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-carbamic acid methyl ester;

[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-carbamic acid ethyl ester;

[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-carbamic acid phenyl ester;

6-(3-Amino-phenyl)-1-benzyl-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Cyclohexylmethyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-phenyl-1-thiophen-2-ylmethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(5-Methyl-furan-2-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-phenyl-1-(2,3,5-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Chloro-2-methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3,4-Dichloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Methyl-benzyl)-6-*m*-tolyl-1H-pyridin-2-one;

1-(4-Methyl-benzyl)-6-phenyl-1H-pyridin-2-one;

1-Benzyl-6-m-tolyl-1H-pyridin-2-one;

1-Benzyl-6-phenyl-1H-pyridin-2-one;

2-Oxo-6-phenyl-1-(2,3,4-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-Cyclohexylmethyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-1-thiophen-2-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-*m*-tolyl-1-(2,3,5-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Chloro-2-methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3,4-Dichloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3,4-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,5-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,3-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,5-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3,4-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,3-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3,4-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,5-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,3-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,5-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3,4-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,3-Difluorol-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(3-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

N-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-methanesulfonamide;

6-(3-Ethyl-phenyl)-1-(4-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Methyl-benzyl)-2-oxo-6-p-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(2-Chloro-phenyl)-1-(4-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(3-Chloro-phenyl)-1-(4-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(4-Chloro-phenyl)-1-(4-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

3-[5-Cyano-1-benzyl-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid;

3-[5-Cyano-1-benzyl-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid tert-butyl ester;

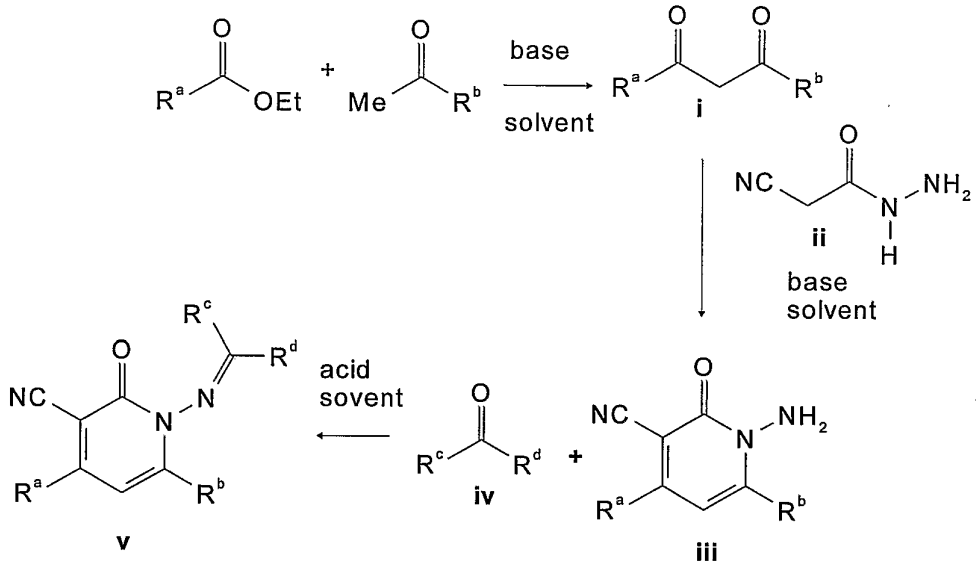
1-Benzyl-6-(3-bromomethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
2-Oxo-6-phenyl-1-(2,2,2-trifluoro-ethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-Benzyl-3-bromo-6-phenyl-1H-pyridin-2-one;
1-Biphenyl-4-ylmethyl-6-phenyl-1H-pyridin-2-one;
1-Benzyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;
3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-N,N-diethyl-benzamide;
1-Benzyl-2-oxo-6-(3-phenoxymethyl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-Benzyl-6-(3-diethylaminomethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-Benzyl-2-oxo-4-pentafluoroethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(4-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-2-oxo-4-pentafluoroethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-2-oxo-6-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-6-(3-ethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-2-oxo-6-p-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-6-(3-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-(4-methoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-6-(2-chloro-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-6-(3-chloro-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;
1-(2,4-Dimethyl-benzyl)-6-(4-chloro-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and
1-Benzyl-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

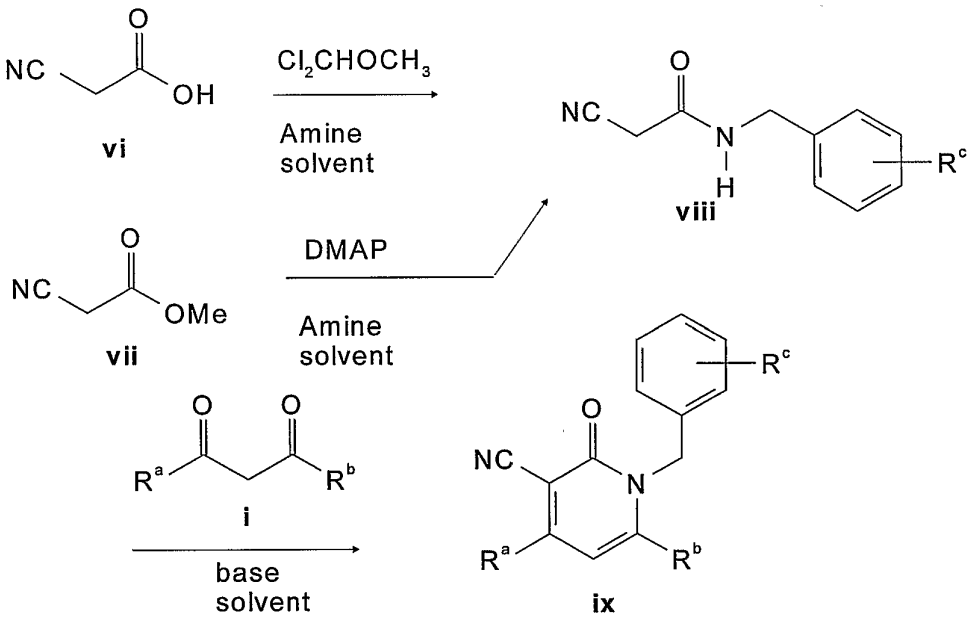
**C. Preparation of the compounds**

The compounds provided herein can be prepared using readily available starting materials or known intermediates. Schemes 1, 2 and 3 (*infra*) provide a summary of the synthetic routes utilized in producing the compounds provided herein.

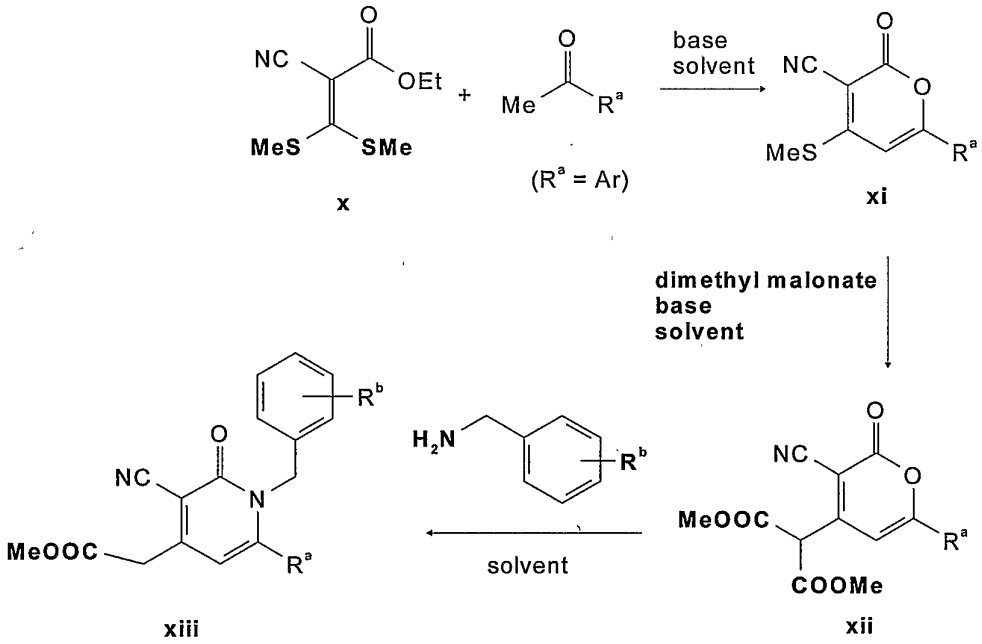
Scheme 1, below, details the synthetic strategy utilized for the construction of N-amino-2-pyridone derivatives **v**. Such hydrazones can be readily obtained via the condensation of N-aminopyridones **iii** with aldehydes ($R^c$ = H) and ketones (as **iv**) in the presence of acids in various solvents. The N-amino-2-pyridone itself is produced by a cyclocondensation reaction between 1,3-diketones **i** and cyanoacetohydrazide **ii** in the presence of various bases (see, *e.g.*, Elgemeie *et al.* (1994) *Org. Prep. Proc. Int. 26*:465-468). The requisite 1,3-dicarbonyl compounds **i** can be obtained from the corresponding esters and methyl ketones using strong bases.




Scheme 2, below, details the synthetic strategy utilized in constructing the N-benzyl-2-pyridone **ix** compounds. These compounds are formed from an analogous cyclocondensation reaction to that used to form the N-aminopyridones. Reaction of cyanoacetamides **viii** with 1,2-diketones **i** using various bases produces N-benzyl-2-pyridones. The requisite cyanoacetamides **viii** are formed from either cyanoacetic acid **vi** or methyl cyanoactate **vii**. Cyanoacetic acid is first activated to its acid chloride using the reagent *α,α*-dichloromethyl methyl ether. The resultant acid chloride is reacted *in situ* with various amines to affect acylation. Direct conversion of methyl cyanoacetate **vii** to the corresponding cyanoacetamides **viii** is carried out with amines and in the presence of the acylation catalyst 4-(dimethylamino)pyridine (DMAP).

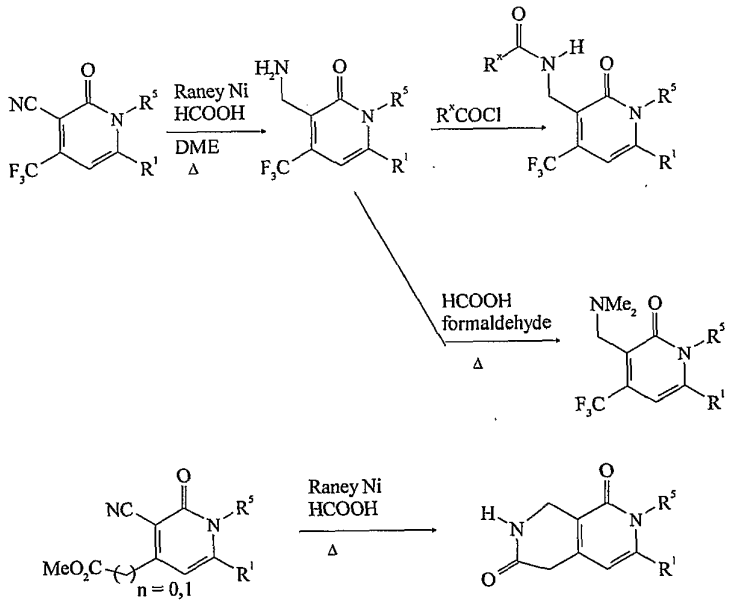



Scheme 3, below, details the synthetic strategy utilized to construct N-benzyl-2-pyridones containing a methoxycarbonylmethyl moiety at the C4-position of the pyridone ring. Compound **xiii** is obtained directly from the diester compound **xii** by reaction with benzylamines (for the conversion of pyrones to *N*-benzyl 2-pyridones, see, *e.g.*, Katrizky *et al.* (1980) *J. Chem. Soc., Perkin Trans. I*:2851-2855). Both pyridone formation and the ester cleavage (via decarboxylation) occur in this single step. The malonate substituted pyrone **xii** derives from the 4-methylsulfide variant **xi** via base-induced substitution with dimethylmalonate (see, *e.g.*, Tominaga *et al.* (1984) *Chem. Pharm. Bull. 32*:3384-3395). Compound **xi** is readily obtained via the cyclocondensation reaction between the commercially available dithiane **x** and methyl ketones.

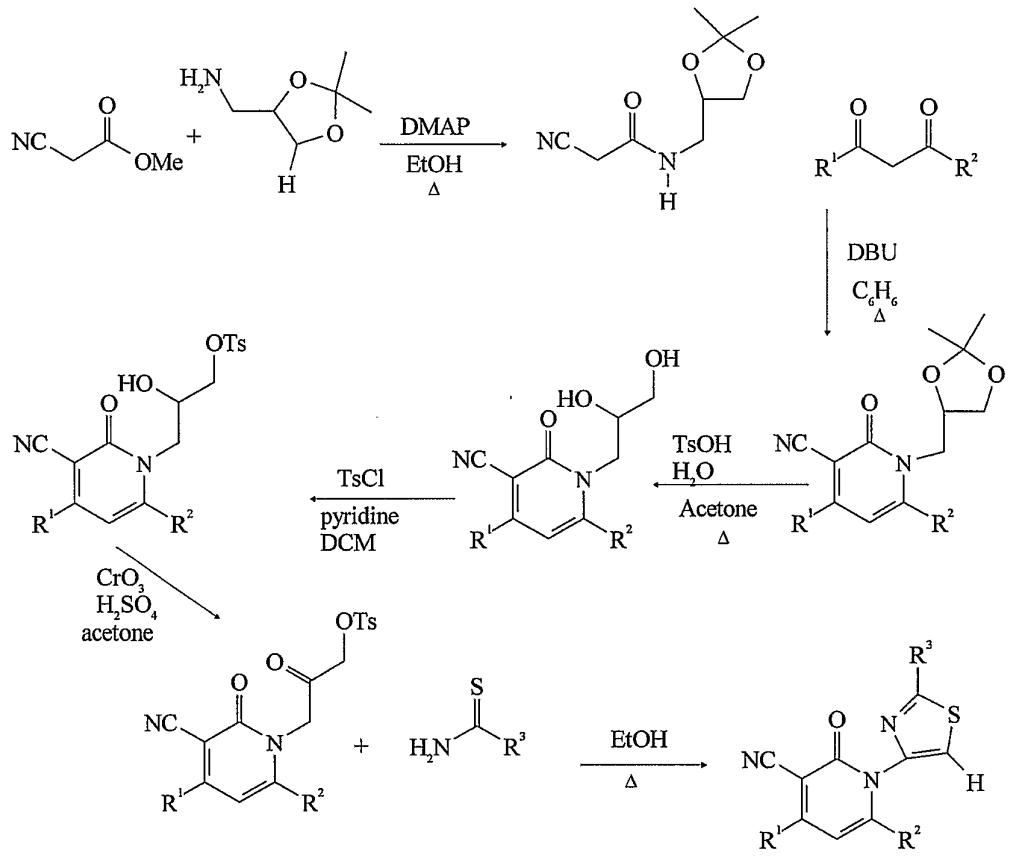



Other methods for the preparation of the compounds provided herein are shown in the Schemes below.

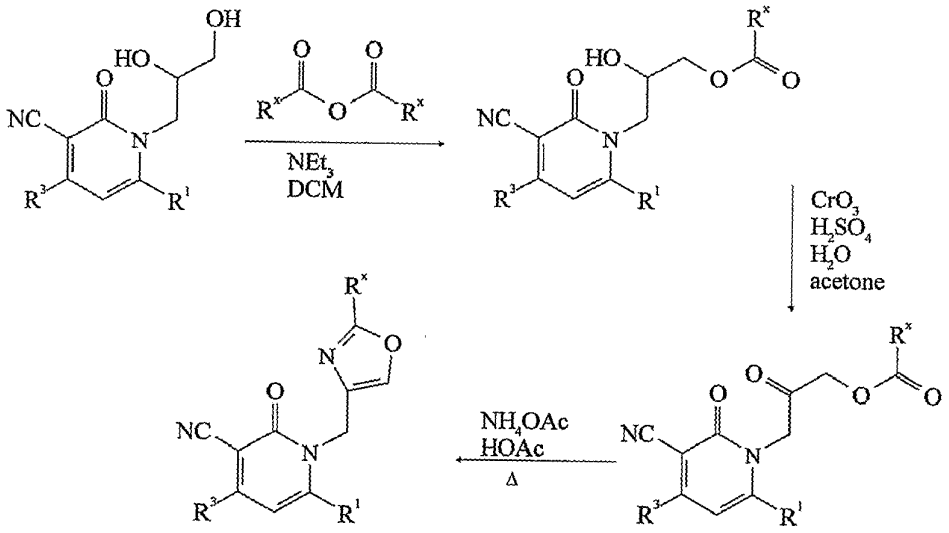
Scheme 4:


Raney Ni
HCOOH
DME
Δ
R*COCl
HCOOH
formaldehyde
Δ
Raney Ni
HCOOH
Δ
n = 0,1

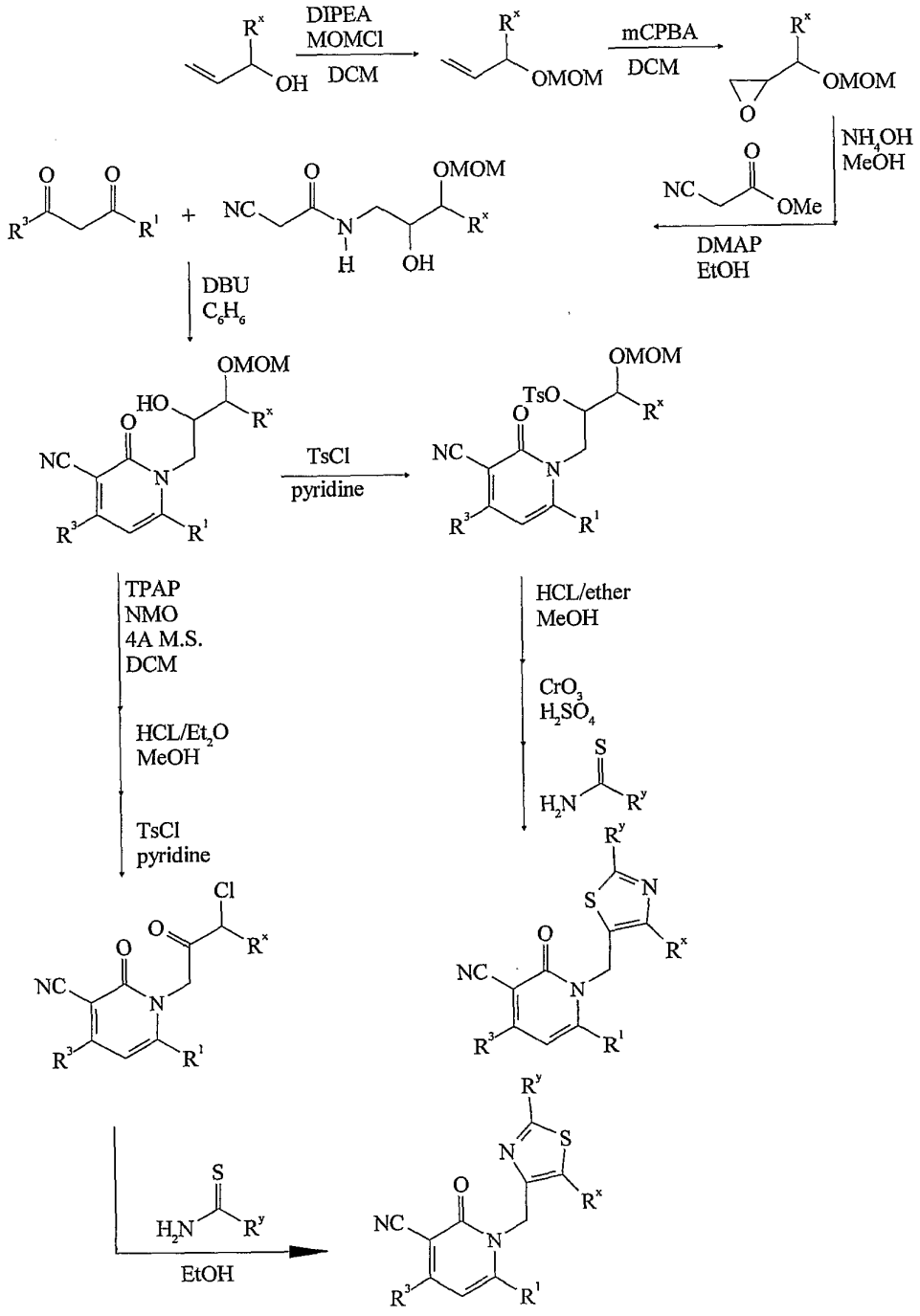
Scheme 5:


DMAP
EtOH
Δ
DBU
$C_6H_6$
Δ
TsOH
$H_2O$
Acetone
Δ
TsCl
pyridine
DCM
$CrO_3$
$H_2SO_4$
acetone
EtOH
Δ

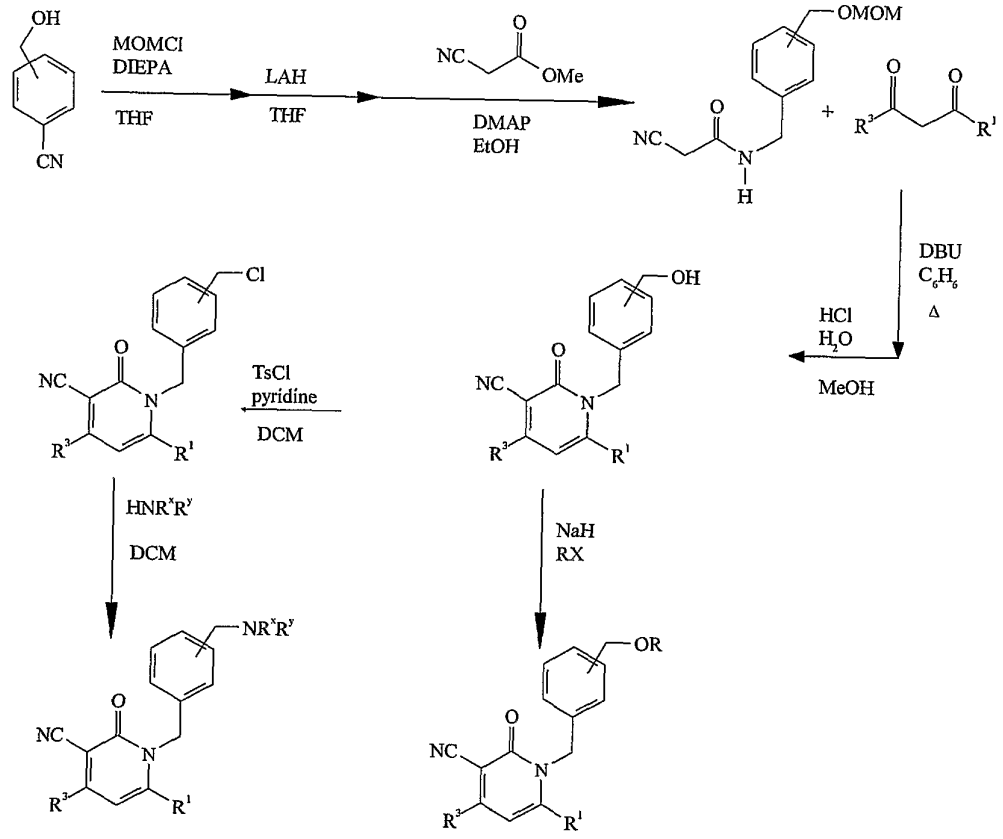
Scheme 6:


OH
HO
O
NC
N
R3
R1
O
O
Rx
O
Rx
NEt3
DCM
R*
HO
O
O
O
NC
N
R3
R1
CrO3
H2SO4
H2O
acetone
R*
O
O
O
NC
N
R3
R1
NH4OAc
HOAc
Δ
Rx
N
O
O
NC
N
R3
R1

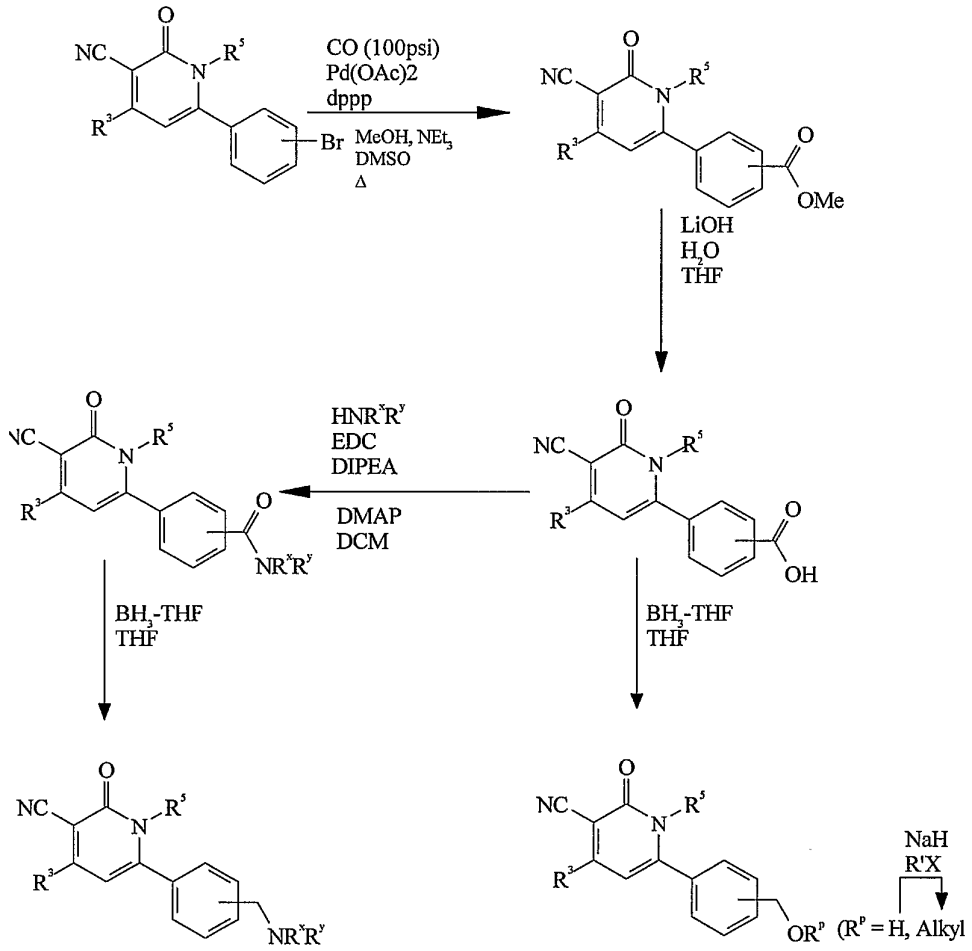
Scheme 7:


DIPEA
MOMCl
DCM
mCPBA
DCM
NH4OH
MeOH
DMAP
EtOH
DBU
C6H6
TsCl
pyridine
TPAP
NMO
4A M.S.
DCM
HCL/Et2O
MeOH
TsCl
pyridine
HCL/ether
MeOH
CrO3
H2SO4
EtOH

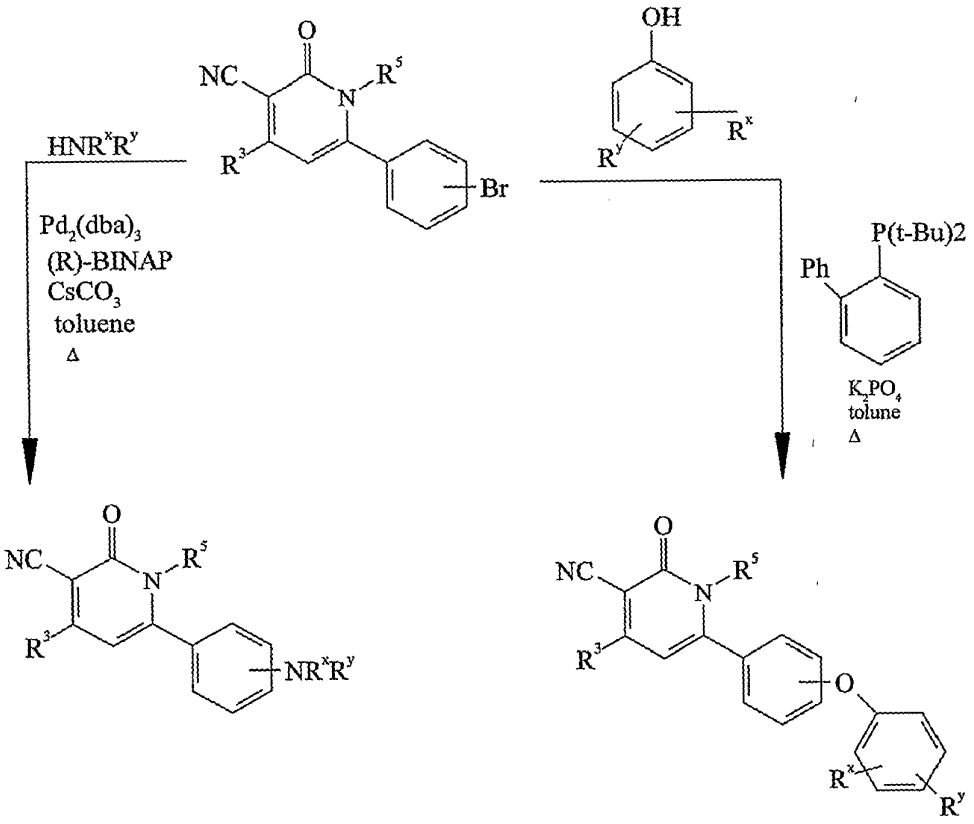
Scheme 8:


OH
CN
MOMCl
DIEPA
THF
LAH
THF
NC
O
OMe
DMAP
EtOH
OMOM
NC
O
N
H
+
O
O
R3
R1
DBU
C6H6
Δ
HCl
H2O
MeOH
OH
NC
O
N
R3
R1
TsCl
pyridine
DCM
Cl
HNRxRy
DCM
NaH
RX
NRxRy
OR

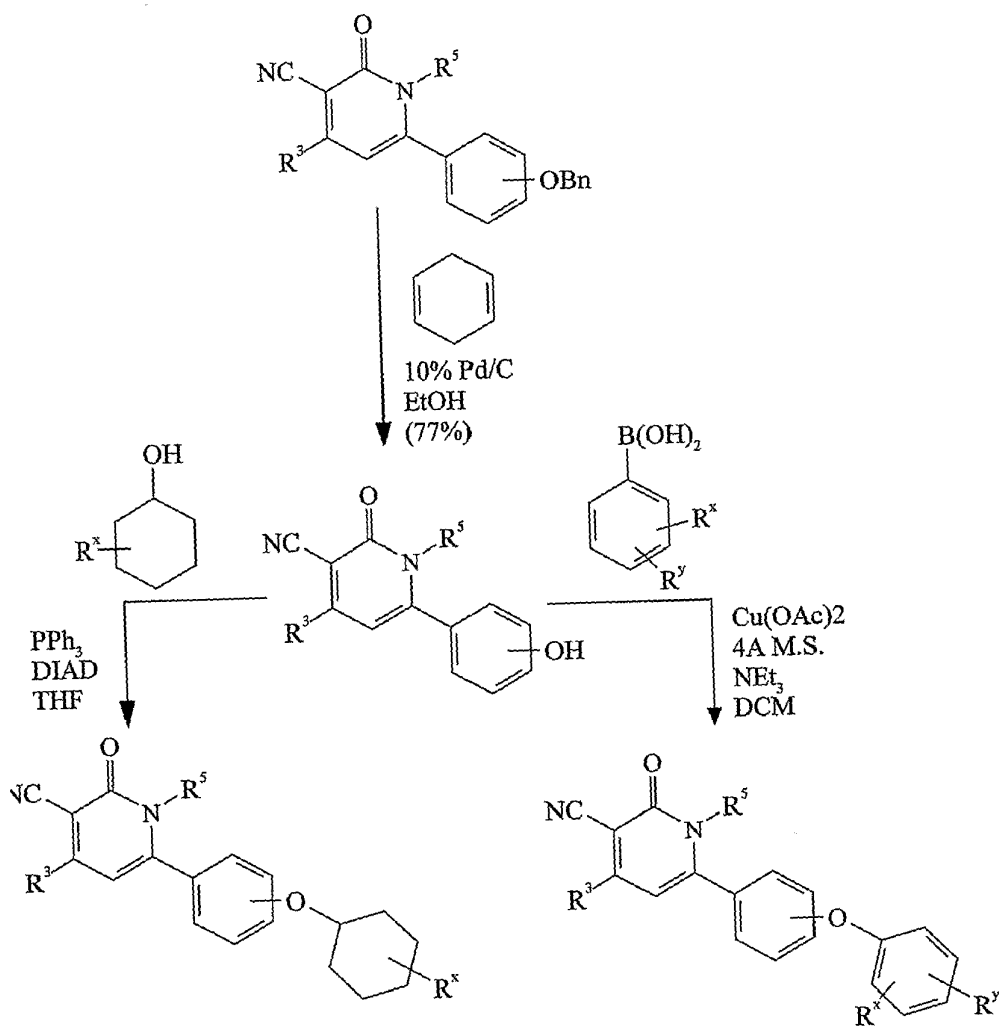
Scheme 9:


CO (100psi)
Pd(OAc)2
dppp
MeOH, NEt3
DMSO
Δ
LiOH
H2O
THF
HNRxRy
EDC
DIPEA
DMAP
DCM
BH3-THF
THF
BH3-THF
THF
NaH
R'X
(Rp = H, Alkyl

Scheme 10:

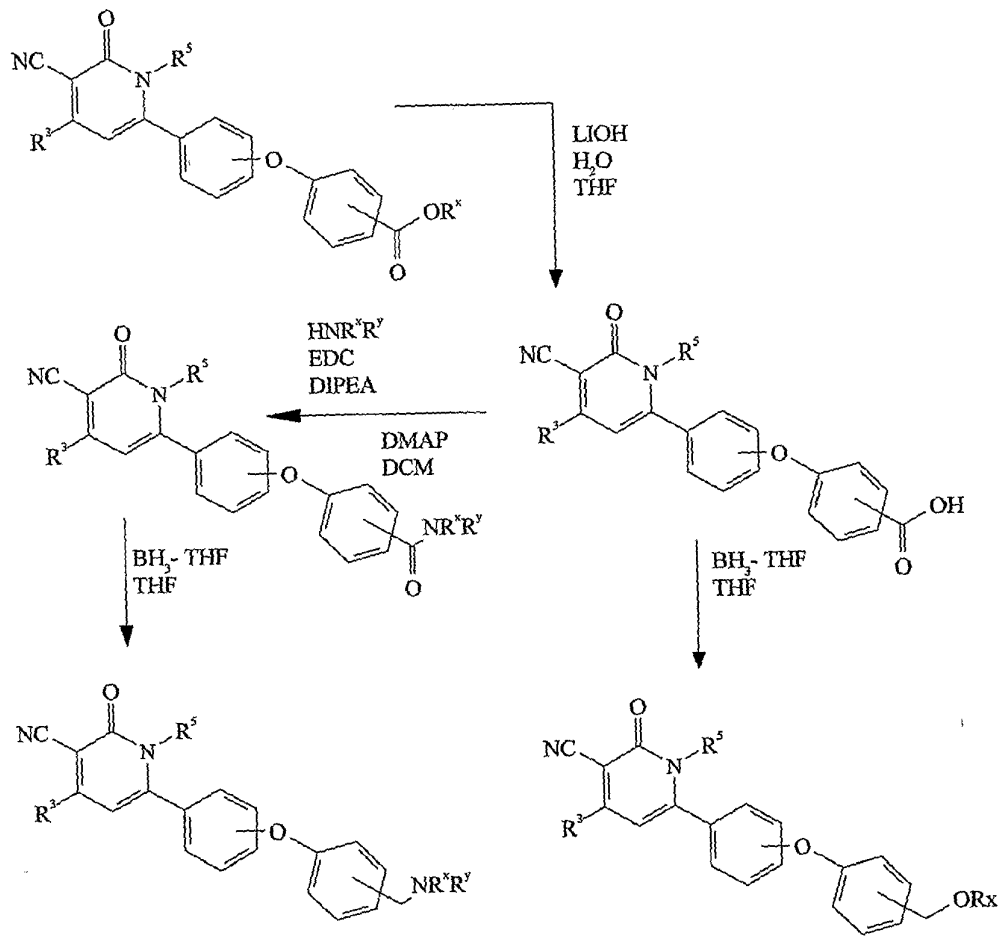

HNR^xR^y
Pd2(dba)3
(R)-BINAP
CsCO3
toluene
Δ
OH
P(t-Bu)2
Ph
K2PO4
tolune
Δ
NC
O
N
R5
R3
Br
NR^xR^y
R^x
R^y

Scheme 11:

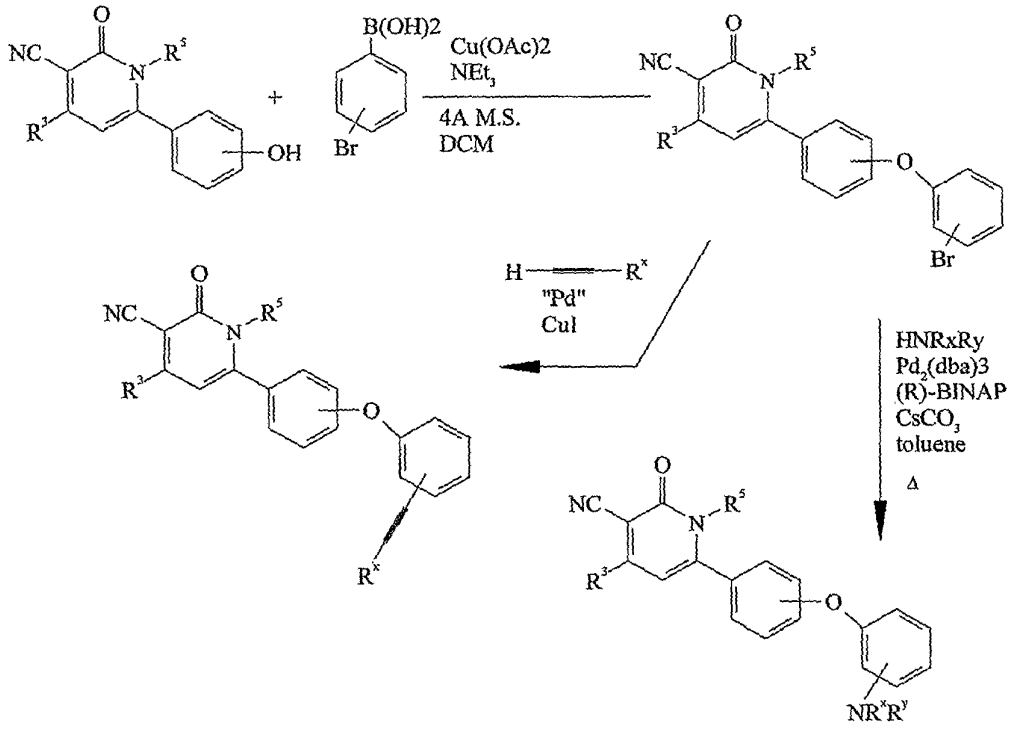

NC
O
N
R5
R3
OBn
10% Pd/C
EtOH
(77%)
OH
Rx
B(OH)2
Ry
PPh3
DIAD
THF
Cu(OAc)2
4A M.S.
NEt3
DCM

5

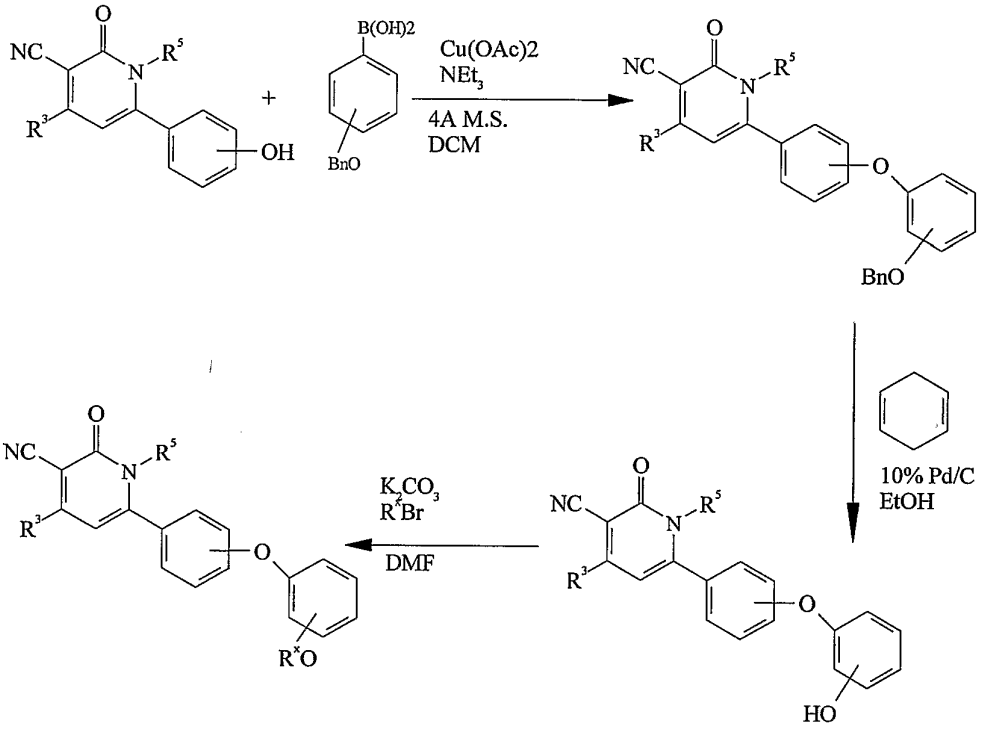
Scheme 12:


LIOH
H2O
THF
HNRxRy
EDC
DIPEA
DMAP
DCM
BH3- THF
THF
BH3- THF
THF
NC
N
R5
R3
O
ORx
OH
NRxRy
ORx

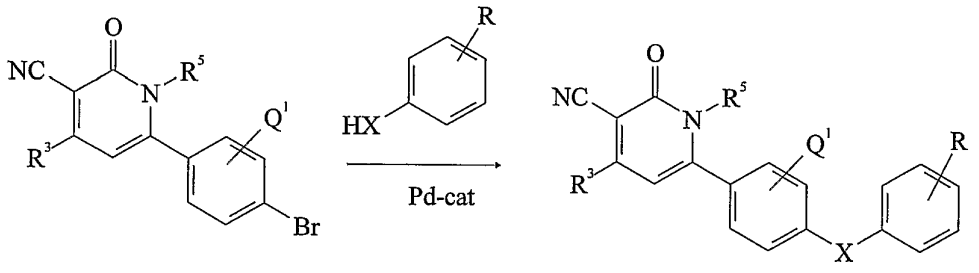
Scheme 13:


B(OH)2
Cu(OAc)2
NEt3
4A M.S.
DCM
OH
Br
H
Rx
"Pd"
CuI
HNRxRy
Pd2(dba)3
(R)-BINAP
CsCO3
toluene
Δ
NRxRy

Scheme 14:

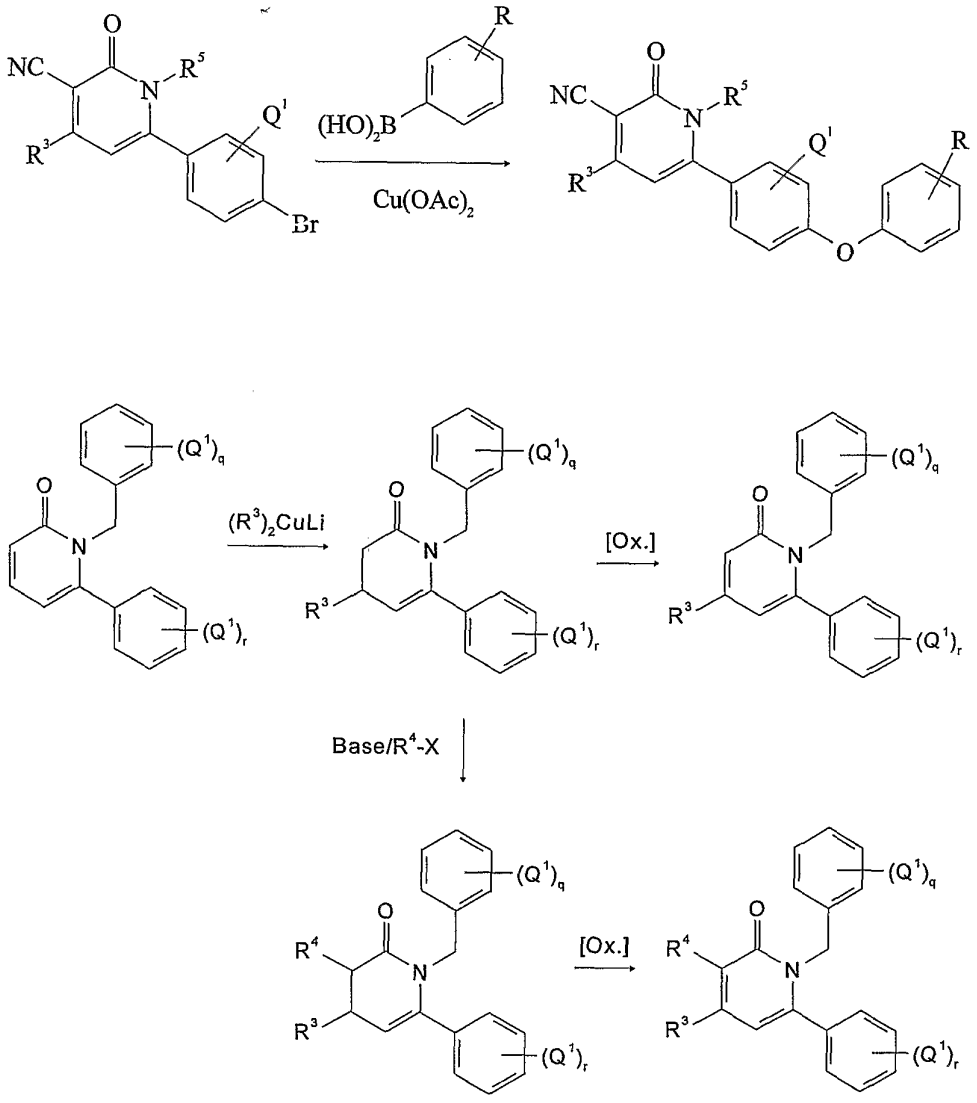


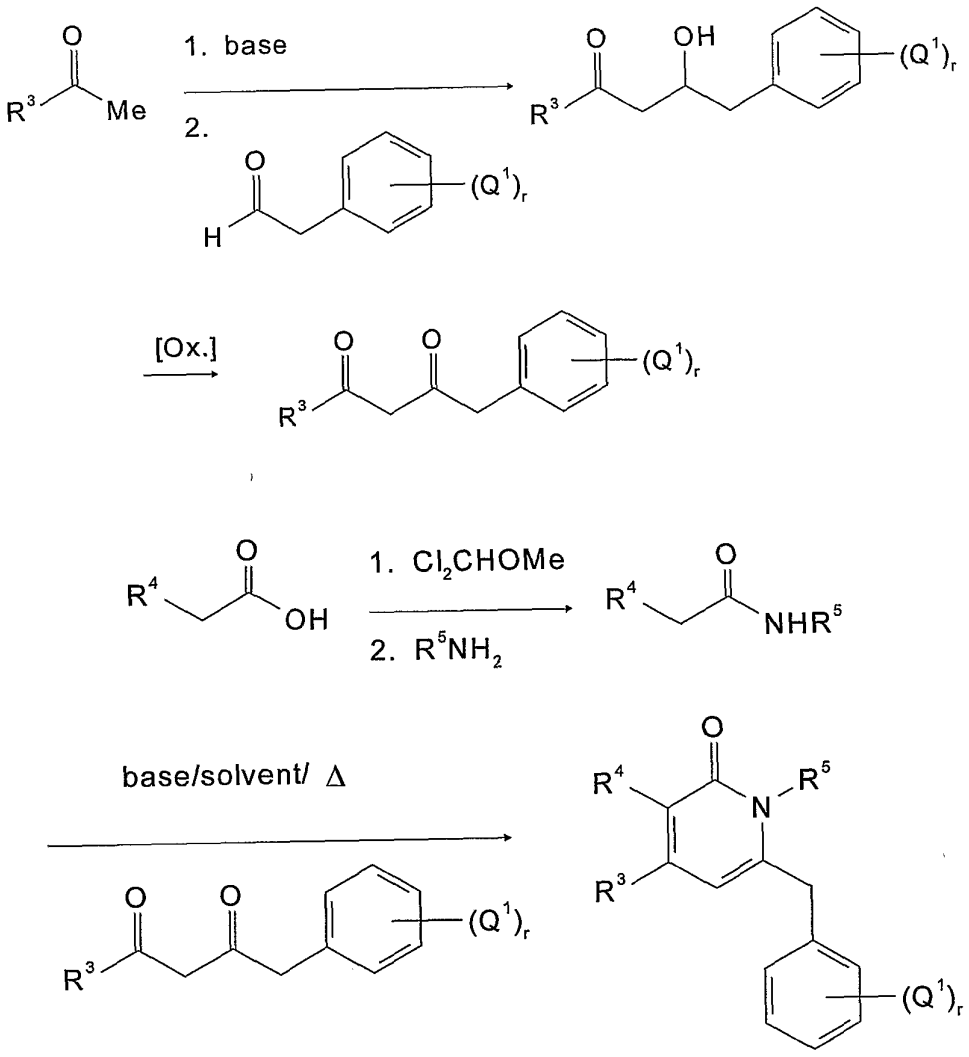

Scheme 15 (see, *e.g.*, Attila *et al.* (1999) *J. Am. Chem. Soc. 121*:4369-4378):

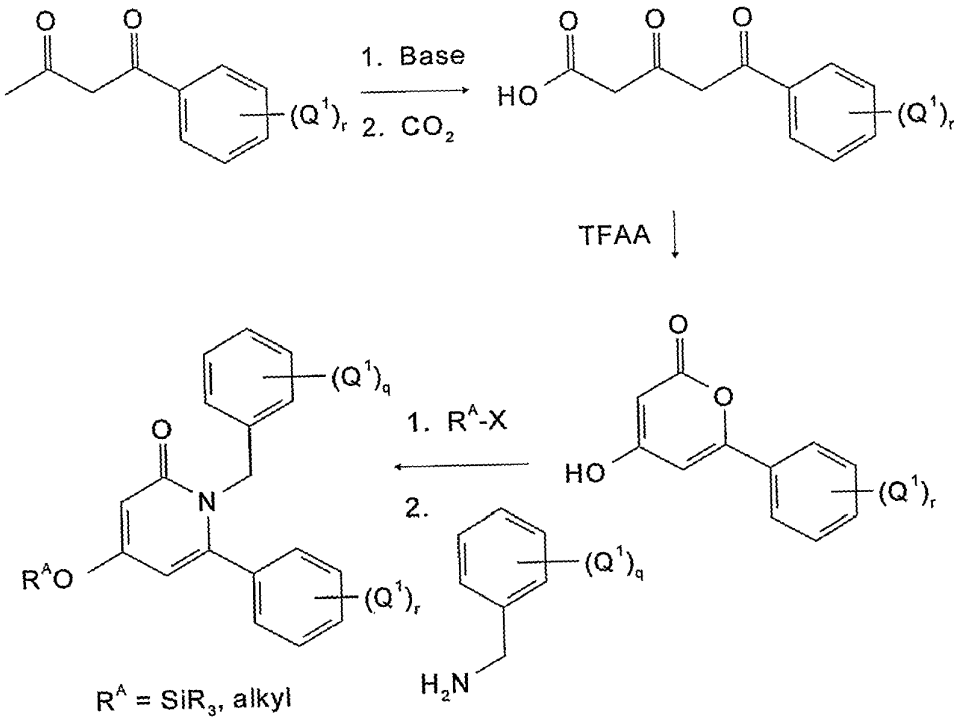


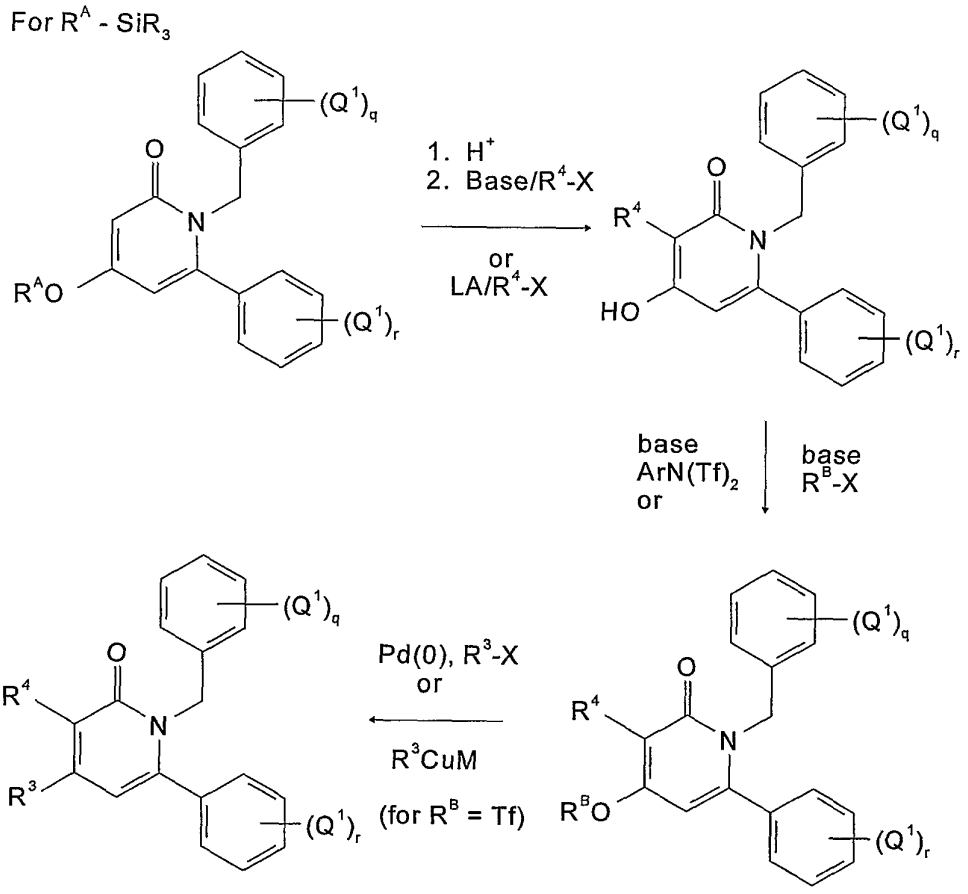

5

Scheme 16 (see, *e.g.*, Evans *et al.* (1998) *Tetrahedron Lett. 39*:2937-2940):




1. base
2.
[Ox.]
1. $Cl_2CHOMe$
2. $R^5NH_2$
base/solvent/ Δ


1. Base
2. $CO_2$
TFAA
1. $R^A$-X
2.
$R^A$ = $SiR_3$, alkyl




Starting materials in the synthesis examples provided herein are either available from commercial sources or via literature procedures. All commercially available compounds were used without further purification unless otherwise indicated. $CDCl_3$ (99.8% D, Cambridge Isotope Laboratories) was used in all experiments as indicated. $^1H$ NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Chemical shifts are reported as parts per million ($\delta$) relative to tetramethylsilane. Mass spectra were recorded on a Perkin-Elmer SCIEX HPLC/MS instrument

using reverse-phase conditions (acetonitrile/water, 0.05% trifluoroacetic acid) and electrospray (ES) ionization. Abbreviations used in the examples below have their accepted meanings in the chemical literature. For example, $CH_2Cl_2$ (dichloromethane), $C_6H_6$ (benzene), TFA (trifluoroacetic acid), EtOAc (Ethyl Acetate), $Et_2O$ (diethyl ether), DMAP (4-dimethylaminopyridine), DMF (N,N-dimethylformamide) and THF (tetrahydrofuran). Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh).

**D. Formulation of pharmaceutical compositions**

The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of the nuclear receptor activity modulators provided herein that are useful in the prevention, treatment, or amelioration of one or more of the symptoms of diseases or disorders associated with nuclear receptor activity, including LXR and/or orphan nuclear receptor activity. Such diseases or disorders include, but are not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

The compositions contain one or more compounds provided herein. The compounds are preferably formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch

preparation and dry powder inhalers. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art (see, *e.g.*, Ansel *Introduction to Pharmaceutical Dosage Forms, Fourth Edition* **1985**, 126).

In the compositions, effective concentrations of one or more compounds or pharmaceutically acceptable derivatives is (are) mixed with a suitable pharmaceutical carrier or vehicle. The compounds may be derivatized as the corresponding salts, esters, enol ethers or esters, acids, bases, solvates, hydrates or prodrugs prior to formulation, as described above. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated. Such diseases or disorders include, but are not limited to, hypercholesterolemia, hyperlipopriteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any

such carriers known to those skilled in the art to be suitable for the particular mode of administration.

In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients. Liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Patent No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulted compound, pelleted by centrifugation, and then resuspended in PBS.

The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein and in International Patent Application Publication Nos. 99/27365 and 00/25134 (see, *e.g.*, EXAMPLES 13 and 14) and then extrapolated therefrom for dosages for humans.

The concentration of active compound in the pharmaceutical composition will depend on absorption, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as

other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated, as described herein.

Typically a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/ml to about 50-100 $\mu$g/ml. The pharmaceutical compositions typically should provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 1000 mg and preferably from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

Pharmaceutically acceptable derivatives include acids, bases, enol ethers and esters, salts, esters, hydrates, solvates and prodrug forms. The derivative is selected such that its pharmacokinetic properties are superior to the corresponding neutral compound.

Thus, effective concentrations or amounts of one or more of the compounds described herein or pharmaceutically acceptable derivatives thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. Compounds are included in an amount effective for ameliorating one or more symptoms of, or for treating or preventing diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated, as described herein. The concentration of active compound in the composition will depend on absorption, inactivation, excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

The compositions are intended to be administered by a suitable route, including orally, parenterally, rectally, topically and locally. For oral administration, capsules and tablets are presently preferred. The compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. Preferred modes of administration include parenteral and oral modes of administration. Oral administration is presently most preferred.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, disposable syringes

or single or multiple dose vials made of glass, plastic or other suitable material.

In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The pharmaceutically therapeutically active compounds and derivatives thereof are typically formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of

unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

The composition can contain along with the active ingredient: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethyl-cellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum acacia-gelatin, glucose, molasses, polvinylpyrrolidine, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event,

contain a quantity of the active compound in an amount sufficient to alleviate the symptoms of the treated subject.

Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain 0.001%-100% active ingredient, preferably 0.1-85%, typically 75-95%.

The active compounds or pharmaceutically acceptable derivatives may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings.

The compositions may include other active compounds to obtain desired combinations of properties. The compounds provided herein, or pharmaceutically acceptable derivatives thereof as described herein, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as diseases or disorders associated with nuclear receptor activity or in which nuclear receptor

activity is implicated. It is to be understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

**1. Compositions for oral administration**

Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

In certain embodiments, the formulations are solid dosage forms, preferably capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any

number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. The active ingredient is a compound or pharmaceutically acceptable derivative

thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

Pharmaceutically acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets are compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film-coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar-coated, multiple compressed and chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in

emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic adds include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule. Such solutions, and the preparation

and encapsulation thereof, are disclosed in U.S. Patent Nos 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be easily measured for administration.

Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. Re 28,819 and 4,358,603. Briefly, such formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more anitoxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are

not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

**2. Injectables, solutions and emulsions**

Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, *e.g.*, U.S. Patent No. 3,710,795) is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and

methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polyporpoylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses throught the outer polymeric membrane in a release rate controlling step. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

The unit-dose parenteral preparations are packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

Injectables are designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, preferably more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the

solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

**3. Lyophilized powders**

Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconsitituted and formulated as solids or gels.

The sterile, lyophilized powder is prepared by dissolving a compound provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbital, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, typically, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Generally, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage (10-1000 mg, preferably 100-500 mg) or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature.

Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, about 1-50 mg, preferably 5-35 mg, more preferably about 9-30 mg of lyophilized powder, is added per mL of sterile water or

other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

**4. Topical administration**

Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

The compounds or pharmaceutically acceptable derivatives thereof may be formulated as aerosols for topical application, such as by inhalation (see, *e.g.*, U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns, preferably less than 10 microns.

The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7, with appropriate salts.

**5. Compositions for other routes of administration**

Other routes of administration, such as topical application, transdermal patches, and rectal administration are also contemplated herein.

For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 gm.

Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

**6. Articles of manufacture**

The compounds or pharmaceutically acceptable derivatives may be packaged as articles of manufacture containing

i) packaging material,

ii) a compound or pharmaceutically acceptable derivative thereof provided herein, which is effective for modulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity is implicated, within the packaging material, and

iii) a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity is implicated.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, *e.g.*, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any disease or disorder in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated as a mediator or contributor to the symptoms or cause.

**E. Evaluation of the Utility of the Compounds**

Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess biological activities that modulate the activity or nuclear receptors, including the LXRs (LXR$\alpha$ and LXR $\beta$). Such assays include, for example, biochemical assays such as binding assays, fluorescence polarization assays, FRET based coactivator recruitment assays (see generally Glickman *et al.*, J. Biomolecular Screening, 7 No. 1 3-10 (2002), as well as cell based assays including the co-transfection assay, the use of LBD-Gal 4 chimeras and protein-protein interaction assays, (see, Lehmann. *et al., J. Biol Chem.,* 272(6) 3137-3140 (1997).

High throughput screening systems are commercially available *(see, e.g.,* Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments Inc., Fullerton, CA; Precision Systems, Inc., Natick, MA) that enable these assays to be run in a high throughput mode. These systems typically automate entire procedures, including all sample and reagent pipetting, liquid dispensing timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. These configurable systems provide high throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for various high throughput systems. Thus, for example, Zymark Corp. provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and the like.

Assays that do not require washing or liquid separation steps are preferred for such high throughput screening systems and include biochemical assays such as fluorescence polarization assays (see for example, Owicki, J., Biomol Screen 2000 Oct; 5(5):297) scintillation

proximity assays (SPA) (see for example, Carpenter *et al.*, Methods Mol Biol 2002; 190:31-49) and fluorescence resonance energy transfer (FRET) or time resolved FRET based coactivator recruitment assays (Mukherjee *et al.*, J Steroid Biochem Mol Biol 2002 Jul;81(3):217-25; (Zhou *et al.*, Mol Endocrinol. 1998 Oct; 12(10):1594-604). Generally such assays can be preformed using either the full length receptor, or isolated ligand binding domain (LBD). In the case of LXR$\alpha$ the LBD comprises amino acids 188-447, for LXR $\beta$ the LDB comprises amino acids 198-461, and for FXR, the LBD comprises amino acids 244 to 472 of the full length sequence.

If a fluorescently labeled ligand is available, fluorescence polarization assays provide a way of detecting binding of compounds to the nuclear receptor of interest by measuring changes in fluorescence polarization that occur as a result of the displacement of a trace amount of the label ligand by the compound. Additionally this approach can also be used to monitor the ligand dependent association of a fluorescently labeled coactivator peptide to the nuclear receptor of interest to detect ligand binding to the nuclear receptor of interest.

The ability of a compound to bind to a receptor, or heterodimer complex with RXR, can also be measured in a homogeneous assay format by assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor using a scintillation proximity assay (SPA). In this approach, the radioactivity emitted by a radiolabelled compound (for example, [$^3$H] 24,25 Epoxycholesterol) generates an optical signal when it is brought into close proximity to a scintillant such as a Ysi-copper containing bead, to which the nuclear receptor is bound. If the radiolabelled compound is displaced from the nuclear receptor the amount of light emitted from the nuclear receptor bound scintillant decreases, and this can be readily

detected using standard microplate liquid scintillation plate readers such as, for example, a Wallac MicroBeta reader.

The heterodimerization of LXR with RXR$\alpha$ can also be measured by fluorescence resonance energy transfer (FRET), or time resolved FRET, to monitor the ability of the compounds provided herein to bind to LXR or other nuclear receptors. Both approaches rely upon the fact that energy transfer from a donor molecule to an acceptor molecule only occurs when donor and acceptor are in close proximity. Typically the purified LBD of the nuclear receptor of interest is labeled with biotin then mixed with stoichiometric amounts of europium labeled streptavidin (Wallac Inc.), and the purified LBD of RXR$\alpha$ is labeled with a suitable fluorophore such as CY5™. Equimolar amounts of each modified LBD are mixed together and allowed to equilibrate for at least 1 hour prior to addition to either variable or constant concentrations of the sample for which the affinity is to be determined. After equilibration, the time-resolved fluorescent signal is quantitated using a fluorescent plate reader. The affinity of the compound can then be estimated from a plot of fluorescence versus concentration of compound added.

This approach can also be exploited to measure the ligand dependent interaction of a co-activator peptide with a nuclear receptor in order to characterize the agonist or antagonist activity of the compounds disclosed herein. Typically the assay in this case involves the use a recombinant Glutathione-S-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide sequence derived from the receptor interacting domain of a co-activator peptide such as the steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

In the presence of an agonist for the nuclear receptor, the peptide is recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the allophycocyanin. Upon excitation of the complex with light at 340 nm excitation energy absorbed by the europium chelate is transmitted to the allophycocyanin moiety resulting in emission at 665 nm. If the europium chelate is not brought into close proximity to the allophycocyanin moiety there is little or no energy transfer and excitation of the europium chelate results in emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an indication of the strength of the protein-protein interaction. The activity of a nuclear receptor antagonist can be measured by determining the ability of a compound to competitively inhibit (*i.e.*, $IC_{50}$) the activity of an agonist for the nuclear receptor.

In addition a variety of cell based assay methodologies may be successfully used in screening assays to identify and profile the specificity of compounds claimed herein. These approaches include the co-transfection assay, translocation assays, complementation assays and the use of gene activation technologies to over express endogenous nuclear receptors.

Three basic variants of the co-transfection assay strategy exist, co-transfection assays using full-length nuclear receptor, co transfection assays using chimeric nuclear receptors comprising the ligand binding domain of the nuclear receptor of interest fused to a heterologous DNA binding domain, and assays based around the use of the mammalian two hybrid assay system.

The basic co-transfection assay is based on the co-transfection into the cell of an expression plasmid to express the nuclear receptor of interest in the cell with a reporter plasmid comprising a reporter gene

whose expression is under the control of DNA sequence that is capable of interacting with that nuclear receptor. (See for example US Patents Nos. 5,071,773; 5,298,429 and 6,416,957). Treatment of the transfected cells with an agonist for the nuclear receptor increases the transcriptional activity of that receptor which is reflected by an increase in expression of the reporter gene, which may be measured by a variety of standard procedures.

For those receptors that function as heterodimers with RXR, such as the LXRs, the co-transfection assay typically includes the use of expression plasmids for both the nuclear receptor of interest and RXR. Typical co-transfection assays require access to the full length nuclear receptor and suitable response elements that provide sufficient screening sensitivity and specificity to the nuclear receptor of interest.

Genes encoding the following full-length previously described proteins, which are suitable for use in the co-transfection studies and profiling the compounds described herein, include human LXR $\alpha$ (SEQ ID 1), human LXR $\beta$ (SEQ ID 3), rat FXR (SEQ ID 5), human FXR (SEQ ID 7), human RXR $\alpha$ (SEQ ID 9), human RXR $\beta$ (SEQ ID 17), human RXR$\gamma$ (SEQ ID 15), human PPAR$\alpha$ (SEQ ID 11) and human PPAR $\delta$ (SEQ ID 13). All accession numbers in this application refer to GenBank accession numbers.

Reporter plasmids may be constructed using standard molecular biological techniques by placing cDNA encoding for the reporter gene downstream from a suitable minimal promoter. For example luciferase reporter plasmids may be constructed by placing cDNA encoding firefly luciferase immediately down stream from the herpes virus thymidine kinase promoter (located at nucleotides residues-105 to +51 of the thymidine kinase nucleotide sequence) which is linked in turn to the various response elements.

Numerous methods of co-transfecting the expression and reporter plasmids are known to those of skill in the art and may be used for the co-transfection assay to introduce the plasmids into a suitable cell type. Typically such a cell will not endogenously express nuclear receptors that interact with the response elements used in the reporter plasmid.

Numerous reporter gene systems are known in the art and include, for example, alkaline phosphatase Berger, J., *et al.* (1988) Gene **66** 1-10; Kain, S.R. (1997) Methods. Mol. Biol. 63 49-60), β-galactosidase (See, U.S. Patent No. 5,070,012, issued Dec, 3, 1991 to Nolan *et al.*, and Bronstein, I., et al., (1989) J. Chemilum. Biolum. 4 99-111), chloramphenicol acetyltransferase (See Gorman et al., Mol Cell Biol. (1982) 2 1044-51), β-glucuronidase, peroxidase, β-lactamase (U.S. Patent Nos. 5,741,657 and 5,955,604), catalytic antibodies, luciferases (U.S. Patents 5,221,623; 5,683,888; 5,674,713; 5,650,289; 5,843,746) and naturally fluorescent proteins (Tsien, R.Y. (1998) Annu. Rev. Biochem. **67** 509-44).

The use of chimeras comprising the ligand binding domain (LBD) of the nuclear receptor of interest fused to a heterologous DNA binding domain (DBD) expands the versatility of cell based assays by directing activation of the nuclear receptor in question to defined DNA binding elements recognized by defined DNA binding domain (see WO95/18380). This assay expands the utility of cell based co-transfection assays in cases where the biological response or screening window using the native DNA binding domain is not satisfactory.

In general the methodology is similar to that used with the basic co-transfection assay, except that a chimeric construct is used in place of the full length nuclear receptor. As with the full length nuclear receptor, treatment of the transfected cells with an agonist for the nuclear receptor LBD increases the transcriptional activity of the

heterologous DNA binding domain which is reflected by an increase in expression of the reporter gene as described above. Typically for such chimeric constructs, the DNA binding domains from defined nuclear receptors, or from yeast or bacterially derived transcriptional regulators such as members of the GAL 4 and Lex A/Umud super families are used.

A third cell based assay of utility for screening compounds claimed herein is a mammalian two-hybrid assay that measures the ability of the nuclear hormone receptor to interact with a cofactor in the presence of a ligand. (See for example, US Patent Nos. US 5,667,973, 5,283,173 and 5,468,614). The basic approach is to create three plasmid constructs that enable the interaction of the nuclear receptor with the interacting protein to be coupled to a transcriptional readout within a living cell. The first construct is an expression plasmid for expressing a fusion protein comprising the interacting protein, or a portion of that protein containing the interacting domain, fused to a GAL4 DNA binding domain. The second expression plasmid comprises DNA encoding the nuclear receptor of interest fused to a strong transcription activation domain such as VP16, and the third construct comprises the reporter plasmid comprising a reporter gene with a minimal promoter and GAL4 upstream activating sequences.

Once all three plasmids are introduced into a cell, the GAL4 DNA binding domain encoded in the first construct allows for specific binding of the fusion protein to GAL4 sites upstream of a minimal promoter. However because the GAL4 DNA binding domain typically has no strong transcriptional activation properties in isolation, expression of the reporter gene occurs only at a low level. In the presence of a ligand, the nuclear receptor-VP16 fusion protein can bind to the GAL4-interacting protein fusion protein bringing the strong transcriptional activator VP16 in close proximity to the GAL4 binding sites and minimal promoter region of the

reporter gene. This interaction significantly enhances the transcription of the reporter gene, which can be measured for various reporter genes as described above. Transcription of the reporter gene is thus driven by the interaction of the interacting protein and nuclear receptor of interest in a ligand dependent fashion.

Any compound which is a candidate for activation of LXR $\alpha$ or LXR $\beta$ may be tested by these methods. Generally, compounds are tested at several different concentrations to optimize the chances that activation of the receptor will be detected and recognized if present. Typically assays are performed in triplicate and vary within experimental error by less than 15%. Each experiment is typically repeated three or more times with similar results.

Activity of the reporter gene can be conveniently normalized to the internal control and the data plotted as fold activation relative to untreated cells. A positive control compound (agonist) may be included along with DMSO as high and low controls for normalization of the assay data. Similarly, antagonist activity can be measured by determining the ability of a compound to competitively inhibit the activity of an agonist.

Additionally the compounds and compositions can be evaluated for their ability to increase or decrease the expression of genes known to be modulated by LXR $\alpha$ or $\beta$ and other nuclear receptors in *vivo*, using Northern-blot, RT PCR or oligonucleotide microarray analysis to analyze RNA levels. Western-blot analysis can be used to measure expression of proteins encoded by LXR target genes. Genes that are known to be regulated by the LXRs include the ATP binding cassette transporters ABCA1, ABCG1, ABCG5, ABCG8, the sterol response element binding protein 1c (SREBP1c) gene, stearoyl CoA desaturase 1 (SCD-1) and the apolipoprotein apoE gene (ApoE).

Established animal models exist for a number of diseases of direct relevance to the claimed compounds and these can be used to further profile and characterize the claimed compounds. These model systems include diabetic dislipidemia using Zucker (fa/fa) rats or (db/db) mice, spontaneous hyperlipidemia using apolipoprotein E deficient mice ($ApoE^{-/-}$), diet-induced hyperlipidemia, using low density lipoprotein receptor deficient mice ($LDR^{-/-}$) and atherosclerosis using both the Apo $E(^{-/-})$ and $LDL(^{-/-})$ mice fed a western diet. (21% fat, 0.05% cholesterol). Additionally LXR or FXR animal models (e.g., knockout mice) can be used to further evaluate the present compounds and compositions *in vivo* (*see*, for example, Peet, *et al., Cell,* 93:693-704 (1998), Sinal, *et al., Cell,* 102: 731-744 (2000)).

**F. Methods of Use of the compounds and compositions**

Methods and compounds for selectively regulating LXR $\alpha$ or LXR $\beta$ are also provided. In one embodiment, such compounds exhibit at least a 10 fold difference in $IC_{50}$, or $EC_{50}$ for LXR $\alpha$ compared to LXR $\beta$.

**F. Methods of use of the compounds and compositions**

Methods of use of the compounds and compositions provided herein are also provided. The methods involve both *in vitro* and *in vivo* uses of the compounds and compositions for altering nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, and for treatment, prevention, or amelioration of one or more symptoms of diseases or disorder that are modulated by nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, or in which nuclear receptor activity, including LXR and/or orphan nuclear receptor activity, is implicated.

Methods of reducing cholesterol levels and of modulating cholesterol metabolism are provided. As described above, LXR is

implicated in modulated cholesteral metabolism and catabolism. See, *e.g.*, International Patent Application Publication No. 00/40965.

Method of altering nuclear receptor activity, including liver X receptor (LXR) and/or orphan nuclear receptor activity, by contacting the receptor with one or more compounds or compositions provided herein, are provided.

Methods of treatment, prevention, or amelioration of one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels are provided.

Methods of treatment, prevention, or amelioration of one or more symptoms of hypercholesterolemia (see, *e.g.*, International Patent Application Publication No. WO 00/57915); hyperlipoproteinemia (see, *e.g.*, International Patent Application Publication No. WO 01/60818); hypertriglyceridemia, lipodystrophy, hyperglycemia or diabetes mellitus (see, *e.g.*, International Patent Application Publication No. WO 01/82917); dyslipidemia, obesity, atherosclerosis, lipid disorders, cardiovascular disorders, or gallstone disease (see, *e.g.*, International Patent Applciation Publication No. WO 00/37077); acne vulgaris or acneiform skin conditions (see, *e.g.*, International Patent Application Publication No. WO 00/49992); atherosclerosis, diabetes, Parkinson's disease, inflammation, immunological disorders, obesity, cancer or Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334); conditions characterized by a perturbed epidermal barrier function or conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. Wo 98/32444) are provided.

Methods of increasing cholesterol efflux from mammalian cells using the compounds and compositions provided herein are provided

(see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Methods of increasing the expression of ATP-Binding Cassette (ABC1) in mammalian cells using the compounds and compositions provided herein are provided (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Methods of treating, preventing, or ameliorating one or more symptoms of hypocholesterolemia using the compounds and compositions provided herein are also provided.

Methods of post-myocardial infarction therapy using the compounds and compositions provided herein are also provided (see, *e.g.*, International Patent Application Publication No. WO 01/03705).

Methods and compounds for selectively regulating LXR $\alpha$ or LXR $\beta$ are also provided. In one embodiment, such compounds exhibit at least a 10 fold difference in $IC_{50}$, or $EC_{50}$ for LXR $\alpha$ compared to LXR $\beta$.

**G. Combination Therapy**

Also contemplated herein is combination therapy using a compound provided herein, or a pharmaceutically acceptable derivative thereof, in combination with one or more of the following: antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors (such as HMG CoA reductase inhibitors, such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin), acyl-coenzyme A:cholesterol acyltransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants (such as anion exchange resins, or quaternary amines (*e.g.*, cholestyramine or colestipol)), low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin $B_6$, vitamin $B_{12}$, anti-oxidant vitamins, $\beta$-blockers, anti-diabetes agents,

angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, aspirin or fibric acid derivatives. The compound provided herein, or pharmaceutically acceptable derivative thereof, is administered simultaneously with, prior to, or after administration of one or more of the above agents. Pharmaceutical compositions containing a compound provided herein and one or more of the above agents are also provided.

Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a LXR selective compound and one or more additional active agents, as well as administration of the LXR selective compound and each active agent in its own separate pharmaceutical dosage formulation. For example, a LXR agonist or antagonist claimed herein and an HMG-CoA reductase inhibitor can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, the compounds described herein and one or more additional active agents can be administered at essentially the same time, *i.e.,* concurrently, or at separately staggered times, *i.e.,* sequentially; combination therapy is understood to include all these regimens.

The compound is, in one embodiment, administered with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor. The term HMG-CoA reductase inhibitor is intended to include all pharmaceutically acceptable salts, esters, free acids and lactone forms of compounds which have HMG-CoA reductase inhibitory activity and, therefore, the use of such salts, esters, free acids and lactone forms is included within the scope the compounds claimed herein. Compounds which have inhibitory activity for HMG-CoA reductase can be readily

identified using assays well-known in the art. For instance, suitable assays are described or disclosed in U.S. Patent No. 4,231,938 and WO 84/02131. Examples of suitable HMG-CoA reductase inhibitors include, but are not limited to, lovastatin (MEVACOR®; *see,* U.S. Patent No. 4,231,938); simvastatin (ZOCOR®; *see,* U.S. Patent No. 4,444,784); pravastatin sodium (PRAVACHOL®; *see,* U.S. Patent No. 4,346,227); fluvastatin sodium (LESCOL®; *see,* U.S. Patent No. 5,354,772); atorvastatin calcium (LIPITOR®; *see,* U.S. Patent No. 5,273,995) and rivastatin (also known as cerivastatin; *see*, U.S. Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that can be used in the methods claimed herein are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs," *Chemistry & Industry,* pp. 85-89 (5 February 1996). In one embodiments, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

Dosage information for HMG-CoA reductase inhibitors is well known in the art, since several HMG-CoA reductase inhibitors are marketed in the U.S. In particular, the daily dosage amounts of the HMG-CoA reductase inhibitor may be the same or similar to those amounts which are employed for anti-hypercholesterolemic treatment and which are described in the *Physicians' Desk Reference* (PDR). For example, see the 50th Ed. of the PDR, 1996 (Medical Economics Co); in particular, see at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase Inhibitors," and the reference pages cited therein. In one embodiment, the oral dosage amount of HMG-CoA reductase inhibitor is from about 1 to 200 mg/day and, in another embodiment, from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA reductase

inhibitor which has sufficiently greater potency may be given in sub-milligram daily dosages.

As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg; for lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; and for pravastatin sodium, 10 mg, 20 mg, and 40 mg. The daily dosage amount for atorvastatin calcium may be in the range of, in one embodiment, from 1 mg to 160 mg and, in another embodiment, from 5 mg to 80 mg. Oral administration may be in a single or divided doses of two, three, or four times daily, although a single daily dose of the HMG-CoA reductase inhibitor is preferred.

The compounds claimed herein can be utilized in methods for decreasing hyperglycemia and insulin resistance or for methods of treating type II diabetes. The compounds can be identified, formulated, and administered as described above.

The methods claimed herein can be used effectively in combination with one or more additional active diabetes agents depending on the desired target therapy (see, e.g., Turner, N. et al. Prog. Drug Res. (1998) 51: 33-94; Haffner, S. Diabetes Care (1998) 21: 160-178; and DeFronzo, R. et al. (eds.), Diabetes Reviews (1997) Vol. 5 No. 4). A number of studies have investigated the benefits of combination therapies with oral agents (see, e.g., Mahler, R., J. Clin. Endocrinol. Metab. (1999) 84: 1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, Diabetes Care (1998) 21: 87-92; Bardin, C. W.,(ed.), CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM, 6th Edition (Mosby--Year Book, Inc., St. Louis, Mo. 1997); Chiasson, J. et al., Ann. Intern. Med. (1994) 121: 928-935; Coniff, R. et al., Clin. Ther. (1997) 19: 16-26; Coniff, R. et al., Am. J. Med. (1995) 98: 443-451; and Iwamoto, Y. et al, Diabet. Med. (1996) 13 365-370; Kwiterovich, P.

Am. J. Cardiol (1998) 82(12A): 3U-17U). These studies indicate that diabetes and hyperlipidemia modulation can be further improved by the addition of a second agent to the therapeutic regimen.

An example of combination therapy that modulates (prevents the onset of the symptoms or complications associated) atherosclerosis, is administered with one or more of the following active agents: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as $\beta$-sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrizol; vitamin $B_6$ (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin $B_{12}$ (also known as cyanocobalamin); vitamin $B_3$ (also known as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, such as vitamin C and E and beta carotene; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin.

Still another example of combination therapy can be seen in modulating diabetes (or treating diabetes and its related symptoms,

complications, and disorders) with, for example, sulfonylureas (such as chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, gliclazide, glynase, glimepiride, and glipizide), biguanides (such as metformin), thiazolidinediones (such as ciglitazone, pioglitazone, troglitazone, and rosiglitazone); and related insulin sensitizers, such as selective and non-selective activators of PPAR$\alpha$, PPAR$\beta$ and PPAR$\gamma$; dehydroepiandrosterone (also referred to as DHEA or its conjugated sulphate ester, DHEA-$SO_4$); antiglucocorticoids; TNF$\alpha$inhibitors; $\alpha$-glucosidase inhibitors (such as acarbose, miglitol, and voglibose), pramlintide (a synthetic analog of the human hormone amylin), other insulin secretagogues (such as repaglinide, gliquidone, and nateglinide), insulin, as well as the active agents discussed above for treating atherosclerosis.

Further provided herein are methods for treating obesity, as well as treating the complications of obesity, by administering a compound claimed herein. The antagonists can be identified, formulated, and administered similarly to the information described above. A LXR selective antagonist includes a partial agonist/antagonist or antagonist that exhibits about a two to about a ten-fold preference for LXR $\alpha$ or $\beta$ compared to another nuclear receptor such as, for example FXR with respect to potency ($IC_{50}$, the concentration of compound that achieves 50% of the maximum reduction in the transcription activity achieved by the compound of interest observed in the presence of a sub-maximal concentration of LXR agonist) and/or efficacy (the maximum percent inhibition of transcription observed with the compound in question).

Another example of combination therapy can be seen in treating obesity or obesity-related disorders, wherein the methods can be effectively used in combination with, for example, phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine, dexfenfluramine,

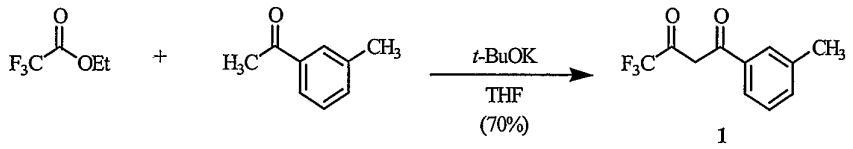
phentiramine, $\beta_3$ adrenoceptor agonist agents; sibutramine, gastrointestinal lipase inhibitors (such as orlistat), and leptins. Other agents used in treating obesity or obesity-related disorders include neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine $H_3$ receptors, dopamine $D_2$ receptors, melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

The following examples are offered by way of illustration and not by way of limitation.

Starting materials in the synthesis examples below are either available from commercial sources or via literature procedures. All commercially available compounds were used without further purification unless otherwise indicated. $CDCl_3$ (99.8% D, Cambridge Isotope Laboratories) was used in all experiments as indicated. $^1H$ NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Chemical shifts are reported as parts per million ($\delta$) relative to tetramethylsilane. Electron Ionization (EI) mass spectra were recorded on a Perkin-Elmer SCIEX HPLC/MS instrument using reverse-phase conditions (acetonitrile/water, 0.05% trifluoroacetic acid). Abbreviations used in the examples below have their accepted meanings in the chemical literature. For example, $CH_2Cl_2$ (dichloromethane), $C_6H_6$ (benzene), TFA (trifloroacetic acid), EtOAc (Ethyl Acetate), $Et_2O$ (diethyl ether), DMAP (4-dimethylaminopyridine), DMF (N,N-dimethylformamide) and THF (tetrahydrofuran). Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh) according to Still *et. al.*[1]

## EXAMPLE 1

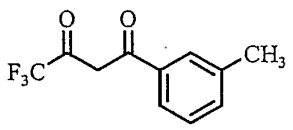
This example illustrates the preparation of compound **1**.




1

Potassium *tert*-butoxide (3.3 g, 28 mmoles, 95% powder) was slowly added to a solution of 3-methylacetophenone (3.2 mL, 23.5 mmoles) in anhydrous THF at 0 °C under nitrogen. The vigorously stirred mixture was

allowed to warm to ambient temperature and was stirred at this temperature for 15 min. After this period the mix was chilled to 0 °C and to it was added ethyl trifluoroacetate (3.4 mL, 28.6 mmoles). The stirring mixture was next allowed the warm to ambient temp and was stirred for 12 hours. After this period the reaction was evaporated *in vacuo* (-THF) and the resulting residue was combined with 30 mL of water. 10% sulfuric acid was carefully added to the stirring mixture to adjust the to pH 6-7 (as indicated using EM Science colorpHast indicator strips, pH 0-14). The mixture was then extracted with $Et_2O$ (3 x 15mL). The combined ether layer was next washed with water (2 x 15 mL) and brine (15 mL). After drying the ether layer over anhydrous $Na_2SO_4$ the solution was evaporated *in vacuo* to yield the crude product as a yellow liquid. The product was purified via vacuum fractional distillation to yield 3.7 g (70% yield) of product as a clear liquid. B.P. 64 °C @ 0.05 mmHg

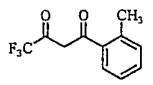


1

4,4,4-Trifluoro-1-*m*-tolyl-butane-1,3-dione

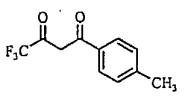
$^1$H-NMR ($CDCl_3$): $\delta$ 15.16 (bs, 1H), 7.76 (s, 1H), 7.74 (d, J=7.2Hz, 1H), 7.45-7.38 (m, 2H), 6.56 (s, 1H), 2.44 (s, 3H).

The following compounds were prepared in a manner similar to that described above.



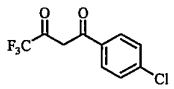
1.1

$^1$H-NMR ($CDCl_3$): $\delta$ 15.0 (br, 1H), 7.60 (m, 1 H), 7.47 (m, 1 H), 7.33 (m, 2 H), 6.36 (s, 1 H), 2.57 (s, 3 H).



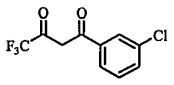
1.2

$^1$H-NMR ($CDCl_3$): $\delta$ 15.1 (br, 1 H), 7.83 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 8.2 Hz, 2 H), 6.52 (s, 1 H), 2.43 (s, 3 H).



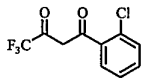
1.3

$^1$H-NMR ($CDCl_3$): $\delta$ 14.8 (br, 1 H), 7.71 (d, J = 8.6 Hz, 2 H), 7.33 (d, J = 8.6 Hz, 2 H), 6.30 (s, 1 H).



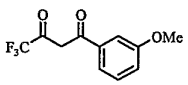
1.4

$^1$H-NMR ($CDCl_3$): $\delta$ 14.7 (br, 1 H), 7.90 (m, 1 H), 7.80 (d, J = 8.0 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.44 (m, 1 H), 6.52 (s, 1 H).



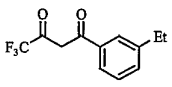
1.5

$^1$H-NMR ($CDCl_3$): $\delta$ 14.4 (br, 1 H), 7.68 (m, 1H), 7.48 (m, 1 H), 7.47 (m, 1 H), 7.39 (m, 1 H), 6.56 (s, 1 H).



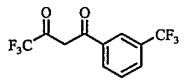
1.6

$^1$H-NMR ($CDCl_3$): $\delta$ 15.09 (br, 1 H), 7.51 (m, 1 H), 7.46 (m, 1 H), 7.41 (m, 1 H), 7.16 (m, 1 H), 6.56 (s, 1 H), 3.88 (s, 3 H).



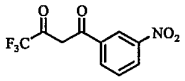
1.7

$^1$H-NMR ($CDCl_3$): $\delta$ 15.18 (br, 1 H), 7.77 (m, 1 H), 7.75 (m, 1 H), 7.46 (m, 1 H), 7.43 (m, 1 H), 6.57 (s, 1 H), 2.73 (q, J = 7.7 Hz, 2 H), 1.28 (t, J = 7.7 Hz, 3 H).



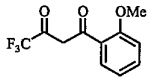
1.8

$^1$H-NMR ($CDCl_3$): $\delta$ 14.89 (br, 1 H), 8.19 (s, 1 H), 8.13 (d, J = 8.1, 1 H), 7.88 (d, J = 8.3 Hz, 1 H), 7.67 (m, 1 H), 6.60 (s, 1 H).



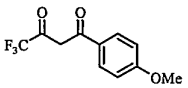
1.9

$^1$H-NMR ($CDCl_3$): $\delta$ 14.75 (br, 1H), 8.78 (m, 1H), 8.48 (m, 1H), 8.29 (m, 1 H), 7.76 (t, J = 8 Hz, 1 H), 6.66 (s, 1H).



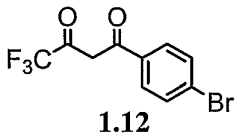
1.10

$^1$H-NMR ($CDCl_3$): $\delta$ 15.25 (br, 1H), 8.0 (m, 1 H), 7.56 (m, 1 H), 7.10 (m, 1 H), 7.02 (m, 1 H), 3.98 (s, 3 H).



1.11

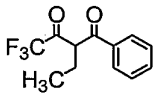
$^1$H-NMR ($CDCl_3$): $\delta$ 15.4 (br, 1H), 7.92 (d, J = 8.8 Hz, 2 H), 6.97 (d, J = 8.8 Hz, 2 H), 6.48 (s, 1 H), 3.89 (s, 3 H).



1.12

1-(4-Bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione

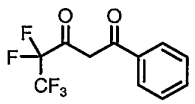
$^{31}$H-NMR ($CDCl_3$): δ 15.0 (s, 1H), 7.82 (d, J=8.6Hz, 2H), 7.66 (d, J=8.6Hz, 2H), 6.54 (s, 1H).



1.13

2-Ethyl-4,4,4-trifluoro-1-phenyl-butane-1,3-dione

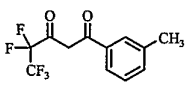
$^{1}$H-NMR ($CDCl_3$): δ 8.05 (bd, J'=8.1Hz, 2H), 7.55 (tt, J'=7.6Hz, J"=1.3Hz, 1H), 7.45 (bt, J=7.3hz, 2H), 4.38 (q, J=7.1Hz, 2H), 1.4 (t, J=7.1Hz, 3H).



1.14

4,4,5,5,5-Pentafluoro-1-phenyl-pentane-1,3-dione

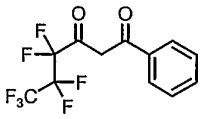
$^{1}$H-NMR ($CDCl_3$): δ 15.32 (bs, 1H), 7.99-7.94 (m, 2H), 7.64 (m, 1H), 7.55-7.48 (m, 2H), 6.64 (s, 1H).



1.15

4,4,5,5,5-Pentafluoro-1-*m*-tolyl-pentane-1,3-dione

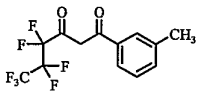
$^1$H-NMR ($CDCl_3$): δ 15.35 (bs, 1H), 7.79-7.73 (m, 2H), 7.47-7.36 (m, 2H), 6.63 (s, 1H), 2.44 (s, 3H).



**1.16**

4,4,5,5,6,6,6-Heptafluoro-1-phenyl-hexane-1,3-dione

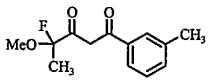
$^1$H-NMR ($CDCl_3$): δ 15.33 (bs, 1H), 7.99-7.94 (m, 2H), 7.67-7.61 (m, 1H), 7.55-7.50 (m, 2H), 6.62 (s, 1H),



**1.17**

4,4,5,5,6,6,6-Heptafluoro-1-*m*-tolyl-hexane-1,3-dione

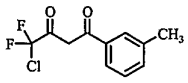
$^1$H-NMR ($CDCl_3$): δ 15.33 (bs, 1H), 7.79-7.73 (m, 2H), 7.47-7.36 (m, 2H), 6.61 (s, 1H), 2.45 (s, 3H).



**1.18**

4-Fluoro-4-methoxy-1-*m*-tolyl-pentane-1,3-dione

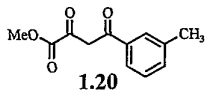
$^1$H-NMR ($CDCl_3$): δ 15.65 (s, 1H), 7.79-7.74 (m, 2H), 7.45-7.36 (m, 2H), 6.68 (d, J=2.0Hz, 1H), 3.61 (s, 3H), 2.44 (s, 3H).



**1.19**

4-Chloro-4,4-difluoro-1-*m*-tolyl-butane-1,3-dione

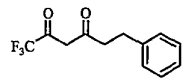
$^1$H-NMR ($CDCl_3$): δ 14.95 (s, 1H), 7.76-7.71 (m, 2H), 7.45-7.36 (m, 2H), 6.52 (s, 1H), 2.44 (s, 3H).



1.20

2,4-Dioxo-4-*m*-tolyl-butyric acid methyl ester

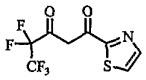
$^1$H-NMR ($CDCl_3$): δ 15.3 (s, 1H), 7.83-7.78 (m, 2H), 7.45-7.36 (m, 2H),7.08 (s, 1H)3.95 (s, 3H), 2.44 (s, 3H).



1.21

1,1,1-Trifluoro-6-phenyl-hexane-2,4-dione

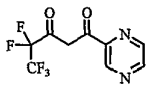
$^1$H-NMR ($CDCl_3$): δ 14.3 (s, 1H), 7.34-7.15 (m, 5H), 5.89 (s, 1H), 2.98 (t, 8.1Hz, 2H), 2.76 (t, J=7.6Hz, 2H).



1.22

4,4,5,5,5-Pentafluoro-1-thiazol-2-yl-pentane-1,3-dione

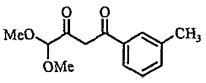
$^1$H-NMR ($CDCl_3$): δ 14.3 (bs, 1H), 8.09 (d, J=3.0Hz, 1H), 7.80 (d, J=3.0Hz, 1H), 7.04 (bs, 1H).



1.23

4,4,5,5,5-Pentafluoro-1-pyrazin-2-yl-pentane-1,3-dione

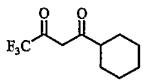
$^1$H-NMR ($CDCl_3$): δ 14.5 (bs, 1H), 9.34 (d, J=1.3Hz, 1H), 8.81 (d, J=2.3Hz, 1H), 8.71 (dd, J'=2.3Hz, J"=1.3Hz, 1H), 7.32 (s, 1H).



1.24

4,4-Dimethoxy-1-*m*-tolyl-butane-1,3-dione

$^1$H-NMR ($CDCl_3$): δ 15.8 (s, 1H), 7.75 (s, 2H), 7.36 (m, 3H), 6.56 (s, 1H), 4.83 (s, 1H), 3.45 (s, 3H).



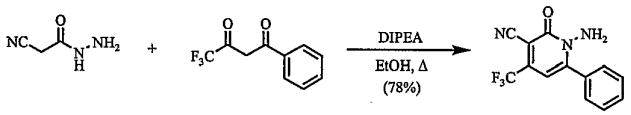
1.27

1-Cyclohexyl-4,4,4-trifluoro-butane-1,3-dione

$^1$H-NMR ($CDCl_3$): δ 5.92 (s, 1H), 2.33 (tt, J'=3.3Hz, J"=11.4Hz, 1H), 1.94-1.63 (m, 5H), 1.47-1.16 (m, 5H).

## EXAMPLE 2

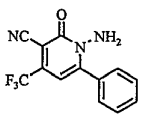
This example illustrates the preparation of compound **2**.




2

4,4,4-Trifluoro-1-phenyl-1,3-butanedione (2.0 g, 9.25 mmoles) and cyanoacetohydrazide (0.92 g, 9.28 mmoles) were combined within a round-bottom flask.

The mixture was dissolved into 30 mL of ethanol and the flask was equipped with a reflux condensor. To the stirring solution was added diisopropylethylamine (0.81 mL, 4.7 mmoles) and the mixture was stirred at 80 °C for 3 hours. After this period the mixture was evaporated and the resulting crude mixture was purified directly by flash silica chromatography using 30% EtOAc/Hexane to yield product 2.01 g (78% yield) as a yellow solid.

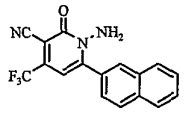


2

1-Amino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): $\delta$ 7.63-7.54 (m, 5H), 6.53 (s, 1H), 5.68 (s, 2H). MS (ES+): 280.0 (M+H).

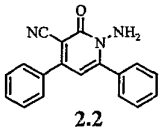
The following compounds were prepared in a manner similar to that described above.



2.1

1-Amino-6-naphthalen-2-yl-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

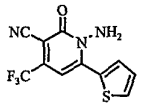
$^1$H-NMR ($CDCl_3$): $\delta$ 8.03 (s, 1H), 7.93 (d, J=8.6Hz, 1H), 7.89-7.85 (m, 2H), 7.62-7.52 (m, 3H), 6.56 (s, 1H), 5.67 (s, 2H).



2.2

1-Amino-2-oxo-4,6-diphenyl-1,2-dihydro-pyridine-3-carbonitrile

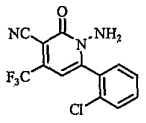
$^1$H-NMR ($CDCl_3$): $\delta$ 7.65 – 7.58 (m, 4 H), 7.56 – 7.46 (m, 6 H), 6.38 (s, 1H), 5.40 (s, 2 H). MS (ES+):288.0 (M+H)



2.3

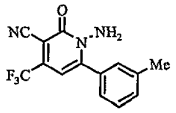
1-Amino-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): $\delta$ 7.95 (m, 1 H), 7.79 (m, 1 H), 7.26 (m, 1 H), 6.91 (s, 1 H), 5.47 (s, 2H). MS (ES+):286.0 (M+H)



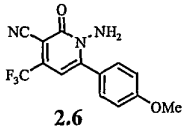
2.4

$^1$H-NMR ($CDCl_3$): $\delta$ 7.57 (m, 1H), 7.56 (m, 1H), 7.49 (m, 1H), 7.39 (m, 1 H), 6.50 (s, 1H), 5.54 (s, 2H).



2.5

$^1$H-NMR ($CDCl_3$): $\delta$ 7.46 – 7.37 (m, 4H), 6.52 (s, 1H), 5.81 (s, 2H), 2.45 (s, 3H).

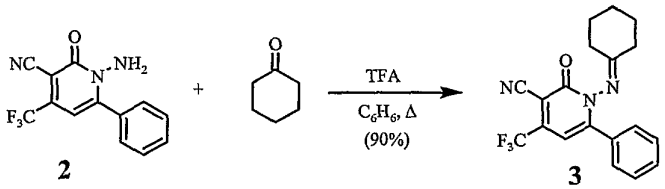


2.6

$^1$H-NMR ($CDCl_3$): $\delta$ 7.64 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 6.51 (s, 1H), 5.78 (s, 2H), 3.90 (s, 3H).

## EXAMPLE 3

This example illustrates the preparation of compound **3**.

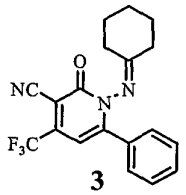



2 3

N-Aminopyridone **2** (70 mg, 0.25 mmoles) was dissolved into 3.0 mL of benzene* within a screw capped vial. To this solution was added cyclohexanone 0.4 mL, 3.9 mmoles) and 2□L of trifluoroacetic acid. The sealed reaction was then shaken at 85 °C for 2 hours. After this period the reaction mixture was evaporated *in vacuo* and the resulting residue was

combined with DCM. The DCM solution was washed with sat'd $NaHCO_3$ (2 x 10 mL), dried over anhydrous $Na_2SO_4$, and was evaporated to yield the crude product. The crude product was purified using flash silica chromatography (30% EtOAc/Hexane) to yield 82 mg (90% yield) of product as a yellow residue.

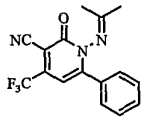
(* - DCM may be used as an alternative with heating at 50 °C)



3

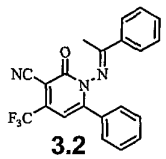
$^1$H-NMR ($CDCl_3$): $\delta$ 7.53-7.45 (m, 3H), 7.41-7.39 (m, 2H), 6.50 (s, 1H), 2.47-2.44 (m, 1H), 2.39-2.34 (m, 1H), 2.20-2.14 (m, 1H), 2.07-2.02 (m, 1H), 1.88-1.85 (m, 2H), 1.60-1.55 (m, 2H), 1.44-1.42 (m, 1H), 1.35-1.31 (m, 1H). MS (ES+): 360.0 (M+H)

The following compounds were prepared in a manner similar to that described above.



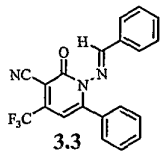
3.1

$^1$H-NMR ($CDCl_3$): $\delta$ 7.52-7.47 (m, 3H), 7.40-7.37 (m, 2H), 6.50 (s, 1H), 2.12 (s, 3H), 1.85 (s, 3H). MS (ES+): 320.0 (M+H).



3.2

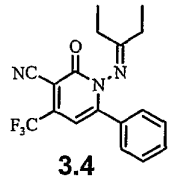
$^1$H-NMR ($CDCl_3$): $\delta$ 7.68 (dd, J'=8.4Hz, J"=1.2Hz, 2H), 7.49-7.43 (m, 6H), 7.38 (t, J= 8Hz, 2H), 6.58 (s, 1H), 2.27 (s, 3H). MS (ES+): 382.0 (M+H).



3.3

1-(Benzylidene-amino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

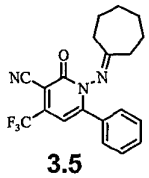
$^1$H-NMR ($CDCl_3$): $\delta$ 8.97 (s, 1H), 7.66 (dd, J'=7.6Hz, J"=0.8Hz, 2H), 7.54-7.41 (m, 8H), 6.57 (s, 1H). MS (ES+): 368.0 (M+H).



3.4

1-(1-Ethyl-propylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): $\delta$ 7.52-7.41 (m, 5H), 6.49 (s, 1H), 2.52-2.44 (m, 1H), 2.38-2.31 (m, 1H), 2.18-2.10 (m, 1H), 2.01-1.92 (m, 1H), 1.02-0.97 (m, 6H). MS (ES+): 348.0 (M+H).



3.5

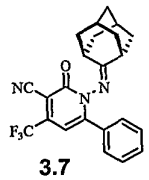
1-Cycloheptylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): $\delta$ 7.54-7.44 (m, 5H), 6.49 (s, 1H), 2.62-2.54 (m, 2h), 2.45-2.39 (m, 1H), 2.08-2.00 (m, 1H), 1.75-1.45 (m, 6H), 1.12-1.06 (m, 2H). MS (ES+): 374.0 (M+H).

3.6

1-Cyclopentylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

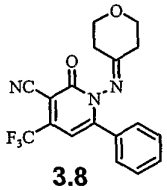
$^1$H-NMR ($CDCl_3$): $\delta$ 7.54-7.45 (m, 3H), 7.40 (dd, J'=8Hz, J"=1.2Hz, 2H), 2.85-2.0 (m, 8H). MS (ES+): 346.0 (M+H).



3.7

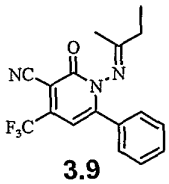
1-(Adamantan-2-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): $\delta$ 7.53-7.45 (m, 5H), 6.49 (s, 1H), 2.82 (bs, 1H), 2.37 (bs, 1H), 2.21 (d, J=12.5Hz, 1H), 2.14 (d, J=12.8Hz, 1H), 2.03-1.99 (m, 2H), 1.90-1.76 (m, 6H), 1.25 (d, J=12.8Hz, 1H), 1.08 (d, J=12.5Hz, 1H). MS (ES+): 412.2 (M+H).



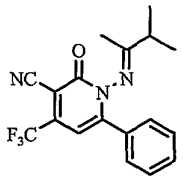
3.8

$^1$H-NMR ($CDCl_3$): $\delta$ 7.56-7.47 (m, 3H), 7.40-7.37 (m, 2H), 6.52 (s, 1H), 3.95-3.89 (m, 2H), 3.69-3.65 (m, 1H), 3.58-3.54 (m, 1H), 2.68-2.63 (m, 1H), 2.47-2.35 (m, 2H), 2.16-2.12 (m, 1H). MS (ES+): 261.8 (M+H).



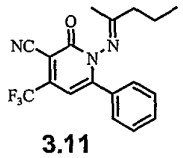
3.9

$^1$H-NMR ($CDCl_3$): $\delta$ 7.51-7.44 (m, 3H), 7.42-7.38 (2H), 6.50 (s, 1H), 2.55-2.45 (m, 1H), 2.40-2.25 (m, 1H), 1.81 (s, 3H), 1.01 (t, J=7.6Hz, 3H). MS (ES+): 334.2 (M+H).



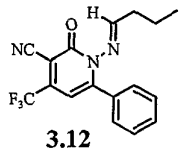
**3.10**

$^1$H-NMR ($CDCl_3$): $\delta$ 7.51-7.43 (m, 3H), 7.39-7.37 (m, 2H), 6.50 (s, 1H), 2.63 (m, J=6.9Hz, 1H), 1.78 (s, 3H), 1.04 (d, J=6.9Hz, 3H), 1.00 (d, J=6.9Hz, 3H).



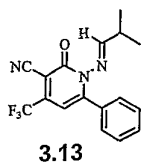
**3.11**

$^1$H-NMR ($CDCl_3$): $\delta$ 7.52-7.44 (m, 3H), 7.40-7.37 (m, 2H), 6.50 (s, 1H), 2.40-2.30 (m, 2H), 1.81 (s, 3H), 1.53-1.45 (m, 2H), 0.80 (t, J=7.4hz, 3H).



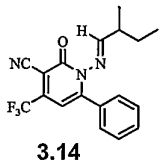
**3.12**

$^1$H-NMR ($CDCl_3$): $\delta$ 8.16 (t, J=5.4Hz, 1H), 7.53-7.45 (m, 3H), 7.42-7.38 (m, 2H), 6.48 (s, 1H), 2.47-2.42 (m, 2H), 1.61-1.52 (m, 2H), 0.89 (t, J=7.4Hz, 3H). MS (ES+): 334.2 (M+H).



**3.13**

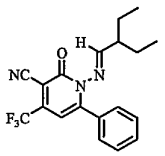
$^1$H-NMR ($CDCl_3$): $\delta$ 8.07 (d, J=5.2Hz, 1H), 7.51-7.45 (m, 3H), 7.41-7.38 (m, 2H), 6.49 (s, 1H), 2.78-2.65 (m, 1H), 1.09 (d, J=6.8Hz, 6H).



**3.14**

1-(2-Methyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

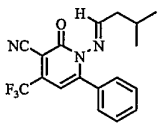
$^1$H-NMR ($CDCl_3$): $\delta$ 8.01 (d, J=6.2Hz, 1H), 7.53-7.44 (m, 3H), 7.42-7.39 (m, 2H), 6.48 (s, 1H), 2.53-2.44 (m, J=6.8Hz, 1H), 1.53-1.40 (m, 2H), 1.06 (d, J=6.8Hz, 3H), 0.86 (t, J=7.5Hz, 3H).



**3.15**

1-(2-Ethyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

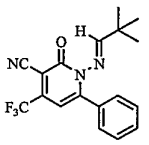
$^1$H-NMR ($CDCl_3$): $\delta$ 7.92 (d, J=7.4Hz, 1H), 7.52-7.40 (m, 5H), 6.47 (s, 1H), 2.29-2.23 (m, 1H), 1.57-1.44 (m, 4H), 0.81 (t, J=7.4, 6H). MS (ES+): 362.0 (M+H).



**3.16**

1-(3-Methyl-butylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

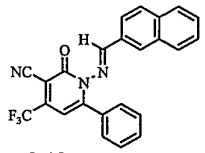
$^1$H-NMR ($CDCl_3$): $\delta$ 8.15 (t, J=5.9Hz, 1H), 7.53-7.44 (m, 3H), 7.42-7.39 (m, 2H), 6.48 (s, 1H), 2.34 (t, J=5.9Hz, 2H), 1.96 (m, J=6.7Hz, 1H), 0.91 (d, J=6.7Hz, 6H).



3.17

1-(2,2-Dimethyl-propylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

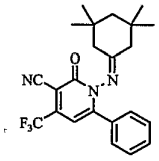
$^1$H-NMR ($CDCl_3$): $\delta$ 8.03 (s, 1H), 7.51-7.44 (m, 3H), 7.40-7.38 (m, 2H), 6.49 (s, 1H), 1.08 (s, 9H). MS (ES+): 348.0 (M+H).



3.18

1-[(Naphthalen-2-ylmethylene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

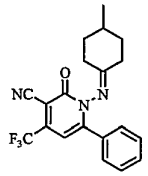
$^1$H-NMR ($CDCl_3$): $\delta$ 9.12 (s, 1H), 8.09 (s, 1H), 7.91-7.74 (m, 4H), 7.62-7.44 (m, 7H), 6.59 (s, 1H). MS (ES+): 418.0 (M+H).



3.19

2-Oxo-6-phenyl-1-(3,3,5,5-tetramethyl-cyclohexylideneamino)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

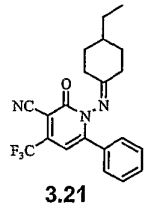
MS(ES+): 416.0 (M+H)



3.20

1-(4-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

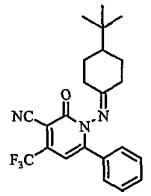
MS(ES+): 374.0 (M+H)



3.21

1-(4-Ethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

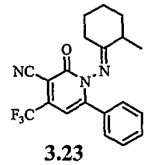
MS(ES+): 388.0 (M+H)



3.22

1-(4-*tert*-Butyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

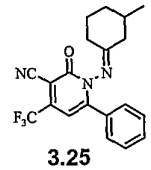
MS(ES+): 416.2 (M+H)



3.23

1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

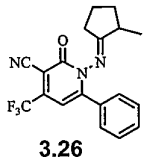
MS(ES+): 374.0 (M+H)



3.25

1-(3-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

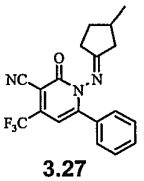
MS(ES+): 374.0 (M+H)



3.26

1-(2-Methyl-cyclopentylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

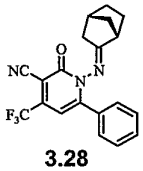
MS(ES+): 360.0 (M+H)



3.27

1-(3-Methyl-cyclopentylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

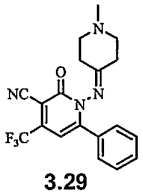
MS(ES+): 360.0 (M+H)



3.28

1-(Bicyclo[2.2.1]hept-2-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

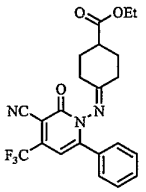
MS(ES+): 372.0 (M+H)



3.29

1-(1-Methyl-piperidin-4-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

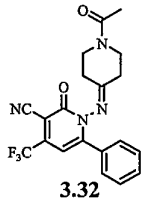
MS(ES+): 375.0 (M+H)



3.30

4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2*H*-pyridin-1-ylimino)-cyclohexanecarboxylic acid ethyl ester

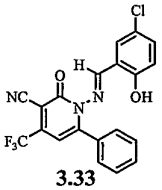
MS(ES+): 432.2 (M+H)



3.32

1-(1-Acetyl-piperidin-4-ylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

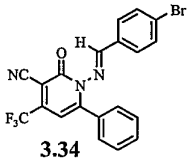
MS(ES+): 403.0 (M+H)



3.33

1-[(5-Chloro-2-hydroxy-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

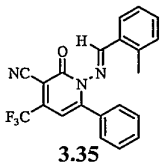
MS(ES+): 418.0 (M+H)



3.34

1-[(4-Bromo-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbon

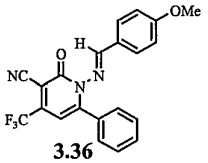
MS(ES+): 446.0 (M+H)



3.35

1-[(2-Methyl-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

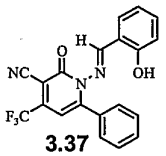
MS(ES+): 382.2 (M+H)



3.36

1-[(4-Methoxy-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

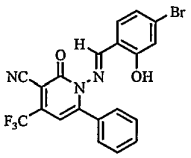
MS(ES+): 398.0 (M+H)



3.37

1-[(2-Hydroxy-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

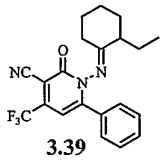
MS(ES+): 384.0 (M+H)



3.38

1-[(4-Bromo-2-hydroxy-benzylidene)-amino]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

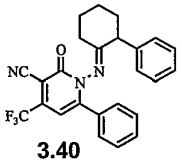
MS(ES+): 462.0 (M+H)



3.39

1-(2-Ethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

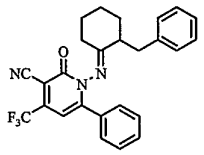
MS(ES+): 388.0 (M+H)



3.40

2-Oxo-6-phenyl-1-(2-phenyl-cyclohexylideneamino)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

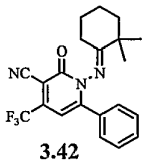
MS(ES+): 436.2 (M+H)



3.41

1-(2-Benzyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

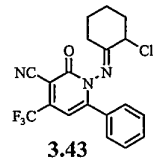
MS(ES+): 450.2 (M+H)



3.42

1-(2,2-Dimethyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

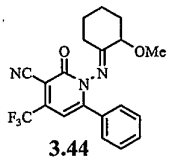
MS(ES+): 388.0 (M+H)



3.43

1-(2-Chloro-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

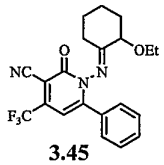
MS(ES+): 393.8 (M+H)



3.44

1-(2-Methoxy-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

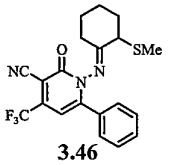
MS(ES+): 390.2 (M+H)



3.45

1-(2-Ethoxy-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

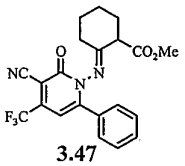
MS(ES+): 404.0 (M+H)



3.46

1-(2-Methylsulfanyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

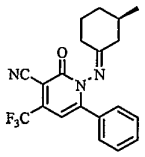
MS(ES+): 406.2 (M+H)



3.47

2-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2*H*-pyridin-1-ylimino)-cyclohexanecarboxylic acid methyl ester

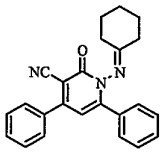
MS(ES+): 418.0 (M+H)



3.48

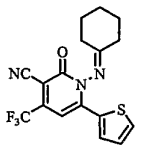
1-(3-Methyl-cyclohexylideneamino)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 374.0 (M+H)



3.49

$^1$H-NMR ($CDCl_3$): $\delta$ 7.60 (m, 2H), 7.44 (m, 4 H), 7.36 (m, 4H), 6.30 (s, 1H), 2.40 (m, 1H), 2.30 (m, 1H), 2.16 (m, 1H), 2.10 (m, 1H), 1.80 (m, 2H), 1.63 (m, 1H), 1.53 (m, 1H), 1.32 (m, 1H).

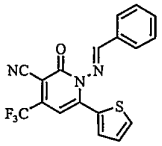


3.50

1-Cyclohexylideneamino-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

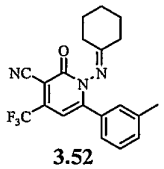
MS (ES+):366.2 (M+H)

$^1$H-NMR ($CDCl_3$): $\delta$ 7.77 (m, 2H), 7.74 (m, 1H), 7.21 (m, 1H), 6.89 (s, 1H), 2.72 (m, 2H), 2.23 (m, 1H), 2.10 (m, 1H), 2.03 (m, 1H), 1.87 (m, 2H), 1.68 (m, 2H), 1.44 (m, 1H).



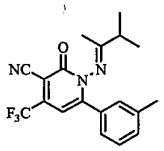
3.51

$^1$H-NMR ($CDCl_3$): $\delta$ 8.89 (s, 1H), 7.88 (m, 1H), 7.86 (m, 1H), 7.74 (m, 1H), 7.66 (m, 1H), 7.56 (m, 1H), 7.46 (m, 2H), 7.12 (m, 1H), 6.89 (s, 1H).



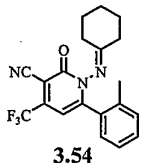
3.52

$^1$H-NMR ($CDCl_3$): $\delta$ 7.35 (m, 1H), 7.32 (m, 1H), 7.20 (m, 1H), 7.19 (m, 1H), 6.49 (s, 1H), 2.48 (m, 1H), 2.41 (s, 3H), 2.38 (m, 1H), 2.20 (m, 1H), 2.07 (m, 1H), 1.88 (m, 2H), 1.61 (m, 2H), 1.46 (m, 1H), 1.37 (m, 1H).



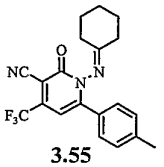
3.53

$^1$H-NMR ($CDCl_3$): $\delta$ 7.33 (m, 1H), 7.31 (m, 1H), 7.19 (m, 1H), 7.17 (m, 1H), 6.49 (s, 1H), 2.64 (m, J = 6.8 Hz, 1H), 2.40 (s, 3H), 1.79 (s, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H).



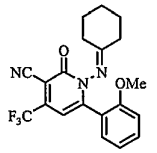
3.54

$^1$H-NMR ($CDCl_3$): $\delta$ 7.39 (m, 1H), 7.29 (m, 1H), 7.23 (m, 1H), 6.96 (m, 1H), 6.43 (s, 1H), 2.37 (m, 1H), 2.29 (s, 3H), 2.19 (m, 1H), 2.15 (m, 1H), 2.10 (m, 1H), 1.96 (m, 1H), 1.80 (m, 2H), 1.53 (m, 1H), 1.36 (m, 1H), 1.24 (m, 1H).



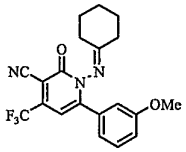
3.55

$^1$H-NMR ($CDCl_3$): $\delta$ 7.33 – 7.24 (m, 4H), 6.48 (s, 1H), 2.49 (m, 1H), 2.42 (s, 3H), 2.38 (m, 1H), 2.19 (m, 1H), 2.04 (m, 1H), 1.87 (m, 2H), 1.59 (m, 2H), 1.49 (m, 1H), 1.36 (m, 1H).



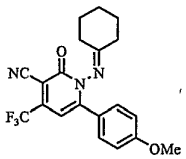
3.56

$^1$H-NMR ($CDCl_3$): $\delta$ 7.47 (m, 1H), 7.16 (m, 1H), 7.05 (m, 1H), 6.95 (m, 1H), 6.45 (s, 1H), 3.79 (s, 3H), 2.40 (m, 1H), 2.22 (m, 2H), 2.06 (m, 1H), 1.91 (m, 1H), 1.81 (m, 1H), 1.58 (m, 2H), 1.46 (m, 2H).



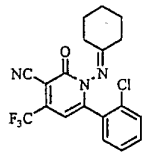
3.57

$^1$H-NMR ($CDCl_3$): $\delta$ 7.37 (m, 1H), 7.03(m, 1H), 6.95 (m, 1H), 6.93 (m, 1H), 6.50 (s, 1H), 3.84 (s, 3H), 2.49 (m, 1H), 2.38 (m, 1H), 2.18 (m, 1H), 2.05 (m, 1H), 1.86 (m, 2H), 1.60 (m, 2H), 1.49 (m, 1H), 1.37 (m, 1H).



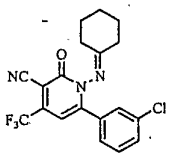
3.58

$^1$H-NMR ($CDCl_3$): $\delta$ 7.39 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 6.48 (s, 1H), 3.87 (s, 3H), 2.52 (m, 1H), 2.41 (m, 1H), 2.18 (m, 1H), 2.02 (m, 1H), 1.87 (m, 2H), 1.60 (m, 2H), 1.52 (m, 1H), 1.34 (m, 1H).



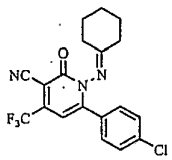
3.59

$^1$H-NMR ($CDCl_3$): $\delta$ 7.57 – 7.30 (m, 4H), 6.46 (s, 1H), 2.37 (m, 1H), 2.23 (m, 2H), 2.05 (m, 1H), 1.91 (m, 1H), 1.83 (m, 1H), 1.60 (m, 2H), 1.54 (m, 1H), 1.44 (m, 1H).



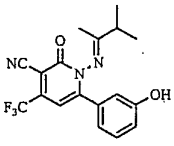
3.60

$^1$H-NMR ($CDCl_3$): $\delta$ 7.50 (m, 1H), 7.43 (m, 1H), 7.37 (m, 1H), 7.31 (m, 1H), 6.49 (s, 1H), 2.48 (m, 1H), 2.40 (m, 1H), 2.22 (m, 1H), 2.11 (m, 1H), 1.92 (m, 2H), 1.63 (m, 2H), 1.51 (m, 1H), 1.42 (m, 1H).



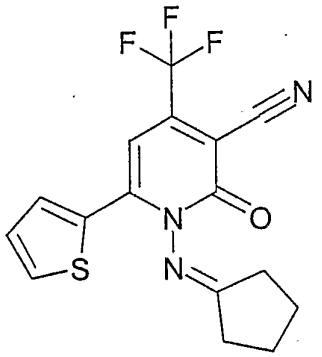
3.61

$^1$H-NMR ($CDCl_3$): $\delta$ 7.46 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 6.47 (s, 1H), 2.49 (m, 1H), 2.38 (m, 1H), 2.19 (m, 1H), 2.02 (m, 1H), 1.88 (m, 2H), 1.61 (m, 2H), 1.51 (m, 1H), 1.37 (m, 1H).



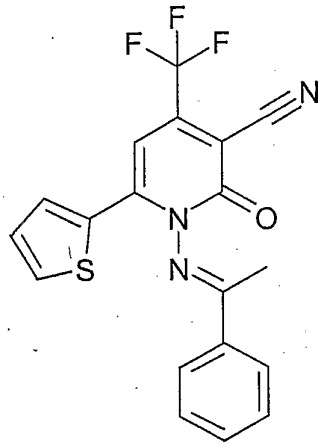
3.62

$^1$H-NMR ($CDCl_3$): $\delta$ 7.31 (m, 1H), 6.98 (m, 1H), 6.95 (m, 1H), 2.08 (m, 1H), 6.53 (s, 1H), 2.62 (m, J = 7.0 Hz, 1H), 1.76 (s, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H).



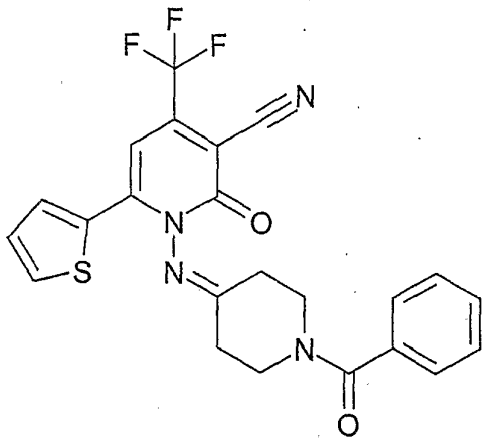
3.63

1-Cyclopentylideneamino-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile
MS (ES+):352.2 (M+H)



3.64

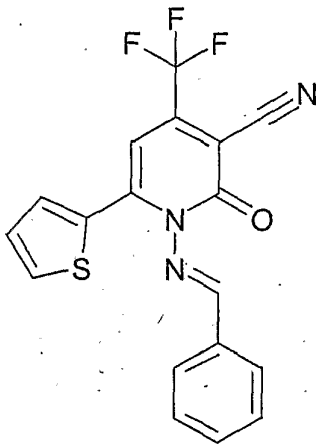
2-Oxo-1-(1-phenyl-ethylideneamino)-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile
MS (ES+):388.0 (M+H)



3.65

1-(1-Benzoyl-piperidin-4-ylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

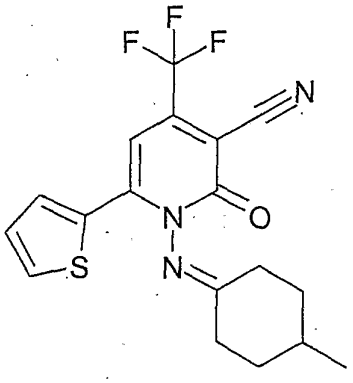
MS (ES+):471.3 (M+H)



3.66

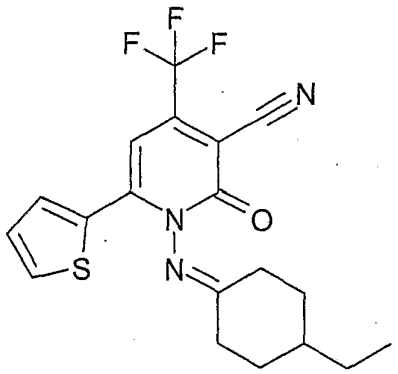
1-(Benzylidene-amino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS (ES+):374.1 (M+H)



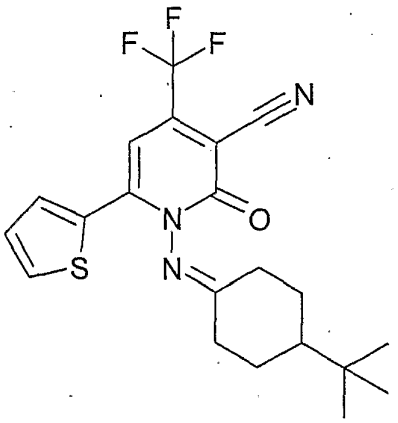
3.67

1-(4-Methyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile
MS (ES+):380.1 (M+H)



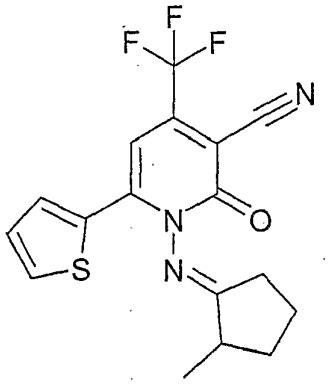
3.68

1-(4-Ethyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile
MS (ES+):394.0 (M+H)



3.69

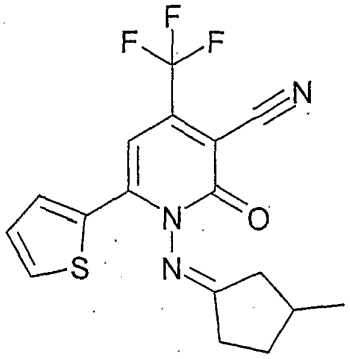
1-(4-tert-Butyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile
MS (ES+):422.0 (M+H)



3.70

1-(2-Methyl-cyclopentylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

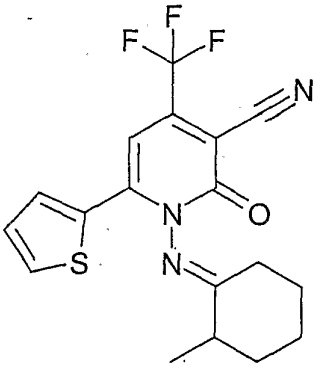
MS (ES+):366.1 (M+H)



3.71

1-(3-Methyl-cyclopentylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

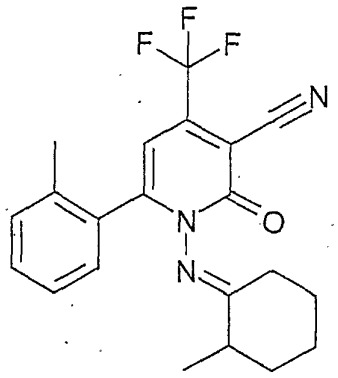
MS (ES+):366.2 (M+H)



3.72

1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS (ES+):380.3 (M+H)



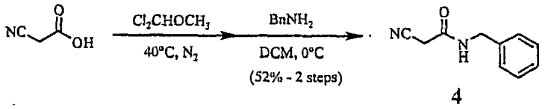
3.73

1-(2-Methyl-cyclohexylideneamino)-2-oxo-6-o-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS (ES+):388.2 (M+H)

## EXAMPLE 4

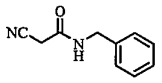
This example illustrates the preparation of compound **4**.



4

Cyanoacetic acid (8.0 g, 94.1 mmoles) and □□-dichloromethyl methyl ether were measured out into a 30 mL round-bottom flask equipped with a magnetic stirbar. The flask was sealed with a septum, and the vessel was continuously flushed with dry $N_2$ gas. The temperature was carefully raised to 40 °C at which temperature the mixture began to liquify and bubble. Nitrogen flushing was maintained throughout this period with adequate venting to atmosphere to permit the release of gases formed during the reaction. The temperature was maintained at 40 °C for 45 minutes while adequate stirring was maintained by vigilant monitoring. After this period the nitrogen line was submerged into the stirring reaction mixture to facilitate the purging of gases (HCl) from the solution. The nitrogen purge was carried out

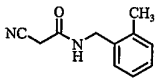
dissolved into 100 mL of anhydrous DCM. To the stirring acid chloride solution at 0 °C was slowly added benzylamine (21 mL, 192.2 mmoles) and the resulting mixture was stirred at ambient temperature for 30 min. After this period the reaction mixture was washed with 1N HCl (2 x 20 mL), sat'd $NaHCO_3$ (2 x 20 mL) and brine. The DCM solution was dried over anhydrous $Na_2SO_4$ and was evaporated *in vacuo* to yield the crude product as a yellowish solid. The crude material was purified by recrystallization in DCM/Hexane to yield 8.5 g (52% yield) of product as yellow, needlelike crystals. (Alternatively, the product can be purified using flash silica chromatography in 60% EtOAc/Hexane).



4

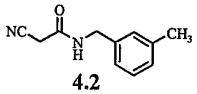
$^1$H-NMR ($CDCl_3$): $\delta$ 7.39-7.28 (m, 5H), 6.39 (bs, 1H), 4.48 (d, J=5.7Hz, 2H), 3.40 (s, 2H).

The following compounds were prepared in a manner similar to that described above.



4.1

$^1$H-NMR ($CDCl_3$): $\delta$ 7.25-7.19 (m, 4H), 6.15 (bs, 1H), 4.49 (d, J=5.4Hz, 2H), 3.41 (s, 2H), 2.34 (s, 3H).

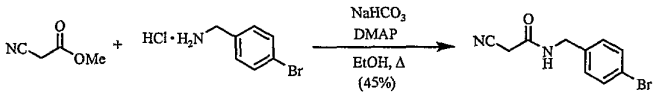


4.2

$^1$H-NMR ($CDCl_3$): $\delta$ 7.27-7.23 (m, 1H), 7.14-7.07 (m, 3H), 6.29 (bs, 1H), 4.45 (d, J=5.6Hz, 2H), 3.41 (s, 2H), 2.36 (s, 3H).

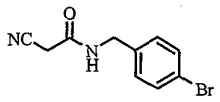
An alternative procedure utilizing commercially available methyl cyanoacetate illustrates the preparation of compound **4**.

## EXAMPLE 5




5

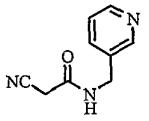
Methyl cyanoacetate (0.8 mL, 9.1 mmoles) and 4-Bromobenzylammonium chloride (0.97 g, 4.4 mmoles) were mixed with 10 mL of anhydrous ethanol within a round-bottom flask. To the stirring mixture at room temp was added sodium bicarbonate (0.55 g, 6.5 mmoles) and 4-(dimethylamino)pyridine (0.25 g, 2.0 mmoles). The mixture was then stirred at 80 °C for 5 hours. After this period the reaction was evaporated *in vacuo*, combined with DCM, and was washed with 1N HCl (2 x 15 mL), sat'd $NaHCO_3$ (2 x 15 mL) and brine. The DCM solution was dried over anhydrous $Na_2SO_4$ and was evaporated *in vacuo* to yield the crude product residue. The crude residue was purified using flash silica chromatography (60% EtOAc/Hexane) to yield 0.49 g (45% yield) of product as a yellow solid.




5

$^1$H-NMR ($CDCl_3$): $\delta$ 7.49 (d, J=8.3Hz, 2H), 7.17 (d, J=8.3Hz, 2H), 6.38 (bs, 1H), 4.44 (d, J=5.8Hz, 2H), 3.42 (s, 2H).

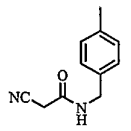
The following compounds were prepared in a manner similar to that described above.




5.1

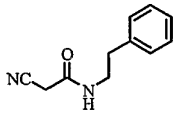
2-Cyano-*N*-pyridin-3-ylmethyl-acetamide

$^1$H-NMR ($CDCl_3$): $\delta$ 8.53-8.48 (m, 2H), 7.65 (dt, J'=7.8Hz, J"=1.8Hz, 1H), 7.29 (dd, J'=7.8hz, J"=4.8Hz, 1H), 7.25 (bs, 1H), 4.47 (d, J=5.8Hz, 2H), 3.43 (s, 2H).



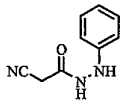
**5.2**
2-Cyano-*N*-(4-methyl-benzyl)-acetamide

$^1$H-NMR ($CDCl_3$): $\delta$ 7.18 (m, 4H), 6.27 (bs, 1H), 4.44 (d, J=5.6Hz, 2H), 3.40 (s, 2H), 2.35 (s, 3H).



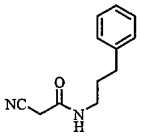
**5.3**
2-Cyano-*N*-phenethyl-acetamide

$^1$H-NMR ($CDCl_3$): $\delta$ 7.34 (m, 2H), 7.29-7.16 (m, 3H), 6.06 (bs, 1H), 3.58 (m, 2H), 3.32 (s, 2H), 2.86 (t, J=7.1Hz, 2H).



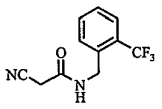
**5.4**
Cyano-acetic acid *N'*-phenyl-hydrazide

$^1$H-NMR ($CDCl_3$): {rotamers} $\delta$ 7.93 (bs, 0.36H), 7.53-7.39 (m, 1.1H), 7.36-7.20 (m, 3.4H), 7.11-6.91 (m, 1.4H), 6.89-6.76 (m, 1.7H), 6.08 (m, 0.40H), 5.92 (m, 0.50H), 4.88 (m, 0.25H), 4.44 (m, 0.33H), 3.90 (s, 0.50H), 3.60 (s, 1H), 3.48 (s, 1H), 3.33 (s, 0.25H).



**5.5**
2-Cyano-*N*-(3-phenyl-propyl)-acetamide

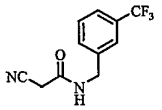
$^1$H-NMR ($CDCl_3$): δ 7.34-7.27 (m, 2H), 7.24-7.14 (m, 3H), 6.07 (bs, 1H), 3.34 (bq, J=5.1Hz, 2H), 3.30 (s, 2H), 2.68 (bt, J=7.5Hz, 2H), 1.90 (m, J=7.5Hz, 2H).



**5.6**

2-Cyano-*N*-(2-trifluoromethyl-benzyl)-acetamide

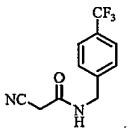
$^1$H-NMR ($CDCl_3$): δ 7.69 (bd, J=7.8Hz, 1H), 7.59-7.53 (m, 2H), 7.48-7.41 (m, 1H), 6.40 (bs, 1H), 4.67 (d, J=6.1Hz, 2H), 3.40 (s, 2H).



**5.7**

2-Cyano-*N*-(3-trifluoromethyl-benzyl)-acetamide

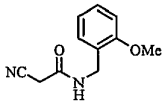
$^1$H-NMR ($CDCl_3$): δ 7.62-7.47 (m, 4H), 6.49 (bs, 1H), 4.55 (d, J=5.8Hz, 2H), 3.44 (s, 2H).



**5.8**

2-Cyano-*N*-(4-trifluoromethyl-benzyl)-acetamide

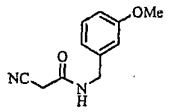
$^1$H-NMR ($CDCl_3$): δ 7.62 (d, J=8.1Hz, 2H), 7.42 (d, J=8.1Hz, 2H), 6.48 (bs, 1H), 4.55 (d, J=6.1Hz, 2H), 3.44 (s, 2H).



**5.9**

2-Cyano-*N*-(2-methoxy-benzyl)-acetamide

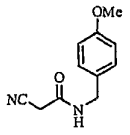
$^1$H-NMR ($CDCl_3$): δ 7.35-7.23 (m, 2H), 6.97-6.89 (m, 2H), 6.80 (bs, 1H), 4.48 (d, J=5.8Hz, 2H), 3.89 (s, 3H), 3.34 (s, 2H).



5.10

2-Cyano-*N*-(3-methoxy-benzyl)-acetamide

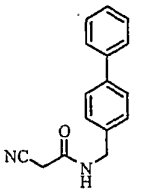
$^1$H-NMR ($CDCl_3$): δ 7.30-7.25 (m, 1H), 6.89-6.81 (m, 3H), 6.36 (bs, 1H), 4.45 (d, J=5.8Hz, 2H), 3.81 (s, 3H), 3.40 (s, 2H).



5.11

2-Cyano-*N*-(4-methoxy-benzyl)-acetamide

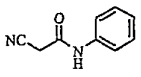
$^1$H-NMR ($CDCl_3$): δ 7.22 (d, J=8.6Hz, 2H), 6.89 (d, J=8.6Hz, 2H), 6.26 (bs, 1H), 4.42 (d, J=5.3Hz, 2H), 3.81 (s, 3H), 3.40 (s, 2H).



5.12

*N*-Biphenyl-4-ylmethyl-2-cyano-acetamide

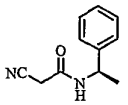
$^1$H-NMR ($CDCl_3$): δ 7.62-7.55 (m, 4H), 7.48-7.42 (m, 2H), 7.40-7.33 (m, 3H), 6.40 (bs, 1H), 4.53 (d, J=5.8Hz, 2H), 3.43 (s, 2H).



5.13

2-Cyano-*N*-phenyl-acetamide

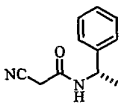
$^1$H-NMR ($CDCl_3$): δ 7.66 (bs, 1H), 7.53-7.48 (m, 2H), 7.41-7.35 (m, 2H), 7.23-7.18 (m, 1H), 3.57 (s, 2H).



**5.14**

2-Cyano-*N*-(1-phenyl-ethyl)-acetamide

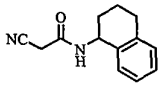
$^1$H-NMR ($CDCl_3$): δ 7.41-7.23 (m, 5H), 6.24 (bs, 1H), 5.12 (m, 1H), 3.37 (m, 2H), 1.55 (d, J=7.1Hz, 3H).



**5.15**

2-Cyano-*N*-(1-phenyl-ethyl)-acetamide

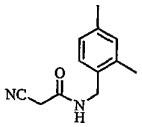
$^1$H-NMR ($CDCl_3$): δ 7.41-7.23 (m, 5H), 6.24 (bs, 1H), 5.12 (m, 1H), 3.37 (m, 2H), 1.55 (d, J=7.1Hz, 3H).



**5.16**

2-Cyano-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide

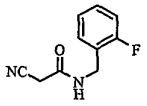
$^1$H-NMR ($CDCl_3$): δ 7.28-7.09 (m, 4H), 6.26 (bs, 2H), 5.22-5.14 (m, 1H), 3.40 (s, 2H), 2.90-2.71 (m, 2H), 2.12-2.00 (m, 1H), 1.93-1.77 (m, 3H).



5.17

2-Cyano-*N*-(2,4-dimethyl-benzyl)-acetamide

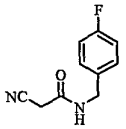
$^1$H-NMR ($CDCl_3$): δ 7.14-7.08 (m, 1H), 7.05-6.98 (m, 2H), 6.13 (bs, 1H), 4.44 (d, J=5.3Hz, 2H), 3.38 (s, 2H), 2.32 (s, 3H), 2.30 (s, 3H).



5.18

2-Cyano-*N*-(2-fluoro-benzyl)-acetamide

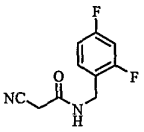
$^1$H-NMR ($CDCl_3$): δ 7.40-7.27 (m, 2H), 7.16-7.05 (m, 2H), 6.45 (bs, 1H), 4.54 (d, J=5.8Hz, 2H), 3.39 (s, 2H).



5.19

2-Cyano-*N*-(4-fluoro-benzyl)-acetamide

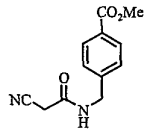
$^1$H-NMR ($CDCl_3$): δ 7.30-7.23 (m, 2H), 7.08-7.00 (m, 2H), 6.40 (bs, 1H), 4.45 (d, J=5.8Hz, 2H), 3.41 (s, 2H).



5.20

2-Cyano-*N*-(2,4-difluoro-benzyl)-acetamide

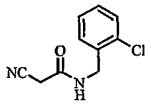
$^1$H-NMR ($CDCl_3$): δ 7.38-7.29 (m, 1H), 6.90-6.80 (m, 2H), 6.51 (bs, 1H), 4.48 (d, J=6.1Hz, 2H), 3.39 (s, 2H).



5.21

4-[(2-Cyano-acetylamino)-methyl]-benzoic acid methyl ester

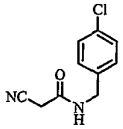
$^1$H-NMR ($CDCl_3$): δ 8.03 (d, J=8.1Hz, 2H), 7.36 (d, J=8.1Hz, 2H), 6.46 (bs, 1H), 4.55 (d, J=5.8Hz, 2H), 3.92 (s, 3H), 3.45 (s, 2H).



5.22

*N*-(2-Chloro-benzyl)-2-cyano-acetamide

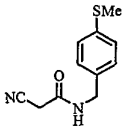
$^1$H-NMR ($CDCl_3$): δ 7.43-7.36 (m, 2H), 7.31-7.23 (m, 2H), 6.53 (bs, 1H), 4.58 (d, J=5.8Hz, 2H), 3.40 (s, 2H).



5.23

*N*-(4-Chloro-benzyl)-2-cyano-acetamide

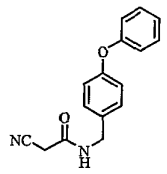
$^1$H-NMR ($CDCl_3$): δ 7.36-7.30 (d, J=8.6Hz, 2H), 7.25-7.20 (d, J=8.6Hz, 2H), 6.43 (bs, 1H), 4.45 (d, J=5.81Hz, 2H), 3.42 (s, 2H).



5.24

2-Cyano-*N*-(4-methylsulfanyl-benzyl)-acetamide

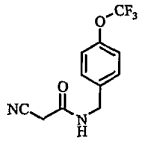
$^1$H-NMR ($CDCl_3$): δ 7.26-7.18 (m, 4H), 6.34 (bs, 1H), 4.43 (d, J=5.6Hz, 2H), 3.40 (s, 2H), 2.48 (s, 3H).



5.25

2-Cyano-*N*-(4-phenoxy-benzyl)-acetamide

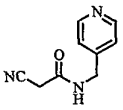
$^1$H-NMR ($CDCl_3$): δ 7.38-7.32 (m, 2H), 7.28-7.23 (m, 3H), 7.16-7.09 (m, 1H), 7.04-6.96 (m, 4H), 6.35 (bs, 1H), 4.45 (d, J=5.6Hz, 2H), 3.42 (s, 2H).



5.26

2-Cyano-*N*-(4-trifluoromethoxy-benzyl)-acetamide

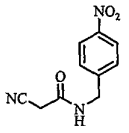
$^1$H-NMR ($CDCl_3$): δ 7.36-7.29 (m, 2H), 7.23-7.17 (m, 2H), 6.46 (bs, 1H), 4.48 (d, J=5.8Hz, 2H), 3.42 (s, 2H).



5.27

2-Cyano-*N*-pyridin-4-ylmethyl-acetamide

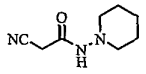
$^1$H-NMR ($CDCl_3$): δ 8.61-8.51 (m, 2H), 7.24-7.18 (m, 2H), 6.99 (bs, 1H), 4.49 (d, J=5.8Hz, 2H), 3.48 (s, 2H).



5.28

2-Cyano-*N*-(4-nitro-benzyl)-acetamide

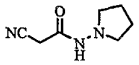
$^1$H-NMR ($CDCl_3$): δ 8.23 (d, J=8.6Hz, 2H), 7.47 (d, J=8.6Hz, 2H), 6.55 (bs, 1H), 4.60 (d, J=6.1Hz, 2H), 3.47 (s, 2H).



**5.29**

2-Cyano-*N*-piperidin-1-yl-acetamide

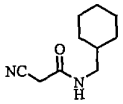
$^1$H-NMR ($CDCl_3$): δ 6.51 (bs, 1H), 3.54 (s, 2H), 3.16-3.04 (m, 2H), 2.43-2.29 (m, 2H)1.81-1.54 (m, 6H).



**5.30**

2-Cyano-*N*-pyrrolidin-1-yl-acetamide

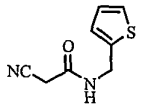
$^1$H-NMR ($CDCl_3$): δ 6.85 (bs, 1H), 3.59 (s, 2H), 3.46-3.03 (bm, 2H), 2.78-2.22 (bm, 2H), 1.96-1.78 (m, 4H).



**5.31**

2-Cyano-*N*-cyclohexylmethyl-acetamide

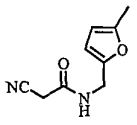
$^1$H-NMR ($CDCl_3$): δ 6.20 (bs, 1H), 3.38 (s, 2H), 3.15 (bt, J=6.3Hz, 2H), 1.79-1.68 (m, 5H), 1.58-1.44 (m, 1H), 1.36-1.09 (m, 3H), 1.02-0.86 (m, 2H).



**5.32**

2-Cyano-*N*-thiophen-2-ylmethyl-acetamide

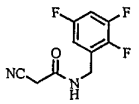
$^1$H-NMR ($CDCl_3$): δ 7.26 (dd, J'=5.1Hz, J"=1.3Hz, 1H), 7.03-6.99 (m, 1H), 6.99-6.95 (m, 1H), 6.57 (bs, 1H), 4.64 (d, J=5.6Hz, 2H), 3.39 (s, 2H).



5.33

2-Cyano-*N*-(5-methyl-furan-2-ylmethyl)-acetamide

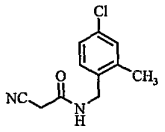
$^1$H-NMR ($CDCl_3$): δ 6.52 (bs, 1H), 6.14 (d, J=3.0Hz, 1H), 5.93-5.88 (m, 1H), 4.40 (d, J=5.3Hz, 2H), 3.39 (s, 2H), 2.27 (s, 3H).



5.34

2-Cyano-*N*-(2,3,5-trifluoro-benzyl)-acetamide

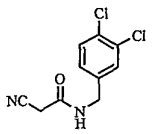
$^1$H-NMR ($CDCl_3$): δ 6.94-6.83 (m, 2H), 6.66 (bs, 1H), 4.53 (bd, J=6.1Hz, 2H), 3.44 (s, 2H).



5.35

*N*-(4-Chloro-2-methyl-benzyl)-2-cyano-acetamide

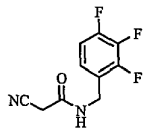
$^1$H-NMR ($CDCl_3$): δ 7.22-7.13 (m, 3H), 6.28 (bs, 1H), 4.43 (d, J=5.6Hz, 2H), 3.40 (s, 2H), 2.31 (s, 3H).



5.36

2-Cyano-*N*-(3,4-dichloro-benzyl)-acetamide

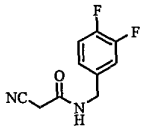
$^1$H-NMR ($CDCl_3$): δ 8.37 (bs, 1H), 7.14-7.09 (m, 2H), 6.87 (dd, J'=8.1Hz, J"=2.0Hz, 1H), 4.02 (d, J=5.8Hz, 2H), 3.20 (s, 2H).



5.37

2-Cyano-*N*-(2,3,4-trifluoro-benzyl)-acetamide

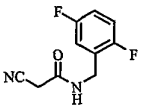
$^1$H-NMR ($CDCl_3$): δ 7.14-7.06 (m, 1H), 7.01-6.90 (m, 1H), 6.54 (bs, 1H), 4.51 (d, J=5.8Hz, 2H), 3.41 (s, 2H).



5.38

2-Cyano-*N*-(3,4-difluoro-benzyl)-acetamide

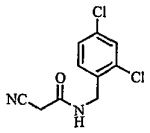
$^1$H-NMR ($CDCl_3$): δ 7.19-7.08 (m, 2H), 7.06-6.98 (m, 1H), 6.46 (bs, 1H), 4.44 (d, J=5.8Hz, 2H), 3.43 (s, 2H).



5.39

2-Cyano-*N*-(2,5-difluoro-benzyl)-acetamide

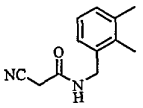
$^1$H-NMR ($CDCl_3$): δ 7.09-6.94 (m, 3H), 6.58 (bs, 1H), 4.50 (d, J=6.1Hz, 2H), 3.42 (s, 2H).



5.40

2-Cyano-*N*-(2,4-dichloro-benzyl)-acetamide

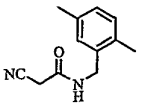
$^1$H-NMR ($CDCl_3$): δ 7.42 (d, J=2.0Hz, 1H), 7.35-7.23 (m, 2H), 6.58 (bs, 1H), 4.53 (d, J=6.1Hz, 2H), 3.40 (s, 2H).



5.41

2-Cyano-*N*-(2,3-dimethyl-benzyl)-acetamide

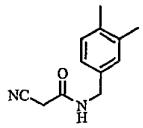
$^1$H-NMR ($CDCl_3$): δ 7.18-7.06 (m, 3H), 6.18 (bs, 1H), 4.49 (d, J=5.3Hz, 2H), 3.37 (s, 2H), 2.30 (s, 3H), 2.22 (s, 3H).



5.42

2-Cyano-*N*-(2,5-dimethyl-benzyl)-acetamide

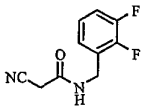
$^1$H-NMR ($CDCl_3$): δ 7.11-7.01 (m, 3H), 6.16 (bs, 1H), 4.44 (d, J=5.3Hz, 2H), 3.40 (d, 2H), 2.32 (s, 3H), 2.29 (s, 3H).



5.43

2-Cyano-*N*-(3,4-dimethyl-benzyl)-acetamide

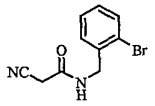
$^1$H-NMR ($CDCl_3$): δ 7.12 (d, J=7.6Hz, 1H), 7.05 (bs, 1H), 7.01 (dd, J'=7.6Hz, J"=1.3Hz, 1H), 6.34 (bs, 1H), 4.40 (d, J=5.8Hz, 2H), 3.38 (d, 2H), 2.26 (s, 3H), 2.25 (s, 3H).



5.44

2-Cyano-*N*-(2,3-difluoro-benzyl)-acetamide

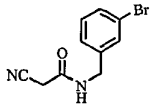
$^1$H-NMR ($CDCl_3$): δ 7.19-7.0 (m, 3H), 6.46 (bs, 1H), 4.56 (dd, J'=6.1 Hz, J"=0.8Hz, 2H), 3.41 (s, 2H).



5.45

*N*-(2-Bromo-benzyl)-2-cyano-acetamide

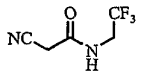
$^1$H-NMR ($CDCl_3$): δ 7.48-7.41 (m, 2H), 7.25-7.19 (m, 2H), 6.45 (bs, 1H), 4.45 (d, J=5.8Hz, 2H), 3.43 (s, 2H).



5.46

*N*-(3-Bromo-benzyl)-2-cyano-acetamide

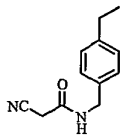
$^1$H-NMR ($CDCl_3$): δ 7.58 (dd, J'=8.1Hz, J"=1.0Hz, 1H), 7.39 (dd, J'=7.8Hz, J"=1.5Hz, 1H), 7.31 (dt, J'=7.6Hz, J"=1.0Hz, 1H), 7.20 (dt, J'=7.6Hz, J"=1.5Hz, 1H), 6.59 (bs, 1H), 4.56 (d, J=5.8Hz, 2H), 3.39 (s, 2H).



5.47

2-Cyano-*N*-(2,2,2-trifluoro-ethyl)-acetamide

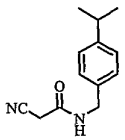
$^1$H-NMR ($CDCl_3$): δ 6.38 (bs, 1H), 3.98 (m, 2H), 3.48 (s, 2H).



5.48

2-Cyano-*N*-(4-ethyl-benzyl)-acetamide

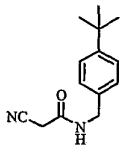
$^1$H-NMR ($CDCl_3$): δ 7.23-7.16 (m, 4H), 6.47 (bs, 1H), 4.42 (d, J=5.6Hz, 2H), 3.36 (s, 2H), 2.64 (q, J=7.6Hz, 2H), 1.23 (t, J=7.6Hz, 3H).



5.49

2-Cyano-*N*-(4-isopropyl-benzyl)-acetamide

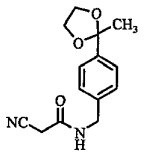
$^1$H-NMR ($CDCl_3$): δ 7.23-7.16 (m, 4H), 6.65 (bs, 1H), 4.39 (d, J=5.6Hz, 2H), 3.33 (s, 2H), 2.90 (m, J=6.8Hz, 1H), 1.24 (d, J=6.8Hz, 6H).



5.50

*N*-(4-*tert*-Butyl-benzyl)-2-cyano-acetamide

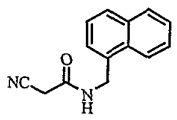
$^1$H-NMR ($CDCl_3$): δ 7.37 (d, J=8.3Hz, 2H), 7.21 (d, J=8.3hz, 2H), 6.59 (bs, 1H), 4.40 (d, J=5.6hz, 2H), 3.33 (s, 2H), 1.31 (s, 9H).



5.51

2-Cyano-*N*-[4-(2-methyl-[1,3]dioxolan-2-yl)-benzyl]-acetamide

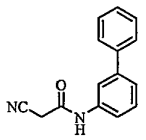
$^1$H-NMR ($CDCl_3$): δ 7.48 (d, J=8.1Hz, 2H), 7.27 (d, J=8.1Hz, 2H), 6.37 (bs, 1H), 4.47 (d, J=5.6Hz, 2H), 4.04 (m, 2H), 3.77 (m, 2H), 3.41 (s, 2H), 1.65 (s, 3H).



5.52

2-Cyano-*N*-naphthalen-1-ylmethyl-acetamide

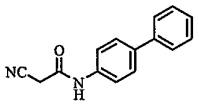
$^1$H-NMR ($CDCl_3$): δ 7.98-7.83 (m, 3H), 7.61-7.50 (m, 2H), 7.48-7.41 (m, 2H), 6.27 (bs, 1H), 4.94 (d, J=5.3Hz, 2H), 3.39 (s, 2H).



5.53

*N*-Biphenyl-3-yl-2-cyano-acetamide

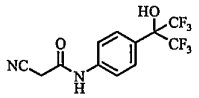
$^1$H-NMR ($CDCl_3$): δ 7.75-7.33 (m, 10H), 3.59 (s, 2H).



5.54

*N*-Biphenyl-4-yl-2-cyano-acetamide

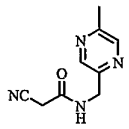
$^1$H-NMR ($CDCl_3$): δ 7.74-7.67 (bs, 1H), 7.63-7.55 (m, 6H), 7.44 (t, J=7.3Hz, 2H), 7.38-7.32 (m, 1H), 3.59 (s, 2H).



5.55

2-Cyano-*N*-[4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-phenyl]-acetamide

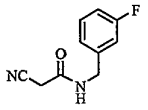
$^1$H-NMR ($CDCl_3$): δ 9.59 (bs, 1H), 7.68-7.55 (m, 4H), 3.75 (s, 2H).



5.56

2-Cyano-*N*-(5-methyl-pyrazin-2-ylmethyl)-acetamide

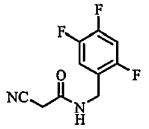
$^1$H-NMR ($CDCl_3$): δ 8.48 (s, 1H), 8.42 (s, 1H), 7.16 (bs, 1H), 4.61 (d, J=5.1Hz, 2H), 3.45 (s, 2H), 2.58 (s, 3H).



5.57

2-Cyano-*N*-(3-fluoro-benzyl)-acetamide

$^1$H-NMR ($CDCl_3$): δ 7.36-7.29 (m, 1H), 7.10-6.97 (m, 3H), 6.54 (bs, 1H), 4.47 (d, J=5.8Hz, 2H), 3.43 (s, 2H).



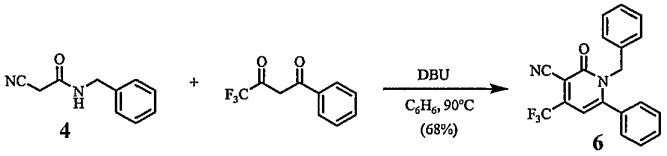
5.58

2-Cyano-*N*-(2,4,5-trifluoro-benzyl)-acetamide

$^1$H-NMR ($CDCl_3$): 7.25-7.17 (m, 1H), 7.00-6.92 (m, 1H), 6.50 (bs, 1H), 4.47 (d, J=6.1Hz, 2H), 3.41 (s, 2H).

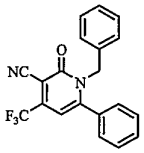
## EXAMPLE 6

This example illustrates the preparation of compound **6**.




4 6

Benzyl cyanoacetamide (0.2 g, 1.2 mmoles) was combined with 4,4,4-trifluoro-1-phenyl-1,3-butanedione (0.24 g, 1.2 mmoles) and 1,8-diazabicyclo[5.4.0]undec-7-ene (90 μL, 0.6 mmoles) in 2.5 mL of benzene. The mixture was stirred at 90 °C for 12 hours. After this period the reaction mixture was evaporated *in vacuo* and the residue was purified directly using flask silica chromatography (20% EtOAc/Hexane) to yield 289 mg (68% yield) of product **6** as a white solid.

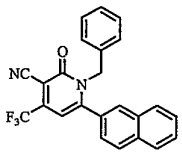


6

1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): $\delta$ 7.54 (t, J=7.6Hz, 1H), 7.45 (t, J=8Hz, 2H), 7.25-7.17 (m, 5H), 6.88 (dd, J'=6.9Hz, J"=1.5Hz, 2H), 6.39 (s, 1H), 5.26 (s, 2H). MS (ES+): 355.2 (M+H).

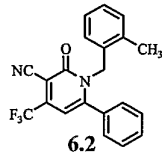
The following compounds were prepared in a manner similar to that described above.



6.1

1-Benzyl-6-naphthalen-2-yl-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

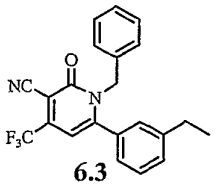
$^1$H-NMR ($CDCl_3$): $\delta$ 7.92 (d, J=8.3Hz, 2H), 7.77 (d, J=8.2Hz, 1H), 7.65-7.57 (m, 3H), 7.24-7.18 (m, 4H), 6.88 (d, J=8.2Hz, 2H), 6.49 (s, 1H), 5.29 (s, 2H).



6.2

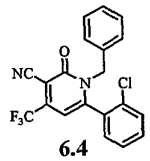
1-(2-Methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): $\delta$ 7.49 (t, J=7.4Hz, 1H), 7.36 (t, J=7.8Hz, 2H), 7.16-7.05 (m, 5H), 6.74-6.72 (m, 1H), 6.45 (s, 1H), 5.15 (s, 2H), 1.93 (s, 3H). MS(ES+): 369.0 (M+H)



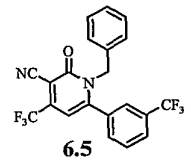
6.3

$^1$H-NMR ($CDCl_3$): $\delta$ 7.36 (m, 2H), 7.24 (m, 3H), 7.03 (m, 1H), 6.92 (m, 1H), 6.90 (m, 1H), 6.88 (m, 1H), 6.40 (s, 1H), 5.25 (s, 2H), 2.60 (q, J = 7.7 Hz, 2H), 1.15 (t, J = 7.7 Hz, 3H).



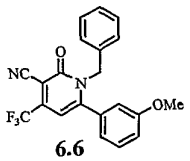
6.4

$^1$H-NMR ($CDCl_3$): $\delta$ 7.53 (m, 1H), 7.50 (m, 1H), 7.28 (m, 1H), 7.21 (m, 1H), 7.18 (m, 2H), 6.97 (m, 1H), 6.84 (m, 1H), 6.82 (m, 1H), 6.35 (s, 1H), 5.68 (d, J = 14.6 Hz, 2H), 4.68 (d, J = 14.6 Hz, 2H).



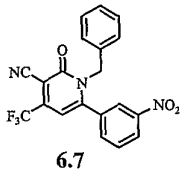
6.5

$^1$H-NMR ($CDCl_3$): $\delta$ 7.80 (m, 1H), 7.60 (m, 1H), 7.38 (m, 1H), 7.32 (s, 1H), 7.24 (m, 3H), 6.81 (m, 2H), 6.39 (s, 1H), 5.21 (s, 2H).



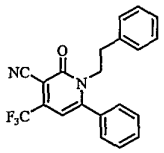
6.6

$^1$H-NMR ($CDCl_3$): $\delta$ 7.36 (m, 1H), 7.25 (m, 3H), 7.05 (m, 1H), 6.92 (m, 2H), 6.79 (m, 1H), 6.60 (m, 1H), 6.42 (s, 1H), 5.25 (s, 2H), 3.64 (s, 3H).



6.7

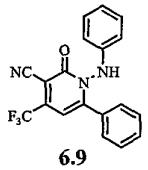
$^1$H-NMR ($CDCl_3$): $\delta$ 8.38 (m, 1H), 7.97 (m, 1H), 7.65 (m, 1H), 7.48 (m, 1H), 7.25 (m, 3H), 6.81 (m, 2H), 6.40 (s, 1H), 5.23 (s, 2H).



6.8

2-Oxo-1-phenethyl-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

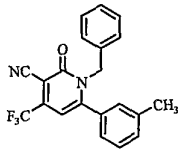
$^1$H-NMR ($CDCl_3$): $\delta$ 7.60-7.54 (m, 1H), 7.53-7.47 (m, 2H), 7.23-7.18 (m, 3H), 7.16-7.11 (m, 2H), 6.88-6.82 (m, 2H), 6.33 (s, 1H), 4.22-4.16 (m, 2H), 2.95-2.89 (m, 2H). MS(ES+): 368.7 (M+H)



6.9

2-Oxo-6-phenyl-1-phenylamino-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

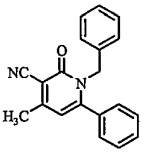
$^1$H-NMR ($CDCl_3$): $\delta$ 7.59-7.54 (m, 2H), 7.53 (bs, 1H), 7.5-7.44 (m, 1H), 7.43-7.38 (m, 2H), 7.21-7.15 (m, 2H), 7.01-6.96 (m, 1H), 6.60 (d, J=7.1Hz, 2H), 6.59 (s, 1H). MS(ES+): 356.0 (M+H)



6.10

1-Benzyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

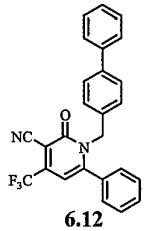
$^1$H-NMR ($CDCl_3$): $\delta$ 7.34 (d, J=5.1Hz, 2H), 7.25-7.22 (m, 4H), 7.02-6.96 (m, 1H), 6.92-6.87 (m, 3H), 6.39 (s, 1H), 5.24 (bs, 2H), 2.32 (s, 3H). MS(ES+): 368.9 (M+H)



**6.11**

1-Benzyl-4-methyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

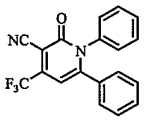
$^1$H-NMR ($CDCl_3$): $\delta$ 7.50-7.44 (m, 1H), 7.38 (t, J=8.1Hz, 2H), 7.24-7.17 (m, 3H), 7.11 (d, J=7.3Hz, 2H), 6.91-6.83 (m, 2H), 6.08 (s, 1H), 5.17 (bs, 2H), 2.47 (s, 3H).



**6.12**

1-Biphenyl-4-ylmethyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

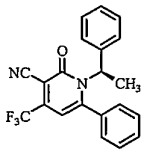
$^1$H-NMR ($CDCl_3$): $\delta$ 7.59-7.51 (m, 3H), 7.51-7.40 (m, 6H), 7.38-7.32 (m, 1H), 7.23 (d, J=6.8Hz, 2H), 6.97 (d, J=8.1Hz, 2H), 6.42 (s, 1H), 5.30 (s, 2H). MS (ES+): 453.0 (M+Na).



**6.13**

2-Oxo-1,6-diphenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

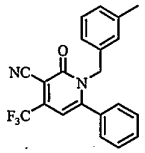
$^1$H-NMR ($CDCl_3$): $\delta$ 7.35-7.27 (m, 4H), 7.26-7.20 (m, 2H), 7.13-7.03 (m, 4H), 6.56 (s, 1H). MS(ES+): 341.1 (M+H)



6.14

2-Oxo-6-phenyl-1-(1-phenyl-ethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

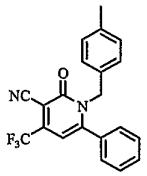
$^1$H-NMR ($CDCl_3$): $\delta$ 7.6-7.39 (m, 5H), 7.34-7.20 (m, 3H), 7.15 (d, J=6.8Hz, 2H), 6.37 (s, 1H), 5.60-5.49 (m, 1H), 1.95 (d, J=6.8Hz, 3H).



6.15

1-(3-Methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

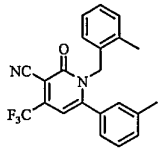
MS(ES+): 369.1 (M+H)



6.16

1-(4-Methyl-benzyl)-6-(1-methylene-but-2-enyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

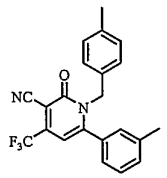
$^1$H-NMR ($CDCl_3$): $\delta$ 7.58-7.51 (m, 1H), 7.49-7.43 (m, 2H), 7.20 (d, J=7.3Hz, 2H), 7.03 (d, J=8.1Hz, 2H), 6.78 (d, J=7.8Hz, 2H), 6.38 (s, 1H), 5.22 (s, 2H), 2.29 (s, 3H), 1.54 (s, 3H).



6.17

1-(2-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

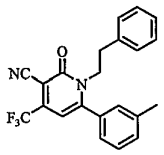
MS(ES+): 383.0 (M+H)



6.18

1-(4-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

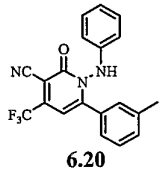
$^1$H-NMR ($CDCl_3$): δ 7.36-7.33 (m, 2H), 7.06-6.98 (m, 3H), 6.93 (bs, 1H), 6.79 (d, J=7.8Hz, 2H), 6.37 (s, 1H), 5.20 (bs, 2H), 2.34 (s, 3H), 2.30 (s, 3H).



6.19

2-Oxo-1-phenethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

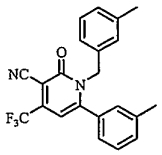
$^1$H-NMR ($CDCl_3$): δ 7.40-7.33 (m, 2H), 7.23-7.18 (m, 3H), 6.97-6.93 (m, 1H), 6.89-6.83 (m, 3H), 6.31 (s, 1H), 4.23-4.16 (m, 2H), 2.97-2.90 (m, 2H), 2.40 (s, 3H).



6.20

2-Oxo-1-phenylamino-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

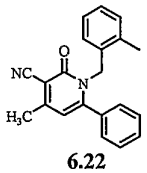
$^1$H-NMR ($CDCl_3$): δ 7.91-7.84 (m, 1H), 7.47 (s, 1H), 7.38-7.32 (m, 2H), 7.18 (t, J=7.6Hz, 2H), 6.97 (t, J=7.3Hz, 1H), 6.62-6.56 (m, 3H), 2.35 (s, 3H)..



6.21

1-(3-Methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

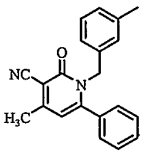
MS(ES+): 383.0 (M+H)



6.22

4-Methyl-1-(2-methyl-benzyl)-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

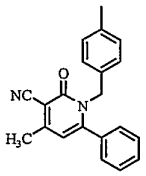
MS(ES+): 315.0 (M+H)



6.23

4-Methyl-1-(3-methyl-benzyl)-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

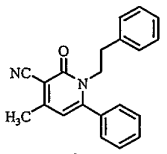
MS(ES+): 315.1 (M+H)



6.24

4-Methyl-1-(4-methyl-benzyl)-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

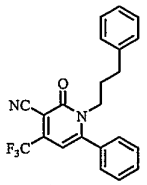
MS(ES+): 315.0 (M+H)



6.25

4-Methyl-2-oxo-1-phenethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

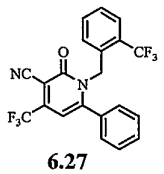
MS(ES+): 315.2 (M+H)



6.26

2-Oxo-6-phenyl-1-(3-phenyl-propyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

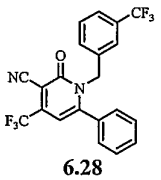
MS(ES+): 383.3 (M+H)



6.27

2-Oxo-6-phenyl-4-trifluoromethyl-1-(2-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile

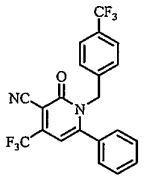
$^1$H-NMR ($CDCl_3$): δ 7.64-7.32 (m, 6H), 7.07 (d, J=6.8Hz, 2H), 6.93 (d, J=7.8Hz, 1H), 6.50 (s, 1H), 5.37 (s, 2H).



6.28

2-Oxo-6-phenyl-4-trifluoromethyl-1-(3-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile

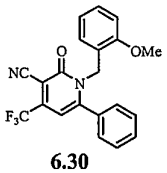
MS(ES+): 422.8 (M+H)



6.29

2-Oxo-6-phenyl-4-trifluoromethyl-1-(4-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile

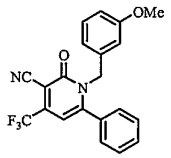
MS(ES+): 422.8 (M+H)



6.30

1-(2-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

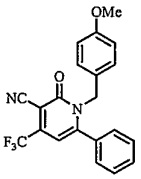
MS(ES+): 383.3 (M+H)



6.31

1-(3-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

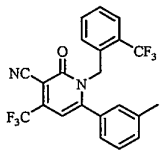
MS(ES+): 384.9 (M+H)



6.32

1-(4-Methoxy-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

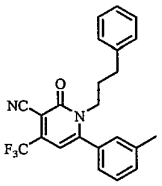
MS(ES+): 385.3 (M+H)



6.33

2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(2-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile

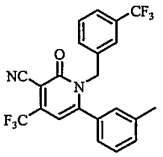
MS(ES+): 459.2 (M+Na)



6.34

2-Oxo-1-(3-phenyl-propyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

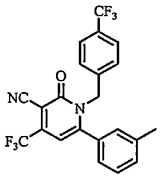
MS(ES+): 397.0 (M+H)



6.35

2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(3-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile

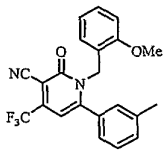
MS(ES+): 438.0 (M+H)



6.36

2-Oxo-6-*m*-tolyl-4-trifluoromethyl-1-(4-trifluoromethyl-benzyl)-1,2-dihydro-pyridine-3-carbonitrile

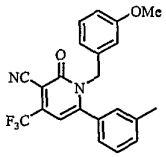
MS(ES+): 437.0 (M+H)



6.37

1-(2-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

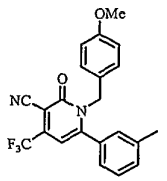
MS(ES+): 420.8 (M+Na)



6.38

1-(3-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

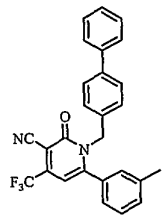
MS(ES+): 398.8 (M+H)



6.39

1-(4-Methoxy-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

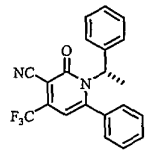
MS(ES+): 421.0 (M+Na)



6.40

1-Biphenyl-4-ylmethyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

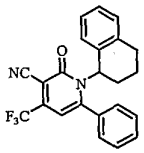
MS(ES+): 467.0 (M+Na)



6.41

2-Oxo-6-phenyl-1-(1-phenyl-ethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

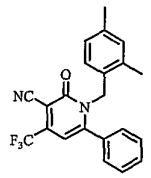
MS(ES+): 369.3 (M+H)



6.42

2-Oxo-6-phenyl-1-(1,2,3,4-tetrahydro-naphthalen-1-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

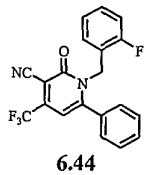
MS(ES+): 395.0 (M+H)



6.43

1-(2,4-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

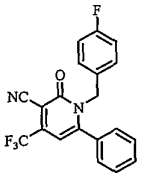
MS(ES+): 405.2 (M+Na)



6.44

1-(2-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

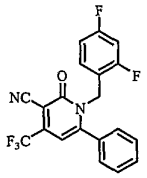
MS(ES+): 373.0 (M+H)



6.45

1-(4-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

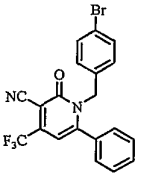
MS(ES+): 373.0 (M+H)



6.46

1-(2,4-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

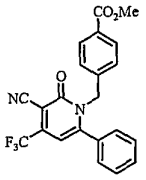
MS(ES+): 390.8 (M+H)



6.47

1-(4-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

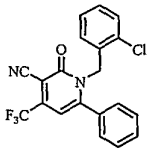
MS(ES+): 435.0 (M+H)



6.48

4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2*H*-pyridin-1-ylmethyl)-benzoic acid methyl ester

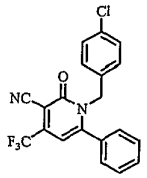
MS(ES+): 413.2 (M+H)



6.49

1-(2-Chloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

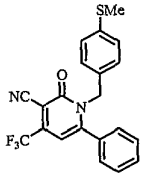
MS(ES+): 389.0 (M+H)



6.50

1-(4-Chloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

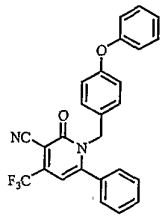
MS(ES+): 389.0 (M+H)



6.51

1-(4-Methylsulfanyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

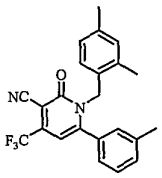
MS(ES+): 423.0 (M+Na)



6.52

2-Oxo-1-(4-phenoxy-benzyl)-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

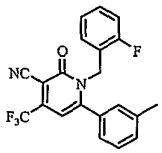
$^1$H-NMR ($CDCl_3$): δ 7.59-7.53 (m, 1H), 7.48 (t, J=7.8Hz, 2H), 7.37-7.30 (m, 2H), 7.25-7.20 (m, 2H), 7.15-7.09 (m, 1H), 7.00-6.95 (m, 2H), 6.88-6.81 (m, 4H), 6.39 (s, 1H), 5.24 (s, 2H).



**6.53**

1-(2,4-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

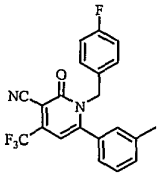
MS(ES+): 397.0 (M+H)



**6.54**

1-(2-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

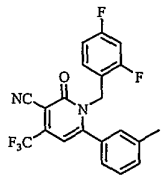
MS(ES+): 387.0 (M+H)



**6.55**

1-(4-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

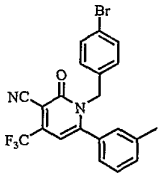
MS(ES+): 387.0 (M+H)



6.56

1-(2,4-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

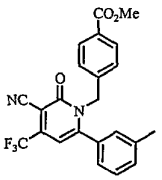
MS(ES+): 405.0 (M+H)



6.57

1-(4-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

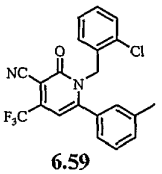
MS(ES+): 449.0 (M+H)



6.58

4-(3-Cyano-2-oxo-6-*m*-tolyl-4-trifluoromethyl-2*H*-pyridin-1-ylmethyl)-benzoic acid methyl ester

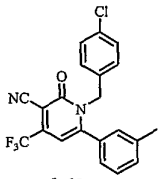
MS(ES+): 427.2 (M+H)



6.59

1-(2-Chloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

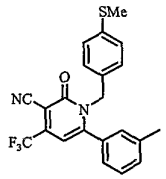
MS(ES+): 403.0 (M+H)



6.60

1-(4-Chloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

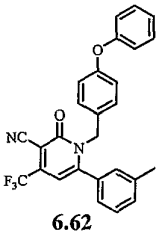
MS(ES+): 402.8 (M+H)



6.61

1-(4-Methylsulfanyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

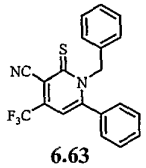
MS(ES+): 437.2 (M+Na)



6.62

2-Oxo-1-(4-phenoxy-benzyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

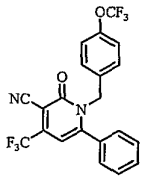
$^1$H-NMR ($CDCl_3$): δ 7.40-7.30 (m, 4H), 7.14-7.09 (m, 1H), 7.05-6.94 (m, 4H), 6.90-6.83 (m, 4H), 6.39 (s, 1H), 5.22 (s, 2H), 2.36 (s, 3H).



6.63

1-Benzyl-6-phenyl-2-thioxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

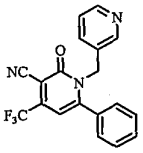
MS(ES+): 370.9 (M+H)



6.64

2-Oxo-6-phenyl-1-(4-trifluoromethoxy-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

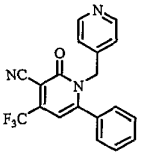
MS(ES+): 439.2 (M+H)



6.65

2-Oxo-6-phenyl-1-pyridin-3-ylmethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

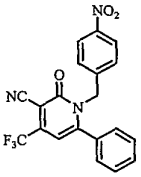
MS(ES+): 355.8 (M+H)



6.66

2-Oxo-6-phenyl-1-pyridin-4-ylmethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

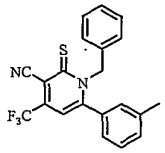
MS(ES+): 355.8 (M+H)



6.67

1-(4-Nitro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

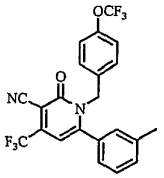
MS(ES+): 400.0 (M+H)



6.68

1-Benzyl-2-thioxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

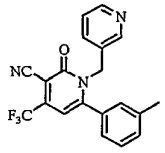
MS(ES+): 385.3 (M+H)



6.69

2-Oxo-6-*m*-tolyl-1-(4-trifluoromethoxy-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

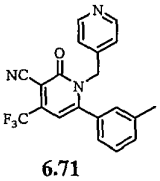
MS(ES+): 453.0 (M+H)



6.70

2-Oxo-1-pyridin-3-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

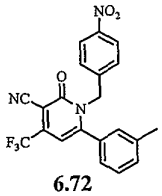
MS(ES+): 369.8 (M+H)



6.71

2-Oxo-1-pyridin-4-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

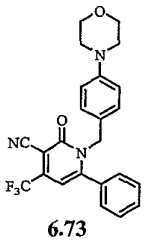
MS(ES+): 369.8 (M+H)



6.72

1-(4-Nitro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

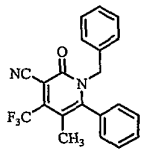
MS(ES+): 414.0 (M+H)



6.73

1-(4-Morpholin-4-yl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

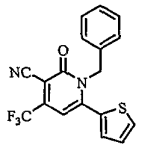
MS(ES+): 440.2 (M+H)



6.74

1-Benzyl-5-methyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

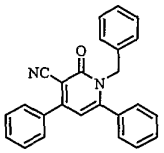
MS(ES+): 369.0(M+H)



6.75

1-Benzyl-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

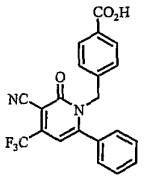
MS(ES+): 383.0 (M+Na)



6.76

1-Benzyl-2-oxo-4,6-diphenyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 385.2 (M+Na)



6.77

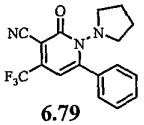
4-(3-Cyano-2-oxo-6-phenyl-4-trifluoromethyl-2*H*-pyridin-1-ylmethyl)-benzoic acid

MS(ES+): 399.4 (M+H)

6.78

2-Oxo-6-phenyl-4-trifluoromethyl-3',4',5',6'-tetrahydro-2*H*,2'*H*-[1,1']bipyridinyl-3-carbonitrile

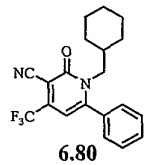
MS(ES+): 348.0 (M+H)



6.79

2-Oxo-6-phenyl-1-pyrrolidin-1-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

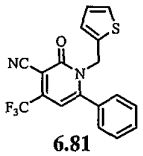
MS(ES+): 334.0 (M+H)



6.80

1-Cyclohexylmethyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

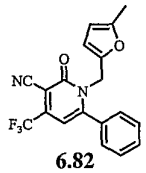
MS(ES+): 361.0 (M+H)



6.81

2-Oxo-6-phenyl-1-thiophen-2-ylmethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

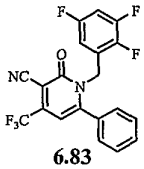
MS(ES+): 361.1 (M+H)



6.82

1-(5-Methyl-furan-2-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

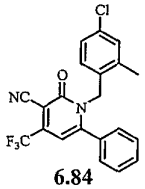
MS(ES+): 381.0 (M+Na)



6.83

2-Oxo-6-phenyl-1-(2,3,5-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

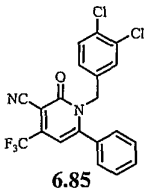
MS(ES+): 409.2 (M+H)



6.84

1-(4-Chloro-2-methyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

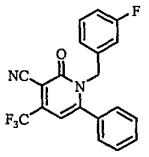
MS(ES+): 403.0 (M+H)



6.85

1-(3,4-Dichloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

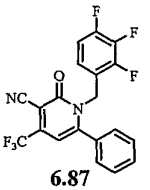
MS(ES+): 423.0 (M+H)



6.86

1-(3-Fluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

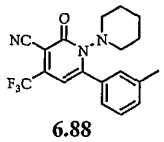
MS(ES+): 373.0 (M+H)



6.87

2-Oxo-6-phenyl-1-(2,3,4-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

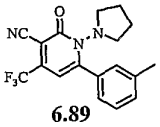
MS(ES+): 409.2 (M+H)



6.88

2-Oxo-6-*m*-tolyl-4-trifluoromethyl-3',4',5',6'-tetrahydro-2*H*,2'*H*-[1,1']bipyridinyl-3-carbonitrile

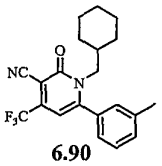
MS(ES+): 362.0 (M+H)



6.89

2-Oxo-1-pyrrolidin-1-yl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 348.0 (M+H)

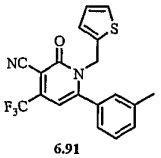


6.90

1-Cyclohexylmethyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 375.0 (M+H)

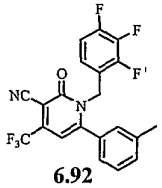
5



6.91

2-Oxo-1-thiophen-2-ylmethyl-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

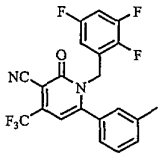
MS(ES+): 375.0 (M+H)



6.92

2-Oxo-6-*m*-tolyl-1-(2,3,4-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

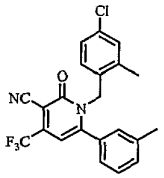
MS(ES+): 423.0 (M+H)



6.93

2-Oxo-6-*m*-tolyl-1-(2,3,5-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

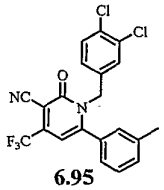
MS(ES+): 423.0 (M+H)



6.94

1-(4-Chloro-2-methyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

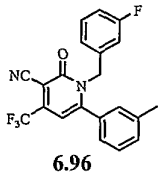
MS(ES+): 417.0 (M+H)



6.95

1-(3,4-Dichloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

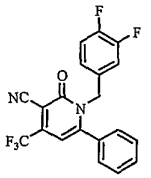
MS(ES+): 437.0 (M+H)



6.96

1-(3-Fluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

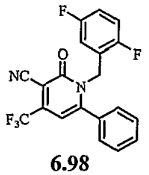
MS(ES+): 387.0 (M+H)



6.97

1-(3,4-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

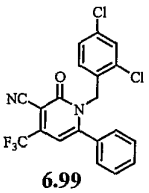
MS(ES+): 390.8 (M+H)



6.98

1-(2,5-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

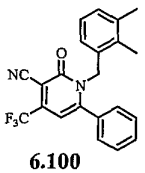
MS(ES+): 390.8 (M+H)



6.99

1-(2,4-Dichloro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

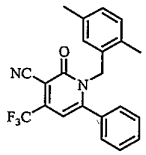
MS(ES+): 423.0 (M+H)



6.100

1-(2,3-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

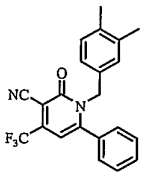
MS(ES+): 383.2 (M+H)



6.101

1-(2,5-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

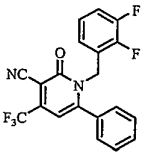
MS(ES+): 383.0 (M+H)



6.102

1-(3,4-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

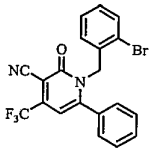
MS(ES+): 383.2 (M+H)



6.103

1-(2,3-Difluoro-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

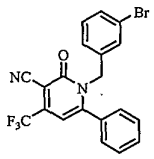
MS(ES+): 391.0 (M+H)



6.104

1-(2-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

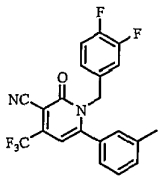
MS(ES+): 433.0 (M+H)



6.105

1-(3-Bromo-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

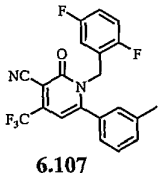
MS(ES+): 435.0 (M+H)



6.106

1-(3,4-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

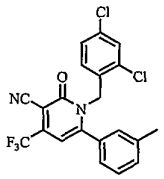
MS(ES+): 405.0 (M+H)



6.107

1-(2,5-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

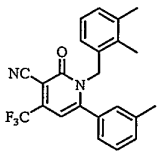
MS(ES+): 405.0 (M+H)



6.108

1-(2,4-Dichloro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

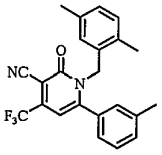
MS(ES+): 437.2 (M+H)



6.109

1-(2,3-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

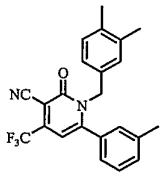
MS(ES+): 397.0 (M+H)



6.110

1-(2,5-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

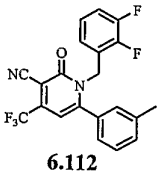
MS(ES+): 397.0 (M+H)



6.111

1-(3,4-Dimethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

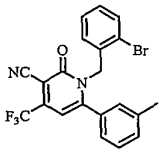
MS(ES+): 397.0 (M+H)



6.112

1-(2,3-Difluoro-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

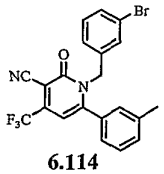
MS(ES+): 405.0 (M+H)



6.113

1-(2-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

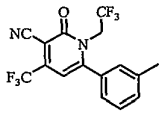
MS(ES+): 449.1(M+H)



6.114

1-(3-Bromo-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

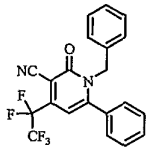
MS(ES+): 447.0 (M+H)



6.115

2-Oxo-6-*m*-tolyl-1-(2,2,2-trifluoro-ethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

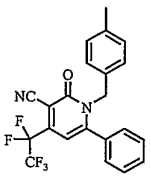
MS(ES+): 347.0 (M+H)



6.116

1-Benzyl-2-oxo-4-pentafluoroethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

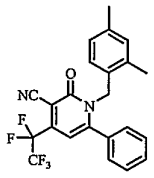
$^1$H-NMR ($CDCl_3$): δ 7.58-7.52 (m, 1H), 7.45 (t, J=7.8Hz, 2H), 7.26-7.16 (m, 5H), 6.92-6.86 (m, 2H), 6.32 (s, 1H), 5.26 (s, 2H).



6.117

1-(4-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

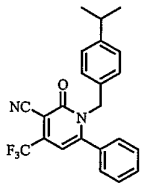
MS(ES+): 419.3 (M+H)



6.118

1-(2,4-Dimethyl-benzyl)-2-oxo-4-pentafluoroethyl-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

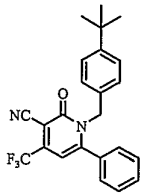
MS(ES+): 433.3 (M+H)



6.119

1-(4-Isopropyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

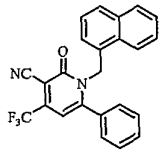
MS(ES+): 397.1 (M+H)



6.120

1-(4-*tert*-Butyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

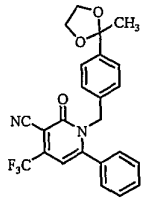
MS(ES+): 411.4 (M+H)



6.121

1-Naphthalen-1-ylmethyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

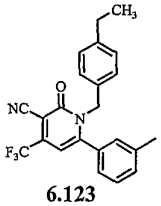
$^1$H-NMR ($CDCl_3$): δ 7.86 (d, J=7.8Hz, 1H), 7.79 (d, J=8.3Hz, 1H), 7.58 (d, J=8.6Hz, 1H), 7.52-7.35 (m, 4H), 7.16-7.14 (m, 2H), 6.87 (d, J=7.3Hz, 1H), 6.49 (s, 1H),5.68 (s, 2H).



6.122

1-[4-(2-Methyl-[1,3]dioxolan-2-yl)-benzyl]-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.59-7.52 (m, 1H), 7.46 (t, J=8.1Hz, 2H), 7.34 (d, J=8.1Hz, 2H), 7.23 (d, J=7.1Hz, 2H), 6.88 (d, J=8.1Hz, 2H), 6.41 (s, 1H), 5.25 (s, 2H), 4.05-3.99 (m, 2H), 3.75-3.70 (m, 2H),1.60 (s, 3H).

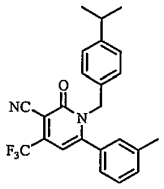


6.123

1-(4-Ethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.36-7.31 (m, 2H), 7.06 (d, J=8.1Hz, 2H), 7.04-6.99 (m, 1H), 6.91 (bs, 1H), 6.81 (d, J=8.1Hz, 2H), 6.37 (s, 1H),

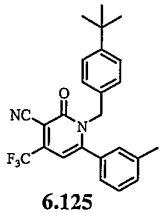
5.21 (bs, 2H), 2.59 (q, J=7.6Hz, 2H), 2.33 (s, 3H), 1.19 (t, J=7.3Hz, 3H).



**6.124**

1-(4-Isopropyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

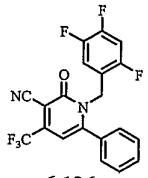
MS(ES+): 411.4 (M+H)



**6.125**

1-(4-*tert*-Butyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

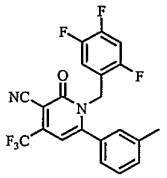
MS(ES+): 424.9 (M+H)



**6.126**

2-Oxo-6-phenyl-1-(2,4,5-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

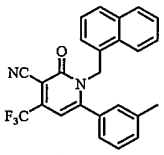
MS(ES+): 409.2 (M+H)



6.127

2-Oxo-6-*m*-tolyl-1-(2,4,5-trifluoro-benzyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

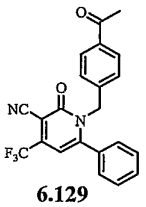
MS(ES+): 423.1 (M+H)



6.128

1-Naphthalen-1-ylmethyl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

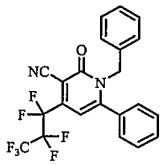
MS(ES+): 419.2 (M+H)



6.129

1-(4-Acetyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

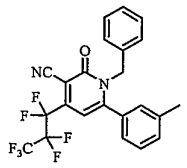
MS(ES+): 397.2 (M+H)



6.130

1-Benzyl-4-heptafluoropropyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile

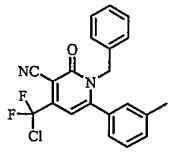
MS(ES+): 455.2 (M+H)



6.131

1-Benzyl-4-heptafluoropropyl-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

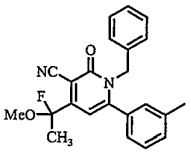
MS(ES+): 469.0 (M+H)



6.132

1-Benzyl-4-(chloro-difluoro-methyl)-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

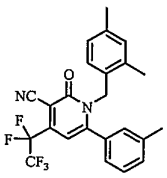
MS(ES+): 385.2 (M+H)



6.133

1-Benzyl-4-(1-fluoro-1-methoxy-ethyl)-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

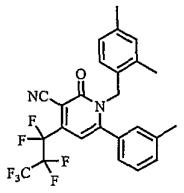
$^1$H-NMR ($CDCl_3$): δ 7.34-7.31 (m, 2H), 7.26-7.22 (m, 2H), 7.02-6.88 (m, 4H), 6.35 (s, 1H), 5.23 (s, 2H), 3.66 (s, 3H), 2.32 (s, 3H).



6.135

1-(2,4-Dimethyl-benzyl)-2-oxo-4-pentafluoroethyl-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

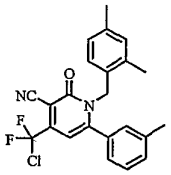
MS(ES+): 447.3 (M+H)



6.136

1-(2,4-Dimethyl-benzyl)-4-heptafluoropropyl-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

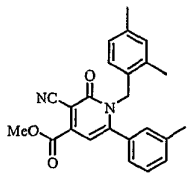
MS(ES+): 497.2 (M+H)



6.137

4-(Chloro-difluoro-methyl)-1-(2,4-dimethyl-benzyl)-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

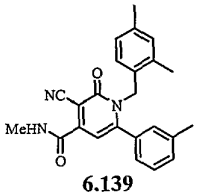
MS(ES+): 413.1 (M+H)



6.138

3-Cyano-1-(2,4-dimethyl-benzyl)-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-4-carboxylic acid methyl ester

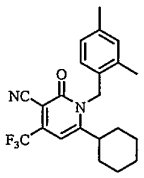
MS(ES+): 387.1 (M+H)



6.139

3-Cyano-1-(2,4-dimethyl-benzyl)-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-4-carboxylic acid methylamide

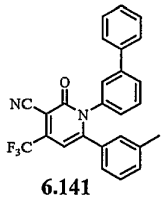
MS(ES+): 386.1 (M+H)



6.140

6-Cyclohexyl-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

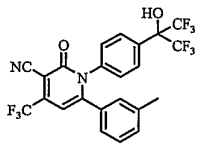
MS(ES+): 389.3 (M+H)



6.141

1-Biphenyl-3-yl-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

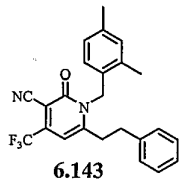
MS(ES+): 431.0 (M+H)



6.142

2-Oxo-6-*m*-tolyl-1-[4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

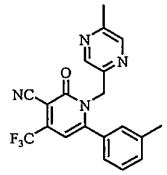
MS(ES+): 521.2 (M+H)



6.143

1-(2,4-Dimethyl-benzyl)-2-oxo-6-phenethyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

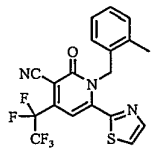
MS(ES+): 411.4 (M+H)



6.144

1-(5-Methyl-pyrazin-2-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

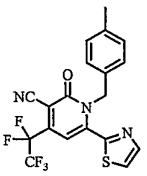
MS(ES+): 385.1 (M+H)



6.145

1-(2-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-thiazol-2-yl-1,2-dihydro-pyridine-3-carbonitrile

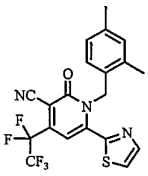
MS(ES+): 426.0 (M+H)



6.145

1-(4-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-thiazol-2-yl-1,2-dihydro-pyridine-3-carbonitrile

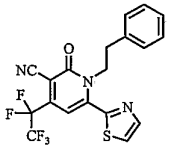
MS(ES+): 426.1 (M+H)



6.146

1-(2,4-Dimethyl-benzyl)-2-oxo-4-pentafluoroethyl-6-thiazol-2-yl-1,2-dihydro-pyridine-3-carbonitrile

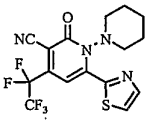
MS(ES+): 440.2 (M+H)



6.147

2-Oxo-4-pentafluoroethyl-1-phenethyl-6-thiazol-2-yl-1,2-dihydro-pyridine-3-carbonitrile

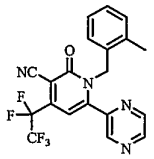
MS(ES+): 426.0 (M+H)



6.148

2-Oxo-4-pentafluoroethyl-6-thiazol-2-yl-3',4',5',6'-tetrahydro-2*H*,2'*H*-[1,1']bipyridinyl-3-carbonitrile

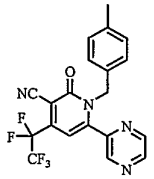
MS(ES+): 404.9 (M+H)



6.149

1-(2-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-pyrazin-2-yl-1,2-dihydro-pyridine-3-carbonitrile

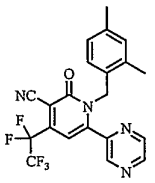
MS(ES+): 421.1 (M+H)



6.150

1-(4-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-pyrazin-2-yl-1,2-dihydro-pyridine-3-carbonitrile

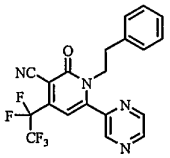
MS(ES+): 421.0 (M+H)



6.151

1-(2,4-Dimethyl-benzyl)-2-oxo-4-pentafluoroethyl-6-pyrazin-2-yl-1,2-dihydro-pyridine-3-carbonitrile

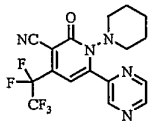
MS(ES+): 435.3 (M+H)



6.152

2-Oxo-4-pentafluoroethyl-1-phenethyl-6-pyrazin-2-yl-1,2-dihydro-pyridine-3-carbonitrile

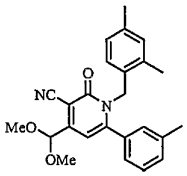
MS(ES+): 421.1 (M+H)



6.153

2-Oxo-4-pentafluoroethyl-6-pyrazin-2-yl-3',4',5',6'-tetrahydro-2*H*,2'*H*-[1,1']bipyridinyl-3-carbonitrile

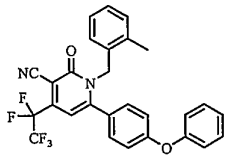
MS(ES+): 400.3 (M+H)



6.154

4-Dimethoxymethyl-1-(2,4-dimethyl-benzyl)-2-oxo-6-*m*-tolyl-1,2-dihydro-pyridine-3-carbonitrile

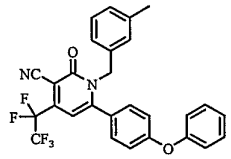
MS(ES+): 402.9 (M+H)



6.155

1-(2-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

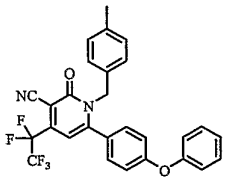
MS(ES+): 511.1 (M+H)



6.156

1-(3-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

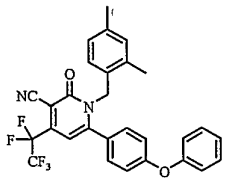
MS(ES+): 511.3 (M+H)



6.157

1-(4-Methyl-benzyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

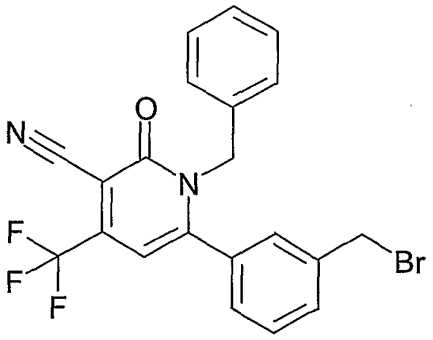
MS(ES+): 510.9 (M+H)



6.158

1-(2,4-Dimethyl-benzyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 525.4 (M+H)



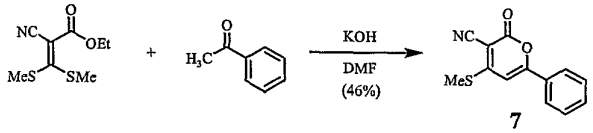
6.159

1-Benzyl-6-(3-bromomethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ7.56 (m), 7.45 (m, 1 H), 7.25 (m, 3 H), 7.15 (m, 2 H), 6.88 (m, 2 H), 6.40 (s, 1 H), 5.24 (s, 2 H), 4.39 (s, 2 H).

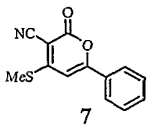
## EXAMPLE 7

This example illustrates the preparation of compound **7**.




7

3,3-Bis(methylthio)-2-cyanoacrylic acid ethyl ester (2.0 g, 9.2 mmoles – TCI America) was combined with acetophenone (1.1 mL, 9.4 mmoles) in 100 mL of DMF within a round-bottom flask. To this stirring mixture at room temp was then added potassium hydroxide (1.0 g, 17.8 mmoles), and the reaction was stirring at this temp for 12 hours. After this period the reaction was combined with 150 mL of ice-water and the mixture was stirred for 2 hours. The resulting heterogeneous mixture was vacuum filtered, and the yellow filter cake was washed with water and dried to yield product 1.04 g (46% yield) as a yellow solid.

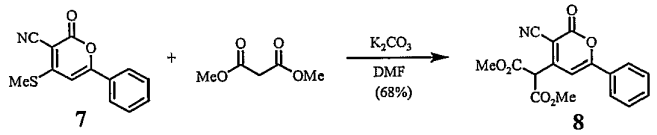



7

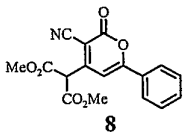
$^1$H-NMR ($CDCl_3$): $\delta$ 7.88 (dt, J'=7.0hz, J"=1.5Hz, 2H), 7.6-7.49 (m, 3H), 6.72 (s, 1H), 2.73 (s, 3H).

## EXAMPLE 8

This example illustrates the preparation of compound **8**.



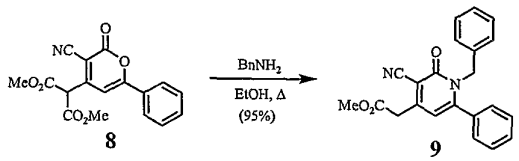

4-Methylsulfanyl-2-oxo-6-phenyl-2H-pyran-3-carbonitrile, **7** (0.11 g, 0.46 mmoles) was combined with dimethyl malonate (0.11 mL, 0.96 mmoles) and potassium carbonate (0.16 g, 1.2 mmoles) in 2.3 mL of anhydrous DMF. The reaction was stirred at room temp for 12 hours. After this period the mixture was combined with water and 1N HCl (to adjust pH < 6) and was extracted with EtOAc (2 x 30 mL). The resulting organic layer was then washed with sat'd NaCl and was dried over anhydrous $Na_2SO_4$. The EtOAc layer was evaporated *in vacuo* to yield the crude product, which was purified using flash silica chromatography to yield product 0.103 g (68% yield) as a yellow solid.



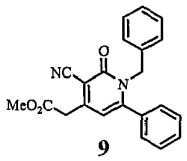

$^1$H-NMR ($CDCl_3$): $\delta$ 7.90 (dt, J'=7.1Hz, J"=1.8Hz, 2H), 7.60-7.49 (m, 3H), 7.14 (s, 1H), 5.06 (s, 1H), 3.86 (s, 6H).

## EXAMPLE 9

This example illustrates the preparation of compound **9**.

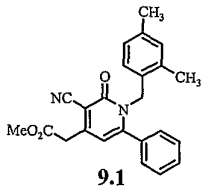



2-(3-Cyano-2-oxo-6-phenyl-2H-pyran-4-yl)-malonic acid dimethyl ester, **8** (26 mg, 0.079 mmoles) was combined with benzylamine (10 μL, 0.092 mmoles) and 1.0 mL of ethanol within a screw cap vial. The mixture was heated to 80 °C and was stirred at this temp for 2 hours. After this period the mixture was evaporated *in vacuo* and was purified directly by flash silica chromatography (0-50% EtOAc/Hexane) to yield product 27 mg (95% yield) as a beige solid.




$^1$H-NMR ($CDCl_3$): $\delta$ 7.5-7.44 (m, 1H), 7.38 (t, J=8.1Hz, 2H), 7.22-7.17 (m, 3H), 7.15 (d, J=7.3Hz, 2H), 6.91-6.85 (m, 2H), 6.31 (s, 1H), 5.19 (s, 2H), 3.96 (s, 3H), 3.86 (s, 2H). MS (ES+): 358.8 (M+H).

The following compounds were prepared in a manner similar to that described above.

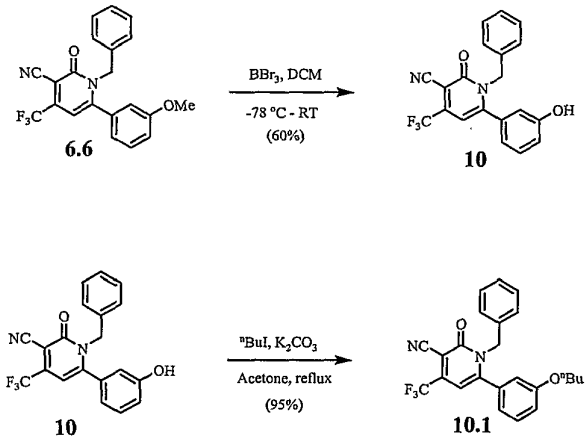



[3-Cyano-1-(2,4-dimethyl-benzyl)-2-oxo-6-phenyl-1,2-dihydro-pyridin-4-yl]-acetic acid methyl ester

$^1$H-NMR ($CDCl_3$): δ 7.28-7.20 (m, 2H), 6.96-6.90 (m, 2H), 6.89-6.82 (m, 2H), 6.67 (s, 1H), 6.62 (d, J=7.8Hz, 1H), 5.09 (s, 2H), 4.01 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H), 1.88 (s, 3H).

## EXAMPLE 10

This example illustrates the preparation of compound **10.1**.

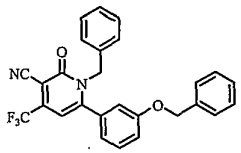



A solution of boron tribromide (4.5 mL, 47.9 mmol) in 10 mL anhydrous THF was slowly added to a solution of 1-benzyl-3-cyano-6-(3-methoxyphenyl)-4-trifluoromethyl-1*H*-pyridin-2-one (**6.6**) (8.37 g, 21.8 mmol) in 62 mL of anhydrous THF at -78 °C under nitrogen. The mixture was vigorously stirred and allowed to warm to ambient temperature overnight. The mixture was then cooled to 0 °C with an ice/water bath and to it was added 100 mL of MeOH in portion. The mixture was stirred at room temperature for 1 h and concentrated *in vacuo*. The residue was dissolved in dichloromethane and neutralized to pH 7 by adding 1 N NaOH. The organic layer was washed with water, separated and dried with anhydrous $MgSO_4$. The dichloromethane was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (50% EtOAc/hexane), providing a bright yellow solid (**10**) (4.8 g, 60% yield). $^1$H-NMR (DMSO-d6): $\delta$ 10.01 (s, 1H), 7.37 (m, 4H), 7.11 (m, 2H), 7.03 (m, 1H), 6.91 (m, 2H), 6.82 (s, 1H), 5.28 (s, 2H).

To a solution of 1-benzyl-3-cyano-6-(3-hydroxyphenyl)-4-trifluoromethyl-1*H*-pyridin-2-one (**10**) (98 mg, 0.27 mmol) in 4 mL of acetone was added 1-iodobutane (59 mg, 0.32 mmol) and $K_2CO_3$ (41 mg, 0.32 mmol). The mixture was stirred and heated to reflux overnight. The salt was removed by filtration

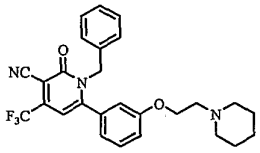
and the solvent was concentrated *in vacuo.* The resulting crude product was purified by column chromatography (25% EtOAc/hexane), providing a yellow solid (**10.1**) (107 mg, 95% yield). $^1$H-NMR ($CDCl_3$): $\delta$ 7.34 (m, 1H), 7.25 (m, 3H), 7.03 (m, 1H), 6.93 (m, 2H), 6.77 (m, 1H), 6.59 (m, 1H), 6.41(s, 1H), 5.25 (s, 2H), 3.73 (m, 2H), 1.71 (m, 2H), 1.45 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H).

The following compounds were prepared in a manner similar to that described above.



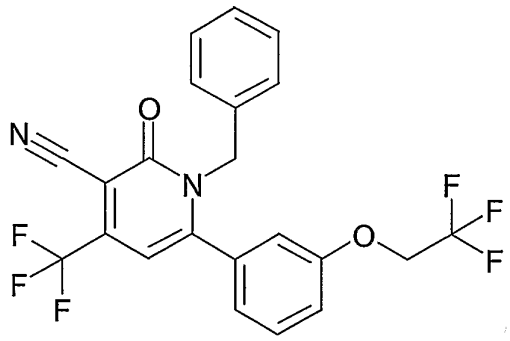
**10.2**

$^1$H-NMR ($CDCl_3$): $\delta$ 7.44 - 7.33 (m, 6H), 7.26 (m, 3H), 7.12 (m, 1H), 6.90 (m, 2H), 6.79 (m, 1H), 6.68 (m, 1H), 6.40 (s, 1H), 5.21 (s, 2H), 4.68 (s, 2H).



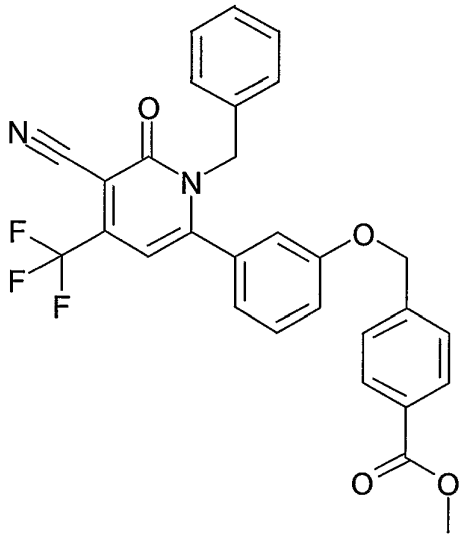
**10.3**

$^1$H-NMR ($CDCl_3$): $\delta$ 7.34 (m, 1H), 7.24 (m, 3H), 7.06 (m, 1H), 6.92 (m, 2H), 6.77 (m, 1H), 6.64 (m, 1H), 6.40 (s, 1H), 5.25 (s, 2H), 3.91 (t, J = 6.1 Hz, 2H), 2.72 (t, J = 6.1 Hz, 2H), 2.48 (m, 4H), 1.61 (m, 4H), 1.45 (m, 2H).



10.4

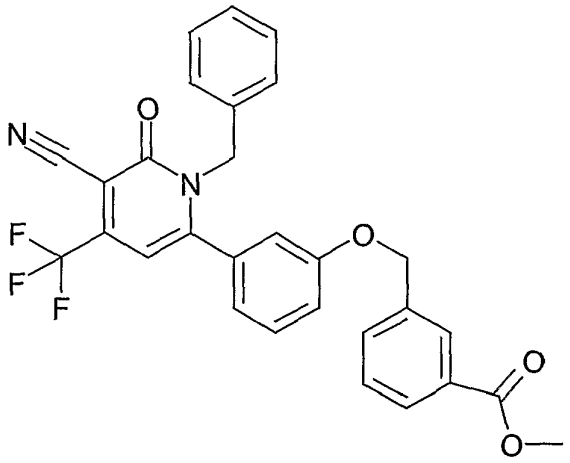
1-Benzyl-2-oxo-6-[3-(2,2,2-trifluoro-ethoxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile $^1$H-NMR ($CDCl_3$): δ7.45 (m, 1 H), 7.25 (m, 4 H), 7.01 (m, 1 H), 6.88 (m, 3 H), 6.40 (s, 1 H), 5.33 (m, 2 H), 5.26 (s, 2 H).



10.5

4-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxymethyl]-benzoic acid methyl ester $^1$H-NMR ($CDCl_3$): δ8.06 (m, 2 H), 7.42 (m, 2 H), 7.36 (m, 1 H), 7.26 (m, 4 H), 7.11 (m, 1 H), 6.92 (m, 2 H), 6.82 (m, 1 H), 6.66 (m, 1 H), 6.40 (s, 1 H), 5.21 (s, 2 H), 4.89 (s, 2 H), 3.93 (s, 3 H)..

XCT0265953

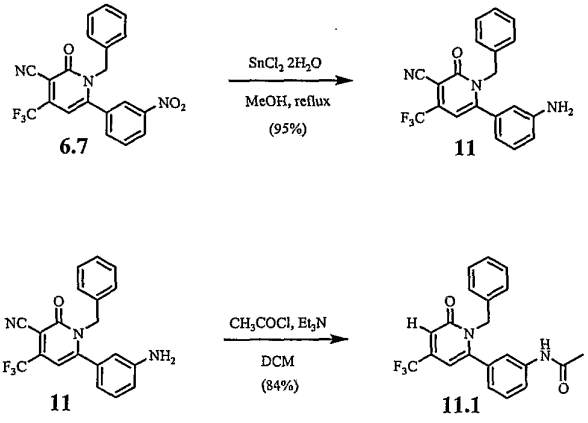


10.6

3-[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenoxymethyl]-benzoic acid methyl ester $^1$H-NMR ($CDCl_3$): δ8.03 (m, 2 H), 7.56 (m, 1 H), 7.48 (m, 1 H), 7.37 (m, 1 H), 7.26 (m, 2 H), 7.11 (m, 1 H), 6.91 (m, 2 H), 6.82 (m, 1 H),, 6.67 (m, 1 H), 6.40 (s, 1 H), 5.22 (s, 2 H), 4.87 (s, 2 H), 3.94 (s, 3 H).

## EXAMPLE 11

This example illustrates the preparation of compound **11.1**.



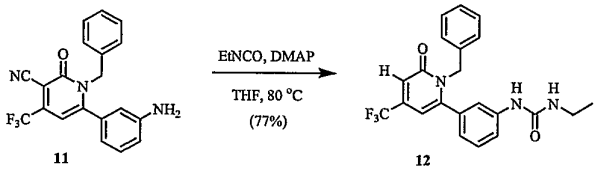

To a solution of 1-benzyl-3-cyano-6-(3-nitrophenyl)-4-trifluoromethyl-1*H*-pyridin-2-one (**6.7**) (200 mg, 0.50 mmol) in 5 mL of MeOH was added

stannous (II) chloride dihydrate (565 mg, 2.5 mmol). The mixture was stirred and heated to reflux for 3 h. The mixture was then concentrated *in vacuo*. The residue was taken in a mixture of ethyl acetate and 5% aqueous $NaHCO_3$. The mixture was stirred for 1 h, and the organic layer was separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layer was dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product (**11**) was relatively pure by analysis of its $^1H$ NMR spectrum and was used for the next reaction without further purification.

To a solution of 6-(3-aminophenyl)-1-benzyl-3-cyano-4-trifluoromethyl-1*H*-pyridin-2-one (**11**) (74 mg, 0.20 mmol) in 2 mL of dichloromethane was added acetyl chloride (48 mg, 0.6 mmol) and triethylamine (81 mg, 0.64 mmol). The mixture was refluxed overnight. The salt was removed by filtration and the solvent was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (60% EtOAc/hexane), providing **11.1** as a yellow oil (69 mg, 84% yield). $^1H$-NMR ($CDCl_3$): $\delta$ 7.57 (m, 2H), 7.43 (s, 1H), 7.35 (m, 1H), 7.23 (m, 3H), 6.90 (m, 2H), 6.85 (m, 1H), 6.41 (s, 1H), 5.27 (s, 2H), 2.19 (s, 3H).

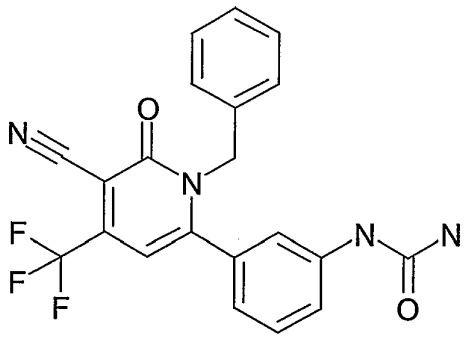
## EXAMPLE 12

This example illustrates the preparation of compound **12**.




To a solution of 6-(3-aminophenyl)-1-benzyl-3-cyano-4-trifluoromethyl-1*H*-pyridin-2-one (**11**) (94 mg, 0.26 mmol) in 2 mL of anhydrous THF was added ethyl isocyanate (90 mg, 1.3 mmol) and DMAP (6 mg, 0.05 mmol). The mixture was refluxed overnight. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the residue purified by column chromatography (50% EtOAc/hexane) providing **12** as a yellow solid (77 mg,

77% yield). $^1$H-NMR ($CDCl_3$): $\delta$ 7.44 (m, 2H), 7.25 (m, 1H), 7.21 (m, 4H), 6.89 (m, 3H), 6.69 (m, 1H), 6.43 (s, 1H), 5.27 (s, 2H), 3.28 (q, J = 7.3 Hz, 2H), 1.16 (t, J = 7.3 Hz, 3H).

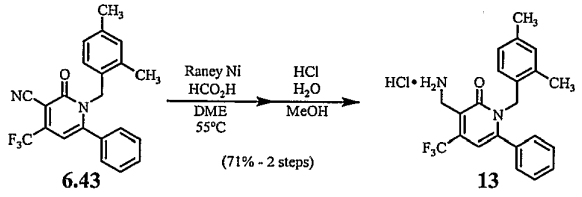


[3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-phenyl]-urea

$^1$H-NMR (DMSO-d6): δ10.20 (s, 1 H), 9.04 (s, 1 H), 7.65 (m, 1 H), 7.58 (m, 1 H), 7.43 (m, 1 H), 7.29 (m, 3 H), 7.07 (m, 1 H), 7.02 (m, 2 H), 6.80 (s, 1 H), 5.23 (s, 2 H). .

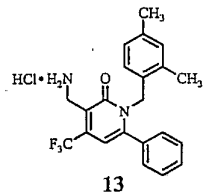
## EXAMPLE 13

This example illustrates the preparation of compound **13**.




Within a 100 mL flask was placed Raney®-type Alloy (Aluminum-nickel catalyst, Aldrich, 2.0 g), a magnetic stir bar and 2N NaOH solution (20 mL). The flask was submerged into a water bath at ambient temperature and the mixture was vigorously stirred for 45 min (bubbling occurs). In a separate pear-shaped flask was placed 1-(2,4-Dimethyl-benzyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **6.43** (100 mg, 0.26 mmoles) and this was dissolved within formic acid (5 mL) and ethylene glycol dimethyl ether (DME, 1.0 mL). After Ra-Ni activation was complete the hydroxide

mixture (heterogeneous) was carefully decanted, washed with water, and sequentially decanted to remove the residual sodium hydroxide. Excess water was removed from the activated Ra-Ni using a pipette. The nitrile solution was carefully added to the stirring Ra-Ni at room temperature, and mixture was heated to 55 °C for 3 hours. After this period the reaction mixture was filtered through Celite (with MeOH washings) and concentrated *in vacuo*. The residue was taken up in ethyl acetate and was washed with 50% v/v aqueous $NH_4OH$ (3x20 mL) and brine. The resulting EtOAc solution was dried over anhydrous $Na_2SO_4$ and was concentrated *in vacuo* to yield crude product as a yellow residue. The crude product was purified using flash silica chromatography (0-10% MeOH/DCM) to yield the free base as a yellow residue. The free base was combined with 2N HCl/MeOH and evaporated to yield the hydrochloride salt. The salt was dissolved in deionized water and freeze-dried to yield 79mg (71% yield) of product **13** as a yellowish powder.

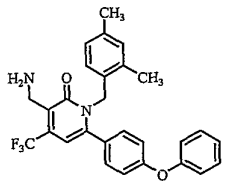



13

(3-Aminomethyl-1-(2,4-dimethyl-benzyl)-6-phenyl-4-trifluoromethyl-1*H*-pyridin-2-one hydrochloride)

$^1$H-NMR ($CDCl_3$): δ (d6-DMSO) 8.38 (bs, 3H), 7.47 (t, J=7.5Hz, 1H), 7.40 (t, J=7.6Hz, 2H), 7.26 (d, J=7.6Hz, 2H), 6.92-6.89 (m, 2H), 6.65 (d, J=7.6Hz, 1H), 6.54 (s, 1H), 5.05 (s, 2H), 4.02 (bs, 2H), 2.21 (s, 3H), 1.87 (s, 3H). MS(ES+): 386.9 (M+H)

The following compound was prepared in a manner similar to that described above.



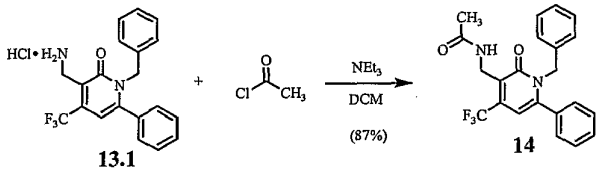
13.2

(3-Aminomethyl-1-(2,4-dimethyl-benzyl)-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1*H*-pyridin-2-one)

$^1$H-NMR ($CDCl_3$): δ 7.20-7.14 (m, 1H), 7.11-6.99 (m, 5H), 6.94-6.87 (m, 5H), 6.58 (d, J=7.3Hz, 1H), 6.34 (s, 1H), 5.09 (s, 2H), 3.93 (s, 2H), 2.26 (s, 3H), 2.01 (s, 3H).

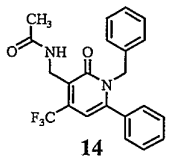
## EXAMPLE 14

This example illustrates the preparation of compound **14**.



**13.1** **14**

3-Aminomethyl-1-(2,4-dimethyl-benzyl)-6-phenyl-4-trifluoromethyl-1H-pyridin-2-one hydrochloride **13.1** (15 mg, 0.039 mmoles) was combined with acetyl chloride (5 μL, 0.070 mmoles) and triethylamine (12 μL, 0.086 mmoles) in 5 mL of anhydrous DCM within a round-bottom flask. The mixture was stirred at room temperature for 10 hours and was evaporated *in vacuo* to yield crude product as a yellow residue. The crude product was purified using flash silica chromatography (0-30% EtOAc /Hexane) to yield 15mg (87% yield) of **14** as a white solid.



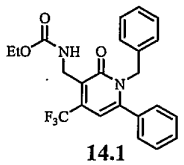
14

*N*-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-acetamide

$^1$H-NMR ($CDCl_3$): δ 7.50-7.43 (m, 1H), 7.38 (t, J=7.8Hz, 2H), 7.25-7.21 (m, 3H), 7.19-7.14 (m, 2H),6.92-6.85 (m, 2H), 6.83-6.75 (m, 1H), 6.36 (s, 1H), 5.21 (bs, 2H), 4.62 (d, J=6.1Hz, 2H), 1.97 (s, 3H).

MS(ES+): 401.2 (M+H)

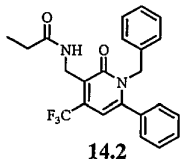
The following compounds were prepared in a manner similar to that described above.



14.1

(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-carbamic acid ethyl ester

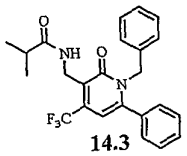
MS(ES+): 431.1 (M+H)



14.2

*N*-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-propionamide

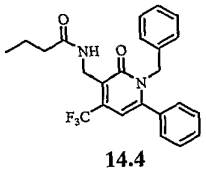
MS(ES+): 415.2 (M+H)



14.3

*N*-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-isobutyramide

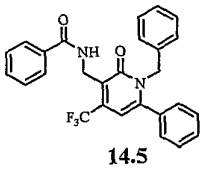
MS(ES+): 429.3 (M+H)



14.4

*N*-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-butyramide

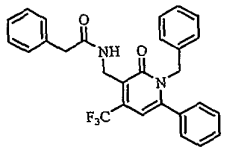
MS(ES+): 429.2 (M+H)



14.5

*N*-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-benzamide

MS(ES+): 463.2 (M+H)



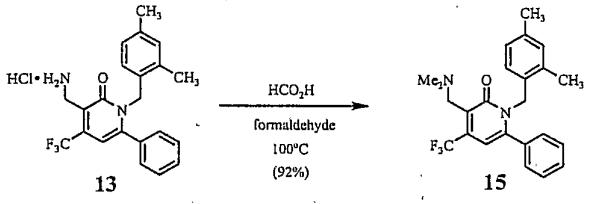
14.6

*N*-(1-Benzyl-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl)-2-phenyl-acetamide

MS(ES+): 477.1 (M+H)

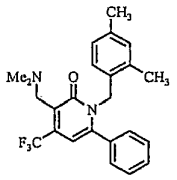
**EXAMPLE 15**

This example illustrates the preparation of compound **15**.




13 15

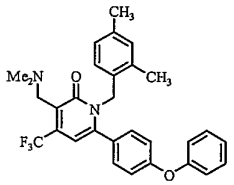
3-Aminomethyl-1-(2,4-dimethyl-benzyl)-6-phenyl-4-trifluoromethyl-1H-pyridin-2-one hydrochloride **13** (39 mg, 0.092 mmoles) was combined with formic acid (96%, 1.0 mL) in 3.0 mL of aqueous formaldehyde (37 wt. % solution in water), and the mixture was stirred at 100 °C for 16 hours. After this period the mixture was poured into a saturated $NaHCO_3$ solution (20 mL) which was extracted with copious $Et_2O$. The combined ether layer was washed with brine, dried over anhydrous $Na_2SO_4$, and was evaporated *in vacuo* to yield crude product as a yellowish residue. The crude product was purified using flash silica chromatography (0-10% MeOH/DCM w/0.1% diethylamine) to yield 35 mg (92% yield) of **15** as a yellowish residue.




15

(3-Dimethylaminomethyl-1-(2,4-dimethyl-benzyl)-6-phenyl-4-trifluoromethyl-1*H*-pyridin-2-one)

$^1$H-NMR ($CDCl_3$): δ 7.43-7.37 (m, 1H), 7.31 (t, J=7.8Hz, 2H), 7.17-7.11 (m, 2H), 6.89 (bd, J=7.8Hz, 1H), 6.85 (bs, 1H), 6.56 (d, J=7.8Hz, 1H), 6.32 (s, 1H), 5.07 (s, 2H), 3.63-3.59 (m, 2H), 2.36 (s, 6H), 2.25 (s, 3H), 1.92 (s, 3H). MS(ES+): 415.4 (M+H)



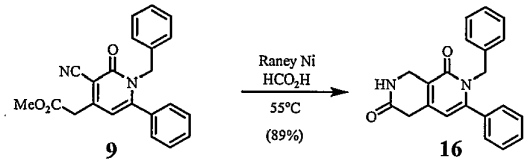
15.1

3-Dimethylaminomethyl-1-(2,4-dimethyl-benzyl)-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1*H*-pyridin-2-one

MS(ES+): 507.2 (M+H)

## EXAMPLE 16

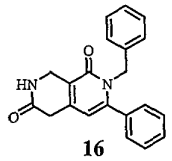
This example illustrates the preparation of compound **16**.



9 16

Within a 100 mL flask was placed Raney®-type Alloy (Aluminum-nickel catalyst, Aldrich, 4.0 g), a magnetic stir bar and 2N NaOH solution (50 mL). The flask was submerged into a water bath at ambient temperature and the mixture was vigorously stirred for 45 min (bubbling occurs). In a separate pear-shaped flask was placed [3-Cyano-1-(2,4-dimethyl-benzyl)-2-oxo-6-phenyl-1,2-dihydro-pyridin-4-yl]-acetic acid methyl ester **9** (183 mg, 0.46 mmoles) and this was dissolved within formic acid (8 mL). After Ra-Ni activation was complete the hydroxide mixture (heterogeneous) was carefully decanted, washed with water, and sequentially decanted to remove the residual sodium hydroxide. Excess water was removed from the activated Ra-Ni using a pipette. The nitrile solution was carefully added to the stirring Ra-Ni at room temperature, and mixture was heated to 55 °C for 90 min. After this period the reaction mixture was filtered through Celite (with MeOH washings) and concentrated *in vacuo*. The residue was taken up in EA and was washed with 50% v/v aqueous $NH_4OH$ (3x20 mL) and brine. The

resulting EA solution was dried over anhydrous $Na_2SO_4$ and was concentrated *in vacuo* to yield 0.151 g (89% yield) of **16** as a yellow residue.

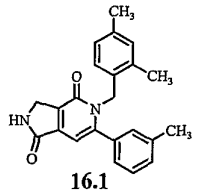


16

2-Benzyl-3-phenyl-7,8-dihydro-2*H*,5*H*-[2,7]naphthyridine-1,6-dione

$^1$H-NMR ($CDCl_3$): δ 7.48-7.41 (m, 1H), 7.40-7.33 (m, 2H), 7.20-7.09 (m, 5H), 6.95-6.89 (m, 2H), 5.95 (s, 1H), 5.84 (bs, 1H), 5.20 (bs, 2H), 3.55-3.47 (m, 2H), 2.81 (t, J=6.6Hz, 2H). MS(ES+): 331.2 (M+H)

The following compound was prepared in a manner similar to that described above.



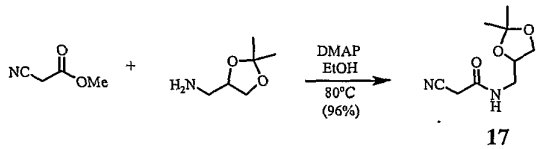
16.1

5-(2,4-Dimethyl-benzyl)-6-*m*-tolyl-3,5-dihydro-2*H*-pyrrolo[3,4-*c*]pyridine-1,4-dione

MS(ES+): 359.2 (M+H)

## EXAMPLE 17

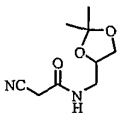
This example illustrates the preparation of compound **17**.




17

Methyl cyanoacetate (6.7 mL, 75.9 mmoles) was combined with 2,2-dimethyl-1,3-dioxolane-4-methanamine (4.6 g, 50.5 mmoles), 4-(N,N-dimethylamino)pyridine (20 mg, 0.16 mmoles) and 20 mL of Ethanol within a

round-bottom flask. The mixture was then stirred at 80 °C for 16 hours. After this period reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-60% EtOAc/hexane) to yield 7.33 g (96% yield) of **17** as a yellowish liquid.



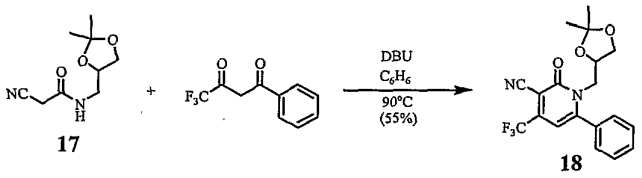
**17**

2-Cyano-*N*-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-acetamide

$^1$H-NMR ($CDCl_3$): δ 6.43 (bs, 1H), 4.31-4.21 (m, 1H), 4.10-4.04 (m, 1H), 3.65 (dd, J'=8.3Hz, J"=5.8Hz, 1H), 3.59 (dq, $J^1$=13.9Hz, $J^2$=5.6Hz, $J^3$=3.5Hz, 1H), 3.41 (s, 2H), 3.39-3.33 (m, 1H), 1.47 (s, 3H), 1.36 (s, 3H).

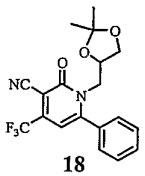
## EXAMPLE 18

This example illustrates the preparation of compound **18**.




**17** **18**

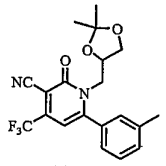
2-Cyano-N-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-acetamide **17** (2.05 g, 10.3 mmoles), 4,4,4-Trifluoro-1-phenyl-butane-1,3-dione (2.2 g, 10.3 mmoles) and DBU (0.77 mL, 5.1 mmoles) were combined with 20 mL of benzene within a round-bottom flask. The mixture was stirred at 90 °C for 16 hours. After this period the reaction mix was purified directly using flash silica chromatography (0-40% EtOAc/Hexane) to yield 2.14g (55% yield) of **18** as a yellow residue.



18

1-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

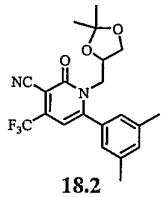
$^1$H-NMR ($CDCl_3$): δ 7.60-7.49 (m, 3H), 7.48-7.37 (m, 2H), 6.42 (s, 1H), 4.59-4.52 (m, 1H), 4.33 (dd, J'=13.1Hz, J"=2.5Hz, 1H), 4.09 (dd, J'=8.8Hz, J"=6.8Hz, 1H), 4.02 (dd, J'=12.9Hz, J"=8.6Hz, 1H), 3.51 (dd, J'=8.6Hz, J"=6.1Hz, 1H), 1.24 (s, 3H), 1.10 (s, 3H). MS(ES+): 379.4 (M+H)



18.1

1-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.43-7.33 (m, 2H), 7.22 (bs, 2H), 6.41 (s, 1H), 4.59-4.51 (m, 1H), 4.34-4.30 (dd, J'=13.1Hz, J"=2.8Hz, 1H), 4.16-4.00 (m, 2H), 3.52 (dd, J'=8.8Hz, J"=5.8Hz, 1H), 2.43 (s, 6H), 1.11 (s, 3H).



18.2

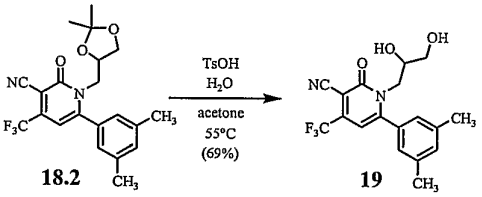
1-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.16 (s, 1H), 6.99 (bs, 2H), 6.40 (s, 1H), 4.59-4.52 (m, 1H), 4.34 (dd, J'=12.9Hz, J"=2.5Hz, 1H), 4.13-4.00 (m,

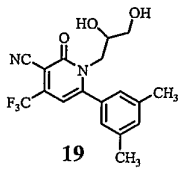
2H), 3.53 (dd, J'=8.6Hz, J"=6.3Hz, 1H), 2.38 (s, 6H), 1.24 (s, 3H), 1.12 (s, 3H).

## EXAMPLE 19

This example illustrates the preparation of compound **19**.



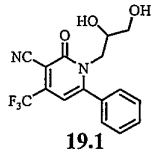

1-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoro-methyl-1,2-dihydro-pyridine-3-carbonitrile **18.2** (0.72 g, 1.78 moles) was combined with p-toluenesulfonic acid monohydrate (0.34 g, 1.78 mmoles), water (2 mL) and 30 mL of actone within a round-bottom flask equipped with a reflux condensor. The mixture was stirred at 55 °C for 3 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified directly using flash silica chromatography (0-80% EtOAc/Hexane) to yield 0.45 g (69% yield) of **19** as a white solid.




1-(2,3-Dihydroxy-propyl)-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.19 (s, 1H), 6.95 (s, 2H), 6.46 (s, 1H), 4.24-4.12 (m, 2H), 3.94-3.86 (m, 1H), 3.63-3.55 (m, 1H), 3.43-3.36 (m, 1H), 3.21 (d, J=6.1Hz, 1H), 2.39 (s, 6H).

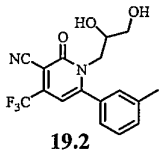
The following compounds were prepared in a manner similar to that described above.



19.1

1-(2,3-Dihydroxy-propyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 339.1 (M+H)



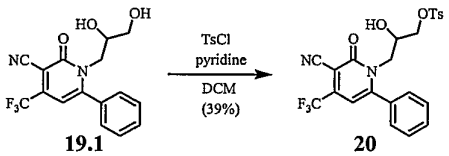
19.2

1-(2,3-Dihydroxy-propyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.47-7.33 (m, 2H), 7.21 (bs, 2H), 6.48 (s, 1H), 4.24-4.09 (m, 2H), 4.04-3.97 (m, 1H), 3.56 (dd, J'=11.6Hz, J"=4.0Hz, 1H), 3.37 (dd, J'=11.9Hz, J"=4.8Hz, 1H), 2.82 (bs, 1H), 2.43 (s, 3H).

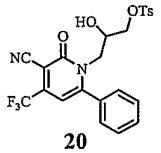
## EXAMPLE 20

This example illustrates the preparation of compound **20**




19.1 20

1-(2,3-Dihydroxy-propyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **19.1** (0.33 g, 0.98 mmoles) was combined with *p*-toluenesulfonyl chloride (0.2 g, 1.05 mmoles), pyridine (0.1 mL, 1.24 mmoles) and 3 mL of anhydrous DCM within a 7 mL reaction vial. The mixture as then stirred at room temp for 24 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified directly using flash silica chromatography (0-30% EtOAc/Hexane) to yield 186 mg (39% yield) of **20** was a yellow residue.

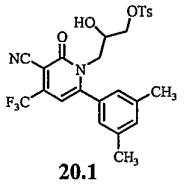


20

Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-phenyl-4-trifluoromethyl-2*H*-pyridin-1-yl)-2-hydroxy-propyl ester

$^1$H-NMR ($CDCl_3$): δ 7.66 (d, J=8.3Hz, 2H), 7.62-7.52 (m, 3H), 7.44-7.38 (m, 2H), 7.33 (d, J=8.1Hz, 2H), 6.46 (s, 1H), 4.30-4.21 (m, 1H), 4.17-4.07 (m, 2H), 3.97-3.87 (m, 2H), 3.38 (d, J=5.8Hz, 1H), 2.45 (s, 3H).

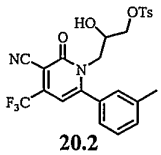
The following compounds were prepared in a manner similar to that described above.



20.1

Toluene-4-sulfonic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2*H*-pyridin-1-yl] -2-hydroxy-propyl ester

$^1$H-NMR ($CDCl_3$): δ 7.67 (d, J=8.3Hz, 2H), 7.33 (d, J=8.1Hz, 2H), 7.20 (s, 1H), 6.97 (bs, 2H), 6.45 (s, 1H), 4.23-4.05 (m, 4H), 3.96-3.87 (m, 2H), 3.38-3.34 (m, 1H), 2.45 (s, 3H), 2.40 (s, 6H).



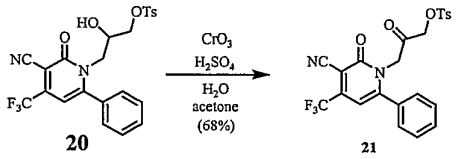
20.2

Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-*m*-tolyl-4-trifluoromethyl-2*H*-pyridin-1-yl)-2-hydroxy-propyl ester

$^1$H-NMR ($CDCl_3$): δ 7.66 d (J=8.3Hz, 2H), 7.48-7.36 (m, 3H), 7.33 (d, J=8.3Hz, 2H), 7.19 (bs, 2H), 6.45 (s, 1H), 4.25-4.05 (m, 3H), 3.96-3.86 (m, 2H), 3.45 (bs, 1H), 2.45 (s, 3H), 2.44 (s, 3H).

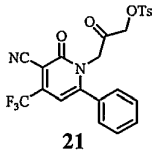
## EXAMPLE 21

This example illustrates the preparation of compound **21**.




**20** **21**

Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-phenyl-4-trifluoromethyl-2H-pyridin-1-yl)-2-hydroxy-propyl ester **20** (46 mg, 0.093 mmoles) was dissolved into actone. To this solution at room temperature was added 2.67 M Jones Reagent (0.15 mL, 0.40 mmoles) and the resulting mixture was stirred at this temperature for 3 hours. After this period the reaction mixture was gravity filtered through paper, evaporated *in vacuo* and was purified directly using flash silica chromatography (0-30% EtOAc/Hexane) to yield 31 mg (68% yield) of **21** as a yellow residue.

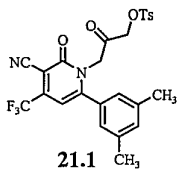



**21**

Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-phenyl-4-trifluoromethyl-2*H*-pyridin-1-yl)-2-oxo-propyl ester

$^1$H-NMR ($CDCl_3$): δ 7.76 (d, J=8.3Hz, 2H), 7.63-7.52 (m, 3H), 7.40-7.32 (m, 4H), 6.50 (s, 1H), 4.84 (s, 2H), 4.59 (s, 2H), 2.47 (s, 3H).

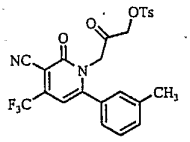
The following compounds were prepared in a manner similar to that described above.




**21.1**

Toluene-4-sulfonic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2*H*-pyridin-1-yl]-2-oxo-propyl ester

$^1$H-NMR ($CDCl_3$): δ 7.76 (d, J=8.3Hz, 2H), 7.38 (d, J=8.3Hz, 2H), 7.21 (bs, 1H), 6.93 (s, 2H), 6.48 (s, 1H), 4.86 (s, 2H), 4.60 (s, 2H), 2.47 (s, 3H), 2.38 (s, 6H).



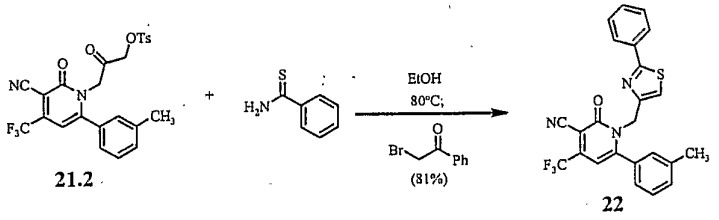
21.2

Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-*m*-tolyl-4-trifluoromethyl-2*H*-pyridin-1-yl)-2-oxo-propyl ester

$^1$H-NMR ($CDCl_3$): δ 7.76 (d, J=8.3Hz, 2H), 7.45-7.35 (m, 4H), 7.17-7.10 (m, 2H), 6.49 (s, 1H), 4.85 (s, 2H), 4.59 (s, 2H), 2.47 (s, 3H), 2.43 (s, 3H).

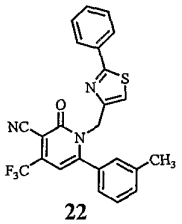
## EXAMPLE 22

This example illustrates the preparation of compound **22**.



21.2 22

Toluene-4-sulfonic acid 3-(3-cyano-2-oxo-6-m-tolyl-4-trifluoromethyl-2H-pyridin-1-yl)-2-oxo-propyl ester **21.2** (11 mg, 0.022 mmoles) was combined with thiobenzamide (6 mg, 0.044 mmoles) and 1.0 mL of EtOH within a 7 mL reaction vial. This mixture was stirred at 80 °C for 16 hours. After this period 2-bromoacetophenone (7 mg, 0.035 mmoles) was added and the mixture was stirred at 80 °C for an additional 3 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 8mg (81% yield) of **22** as a yellowish residue.

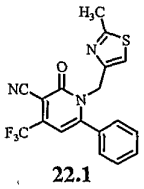


22

2-Oxo-1-(2-phenyl-thiazol-4-ylmethyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.89-7.82 (m, 2H), 7.46-7.34 (m, 7H), 7.30 (s, 1H), 6.44 (s, 1H), 5.28 (s, 2H), 2.41 (s, 3H). MS(ES+): 452.1 (M+H)

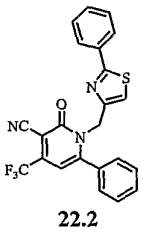
The following compounds were prepared in a manner similar to that described above.



22.1

1-(2-Methyl-thiazol-4-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

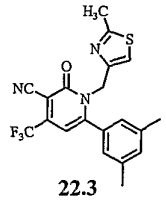
MS(ES+): 398.0 (M+Na)



22.2

2-Oxo-6-phenyl-1-(2-phenyl-thiazol-4-ylmethyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

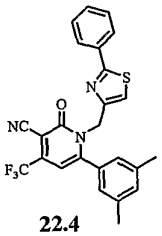
MS(ES+): 438.2 (M+H)



22.3

6-(3,5-Dimethyl-phenyl)-1-(2-methyl-thiazol-4-ylmethyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

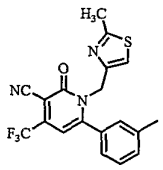
MS(ES+): 404.1 (M+H)



22.4

2-Oxo-1-(2-phenyl-thiazol-4-ylmethyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

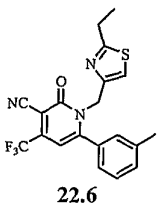
MS(ES+): 466.2 (M+H)



22.5

1-(2-Methyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

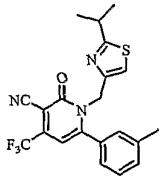
MS(ES+): 389.8 (M+H)



22.6

1-(2-Ethyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

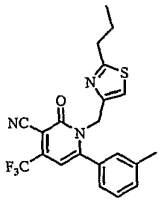
MS(ES+): 404.0 (M+H)



22.7

1-(2-Isopropyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

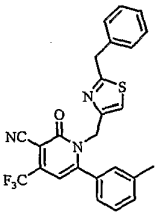
$^1$H-NMR ($CDCl_3$): δ 7.39-7.27 (m, 4H), 7.11 (s, 1H), 6.42 (s, 1H), 5.19 (s, 2H), 3.22 (m, J=6.8Hz, 1H), 2.39 (s, 3H), 1.36 (d, J=6.8Hz, 6H).



22.8

2-Oxo-1-(2-propyl-thiazol-4-ylmethyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 418.3 (M+H)



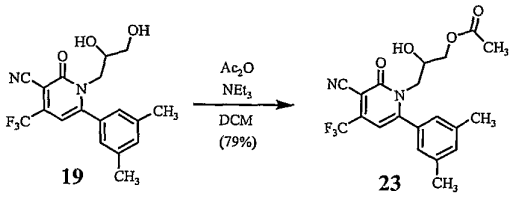
18.9

1-(2-Benzyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

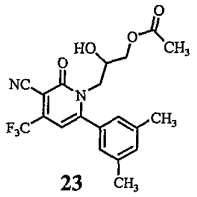
MS(ES+): 466.2 (M+H)

## EXAMPLE 23

This example illustrates the preparation of compound **23**.



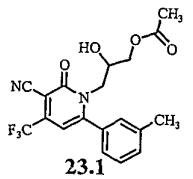

1-(2,3-Dihydroxy-propyl)-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **19** (33 mg, 0.09 mmoles) was combined with acetic acid anhydride (9 μL, 0.095 mmoles), triethylamine (1□□L, 0.11 mmoles) and 2.0 mL of DCM within a 7 mL reaction vial. This mixture was stirred at room temperature for 24 hours. After this period the reaction mixture was purified directly by flash silica chromatography (0-40% EtOAc/Hexane) to yield 29 mg (79% yield) of **23** as a white solid.




Acetic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2*H*-pyridin-1-yl]-2-hydroxy-propyl ester

$^1$H-NMR ($CDCl_3$): δ 7.19 (bs, 1H), 6.98 (bs, 2H), 6.44 (s, 1H), 4.28-3.91 (m, 6H), 3.15 (bs, 1H), 2.39 (s, 6H), 1.94 (s, 3H).

The following compounds were prepared in a manner similar to that described above.

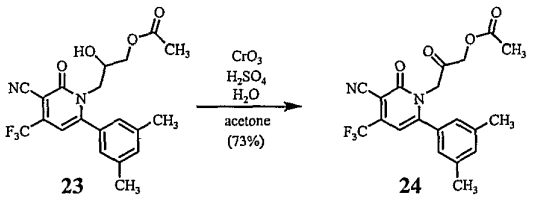



Acetic acid 3-(3-cyano-2-oxo-6-*m*-tolyl-4-trifluoromethyl-2*H*-pyridin-1-yl)-2-hydroxy-propyl ester

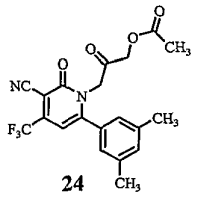
$^1$H-NMR ($CDCl_3$): δ 7.45-7.35 (m, 2H), 7.19 (bs, 2H), 6.45 (s, 1H), 4.27-3.91 (m, 6H), 3.05 (bs, 1H), 2.44 (s, 3H), 1.93 (s, 3H).

## EXAMPLE 24

This example illustrates the preparation of compound **24**.




Acetic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2H-pyridin-1-yl]-2-hydroxy-propyl ester **23** (29 mg, 0.071 mmoles) was dissolved into 3 mL of acetone within a 7 ml reaction vial. To this solution was added 2.67M Jones Reagent (53 mL, 0.142 mmoles) and the mixture was stirred at room temperature for 2 hours. After this period the reaction mixture was gravity filtered through paper and the resulting filtrate was evaporated *in vacuo*, and purified using flash silica chromatography (0-40% EtOAc/Hexane) to yield 21 mg (73% yield) of **24** as a white solid.

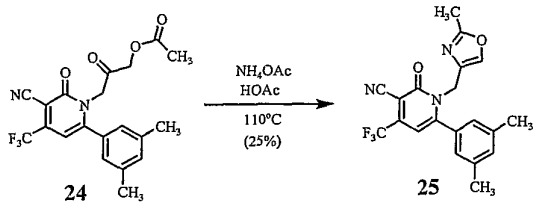



Acetic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2*H*-pyridin-1-yl]-2-oxo-propyl ester

$^1$H-NMR ($CDCl_3$): δ 7.19 (s, 1H), 6.93 (s, 2H), 6.48 (s, 1H), 4.73 (s, 2H), 4.72 (s, 2H), 2.37 (s, 6H), 2.14 (s, 3H).

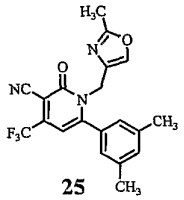
## EXAMPLE 25

This example illustrates the preparation of compound **25**.




24 25

Acetic acid 3-[3-cyano-6-(3,5-dimethyl-phenyl)-2-oxo-4-trifluoromethyl-2H-pyridin-1-yl]-2-oxo-propyl ester **24** (21 mg, 0.052 mmoles) was combined with ammonium acetate (50 mg, 0.64 mmoles) and 1.0 mL of glacial acetic acid within a 7 mL reaction vial, and the mixture was stirred at 110 °C for 16 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-40% EtOAc/Hexane) to yield 5mg (25% yield) of **25** as a white solid.

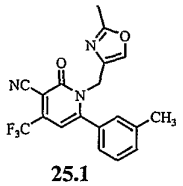


25

6-(3,5-Dimethyl-phenyl)-1-(2-methyl-oxazol-4-ylmethyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.59 (s, 1H), 7.19 (bs, 1H), 7.15 (s, 2H), 6.41 (s, 1H), 4.98 (s, 2H), 2.41 (s, 3H), 2.38 (s, 6H).

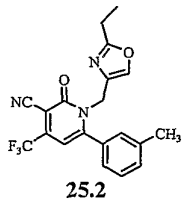
The following compounds were prepared in a manner similar to that described above.



25.1

1-(2-Methyl-oxazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

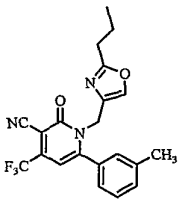
MS(ES+): 374.1 (M+H)



25.2

1-(2-Ethyl-oxazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

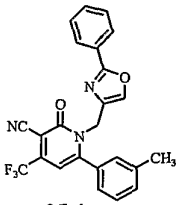
MS(ES+): 388.0 (M+H)



25.2

2-Oxo-1-(2-propyl-oxazol-4-ylmethyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

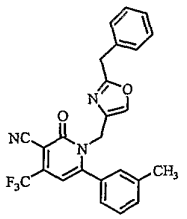
MS(ES+): 402.1 (M+H)



25.4

2-Oxo-1-(2-phenyl-oxazol-4-ylmethyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

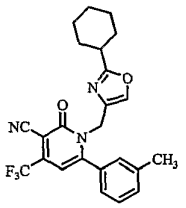
MS(ES+): 436.3 (M+H)



25.5

1-(2-Benzyl-oxazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.64 (s, 1H), 7.37-7.24 (m, 9H), 6.4 (s, 1H), 4.98 (s, 2H), 4.06 (s, 2H), 2.36 (s, 3H). MS(ES+): 449.9 (M+H)



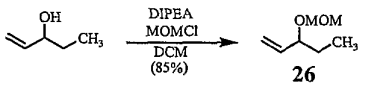
25.6

1-(2-Cyclohexyl-oxazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 442.0 (M+H)

## EXAMPLE 26

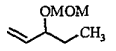
This example illustrates the preparation of compound **26**.




26

Pent-1-en-3-ol (5.0 mL, 48.7 mmoles), N,N-diisopropylethylamine (10.2 mL, 58.6 mmoles) and MOMCl (4.4 mL, 57.9 mmoles) were dissolved in 10 mL of anhydrous DCM within a sealed-tube, and this mixture was stirred at 50 °C for 20 hours. After this period the reaction mixture was combined with $Et_2O$ and the resulting precipitate was removed by gravity filtration. The filtrate was carefully evaporated (-$Et_2O$ and

DCM) and the resulting amber liquid was fractionally distilled to yield 5.4g (85% yield) of **26** as a clear liquid. B.P. 126 °C @ 760mmHg



**26**
3-Methoxymethoxy-pent-1-ene

$^1$H-NMR ($CDCl_3$): δ 5.72-5.61 (m, 1H), 5.23-5.16 (m, 2H), 4.71 (d, J=6.8Hz, 1H), 4.55 (d, J=6.8Hz, 1H), 3.91 (q, J=7.1Hz, 1H), 3.38 (s, 3H), 1.70-1.48 (m, 2H), 0.93 (t, J=7.3Hz, 3H).

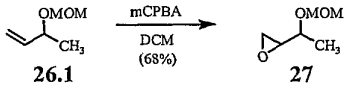
The following compounds were prepared in a manner similar to that described above.

**26.1**
3-Methoxymethoxy-but-1-ene

$^1$H-NMR ($CDCl_3$): δ 5.80-5.70 (m, 1H), 5.24-5.11 (m, 2H), 4.69 (d, J=6.8Hz, 1H), 4.58 (d, J=6.8Hz, 1H), 4.21-4.09 (m, 1H), 3.38 (s, 3H), 1.27 (d, J=6.3Hz, 3H).

## EXAMPLE 27

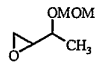
This example illustrates the preparation of compound **27**.




**26.1** **27**

3-Methoxymethoxy-but-1-ene **26.1** (1.73 g, 14.9 mmoles) was dissolved into 100 mL of DCM and to this stirring mixture at 0 °C was added 3-chloroperoxybenzoic acid (77% max, 7.4 g, ~30 mmoles). This mixture was allowed to stir at room temperature for 20 hours. After this period the reaction mixture was combined with DCM and was washed with saturated $Na_2S_2O_3$ (2x20 mL) and 15 mL of saturated $NaHCO_3$. After drying the resulting DCM

solution over anhydrous $Na_2SO_4$ the mixture was carefully evaporated *in vacuo* to yield crude product. The crude product was purified using flash silica chromatography (0-15% EtOAc/Hexane) to yield 1.34 g (68% yield) of **27** as yellowish liquid. Both $^1$H-NMR and TLC analysis show **27** to be a 1:1 mixture of diastereomers.

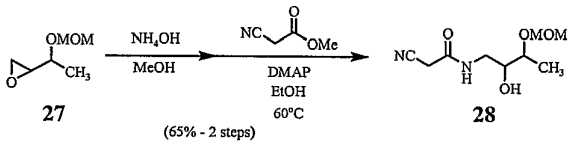


**27**
2-(1-Methoxymethoxy-ethyl)-oxirane

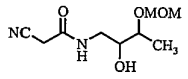
$^1$H-NMR ($CDCl_3$): (diastereomers) δ 4.81 (d, J=6.6Hz, 1H), 4.72-4.67 (m, 2H), 4.64 (d, J=6.6Hz, 1H), 3.65-3.57 (m, 1H), 3.53-3.44 (m, 1H), 3.40 (s, 3H), 3.37 (s, 3H), 3.02-2.98 (m, 1H), 2.95-2.91 (m, 1H), 2.81-2.76 (m, 2H), 2.73-2.70 (m, 1H), 2.57-2.54 (m, 1H).

## EXAMPLE 28

This example illustrates the preparation of compound **28**.



2-(1-Methoxymethoxy-ethyl)-oxirane **27** (1.89 g, 14.3 mmoles) was combined with $NH_4OH$ (28% $NH_3$ in water, 5 mL) and 1 mL of MeOH within a sealed-tube and this mixture was vigorously stirred at room temperature for 48 hours. After this period the reaction mixture was evaporate *in vacuo* (-$NH_3$ and $H_2O$) to yield crude product as an amber liquid. This product was combined with methyl cyanoactate (3.0 mL, 34.0 mmoles), DMAP (10 mg) and 50 mL of anhydrous EtOH. This mixture was stirred at 60 °C for 48 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-100% EtOAc/Hexane) to yield 2.02 g (65% yield) of **28** as an amber residue. Both $^1$H-NMR and TLC analysis show **28** to be a 1:1 mixture of diastereomers.



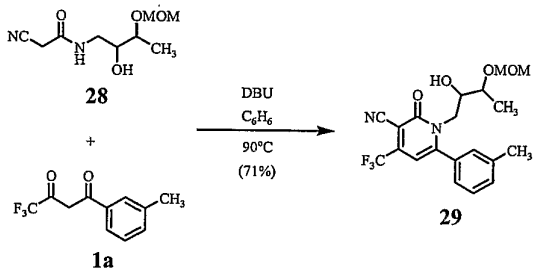
28

2-Cyano-*N*-(2-hydroxy-3-methoxymethoxy-butyl)-acetamide

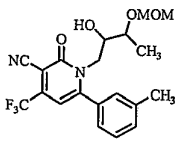
$^1$H-NMR ($CDCl_3$): (diastereomers) δ 6.78 & 6.64 (bs, 1H – both peaks), 4.77-4.65 (m, 2H), 3.84-3.54 (m, 3H), 3.45-3.36 (m, 6H), 3.32-3.14 (m, 2H), 1.13 (d, J=6.3Hz, 3H).

## EXAMPLE 29

This example illustrates the preparation of compound **29**.



2-Cyano-N-(2-hydroxy-3-methoxymethoxy-butyl)-acetamide **28** (0.78 g, 3.6 mmoles) and 4,4,4-Trifluoro-1-m-tolyl-butane-1,3-dione **1a** (0.83 g, 3.6 mmoles) were dissolved in 10 mL of $C_6H_6$ and this mixture was stirred at 90 °C for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-40% EtOAc/Hexane) to yield 1.06 g (71% yield) of **29** as a yellow liquid. $^1$H-NMR analysis shows **29** to be a 1:1 mixture of diastereomers.

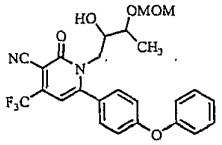


29

1-(2-Hydroxy-3-methoxymethoxy-butyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): (diastereomers) δ 7.44-7.32 (m, 4H), 7.21 (bs, 4H), 6.40 (bs, 2H), 4.58-4.45 (m, 4H), 4.28-4.09 (m, 4H), 3.90-3.82 (m, 1H), 3.81-3.73 (m, 1H), 3.71-3.63 (m, 1H), 3.57-3.49 (m, 1H), 3.22 (s, 3H), 3.10 (s, 3H), 2.43 (s, 6H), 1.14 (d, J=6.3Hz, 3H), 1.07 (d, J=6.6Hz, 3H).

The following compounds were prepared in a manner similar to that described above.



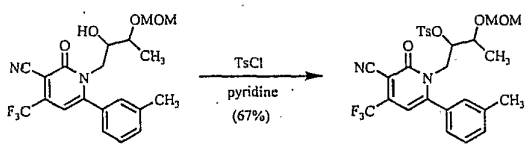
29.1

1-(2-Hydroxy-3-methoxymethoxy-butyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): (diastereomers)δ 7.45-7.33 (m, 8H), 7.24-7.19 (m, 2H), 7.11-7.02 (m, 8H), 6.36 (s, 1H), 6.35 (s, 1H), 4.62-4.51 (m, 4H), 4.30-4.15 (m 4H), 3.96-3.82 (m, 2H), 3.75-3.66 (m 1H), 3.62-3.54 (m, 1H), 3.26 (s, 3H), 3.19 (s, 3H), 1.15 (d, J=6.3Hz, 3H), 1.11 (d, J=6.3Hz, 3H).

## EXAMPLE 30

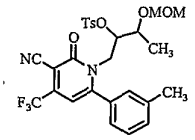
This example illustrates the preparation of compound **30**.




29 30

1-(2-Hydroxy-3-methoxymethoxy-butyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **29** (0.36 g, 0.87 mmoles) was combined with *p*-toluenesulfonyl chloride (0.33 g, 1.73 mmoles) in 2 mL of pyridine and this mixture was stirred at room temperature for 16 hours.

After this period the mixture was evaporated and purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 0.33 g (67% yield) of **30** as a yellow residue. $^1$H-NMR analysis shows **30** to be a 1:1 mixture of diastereomers.



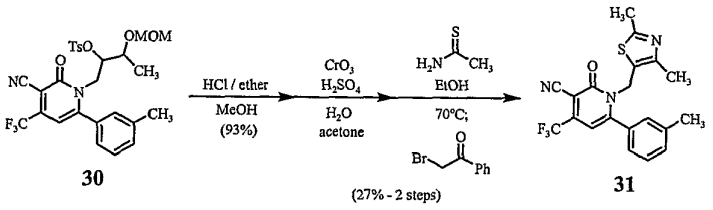
**30**

Toluene-4-sulfonic acid 1-(3-cyano-2-oxo-6-*m*-tolyl-4-trifluoromethyl-2*H*-pyridin-1-ylmethyl)-2-methoxymethoxy-propyl ester

$^1$H-NMR ($CDCl_3$): (diastereomers) δ 7.68-7.61 (m, 4H), 7.46-7.28 (m, 4H), 6.33 (s, 1H), 6.33 (s, 1H), 5.06-5.00 (m, 1H), 4.88-4.82 (m, 1H), 4.52-4.45 (m, 2H), 4.38 (q, J=6.8Hz, 2H), 4.33-4.02 (m, 4H), 3.96-3.89 (m, 1H), 3.28 (s, 3H), 3.14 (s, 3H), 2.49 (s, 3H), 2.49 (s, 3H), 2.44 (s, 3H), 2.43 (s, 3H), 1.14 (d, J=6.8Hz, 3H), 0.85 (d, J=6.6Hz, 3H).

## EXAMPLE 31

This example illustrates the preparation of compound **31**.

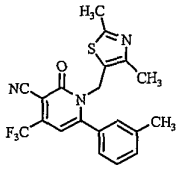


**30** **31**

(27% - 2 steps)

Toluene-4-sulfonic acid 1-(3-cyano-2-oxo-6-m-tolyl-4-trifluoromethyl-2H-pyridin-1-ylmethyl)-2-methoxymethoxy-propyl ester **30** (0.28 g, 0.50 mmoles) was dissolved into 7 mL of anhydrous MeOH and to this solution was added HCl (2.0 M solution in diethyl ether, 1.0 mL) and this mixture was stirred at room temperature for 2 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-40% EtOAc/Hexane) to yield 0.24 g (93% yield) of **31** as a

yellow residue. $^1$H-NMR analysis shows **31** to be a 1:1 mixture of diastereomers.

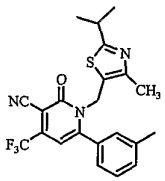


**31**

1-(2,4-Dimethyl-thiazol-5-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.47-7.38 (m, 2H), 7.13-7.06 (m, 2H), 6.37 (s, 1H), 5.28 (s, 2H), 2.58 (s, 3H), 2.43 (s, 3H). MS(ES+): 403.8 (M+H)

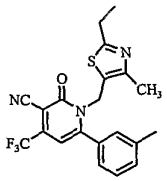
The following compounds were prepared in a manner similar to that described above.



**31.1**

1-(2-Isopropyl-4-methyl-thiazol-5-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 432.3 (M+H)



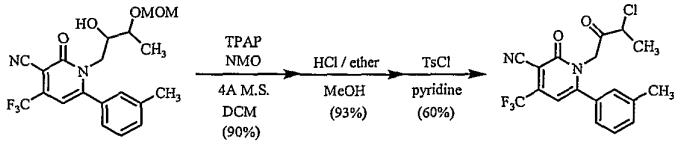
**31.2**

1-(2-Ethyl-4-methyl-thiazol-5-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 418.2 (M+H)

## EXAMPLE 32

This example illustrates the preparation of compound **32**.




29 32

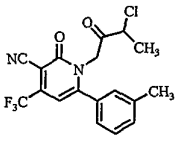
1-(2-Hydroxy-3-methoxymethoxy-butyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **29** (0.21 g, 0.52 mmoles) was combined with N-methylmorpholine N-oxide (NMO, 92 mg, 0.79 mmoles) and 4Å molecular sieves (powder, 170 mg) in 5 mL of anhydrous DCM within a 7 mL reaction vial. The mixture was stirred at room temperature for 10 min. After this period tetrapropylammonium perruthenate (TPAP, 10mg, 0.028 mmoles) was added and the mixture was stirred at room temperature for an additional 3 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-40% EtOAc/Hexane) to yield 0.191 g (90% yield) of 1-(3-Methoxymethoxy-2-oxo-butyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile as a yellow residue.

$^1$H-NMR ($CDCl_3$): δ 7.42-7.35 (m, 2H), 7.14-7.07 (m, 2H), 6.45 (s, 1H), 5.04-4.91(m, 2H), 4.63-4.55 (m, 2H), 4.20 (q, J=6.8Hz, 1H), 3.22 (s, 3H), 2.40 (s, 3H), 1.31 (d, J=7.1Hz, 3H).

1-(3-Methoxymethoxy-2-oxo-butyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (0.191 g, 0.47 mmoles) was dissolved into 25 mL of anhydrous MeOH and to this solution was added HCl (2.0 M solution in diethyl ether, 5.0 mL). The mixture was then stirred at room temperature for 2 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-60% EtOAc/Hexane) to yield 0.16 g (93% yield) of 1-(3-Hydroxy-2-oxo-butyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile as a yellow residue. $^1$H-NMR ($CDCl_3$): δ 7.42-7.35 (m, 2H), 7.14-7.08 (m, 2H), 6.50 (m, 1H), 5.06 (d,

J=17.2Hz, 1H), 4.92 (d, J=17.2Hz, 1H), 4.39-4.31 (m, 1H), 3.48 (bs, 1H), 2.40 (s, 3H), 1.28 (d, J=6.8Hz, 3H).

1-(3-Hydroxy-2-oxo-butyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (98 mg, 0.27 mmoles) was combined with *p*-toluenesulfonyl chloride (0.1 g, 0.52 mmoles) in 2.0 mL of pyridine. The mixture was stirred at room temperature for 16 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 62 mg (60% yield) of **32** as a yellow residue.



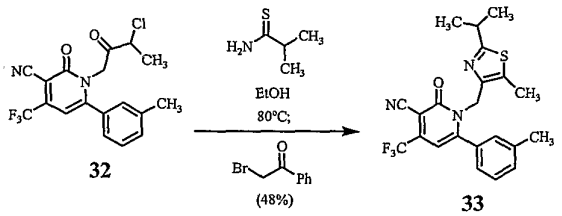
32

1-(3-Chloro-2-oxo-butyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.44-7.35 (m, 2H), 7.16-7.11 (m, 2H), 6.49 (s, 1H), 5.02-4.92 (m, 2H), 4.55 (q, J=6.8Hz, 1H), 2.42 (s, 3H), 1.65 (d, J=6.8Hz, 3H).

## EXAMPLE 33

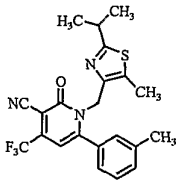
This example illustrates the preparation of compound **33**.




32 33

1-(3-Chloro-2-oxo-butyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **32** (41 mg, 0.11 mmoles) was combined with thioisobutyramide (22 mg, 0.22 mmoles) in 1.0 mL of anhydrous EtOH within a 7 mL reaction vial. This mixture was stirred at 80 °C for 16 hours. After this

period 2-bromoacetophenone (33 mg, 0.17 mmoles) was added and the reaction was stirred at 80 °C for an additional 3 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-40% EtOAc/Hexane) and normal-phase HPLC (YMC-Pack SIL, 250x50 mm I.D., S-5□M: 4-20% EaOAc/Hexane over 30 minutes) to yield 22 mg (48% yield) of **33** as a yellow residue.



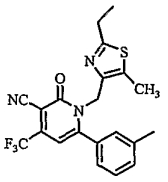
**33**

1-(2-Isopropyl-5-methyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.53-7.29 (4H), 6.40 (s, 1H), 5.03 (s, 2H), 3.13 (m, J=6.6Hz, 1H), 2.40 (s, 3H), 2.38 (s,3H), 1.32 (d, J=6.8Hz, 6H).

MS(ES+): 432.1 (M+H)

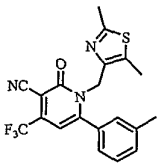
The following compounds were prepared in a manner similar to that described above.



**33.1**

1-(2-Ethyl-5-methyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

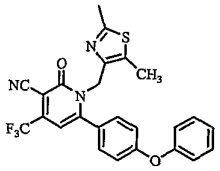
MS(ES+): 417.9 (M+H)



33.2

1-(2,5-Dimethyl-thiazol-4-ylmethyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbo nitrile

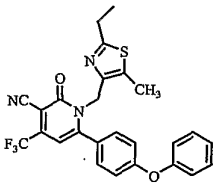
MS(ES+): 404.2 (M+H)



33.3

1-(2,5-Dimethyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

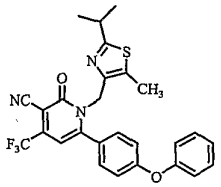
MS(ES+): 482.1 (M+H)



33.4

1-(2-Ethyl-5-methyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

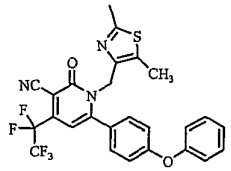
MS(ES+): 496.2 (M+H)



33.5

1-(2-Isopropyl-5-methyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

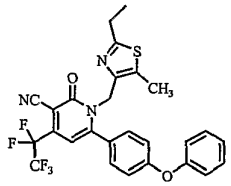
MS(ES+): 510.1 (M+H)



33.6

1-(2,5-Dimethyl-thiazol-4-ylmethyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

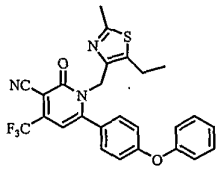
MS(ES+): 532.0 (M+H)



33.7

1-(2-Ethyl-5-methyl-thiazol-4-ylmethyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile

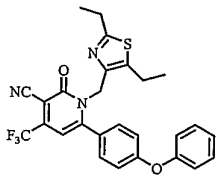
MS(ES+): 546.4 (M+H)



33.8

1-(5-Ethyl-2-methyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 496.1 (M+H)



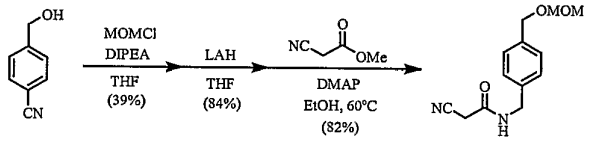
33.9

1-(2,5-Diethyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 510.1 (M+H)

## EXAMPLE 34

This example illustrates the preparation of compound **34**.

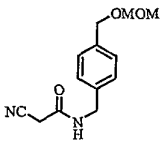


34

4-Hydroxymethyl-benzonitrile (3.1 g, 23.3 mmoles) was combined with N,N-diisopropylethylamine (4.9 mL, 28 mmoles) in 100 mL of anhydrous THF. To this solution was added MOMCl (3.5 mL, 46.1 mmoles) and the mixture was stirred at room temperature for 16 hours. After this period a solution of $NH_4OH/H_2O$ (1:1, 20 mL) was added (-MOMCl) and the solution was stirred for 15 minutes. After this period the reaction mixture was evaporated *in vacuo* (-THF) and the resulting mixture was extracted with DCM (3x30 mL). The combined DCM layer was dried over anhydrous $Na_2SO_4$, evaporated *in vacuo*, and the resulting crude product was purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 1.6 g (39% yield) of 4-Methoxymethoxymethylbenzonitrile as a colorless liquid.

4-Methoxymethoxymethylbenzonitrile (3.7 g, 20.9 mmoles) was dissolved into 100 mL of anhydrous THF and was placed under dry $N_2$ atmosphere. To this solution at 0 °C was added lithium aluminum hydride (LAH, 1.6 g, 42.2 mmoles, bubbling occurs) and this mixture (sealed under

$N_2$) was gentle stirred at 75 °C for 12 hours. After this period the mixture was cooled down and placed into an ice bath under a dry $N_2$ atmosphere. To the vigorously stirring mixture at 0 °C was slowly and carefully sequentially added water (2 mL), 15% NaOH (2 mL) and water (4 mL). The resulting heterogenous mixture was vacuum filtered and the filtrate was evaporated *in vacuo* to yield 3.2 g (17.7 mmoles, 84% yield) of crude amine as a yellowish residue. The crude amine was combined with methyl cyanoacetate (3.1 mL, 35.1 mmoles) and DMAP (10 mg) in 50 mL of anhydrous EtOH. The mixture was then stirred at 60 °C for 16 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-60% EtOAc/Hexane) to 3.6 g (82% yield) of **34** as a white powder.



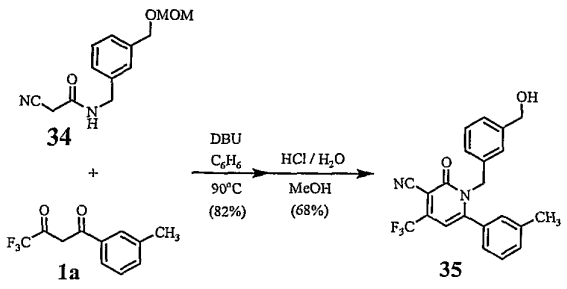
**34**

2-Cyano-*N*-(4-methoxymethoxymethyl-benzyl)-acetamide

$^1$H-NMR ($CDCl_3$): δ 7.36 (d, J=8.1Hz, 2H), 7.28 (d, J=8.3Hz, 2H), 6.34 (bs, 1H), 4.71 (s, 2H), 4.59 (s, 2H), 4.48 (d, J=5.6Hz, 2H), 3.41 (s, 3H), 3.40 (s, 2H).

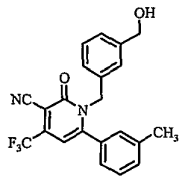
## EXAMPLE 35

This example illustrates the preparation of compound **35**.



2-Cyano-N-(4-methoxymethoxymethyl-benzyl)-acetamide (0.84 g, 3.4 mmoles) was combined with **1a** (0.78g, 3.4 mmoles), DBU (0.25 mL, 1.7 mmoles) and 5 mL of $C_6H_6$ within a 7 mL reaction vial. The mixture was stirred at 90 °C for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to yield 1.23 g (82% yield) of **35** as a yellow residue. $^1$H-NMR ($CDCl_3$): δ 7.37-7.31 (m, 2H), 7.26-7.19 (m, 2H), 7.03-6.97 (m, 1H), 6.93 (bs, 1H), 6.89 (bs, 1H), 6.86-6.81 (m, 1H), 6.39 (s, 1H), 5.24 (bs, 2H), 4.67 (s, 2H), 4.50 (s, 2H), 3.39 (s, 3H), 2.33 (s, 3H). MS(ES+): 443.2 (M+H)

1-(3-Methoxymethoxymethyl-benzyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (0.65 g, 1.47 mmoles) was dissolved into 10 mL of MeOH and to this was added 12N HCl (100□L). This mixture was then stirred at room temperature for 3 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-40% EtOAc/Hexane) to yield 0.40 g (68% yield) of **31** as a yellow residue.

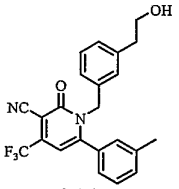



35

1-(3-Hydroxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.36-7.32 (m, 2H), 7.26-7.19 (m, 2H), 7.02-6.97 (m, 1H), 6.92 (d, J=10Hz, 2H), 6.82 (d, J=6.8Hz, 1H), 6.39 (s, 1H), 5.24 (bs, 2H), 4.62 (s, 2H), 2.34 (s, 3H). MS(ES+): 398.8 (M+H)

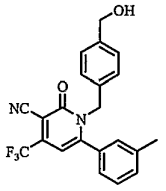
The following compounds were prepared in a manner similar to that described above.



35.1

1-[3-(2-Hydroxy-ethyl)-benzyl]-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

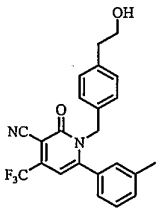
$^1$H-NMR ($CDCl_3$): δ 7.36-7.33 (m, 2H), 7.11 (d, J=8.1Hz, 2H), 7.04-7.00 (m, 1H), 6.95 (s, 1H), 6.87 (d, J=8.1Hz, 2H), 6.39 (s, 1H), 5.22 (bs, 2H), 3.82 (q, J=5.8Hz, 2H), 2.82 (t, J=6.8Hz, 2H), 2.34 (s, 3H).



35.2

1-(4-Hydroxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 398.9 (M+H)



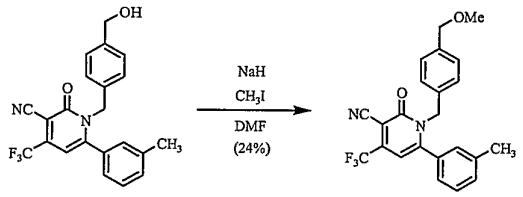
35.3

1-[4-(2-Hydroxy-ethyl)-benzyl]-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 413.3 (M+H)

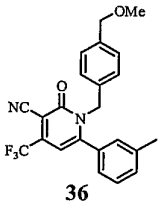
## EXAMPLE 36

This example illustrates the preparation of compound **36**.




35.2 36

1-(4-Hydroxymethyl-benzyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **35.2** (41 mg, 0.10 mmoles) was dissolved into 1.0 mL of anhydrous N,N-dimethyl-formamide. To this solution was then added sodium hydride (60% dispersion in mineral oil, 5 mg, 0.125 mmoles) and the mixture was stirred (bubbling occurs) for 5 min. After this period iodomethane (15 μL, 0.24 mmoles) was added and the mixture was stirred at room temperature for 16 hours. After this period the reaction mixture was combined with 20 mL of water and was extracted with EtOAc (4x15 mL). The combined organic layer was washed with water (4x15 mL), 15 mL of brine, and was dried over $Na_2SO_4$. The EtOAc solution was evaporated *in vacuo* and purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 10 mg (24%) of **36** as a yellow residue.

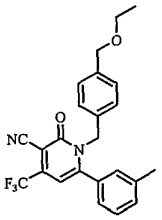



36

1-(4-Methoxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.36-7.32 (m, 2H), 7.21 (d, J=7.8Hz, 2H), 7.02-6.96 (m, 1H), 6.93 (bs, 1H), 6.89 (d, J=7.6Hz, 2H), 6.38 (s, 1H), 5.23 (bs, 2H), 4.41 (s, 3H), 3.37 (s, 3H), 2.33 (s, 3H). MS(ES+): 413.3 (M+H)

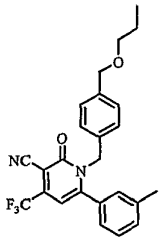
The following compounds were prepared in a manner similar to that described above.



36.1

1-(4-Ethoxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

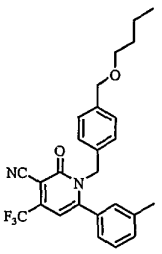
MS(ES+): 427.3 (M+H)



36.2

2-Oxo-1-(4-propoxymethyl-benzyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

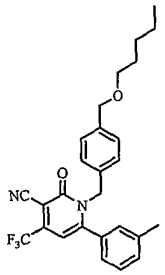
MS(ES+): 441.2 (M+H)



36.3

1-(4-Butoxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

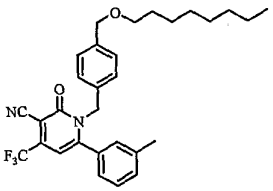
MS(ES+): 455.2 (M+H)



36.4

2-Oxo-1-(4-pentyloxymethyl-benzyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

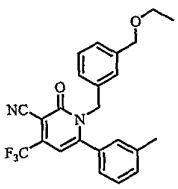
MS(ES+): 469.2 (M+H)



36.5

1-(4-Octyloxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

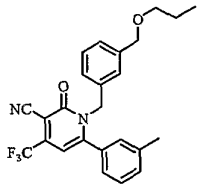
MS(ES+): 511.1 (M+H)δ



36.7

1-(3-Ethoxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

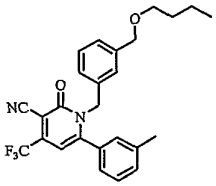
MS(ES+): 427.2 (M+H)



36.8

2-Oxo-1-(3-propoxymethyl-benzyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

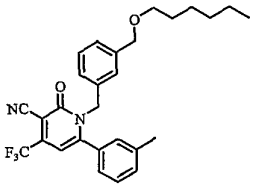
MS(ES+): 441.1 (M+H)



36.9

1-(3-Butoxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

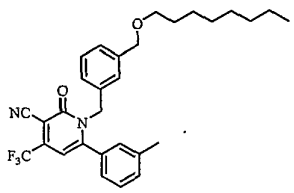
MS(ES+): 455.2 (M+H)



36.10

1-(3-Hexyloxymethyl-benzyl)-6-(3-methyl-1-methylene-but-2-enyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 483.1 (M+H)



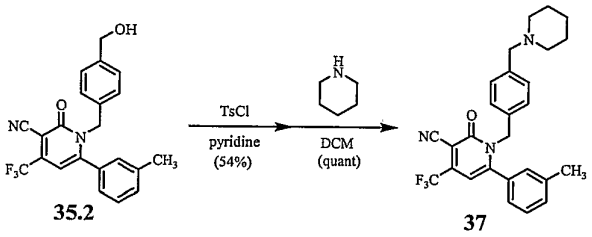
36.11

1-(3-Octyloxymethyl-benzyl)-2-oxo-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 511.0 (M+H)

## EXAMPLE 37

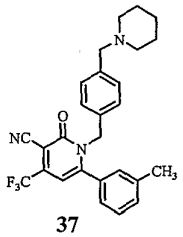
This example illustrates the preparation of compound **37**.




35.2 37

1-(3-Hydroxymethyl-benzyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **35.2** (29 mg, 0.073 mmoles) was combined with *p*-toluenesulfonyl chloride (25 mg, 0.13 mmoles) in 1.0 mL of pyridine and this mixture was stirred at room temperature for 16 hours. After this period the reaction mixture was evaporated *in vacuo* and was purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 16mg (54% yield) of **37a** as a yellow residue. $^1$H-NMR ($CDCl_3$): δ 7.33 (d, J=5.3Hz, 2H), 7.20 (br d, J=7.6Hz, 2H), 7.03-6.99 (m, 1H), 6.91 (s, 1H), 6.85 (d, J=7.8Hz, 2H), 6.38 (br s, 1H), 5.22 (s, 2H), 3.45 (br s, 2H), 2.36 (br s, 4H), 2.32 (s, 3H), 1.57 (br s, 4H), 1.43 (br s, 2H).

1-(4-Chloromethyl-benzyl)-2-oxo-6-m-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **37a** (8 mg, 0.019 mmoles) was combined with 1.0 mL of DCM and piperidine (0.1 mL, 1.0 mmoles) within a 7 mL reaction vial. The mixture was stirred at room temperature for 2 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-10% MeOH/DCM) to yield 9 mg (quantitative yield) of **37** as a yellow residue.



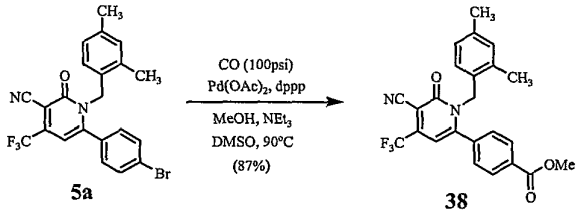
37

2-Oxo-1-(4-piperidin-1-ylmethyl-benzyl)-6-*m*-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.33 (d, J=5.1Hz, 2H), 7.20 (bd, J=7.3Hz, 2H), 7.03-6.98 (m, 1H), 6.91 (m, 1H), 6.85 (d, J=7.8Hz, 2H), 5.22 (bs, 2H), 3.45 (bs, 2H), 2.45-2.28 (m, 4H), 2.32 (s, 3H), 1.63-1.52 (m, 4H), 1.48-1.38 (m, 2H). MS(ES+): 466.2 (M+H)

## EXAMPLE 38

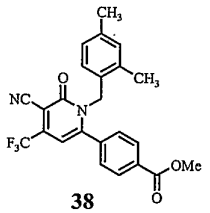
This example illustrates the preparation of compound **38**.




5a 38

Within a Parr high-pressure apparatus were combined 6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **5a** (0.51 g, 1.11 mmoles), $Pd(OAc)_2$ (15 mg, 0.067 mmoles), and 1,3-bis(diphenylphosphino)propane (30 mg, 0.073 mmoles). This mixture was dissolved into 15 mL of anhydrous MeOH, 5 mL of anhydrous DMSO and $NEt_3$ (0.6 mL, 4.3 mmoles), and was pressured to 100 psi with CO. The pressured and stirring reaction mixture was then heated to 90 °C for 48 hours. After this period the reaction mixture was cooled to ambient tempurature, depressurized, and was combined with 100 mL of water. The aqueous mixture was extracted with EtOAc (4x25 mL) and the combined EtOAc layer was washed with water (4x25 mL) and brine. After

drying over anhydrous $Na_2SO_4$ the crude product was purified using flash silica chromatography (0-30% EtOAc/Hexane) to yield 0.43 g (87% yield) of **38** as a yellow solid.



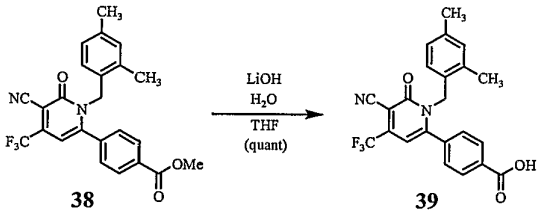
**38**

4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid methyl ester

$^1$H-NMR ($CDCl_3$): δ 8.03 (d, J=8.3Hz, 2H), 7.23 (d, J=8.3Hz, 2H), 6.95 (bd, J=7.8Hz, 1H), 6.89 (bs, 1H), 6.58 (d, J=7.8Hz, 1H), 6.42 (s, 1H), 5.09 (s, 2H), 3.95 (s, 3H), 2.28 (s, 3H), 1.88 (s, 3H).

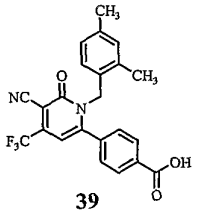
## EXAMPLE 39

This example illustrates the preparation of compound **39**.




**38** **39**

4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid methyl ester **38** (0.105 g, 0.24 mmoles) was combined with LiOH (monohydrate, 22 mg, 0.52 mmoles) in 5 mL of THF and 1 mL of water. The mixture was stirred at room temperature for 90 minutes. After this period the reaction mixture was concentrated *in vacuo* (-THF) and the resulting aqueous mixture was combined with 10 mL of 1N HCl and salt (enough to affect saturation after mixing). The acidic aqueous layer was extracted with $Et_2O$ (3x20 mL) and the combined organic layer was washed with brine. The $Et_2O$ layer was dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to yield 0.102 g (quantitative yield) as a yellowish solid.



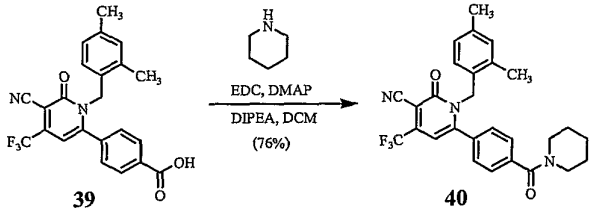
39

4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid

$^1$H-NMR ($CDCl_3$): δ 8.09 (d, J=8.1Hz, 2H), 7.29-7.25 (m, 2H), 6.95 (d, J=7.8Hz, 1H), 6.90 (s, 1H), 6.59 (d, J=7.8Hz, 1H), 6.43 (s, 1H), 5.10 (s, 2H), 2.29 (s, 3H), 1.89 (s, 3H). MS(ES+): 427.2 (M+H)

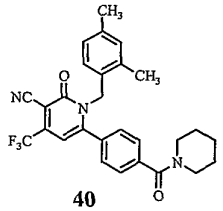
## EXAMPLE 40

This example illustrates the preparation of compound **40**.




39 40

4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid **39** (48 mg, 0.11 mmoles) was combined with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC, 54 mg, 0.28 mmoles), 4-dimethylaminopyridine (DMAP, 2 mg, 0.016 mmoles) in 5 mL of anhydrous DCM. To this mixture was added diisopropylethylamine (DIPEA, 50 μL, 0.29 mmoles) and piperidine (28 μL, 0.28 mmoles). This mixture was then stirred at room temperature for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-60% EtOAc/Hexane) to yield 41 mg (76% yield) of **40** as a yellow residue.

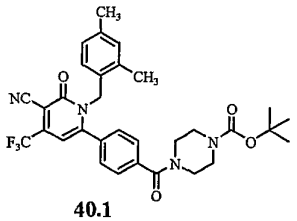


40

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(piperidine-1-carbonyl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.39 (d, J=8.1Hz, 2H), 7.19 (d, J=8.1Hz, 2H), 6.94 (bd, J=8.1Hz, 1H), 6.88 (bs, 1H), 6.59 (d, J=7.8Hz, 1H), 6.42 (s, 1H), 5.11 (s, 2H), 3.75-3.66 (m, 2H), 3.343.24 (m, 2H), 2.28 (s, 3H), 1.93 (s, 3H), 1.75-1.63 (m, 4H), 1.56-1.48 (m, 2H). MS(ES+): 494.3 (M+H)

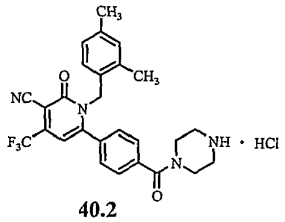
The following compounds were prepared in a manner similar to that described above.



40.1

4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoyl}-piperazine-1-carboxylic acid *tert*-butyl ester

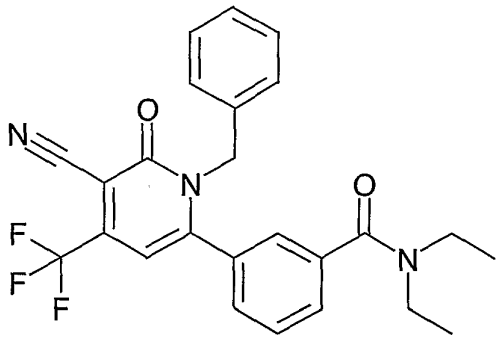
MS(ES+): 595.4 (M+H)



40.2

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(piperazine-1-carbonyl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile hydrochloride

MS(ES+): 495.2 (M+H)



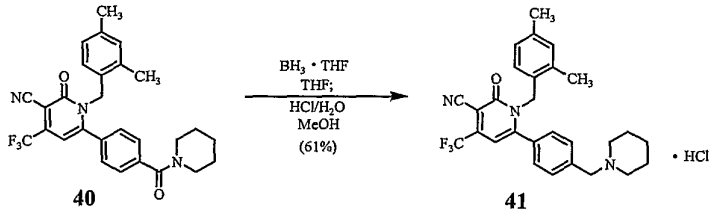
40.3

3-(1-Benzyl-5-cyano-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl)-N,N-diethyl-benzamide

$^1$H-NMR ($CDCl_3$): δ7.54 (m, 1 H), 7.48 (m, 1 H), 7.23 (m, 5 H), 6.89 (m, 2 H), 6.4 (s, 1 H), 5.28 (s, 2 H), 3.52 (br, 2 H), 3.13 (br, 2 H), 1.20 (br, 3 H), 1.06 (br, 3 H).

## EXAMPLE 41

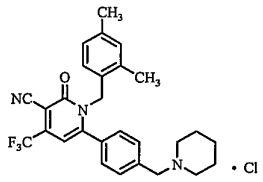
This example illustrates the preparation of compound **41**.




40 41

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(piperidine-1-carbonyl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **40** (20 mg, 0.041 mmoles) was dissolved into 2.0 mL of anhydrous THF within a 7 mL reaction vial. To this stirring mixture at room temperature was added diborane-THF (160 μL, 0.16 mmoles) and the mixture was stirred at room temperature for 16 hours. After this period the reaction was quenched by adding 3 mL of 25% $NH_4Cl$. This aqueous mixture was stirred for 30 min. After this period the resulting mixture was extracted with $Et_2O$ (3x10 mL) and the resulting organic layer was washed with brine and dried over $Na_2SO_4$. The ether layer was evaporated *in vacuo* and the resulting crude product was purified using flash

silica chromatography (0-5% MeOH/DCM w/0.1% $NEt_3$) to yield the free base. The free base was combined with 2N HCl/MeOH, evaporated, dissolved into deionized water and lyopholyzed to yield 12 mg (61% yield) of **41** as a white powder.



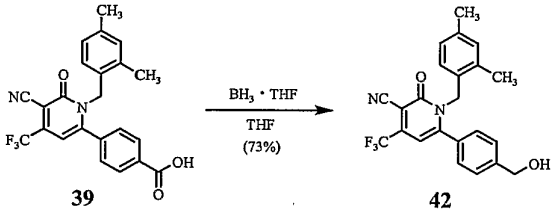
41

1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-piperidin-1-ylmethyl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile hydrochloride

$^1$H-NMR ($D_2O$ – free base): δ 7.31 (d, J=8.1Hz, 2H), 7.21 (d, J=8.1Hz, 2H), 6.86 (d, J=8.3Hz, 1H), 6.82 (s, 1H), 6.51 (d, J=7.3Hz, 1H), 5.09 (s, 2H), 4.14 (s, 2H), 3.27-3.17 (m, 2H), 2.84-2.70 (m, 2H), 2.10 (s, 3H), 1.87-1.24 (m, 6H), 2.10 (s, 3H), 1.75 (s, 3H). MS(ES+): 480.2 (M+H)

## EXAMPLE 42

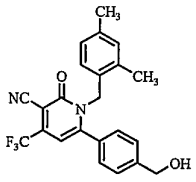
This example illustrates the preparation of compound **42**.



39 42

4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-benzoic acid **39** (27 mg, 0.063 mmoles) was dissolved into 2.0 mL of anhydrous THF within a 7 mL reaction vial. To this stirring solution at 0 °C was added diborane-THF (0.11 mL, 0.11 mmoles). The reaction was then allowed to warm to room temperature and was stirred for 16 hours. After this period the reaction was quenched by adding 3 mL of 25%

$NH_4Cl$, and this mixture was stirred for 30 min. The resulting aqueous mixture was evaporated *in vacuo* (-THF) and extracted with $Et_2O$ (3x10 mL). The combined ether layer was washed with saturated $NaHCO_3$, dried over $Na_2SO_4$ and was evaporated *in vacuo* to yield the crude residue. The crude residue was purified using flash silica chromatography (0-60% EtOAc/Hexane) to yield 19 mg (73% yield) of **42** as a white solid.



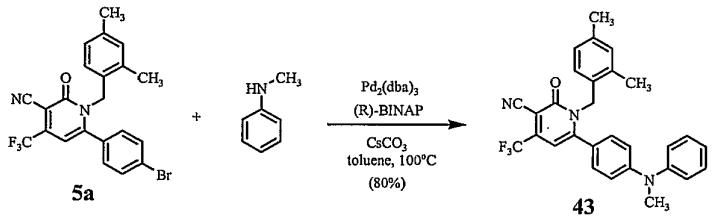
**42**

1-(2,4-Dimethyl-benzyl)-6-(4-hydroxymethyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.39 (d, J=8.1Hz, 2H), 7.17 (d, J=8.1Hz, 2H), 6.95 (bd, J=7.8Hz, 1H), 6.91 (bs, 1H), 6.60 (d, J=7.6Hz, 1H), 6.43 (s, 1H), 5.10 (s, 2H), 4.76 (bd, 2H), 2.28 (s, 3H), 1.94 (s, 3H).
MS(ES+): 413.1 (M+H)

## EXAMPLE 43

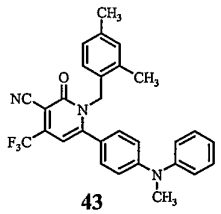
This example illustrates the preparation of compound **43**.




**5a** **43**

6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **5a** (38 mg, 0.082 mmoles) was combined with N-methylaniline (11 μL, 0.10 mmoles) and 0.5 mL of anhydrous toluene within a 7 mL reaction vial. In a separate vial was added tris(dibenzylideneacetone) dipalladium (8 mg, 0.009 mmoles), (R)-BINAP (8

mg, 0.013 mmoles), cesium carbonate (38 mg, 0.12 mmoles) and 0.3 mL of anhydrous toluene. This "catalytic" mixture was stirred at room temperature for 5 min under dry-nitrogen. To the stirring "catalytic" solution under nitrogen was then added the "bromide" solution, and the resulting mixture was sealed under dry-nitrogen and was stirred at 100 °C for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to provide 32 mg (80% yield) of 4**3** as an orange-red residue.

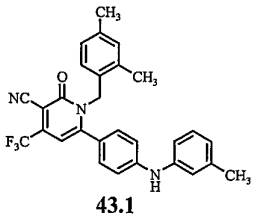


**43**

1-(2,4-Dimethyl-benzyl)-6-[4-(methyl-phenyl-amino)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.44-7.34 (m, 2H), 7.25-7.14 (m, 3H), 7.07-7.02 (m, 2H), 6.97-6.92 (m, 2H), 6.72 (d, J=9.1Hz, 2H), 6.63 (d, J=8.1Hz, 1H), 6.46 (s, 1H), 5.18 (s, 2H), 3.33 (s, 3H), 2.28 (s, 3H), 2.10 (s, 3H). MS(ES+): 488.4 (M+H)

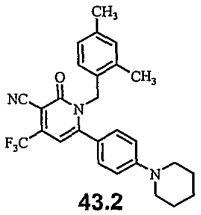
The following compounds were prepared in a manner similar to that described above.



**43.1**

1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-*m*-tolylamino-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

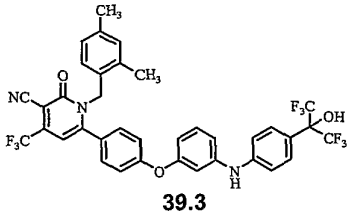
MS(ES+): 488.4 (M+H)



43.2

1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-piperidin-1-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 466.4 (M+H)

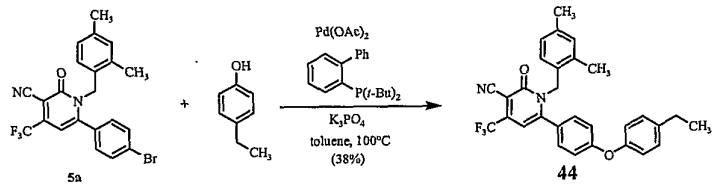


39.3

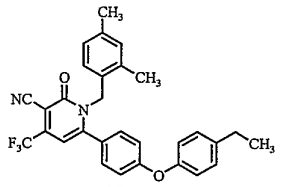
MS(ES+): 640.0 (M+H)

## EXAMPLE 44

This example illustrates the preparation of compound **44**.



6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **5a** (100 mg, 0.22 mmoles) was combined with 4-ethylphenol (32 mg, 0.26 mmoles), palladium acetate (5 mg, 0.022 mmoles), 2-(di-*t*-butylphosphino)biphenyl (12 mg, 0.040 mmoles), potassium phosphate (100 mg, 0.47 mmoles) and 1.0 mL of anhydrous toluene within an oven-dried 7 mL reaction vial. The mixture was sealed and stirred at 100 °C for 16 hours. After this period the mixture was purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to yield 42 mg (38%) of **44** as a yellow residue.

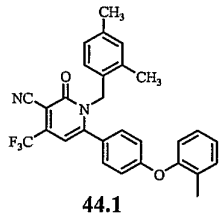


44

1-(2,4-Dimethyl-benzyl)-6-[4-(4-ethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.21 (d, J=8.3Hz, 2H), 7.09 (d, J=8.3Hz, 2H), 6.98-6.89 (m, 6H), 6.60 (d, J=7.8Hz, 1H), 6.44 (s, 1H), 5.14 (s, 2H), 2.66 (q, J=7.6Hz, 2H), 2.27 (s, 3H), 2.01 (s, 3H), 1.25 (t, J=7.6Hz, 3H). MS(ES+): 503.2 (M+H)

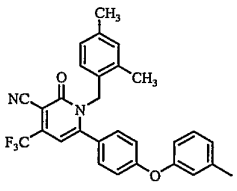
The following compounds were prepared in a manner similar to that described above.



44.1

1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-*o*-tolyloxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

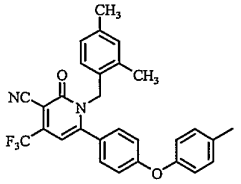
MS(ES+): 489.2 (M+H)



44.2

1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-*m*-tolyloxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

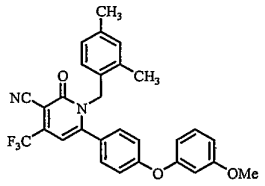
MS(ES+): 489.4 (M+H)



44.3

1-(2,4-Dimethyl-benzyl)-2-oxo-6-(4-*p*-tolyloxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

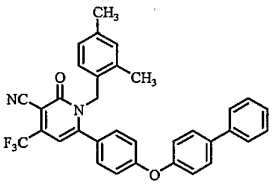
MS(ES+): 489.4 (M+H)



44.4

1-(2,4-Dimethyl-benzyl)-6-[4-(3-methoxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

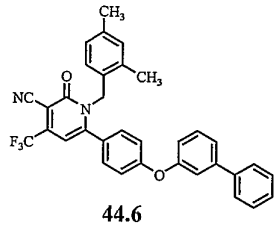
MS(ES+): 505.3 (M+H)



44.5

6-[4-(Biphenyl-4-yloxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

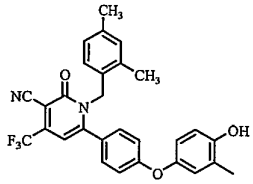
$^1$H-NMR ($CDCl_3$): δ 7.64-7.54 (m, 4H), 7.48-7.42 (m, 2H), 7.40-7.33 (m, 1H), 7.16-7.08 (m, 4H), 7.02-6.87 (m, 4H), 6.61 (d, J=7.8Hz, 1H), 6.46 (s, 1H), 5.15 (s, 2H), 2.28 (s, 3H), 2.02 (s, 3H).



44.6

6-[4-(Biphenyl-3-yloxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

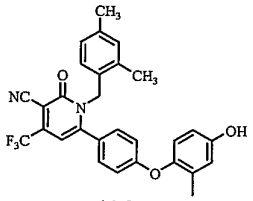
$^1$H-NMR ($CDCl_3$): δ 7.59-7.53 (m, 2H), 7.49-7.35 (m, 4H), 7.15-7.09 (m, 2H), 7.05-6.88 (m, 5H), 6.61 (d, J=8.1Hz, 1H), 6.45 (s, 1H), 5.14 (s, 2H), 2.26 (s, 3H), 2.00 (s, 3H).



44.7

1-(2,4-Dimethyl-benzyl)-6-[4-(4-hydroxy-3-methyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

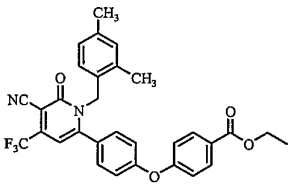
MS(ES+): 505.1 (M+H)



44.8

1-(2,4-Dimethyl-benzyl)-6-[4-(4-hydroxy-2-methyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

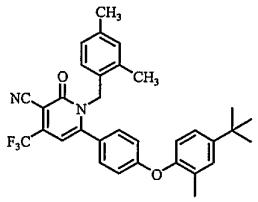
MS(ES+): 505.4 (M+H)



44.9

4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid ethyl ester

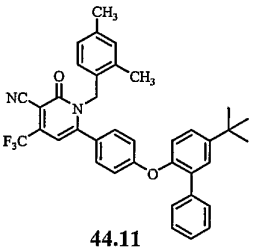
MS(ES+): 547.4 (M+H)



44.10

6-[4-(4-*tert*-Butyl-2-methyl-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

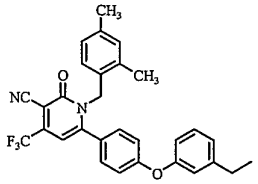
MS(ES+): 545.2 (M+H)



44.11

6-[4-(5-*tert*-Butyl-biphenyl-2-yloxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

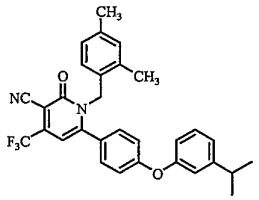
MS(ES+): 607.6 (M+H)



44.12

1-(2,4-Dimethyl-benzyl)-6-[4-(3-ethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

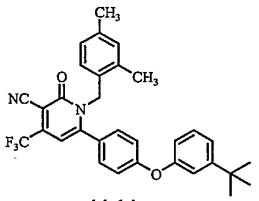
MS(ES+): 503.0 (M+H)



44.13

1-(2,4-Dimethyl-benzyl)-6-[4-(3-isopropyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

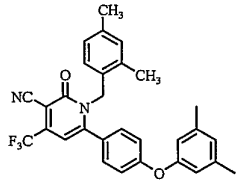
MS(ES+): 517.4 (M+H)



44.14

6-[4-(3-*tert*-Butyl-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

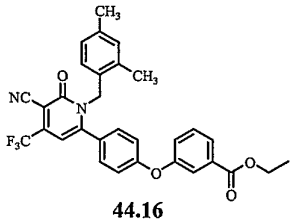
MS(ES+): 531.3 (M+H)



44.15

1-(2,4-Dimethyl-benzyl)-6-[4-(3,5-dimethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

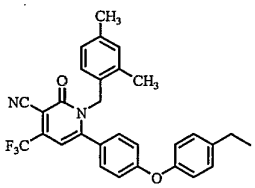
MS(ES+): 503.3 (M+H)



44.16

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid ethyl ester

MS(ES+): 547.3 (M+H)

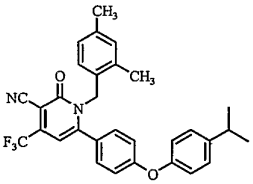


44.17

1-(2,4-Dimethyl-benzyl)-6-[4-(4-ethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

5

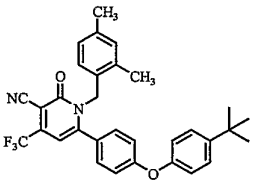
$^1$H-NMR ($CDCl_3$): $\delta$ 7.21 (d, J=8.6Hz, 2H), 7.09 (d, J=8.6Hz, 2H), 6.98-6.89 (m, 6H), 6.60 (d, J=7.8 Hz, 1H), 6.44 (s, 1H), 5.14 (s, 2H), 2.66 (q, J=7.6Hz, 2H), 2.27 (s, 3H), 2.01 (s, 3H), 1.25 (t, J=7.6Hz, 3H).



**44.18**

1-(2,4-Dimethyl-benzyl)-6-[4-(4-isopropyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

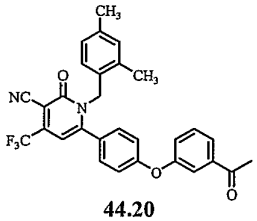
MS(ES+): 517.4 (M+H)



**44.19**

6-[4-(4-*tert*-Butyl-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

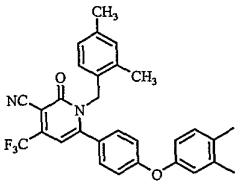
MS(ES+): 531.4 (M+H)



**44.20**

6-[4-(3-Acetyl-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

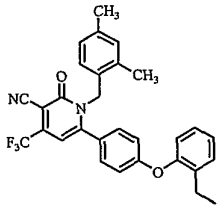
MS(ES+): 517.5 (M+H)



44.21

1-(2,4-Dimethyl-benzyl)-6-[4-(3,4-dimethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

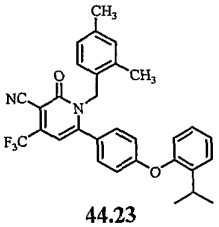
MS(ES+): 503.1 (M+H)



44.22

1-(2,4-Dimethyl-benzyl)-6-[4-(2-ethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

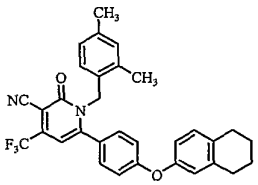
MS(ES+): 503.3 (M+H)



44.23

1-(2,4-Dimethyl-benzyl)-6-[4-(2-isopropyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

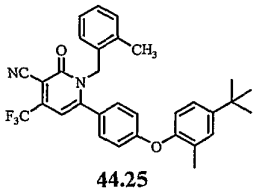
MS(ES+): 517.5 (M+H)



44.24

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(5,6,7,8-tetrahydro-naphthalen-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

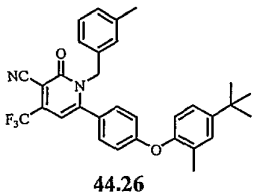
MS(ES+): 529.3 (M+H)



44.25

6-[4-(4-*tert*-Butyl-2-methyl-phenoxy)-phenyl]-1-(2-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

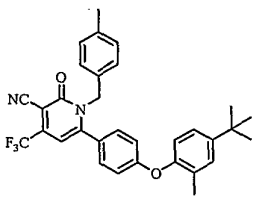
MS(ES+): 531.2 (M+H)



44.26

6-[4-(4-*tert*-Butyl-2-methyl-phenoxy)-phenyl]-1-(3-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

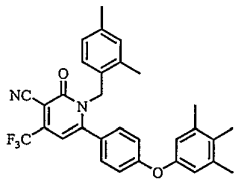
MS(ES+): 531.3 (M+H)



44.27

6-[4-(4-*tert*-Butyl-2-methyl-phenoxy)-phenyl]-1-(4-methyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

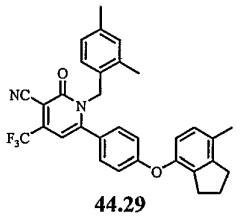
MS(ES+): 531.3 (M+H)



**44.28**

1-(2,4-Dimethyl-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(3,4,5-trimethyl-phenoxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile

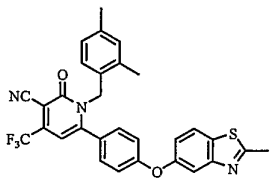
MS(ES+): 517.4 (M+H)



**44.29**

1-(2,4-Dimethyl-benzyl)-6-[4-(7-methyl-indan-4-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

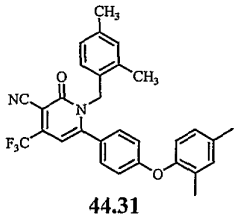
MS(ES+): 529.4 (M+H)



**44.30**

1-(2,4-Dimethyl-benzyl)-6-[4-(2-methyl-benzothiazol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

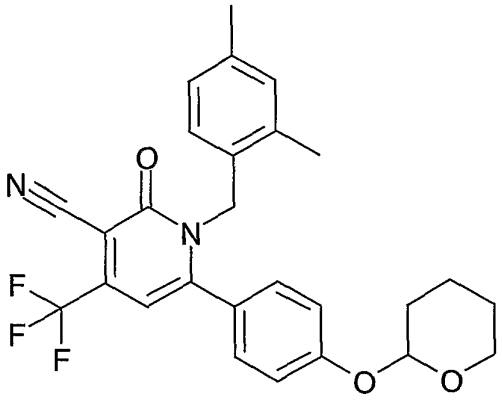
MS(ES+): 546.5 (M+H)



44.31

1-(2,4-Dimethyl-benzyl)-6-[4-(2,4-dimethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

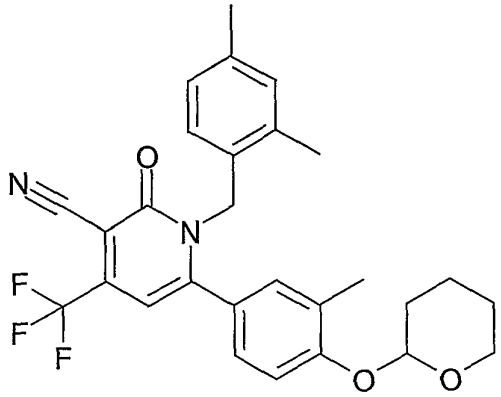
MS(ES+): 503.2 (M+H)



44.32

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(tetrahydro-pyran-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ7.10 (m, 2 H), 7.02 (m, 2 H), 6.94 (m, 2 H), 6.61 (m, 1 H), 6.44 (s, 1 H), 5.45 (m, 1 H), 5.13 (s, 2 H), 3.83 (m, 1 H), 3.61 (m, 1 H), 2.28 (s, 3 H), 2.00 (s, 3 H), 1.87 (m, 2 H), 1.87 (m, 2 H), 1.68 (m, 4 H).



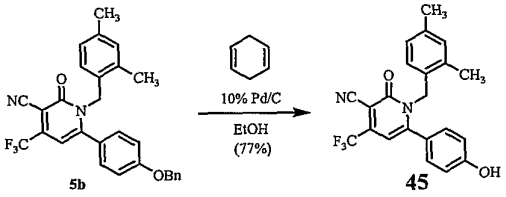
44.33

1-(2,4-Dimethyl-benzyl)-6-[3-methyl-4-(tetrahydro-pyran-2-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

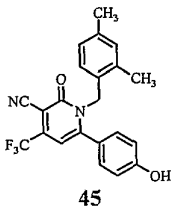
$^1$H-NMR ($CDCl_3$): δ7.03 (m, 1 H), 6.95 (m, 2 H), 6.91 (m, 1 H), 6.86 (m, 1 H), 6.63 (m, 1 H), 6.42 (s, 1 H), 5.46 (m, 1 H), 5.11 (m, 2 H), 3.79 (m, 1 H), 3.60 (m,1 H), 2.27 (s, 3 H), 2.14 (s, 3 H), 2.01 (m, 1 H), 1.97 (s, 3 H), 1.89 (m, 2 H), 1.68 (m, 2 H), 1.60 (m, 1 H).

## EXAMPLE 45

This example illustrates the preparation of compound **45**.




6-(4-Benzyloxy-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **5b** (0.55 g, 1.13 mmoles) was combined with cyclohexadiene (1.6 mL, 16.9 mmoles), 10% Pd/C (0.6 g) and 10 mL of anhydrous EtOH. This mixture was then stirred at room temperature for 24 hours. After this period the reaction mixture was vacuum filtered through Celite and the resulting filtrate was evaporated *in vacuo* to yield 0.35 g (77%) of **45** as a yellowish/orange solid.

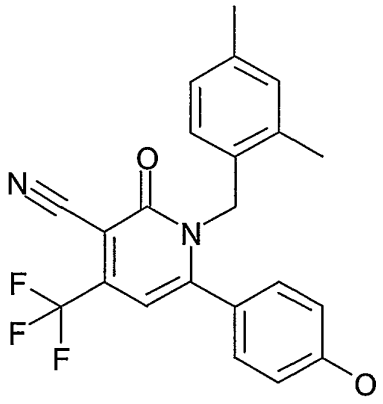



45

1-(2,4-Dimethyl-benzyl)-6-(4-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile

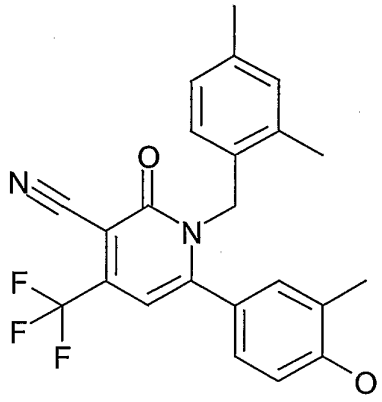
$^1$H-NMR ($CDCl_3$): δ 7.04 (d, J=8.6Hz, 2H), 6.95 (d, J=7.6Hz, 1H), 6.92 (s, 1H), 6.80 (d, J=7.6Hz, 2H), 6.60 (d, J=7.8Hz, 1H), 6.43 (s, 1H), 5.47 (bs, 1H), 5.12 (s, 2H), 2.28 (s, 3H), 1.98 (s, 3H).

Following compounds were prepared in manner similar to that described above.



45.1
1-(2,4-Dimethyl-benzyl)-6-(4-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR (Acetone-d6): δ8.92 (s, 1 H), 7.14 (m, 2 H), 6.85 (m, 2 H), 6.76 (m, 2 H), 6.64 (m, 1 H), 6.50 (s, 1 H), 5.08 (s, 2 H), 2.11 (s, 3 H), 1.92 (s, 3 H).

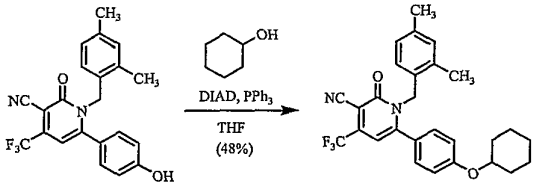


45.2
1-(2,4-Dimethyl-benzyl)-6-(4-hydroxy-3-methyl-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

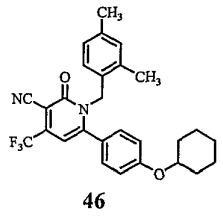
$^1$H-NMR ($CDCl_3$): δ6.91 – 6.78 (m, 4 H), 6.66 (m, 1 H), 6.56 (m, 1 H), 6.35 (s, 1 H), 5.05 (s, 2 H), 2.22 (s, 3 H), 2.07 (s, 3 H), 1.90 (s, 3 H).

## EXAMPLE 46

This example illustrates the preparation of compound **46.**




1-(2,4-Dimethyl-benzyl)-6-(4-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **45** (31 mg, 0.078 mmoles) was combined with triphenylphosphine (29 mg, 0.11 mmoles) in 1.0 mL of anhydrous THF. To this stirring mixture at room temperature was slowly added (over 1 hour using a syringe pump) a solution of cyclohexanol (12 μL, 0.11 mmoles) and diisopropyl azodicarboxylate (22 μL, 0.11 mmoles) in 1.0 mL of anhydrous THF. The mixture was then stirred at room temperature for 24 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to yield 18 mg (48%) of **46** as a yellow residue.

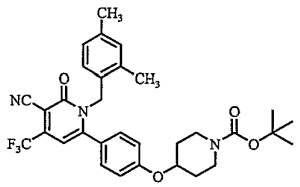



**46**

6-(4-Cyclohexyloxy-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.08 (d, J=8.6Hz, 2H), 6.97-6.91 (m, 2H), 6.85 (d, J=8.6Hz, 2H), 6.61 (d, J=7.8Hz, 1H), 6.44 (s, 1H), 5.14 (s, 2H), 4.32-4.23 (m, 1H), 2.29 (s, 3H), 2.00 (s, 3H), 1.99-1.22 (m, 10H). MS(ES+): 481.4 (M+H)

The following compounds were prepared in a manner similar to that described above.



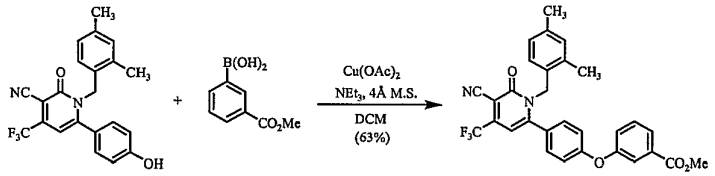
46.1

4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-piperidine-1-carboxylic acid *tert*-butyl ester

MS(ES+): 582.3 (M+H)

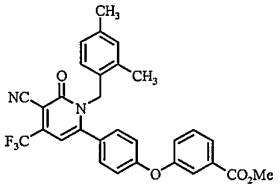
## EXAMPLE 47

This example illustrates the preparation of compound **47**.



45 47

1-(2,4-Dimethyl-benzyl)-6-(4-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **45** (43 mg, 0.11 mmoles) was combined with (3-methoxycarbonylphenyl) boronic acid (62 mg, 0.34 mmoles), copper acetate (22 mg, 0.12 mmoles), 4Å molecular sieves (0.18 g) and 1.0 mL of anhydrous DCM within an oven-dried reaction vial. The mixture was stirred at room temperature for 15 min. After this period triethylamine (75 μL, 0.54 mmoles) was added and the mixture was stirred at room temperature for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to yield 38 mg (63%) of **47** as a yellow residue.

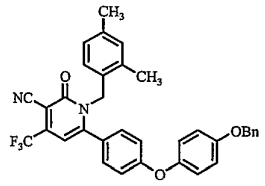


47

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid methyl ester

$^1$H-NMR ($CDCl_3$): δ 7.90-7.85 (m, 1H), 7.71-7.68 (m, 1H), 7.47 (t, J=7.8Hz, 1H), 7.27-7.23 (m, 1H), 7.12 (d, J=8.8Hz, 2H), 6.98-6.91 (m, 4H), 6.61 (d, J=7.8Hz, 1H), 6.45 (s, 1H), 5.14 (s, 2H), 3.92 (s, 3H), 2.27 (s, 3H), 2.01 (s, 3H). MS(ES+): 533.2 (M+H)

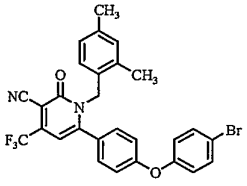
The following compounds were prepared in a manner similar to that described above.



47.1

6-[4-(4-Benzyloxy-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

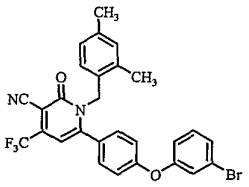
MS(ES+): 581.3 (M+H)



47.2

6-[4-(4-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

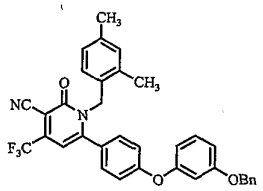
MS(ES+): 555.2 (M+H)



47.3

6-[4-(3-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

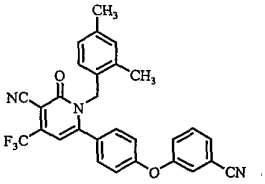
MS(ES+): 555.3 (M+H)



47.4

6-[4-(3-Benzyloxy-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

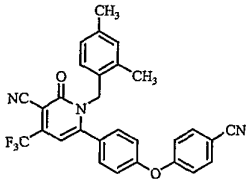
MS(ES+): 581.5 (M+H)



47.5

6-[4-(3-Cyano-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

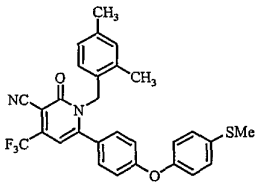
MS(ES+): 500.4 (M+H)



47.6

6-[4-(4-Cyano-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

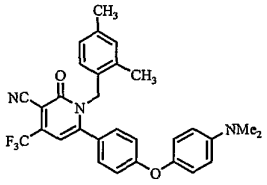
MS(ES+): 500.4 (M+H)



47.7

1-(2,4-Dimethyl-benzyl)-6-[4-(4-methylsulfanyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

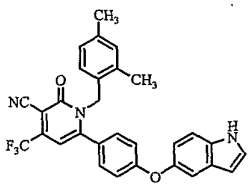
MS(ES+): 521.1 (M+H)



47.8

6-[4-(4-Dimethylamino-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 518.4 (M+H)



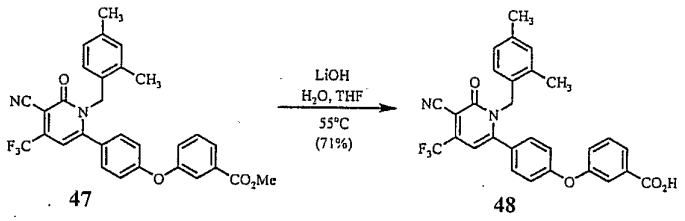
47.9

1-(2,4-Dimethyl-benzyl)-6-[4-(1*H*-indol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 514.4 (M+H)

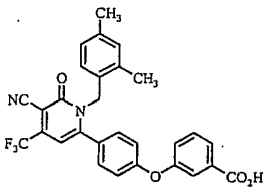
## EXAMPLE 48

This example illustrates the preparation of compound **48**.




47 48

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid methyl ester **47** (0.55 g, 1.01 mmoles) was combined with lithium hydroxide (monohydrate, 93 mg, 2.22 mmoles) in 10 mL of THF/$H_2O$ (4:1). This mixture was then heated at 55 °C for 12 hours. After this period the mixture was evaporated *in vacuo* (-THF) and was combined with 1N HCl (10 mL). The aqueous acidic mixture was combined with enough NaCl to affect saturation and was extracted with $Et_2O$ (4x20 mL). The combined ether layer was washed with brine ,dried over $Na_2SO_4$, and was evaporated *in vacuo* to yield crude product. The crude product was purified using flash silica chromatography (0-60% EtOAc/Hexane) to yield 0.37g (71%) of product as a yellow residue.



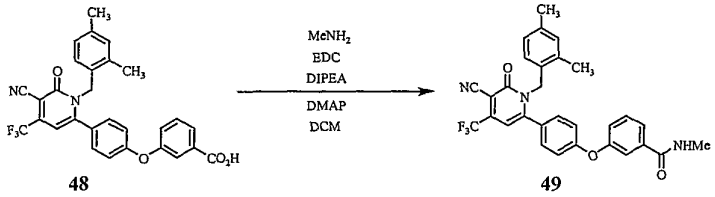
**48**

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid

$^1$H-NMR ($CDCl_3$): δ 7.95-7.91 (m, 1H), 7.74-7.71 (m, 1H), 7.51 (t, J=7.8Hz, 1H), 7.33-7.28 (m, 1H), 7.15-7.10 (m, 2H), 7.00-6.91 (m, 4H), 6.61 (d, J=8.1Hz, 1H), 6.46 (s, 1H), 5.14 (s, 2H), 2.27 (s, 3H), 2.00 (s, 3H). MS(ES+): 519.3 (M+H)

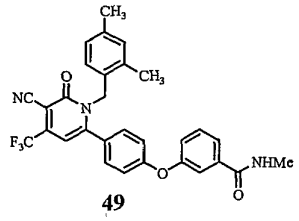
## EXAMPLE 49

This example illustrates the preparation of compound **49**.




48 49

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid **48** (15 mg, 0.029 mmoles) was combined with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC, 14 mg, 0.073 mmoles), 4-dimethylaminopyridine (DMAP, 2 mg, 0.016 mmoles) in 5 mL of anhydrous DCM. To this mixture was added diisopropylethylamine (DIPEA, 13 μL, 0.075 mmoles) and methylamine ([2.0 M] solution in THF, 36 μL, 0.72 mmoles). This mixture was then stirred at room temperature for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-60% EtOAc/Hexane) to yield 13 mg (84% yield) of **49** as a yellow solid.

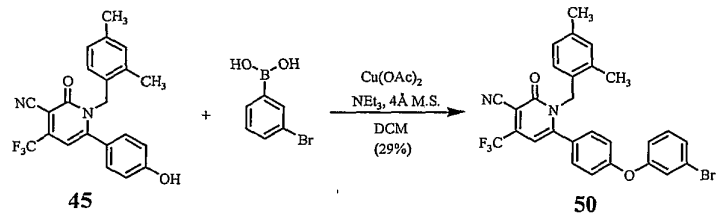



49

$^1$H-NMR ($CDCl_3$): δ7.52-7.41 (m, 3H), 7.19-7.10 (m, 3H), 6.98-6.91 (m, 4H), 6.61 (d, J=7.6Hz, 1H), 6.45 (s, 1H), 6.09 (bs, 1H), 5.14 (s, 2H), 3.01 (d, J=5.1Hz, 3H), 2.27 (s, 3H), 2.01 (s, 3H).

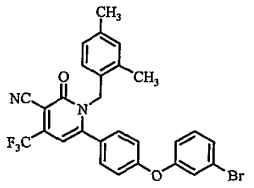
## EXAMPLE 50

This example illustrates the preparation of compound **50**.




45 50

1-(2,4-Dimethyl-benzyl)-6-(4-hydroxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **45** (104 mg, 0.26 mmoles) was combined with (3-bromophenyl) boronic acid (157mg, 0.78 mmoles), copper acetate (57 mg, 0.31 mmoles), 4Å molecular sieves (0.20g) and 1.0 mL of anhydrous DCM within an oven-dried reaction vial. The mixture was stirred at room temperature for 15 min. After this period triethylamine (182 μL, 1.31 mmoles) was added and the mixture was stirred at room temperature for 16 hours. After this period the reaction mixture was purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to yield 41mg (29%) of **50** as a yellow residue.

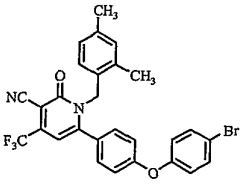


**50**

6-[4-(3-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 555.3 (M+H)

The following compounds were prepared in a manner similar to that described above.



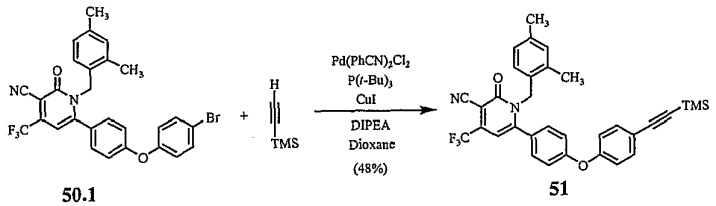
**50.1**

6-[4-(4-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

MS(ES+): 555.2 (M+H)

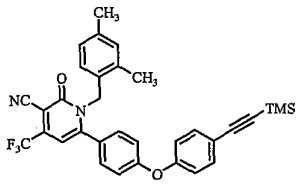
**EXAMPLE 51**

This example illustrates the preparation of compound **51**.




50.1 51

6-[4-(4-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **50.1** (108 mg, 0.195 mmoles) was combined with dichlorobis(benzonitrile)palladium (II) (11 mg, 0.029 mmoles), tri-*t*-butylphosphine (33 mg, 0.065 mmoles), copper iodide (4 mg, 0.021 mmoles), diisopropylethylamine (33 μL, 0.24 mmoles) and trimethylsilylacetylene (□□□□, 0.23 mmoles) in 2.0 mL of anhydrous and thoroughly degassed dioxane. This mixture was then stirred at 50 °C for 24 hours. After this period the reaction mixture was evaporated and purified directly for flash silica chromatography (0-20% EtOAc/Hexane) to yield 53 mg (48% yield) of **51** as a yellow residue.



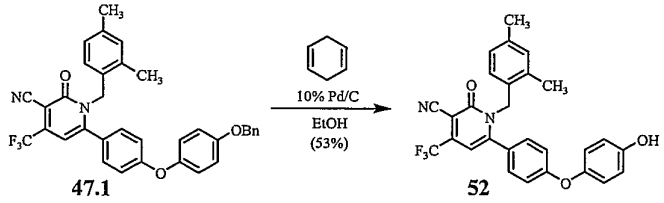

**51**

1-(2,4-Dimethyl-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(4-trimethylsilanylethynyl-phenoxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.52-7.46 (m, 2H), 7.14-7.09 (m, 2H), 6.97-6.89 (m, 6H), 6.60 (d, J=8.1Hz, 1H), 6.44 (s, 1H), 5.13 (s, 2H), 2.28 (s, 3H), 1.99 (s, 3H), 0.25 (s, 9H).

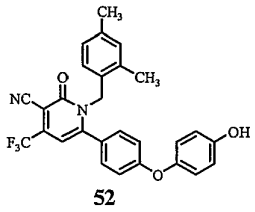
## EXAMPLE 52

This example illustrates the preparation of compound **52**.




47.1 52

6-[4-(4-Benzyloxy-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **47.1** (29 mg, 0.05 mmoles) was combined with cyclohexadiene (0.1 mL, 1.05 mmoles), 10% Pd/C (50 mg) and 10 mL of anhydrous EtOH. This mixture was then stirred at room temperature for 24 hours. After this period the reaction mixture was vacuum filtered through Celite and the resulting filtrate was evaporated *in vacuo* to yield 13 mg (53%) of **52** as a yellow residue.

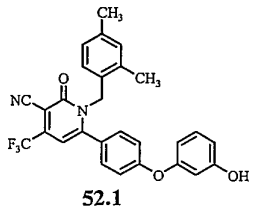


52

1-(2,4-Dimethyl-benzyl)-6-[4-(4-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

$^1$H-NMR ($CDCl_3$): δ 7.12-7.06 (m, 2H), 6.97-6.82 (m, 8H), 6.59 (d, J=7.8Hz, 1H), 6.44 (s, 1H), 5.13 (s, 2H), 4.84 (s, 1H), 2.28 (s, 3H), 2.01 (s, 3H). MS(ES+): 519.3 (M+H)

The following compounds were prepared in a manner similar to that described above.



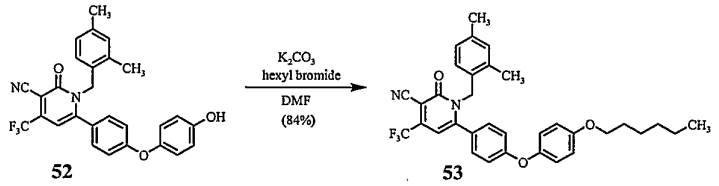
52.1

1-(2,4-Dimethyl-benzyl)-6-[4-(3-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

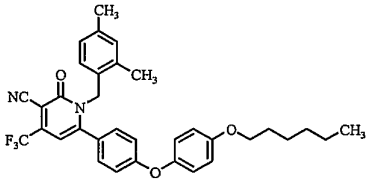
MS(ES+): 519.3 (M+H)

## EXAMPLE 53

This example illustrates the preparation of compound **53**.

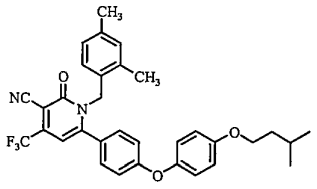



1-(2,4-Dimethyl-benzyl)-6-[4-(4-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile **52** (16 mg, 0.033 mmoles) was combined with potassium carbonate (23 mg, 0.166 mmoles) and hexyl bromide (20 μL, 0.142 mmoles) in 2.0 mL of anhydrous DMF. This mixture was stirred at room temperature for 24 hours. After this period the reaction mixture was combined with 50 mL of water and was extracted with EtOAc (4x15 mL). The combined EtOAc layer was washed with water (4x15 mL) and 15 mL of brine. The resulting EtOAc later was dried over anhydrous $Na_2SO_4$ and was evaporated *in vacuo* to yield the crude product. The crude product was purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 14 mg (84%) of **53** as a yellow residue.




53

$^1$H-NMR ($CDCl_3$): δ 7.05 (d, J=8.8Hz, 2H), 6.97-6.81 (m, 8H), 6.57 (d, J=7.3Hz, 1H), 6.40 (s, 1H), 5.10 (s, 2H), 3.92 (t, J=6.6Hz, 2H), 2.24 (s, 3H), 1.98 (s, 3H), 1.81-1.71 (m, 2H), 1.49-1.39 (m, 2H), 1.35-1.28 (m, 4H), 0.91-0.84 (m, 3H). MS(ES+): 575.5 (M+H)

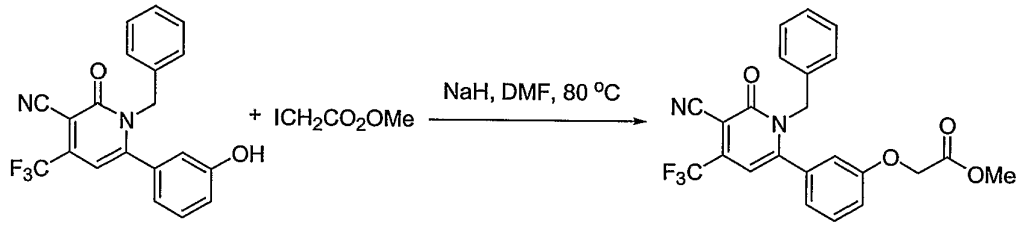


53.1

MS(ES+): 561.3 (M+H)

## EXAMPLE 54

This example illustrates the preparation of compound **54**.

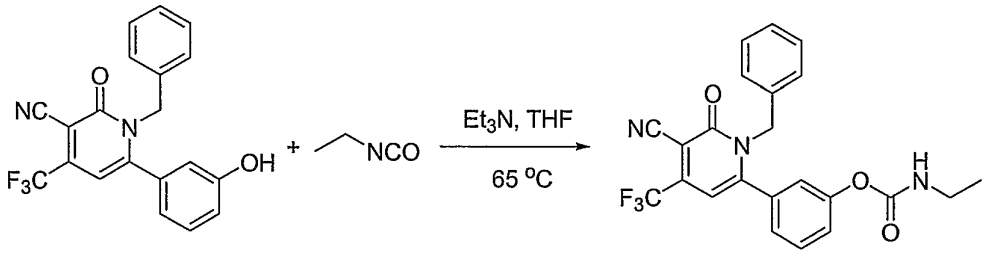


**54a** **54**

Sodium hydride (18 mg, 0.43 mmol) was added to a solution of **54a** (80 mg, 0.22 mmol) and methyl 2-iodoacetate (82 μL, 0.86 mmol) in anhydrous DMF (2 mL). The reaction mixture was stirred under nitrogen atmosphere at 80 °C overnight. After the reaction mixture was cooled off, it was poured into 20 mL of water and extract with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine and water and concentrated *in vacuo*. The crude product was purified by column chromatography (40% ethyl acetate in hexane), providing product **54** (67 mg, 70% yield). $^1$H-NMR ($CDCl_3$): δ7.37 (m, 1H), 7.26 (m, 4 H), 7.06 (m, 1 H), 6.91 (m, 1 H), 6.82 (m, 1 H), 6.62 (m, 1 H), 6.40 (s, 1 H), 5.24 (s, 2 H), 4.46 (s, 2 H), 3.80 (s, 2 H).

## EXAMPLE 55

This example illustrates the preparation of compound **55**.

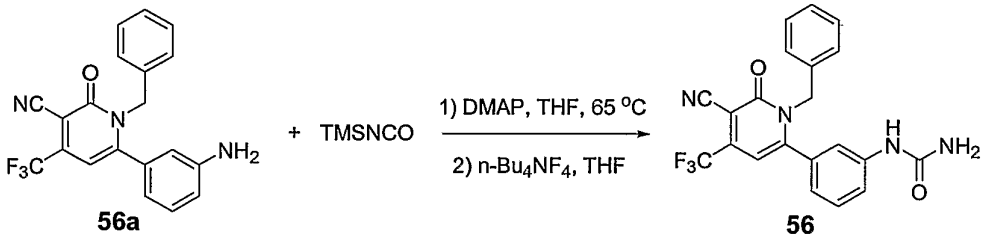



**54a** **55**

To a solution of **54a** (80 mg, 0.22 mmol) and triethylamine (60 μL, 0.43 mmol) in anhydrous THF (2 mL) was added ethyl isocyanate (43 μL, 0.54 mmol). The reaction mixture was stirred at 65 °C under nitrogen atmosphere for overnight. The reaction mixture was then cooled off and concentrated *in vacuo*. The crude product was purified by column chromatography (40% ethyl acetate in hexane) to yield product **55** (91 mg, 95% yield). $^1$H-NMR ($CDCl_3$): δ7.39 (m, 1 H), 7.29 (m, 1 H), 7.24-7.20 (m, 3 H), 7.04 (m, 1 H), 6.91 (m, 3 H), 6.41 (s, 1 H), 5.29 (s, 2 H), 5.05 (s, 1 H), 3.33 (m, 2 H), 1.24 (t, 7.1 Hz, 3H).

## EXAMPLE 56

This example illustrates the preparation of compound **56**.



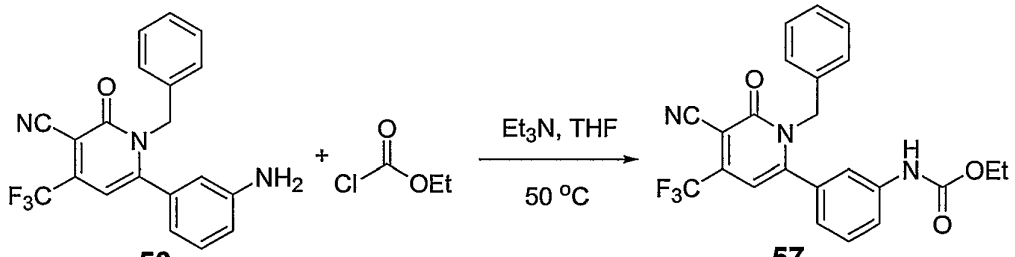

**56a** **56**

To a solution of **56a** (117 mg, 0.32 mmol) in anhydrous THF (4 mL) was added trimethylsilyl isocyanate (0.24 mL, 1.6 mmol) and 4-dimethylaminopyridine (4 mg, 0.03 mmol). The reaction mixture was stirred at 65 °C under nitrogen atmosphere overnight. The mixture was concentrated in vacuo. The resulting residue was dissolved in anhydrous THF (4 mL), and to it was added tetrabutylammonium floride (0.7 mL, 1.0 M) in THF. The reaction mixture was stirred at room temperature overnight. The crude product was purified by column chromatography (60% ethyl acetate in hexane) to yield product **56** (95 mg, 72% over two steps). $^1$H-NMR (DMSO-d6): δ10.20 (s, 1

H), 9.04 (s, 1 H), 7.65 (m, 1 H), 7.58 (m, 1 H), 7.43 (m, 1 H), 7.29 (m, 3 H), 7.07 (m, 1 H), 7.02 (m, 2 H), 6.80 (s, 1 H), 5.23 (s, 2 H).

## EXAMPLE 57

This example illustrates the preparation of compound **57**.

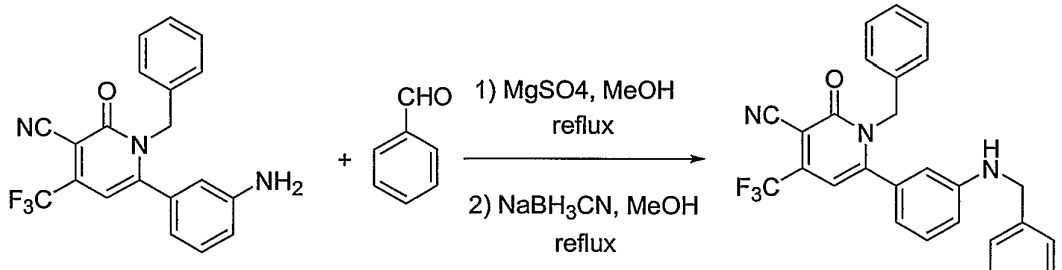



**56a** **57**

To a solution of **56a** (80 mg, 0.22 mmol) and triethyl amine (76 μL, 0.54 mmol) in anhydrous methylene chloride (2 mL) was added ethyl chloroformate (41 μL, 0.54 mmol). The reaction mixture was sealed in a vial and stirred at 50 °C overnight. The mixture was cooled off and concentrated *in vacuo*. The product was purified by column chromatography (40% ethyl acetate in hexane) to yield **57** (40 mg, 42% yield). $^1$H-NMR ($CDCl_3$): δ7.41 (m, 2 H), 7.34 (m, 1 H), 7.25-7.21 (m, 3 H), 6.91 (m, 2 H), 6.81 (m, 1 H), 6.64 (s, 1 H), 6.40 (s, 1 H), 5.27 (s, 2 H), 4.24 (q, 7.1 Hz, 2 H), 1.32 (t, 7.1 Hz, 3 H).

## EXAMPLE 58

This example illustrates the preparation of compound **58**.



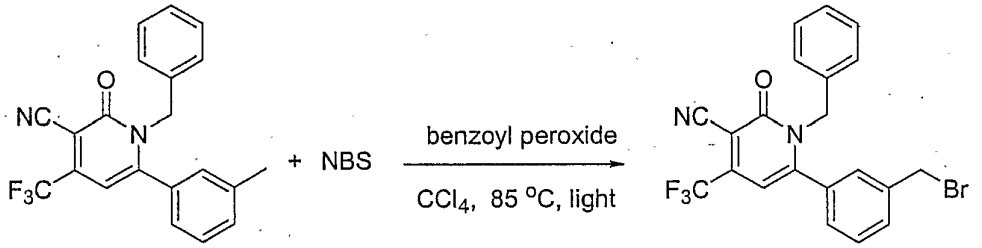

**56a** **58**

To a solution of **56a** (100 mg, 0.27 mmol) in methanol (15 mL) was added benzaldehyde (41 μL, 0.41 mmol) and anhydrous magnesium sulfate (500 mg). The reaction mixture was heated to reflux overnight. Sodium cyanoborohydride (85 mg, 1.36 mmol) was added to the mixture, which was

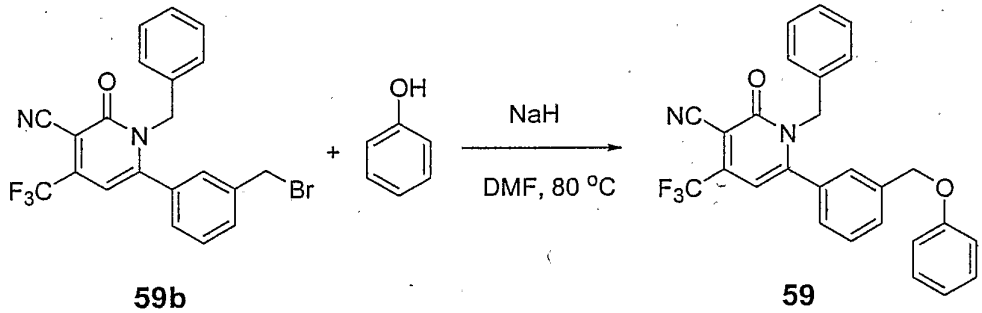
heated to reflux overnight. The reaction mixture was concentrated *in vacuo* and the crude mixture was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The combined ethyl acetate was concentrated *in vacuo*. The crude product was purified by column chromatography (30% ethyl acetate in hexane) to yield compound **58** (24 mg, 19% yield). $^1$H-NMR ($CDCl_3$): δ7.38-7.19 (br, 10 H), 6.93 (m, 2 H), 6.75 (m, 1 H), 6.50 (m, 1 H), 6.38 (s, 1 H), 6.27 (s, 1 H), 5.19 (s, 2 H), 4.17 (s, 2 H).

**EXAMPLE 59**

This example illustrates the preparation of compound **59**.




**59a** **59b**



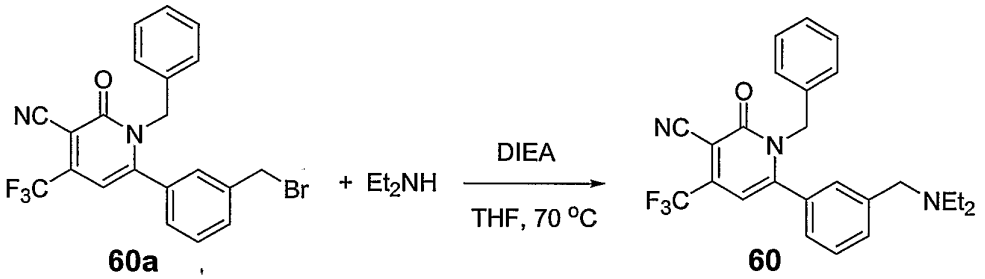

**59b** **59**

A solution of **59a** (0.96 g, 2.61 mmol) in carbon tetrachloride (50 mL) was treated with N-bromosuccinimide (557 mg, 3.13 mmol) and catalytic amount of benzoyl peroxide. The reaction mixture was heated to reflux and irradiated with a 500 W floodlamp for 24 h. It was then cooled off and the white precipitate was filtered off. The solvent was evaporated to dryness, and the residue was purified by column chromatograpy (40% ethyl acetate in hexane) to yield **59b** (0.79 g, 65% yield). $^1$H-NMR ($CDCl_3$): δ7.56 (m, 1 H), 7.43 (m, 1 H), 7.25 (m, 3 H), 7.13 (m, 2 H), 6.88 (m, 2 H), 6.39 (s, 1 H), 5.24 (s, 2 H), 4.38 (s, 2 H).

To a solution of **59b** (151 mg, 0.34 mmol) and phenol (127 mg, 1.35 mmol) in anhydrous DMF was added sodium hydride (54 mg, 60%, 1.35 mmol). The reaction mixture was stirred and heated to 80 °C for overnight. It was cooled off and poured into water and extracted with ether. The ether layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (15-30% ethyl acetate in hexane) to yield product **59** (66 mg, 42% yield). $^1$H-NMR ($CDCl_3$): δ7.60 (m, 1H), 7.46 (m, 1 H), 7.30 (m, 2 H), 7.24-7.20 (br, 4 H), 7.12 (m, 1 H), 7.00 (m, 1 H), 6.92 (m, 2 H), 6.86 (m, 2 H), 6.40 (s, 1 H), 5.22 (s, 1 H), 5.03 (s, 2 H).

## EXAMPLE 60

This example illustrates the preparation of compound **60**.

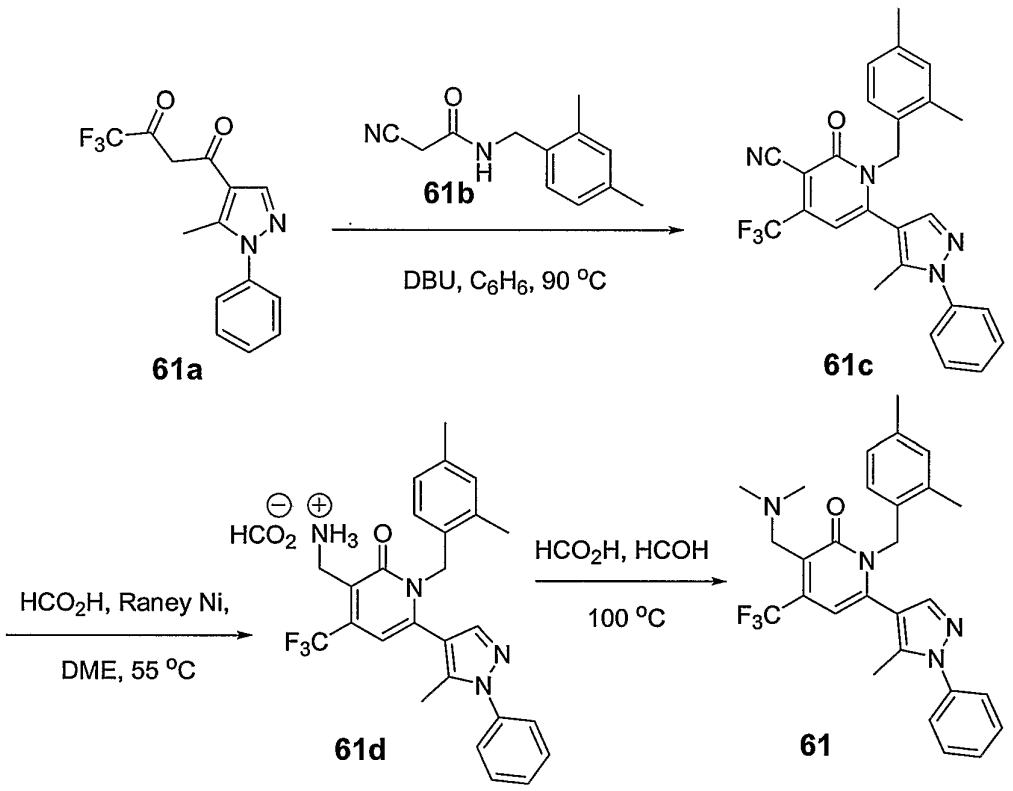



**60a** **60**

To a solution of **60a** (152 mg, 0.34 mmol) and diisopropylethyl amine (89 μL, 0.51 mmol) in THF (2 mL) was added diethyl amine (53 μL, 0.51 mmol). The reaction mixture was heated to 70 °C for overnight. The solvent was evaporated in vacuo and the crude product was purified by column chromatography (50% ethyl acetate in hexane) to yield product **60** (82 mg, 55%). $^1$H-NMR ($CDCl_3$): δ 7.51 (m, 1 H), 7.38 (m, 1 H), 7.24-7.17 (m, 4 H), 7.07 (m, 1 H), 6.88 (m, 2 H), 6.41 (s, 1 H), 5.27 (s, 2 H), 3.52 (m, 2 H), 2.48 (m, 4 H), 1.01 (m, 6 H).

## EXAMPLE 61

This example illustrates the preparation of compound **61**.




2,4-dimethylbenzyl cyanoacetamide **61a** (103 mg, 0.59 mmol) and diketone **61b** (175 mg, 0.59 mmol) were suspended in 2 mL of benzene. To the above reaction mixture was added DBU (45 μL, 0.3 mmol). The mixture was sealed in a vial and stirred at 90 °C for overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by column chromatography (35% ethyl acetate in hexane) to yield **61b** (50 mg, 18%). $^1$H-NMR ($CDCl_3$): δ7.54-7.45 (m, 3 H), 7.34 (m, 3 H), 6.95 (m, 2 H), 6.61 (m, 1 H), 6.44 (s, 1 H), 5.28 (m, 2 H), 2.28 (s, 3 H), 2.08 (s, 3 H), 2.03 (s, 3 H).

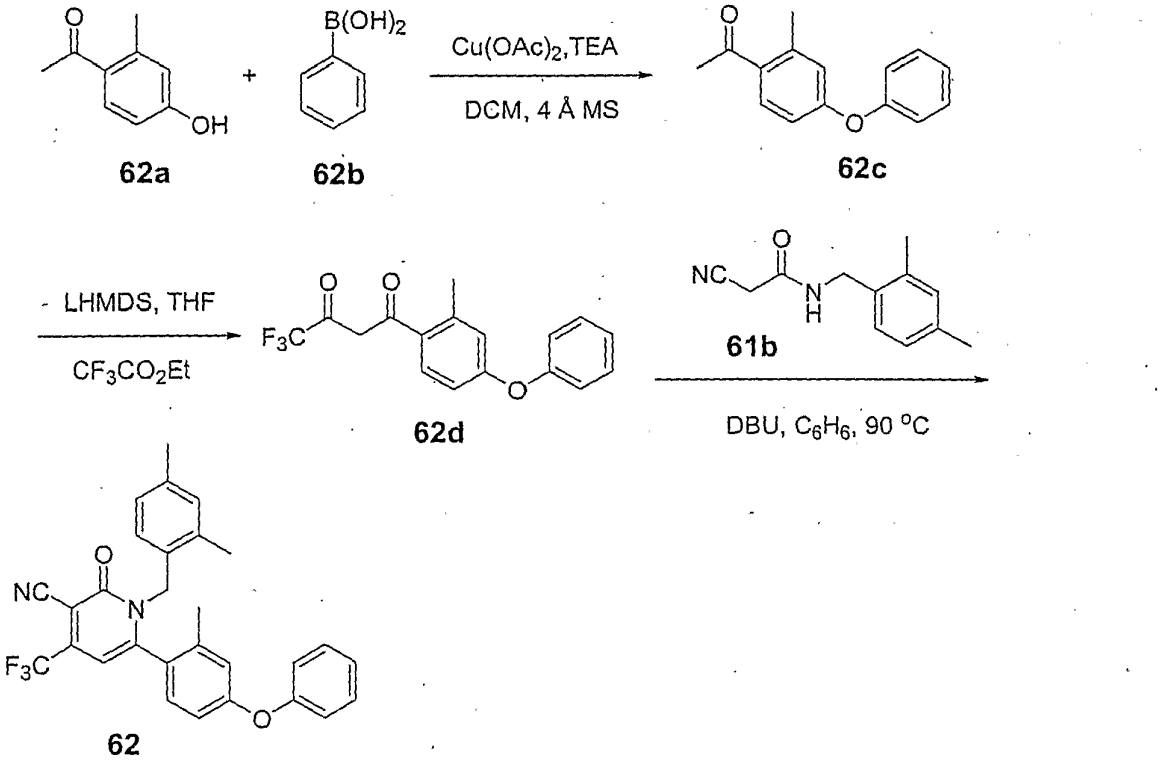
1.0 g of aluminum-nickel catalyst was placed in 10 mL of 2 N aq NaOH and stirred in a flask cooled with ice water. The mixture was stirred for 45 min. The solution was decanted, while the solid Ni catalyst was kept washing with water 8 times until it became clear solution. The water was removed as much as possible, using a pipet. To a solution of **61b** (48 mg, 0.10 mmol) in 5 mL of DME was added 5 mL of formic acid. The reaction mixture was stirred at 55 °C for 4 h under a slow stream of nitrogen. The reaction mixture was filtered through a short pad of celite, and the celite was washed with MeOH. The

filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (10% MeOH in DCM containing 0.1% triethyl amine) to provide product **61d** (26 mg, 50%yield).

The resulting product **61d** (21 mg, 0.04 mmol) was dissolved in a mixture of formic acid (2 mL, 96%) and formaldehyde (6 mL, 37% in water). The reaction mixture was heated at 100 °C for 16 h and then cooled off. The reaction mixture was neutralized by 10% aq NaOH with ice to weekly basic and then extracted with ether (3 x 20 mL). The combined ether was concentrated *in vacuo*. This crude product was purified by HPLC with 30% $CH_3CN$ in water to yield **61** (12 mg, 80% yield) as trifluoroacetic acid salt. $^1$H-NMR ($CDCl_3$): δ7.50 (m, 2 H), 7.45 (m, 1 H), 7.36 (m, 3 H), 6.97 (s, 1 H), 6.91 (m, 1 H), 6.56 (m, 1 H), 6.49 (s, 1 H), 5.23 (s, 2 H), 4.34 (s, 2 H), 3.00 (s, 6 H), 2.27 (s, 3 H), 2.11 (s, 6 H). MS (ES+): 495.2 (M+H).

## EXAMPLE 62

This example illustrates the preparation of compound **62**.



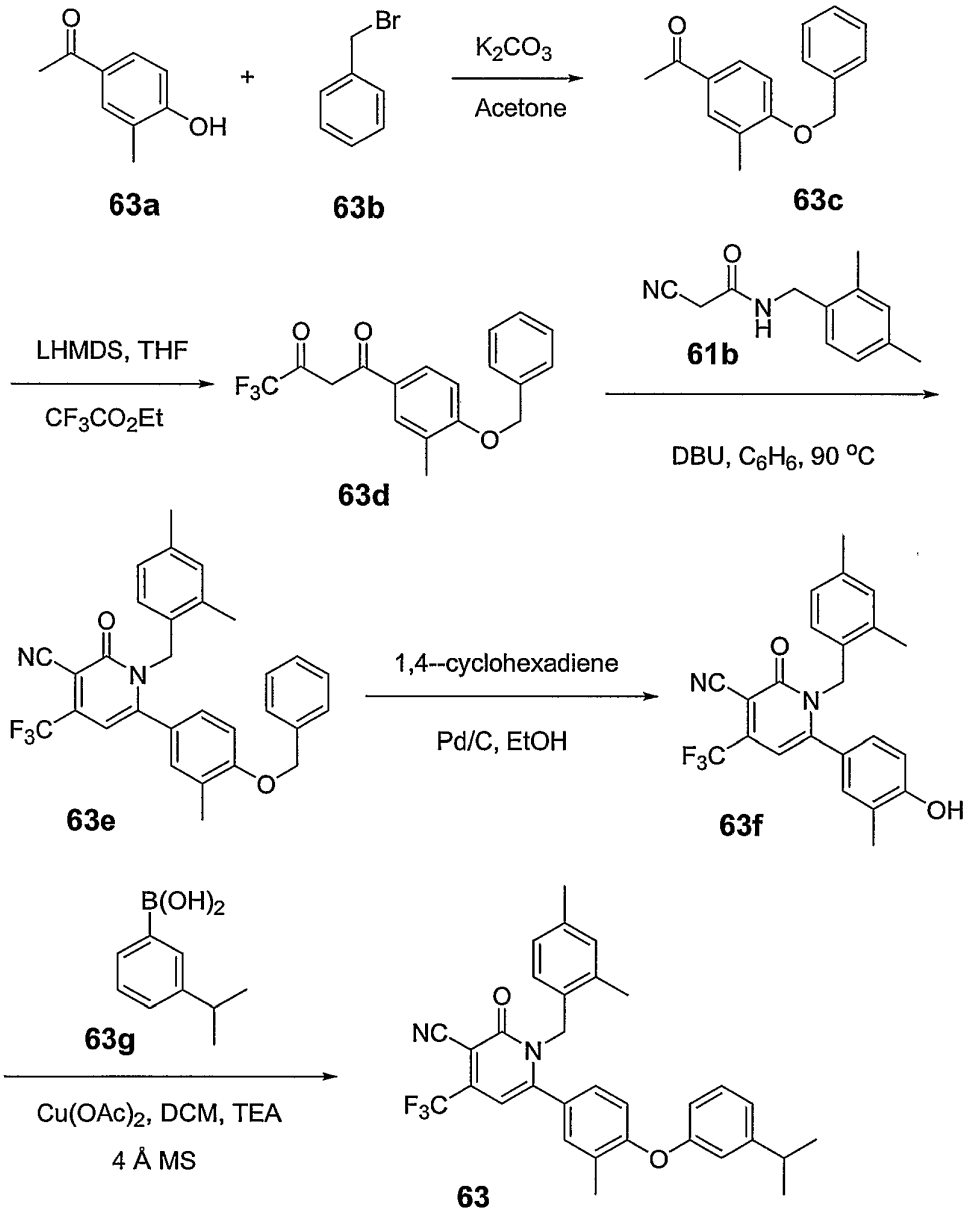
To a solution of 2-methyl-4-hydroxyacetophenone **62a** (0.5 g, 3.33 mmol) in anhydrous methylene chloride (30 mL) was added $Cu(OAc)_2$ (605 mg, 3.33 mmol), phenylboronic acid (812 mg, 6.66 mmol) and powdered 4 Å molecular sieves and triethylamine (2.32 mL, 16.65 ,mmol). The heterogenerous reaction mixture was stirred at ambient temperature for overnight. The resulting slurry was filtered through celite and the diaryl ether was isolated from the organic filtrate by column chromatography (30% ethyl acetate in hexane) to yield **62c** (590 mg, 78% yield). $^1$H-NMR ($CDCl_3$): δ 7.73 (m, 1 H), 7.38 (m, 2 H), 7.19 (m, 1 H), 7.06 (m, 2 H), 6.82 (m, 2 H), 2.56 (s, 3 H), 2.53 (s, 3 H).

The diaryl ether **62c** (530 mg, 2.34 mmol) was dissolved in anhydrous THF (3 mL) and cooled to –78 °C under nitrogen atmosphere. A solution of lithium bis(trimethylsilyl)amide (2.4 mL, 1.0 M) in THF was added slowly. The reaction mixture was stirred at –20 °C under nitrogen atmosphere for 1 h. The reaction mixture was then cooled to –78 °C, and to it was added ethyl trifluoroacetate (417 μL, 3.5 mmol). The vigorously stirred solution was allowed to warm to ambient temperature overnight. The reaction mixture was poured into a mixture of 10% aq HCl and ice and extracted with chloroform three times. The chloroform extract was washed with water. The organic layer was separated and dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give crude product **62d** (1.05 g, 98% yield).

2,4-dimethylbenzyl cyanoacetamide **61b** (101 mg, 0.50 mmol) and diketone **62d** (161 mg, 0.50 mmol) were suspended in 2 mL of benzene. To the above reaction mixture was added DBU (40 μL, 0.25 mmol). The mixture was sealed in a vial and stirred at 90 °C for overnight. The reaction mixture was concentrated in vacuo and the resulting residue was purified by column chromatography (35% ethyl acetate in hexane) to yield product **62** (127 mg, 52% yield). ). $^1$H-NMR ($CDCl_3$): δ 7.40 (m, 2 H), 7.20 (m,1 H), 7.03 (m, 2 H), 6.84 (m, 4 H), 6.73 (m, 1 H), 6.60 (m, 1 H). 6.37 (s, 1 H), 5.31 (m, 1 H), 4.89 (m, 1 H), 2.73 (s, 3 H), 2.25 (s, 3 H, 1.92 (s, 3 H). MS (ES+): 489.2 (M+H).

**EXAMPLE 63**

This example illustrates the preparation of compound **63**.



To a solution of 3-methyl-4-hydroxyacetophenone **63a** (9.01 g, 60 mmol) and benzyl bromide **63b** (7.49 mL, 63 mmol) in acetone (120 mL) was added potassium carbonate (8.71 g, 63 mmol). The reaction mixture was stirred at ambient temperature under nitrogen atmosphere for overnight. The white solid was filtered off and the solvent was concentrated *in vacuo* to yield product **63c** (14.13 g, 98% yield). The product was used for the next reaction without further purification.

The aryl benzyl ether **63c** (14.13 g, 59.3 mmol) was dissolved in anhydrous THF (150 mL) and cooled to –78 °C under nitrogen atmosphere. A solution of lithium bis(trimethylsilyl)amide (59.3 mL, 1.0 M) in THF was added slowly. The reaction mixture was stirred at –20 °C under nitrogen atmosphere for 2 h. The reaction mixture was then cooled to –78 °C, and to it was added ethyl trifluoroacetate (10.58 mL, 89 mmol). The vigorously stirred solution was allowed to warm to ambient temperature overnight. The reaction mixture was poured into a mixture of 10% aq HCl and ice and extracted with chloroform three times. The chloroform extract was washed with water. The organic layer was separated and dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give crude product **63d** (19.5 g, 98% yield). The product was used for the next reaction without purification.

2,4-dimethylbenzyl cyanoacetamide **61b** (3.01 g, 14.88 mmol) and diketone **63d** (5.0 g, 14.87 mmol) were suspended in 50 mL of benzene. To the above reaction mixture was added DBU (1.11 mL, 7.43 mmol). The mixture was heated to reflux under nitrogen atmosphere for overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by column chromatography (20% ethyl acetate in hexane) to yield product **63e** (3.90 g, 45% yield).

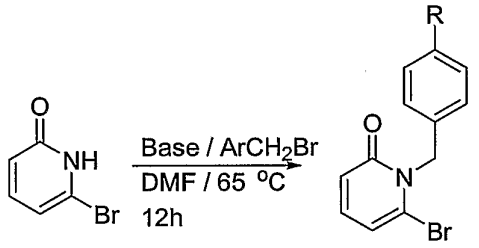
To a solution of **63e** (3.71 g, 7.38 mmol) in anhydrous ethanol (74 mL) was added 2.85 g of 10% Pd/C and 1,4-cyclohexadiene (6.98 mL, 73.8 mmol). The mixture was stirred under nitrogen atmosphere for overnight. The solution

was filtered through a pad of celite and the solvent was concentrated in vacuo to yield product **63f** (2.96 g, 97%).

To a solution of **63f** (103 mg, 0.25 mmol) in anhydrous methylene chloride (3 mL) was added $Cu(OAc)_2$ (91 mg, 0.5 mmol), 3-isopropylphenylboronic acid (82 mg, 0.5 mmol) and powdered 4 Å molecular sieves and triethylamine (174 μL, 1.25 mmol). The heterogenerous reaction mixture was stirred at ambient temperature for overnight. The resulting slurry was filtered through celite and the diaryl ether was isolated from the organic filtrate by column chromatography (20% ethyl acetate in hexane) to yield **63** (63 mg, 47% yield). ). $^1$H-NMR ($CDCl_3$): δ7.27 (m, 1 H), 7.03 (m, 1 H), 6.98-6.85 (m, 5 H), 6.74 (m, 2 H), 6.64 (m, 1 H). 6.46 (s, 1 H), 5.15 (s, 2 H), 2.90 (hep, J = 7.0 Hz, 1 H), 2.27 (s, 3 H), 2.21 (s, 3 H), 1.99 (s, 3 H), 1.25 (d, J = 7.0 Hz, 6 H). MS (ES+): 531.3 (M+H).

## EXAMPLE 64

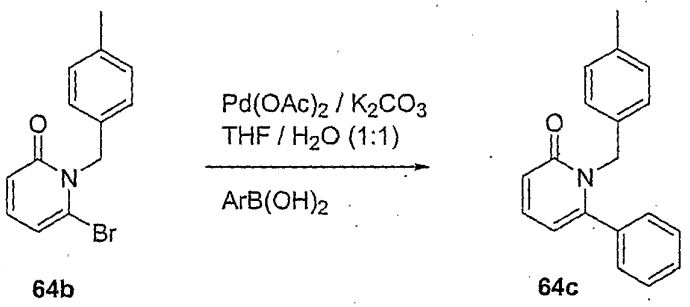
This example illustrates the preparation of compound **64**.




**64a** **64b**

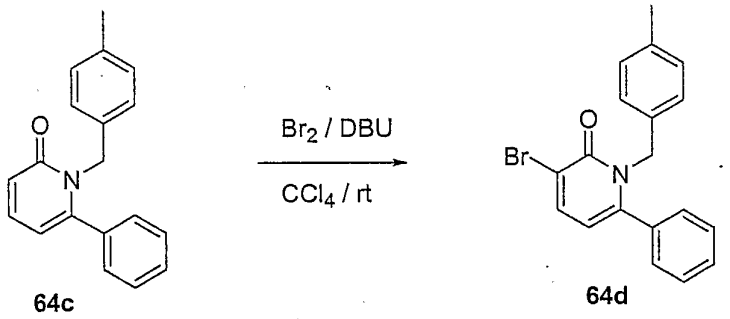
**Method A** (R = Me): To a solution of bromopyridone **64a** (2.12 g, 12.2 mmols) in 60 mL of DMF at room temperature was added LiH (145.0 mg, 18.3 mmols). After stirring for 1 hour at 65 °C, 4-methylbenzyl bromide (2.7 g, 14.6 mmols) was added and heating continued for 12 h. The solution was cooled to room temperature and concentrated under reduced pressure. Pyridone **64b** (R = Me) was isolated from the residue by column chromatography on silica gel (0 to 20% EtOAC / hexanes) as a colorless oil (1.6 g, 47%). $^1$H NMR ($CDCl_3$) δ: 7.34 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 7.6 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 5.24 (s, 2H), 2.29 (s, 3H).

**Method B** (R = H): To a solution of bromopyridone (405.0 mg, 2.3 mmols) in 6.0 mL of DME:DMF (10:1, v/v) at 0 °C was added NaH (92.0 mg, 2.3 mmols, 60% dispersion in mineral oil). After 10 minutes LiBr (800.0 mg, 9.2 mmols) was added and the mixture warmed to room temperature over 15 minutes and then benzyl bromide (786.6 mg, 4.6 mmols) was added. The resulting solution was heated to 65 °C for 12h, cooled to room temperature, diluted with saturated aqueous sodium chloride solution, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Pyridone (R = H) was isolated from the residue by column chromatography on silica gel (0 to 20% EtOAC / hexanes) as a colorless oil (533 mg, 88%). $^1H$ NMR ($CDCl_3$) δ: 7.40-4.24 (m, 6H), 7.00 (d, J = 7.2 Hz, 1H), 6.66 (d, J = 7.6 Hz, 1H), 5.28 (s, 2H).



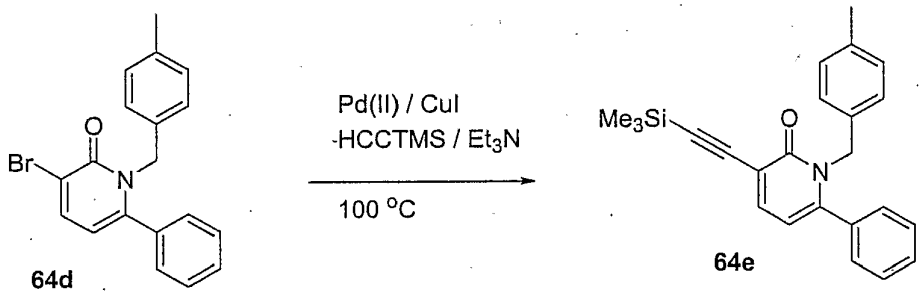

**64b** **64c**

A degassed solution of bromopyridone **64b** (100 mg, 0.4 mmol) and phenylboronic acid (44 mg, 0.4 mmol) in 0.9 mL THF was added $Pd(OAc)_2$ (4 mg, 0.02 mmol). A degassed solution of $Na_2CO_3$ (95 mg, 0.9 mmol) in 0.9 mL $H_2O$ was added and the resulting mixture heated to reflux for 12 h. The mixture was cooled to room temperature, diluted with $H_2O$, and extracted with EtOAc. The combined organic layers were dried over $NaSO_4$ before being concentrated under reduced pressure. The product **64c** (91 mg, 97%) was isolated as a colorless solid from the residual oil by column chromatography on silica (0 to 20% EtOAc / hexanes). $^1H$ NMR ($CDCl_3$) δ: 7.52 (dd, J = 8.6, 1.6 Hz, 1H), 7.39-7.26 (7H), 7.11 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 7.2 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 5.24 (s, 2H), 2.29 (s, 3H).




64c 64d

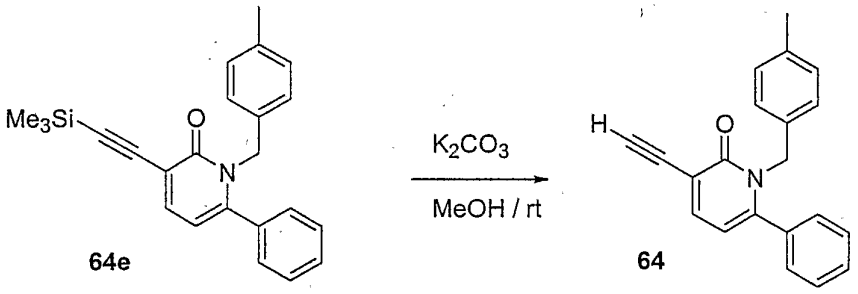
To a solution of pyridone **64c** (70 mg, 0.3 mmol) in 0.54 mL $CCl_4$ at 0 °C in the dark (foil wrapped flask) was added $Br_2$ (62 mg, 0.4 mmol) and DBU (61 mg, 0.4 mmol). The resulting solution was allowed to warm to slowly room temperature and stir for 12 h. The solution was diluted with $CH_2Cl_2$ (25 mL) and washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$, and dried over $Na_2SO_4$ before being concentrated under reduced pressure. The product **64d** (71 mg, 75%) was isolated from the residual oil as a colorless solid by column chromatography on silica (0 to 5% EtOAc / hexanes). $^1H$ NMR ($CDCl_3$) δ: 7.92 (m, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.37 (m, 5H), 7.17 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 5.48 (s, 2H), 2.28 (s, 3H).




64d 64e

To a solution of bromide **64d** (12 mg, 0.03 mmol) in 0.3 mL $Et_3N$ was added CuI (2 mg, 0.01 mmol), dichloro(bis-triphenylphosphine)palladium (II) (4 mg, 0.005 mmol), and 1,3-(bis-diphenylphosphino)propane (2 mg, 0.005). The system was purged with $N_2$, trimethylsilylacetylene (59 mg, 0.6 mmol) added and the resulting mixture heated to 100 °C for 17 h. Upon cooling to room temperature the mixture was concentrated under reduced pressure and

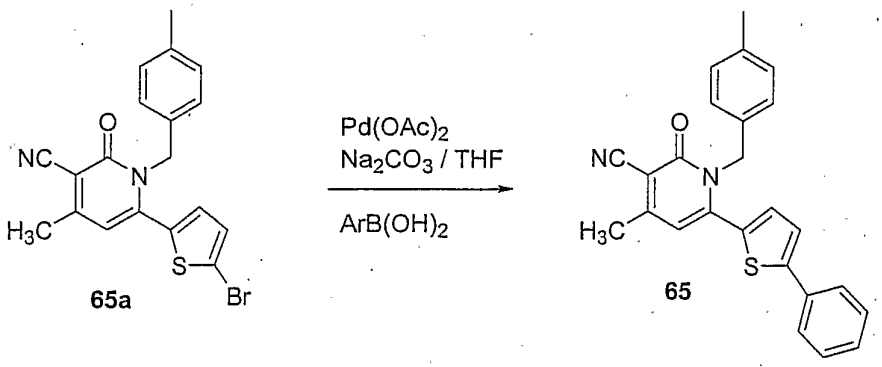
product **64e** (8 mg, 73%) was isolated from the residual oil as a yellow oil by column chromatography on silica (0 to 5% EtOAc / hexanes). $^1$H NMR ($CDCl_3$) δ: 8.09 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.70-7.37 (m, 5H), 7.39 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 5.62 (s, 2H), 2.42 (s, 3H), 0.34 (s, 9H).




Alkyne **64e** (2 mg, 0.005 mmol) was combined with $K_2CO_3$ (3 mg, 0.025 mmol) in 0.1 mL of MeOH and stirred overnight at room temperature. The mixture was concentrated under reduced pressure and product **64** (1 mg) was isolated from the residual oil as a yellow oil by column chromatography on silica (0 to 5% EtOAc / hexanes). $^1$H NMR ($CDCl_3$) δ: 7.95 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.39 (m, 5H), 7.26 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 5.51 (s, 2H), 3.30 (s, 1H), 2.28 (s, 3H).

**Example 65**

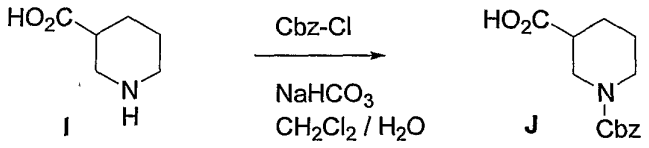
This example illustrates the preparation of compound **65**.



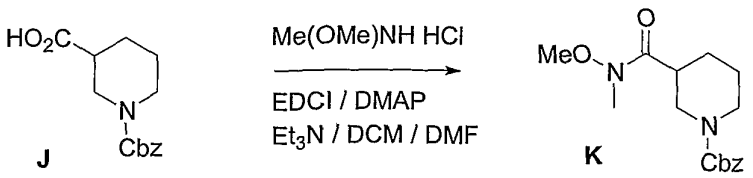
To a degassed solution of thienylbromide **65a** (50 mg, 0.11 mmol) and phenylboronic acid (13 mg, 0.11 mmol) in 0.6 mL THF was added $Pd(OAc)_2$ (1 mg, 0.006 mmol). A degassed solution of $Na_2CO_3$ (30 mg, 0.3 mmol) in 0.6 mL $H_2O$ was added and the resulting mixture heated to reflux for 12 h. The mixture was cooled to room temperature, diluted with $H_2O$ and extracted with EtOAc. The combined organic layers were dried over $NaSO_4$ before being concentrated under reduced pressure. The product **65** (28 mg, 55%) was isolated as a colorless solid from the residual oil by column chromatography on silica (10 to 20% EtOAc / hexanes). $^1H$ NMR ($CDCl_3$) δ: 7.51 (d, J = 8.0 Hz, 2H), 7.35 (m, 5H), 7.35 (d, J = 7.3 Hz, 1H), 7.01 (d, J = 3.8 Hz, 1H), 6.88 (d, J = 8.1 Hz, 2H), 6.56 (s, 1H), 5.38 (s, 2H), 2.25 (s, 3H).

**Example 66**

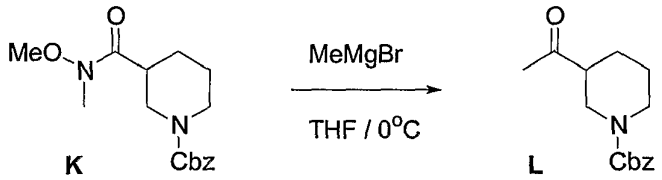
This example illustrates the preparation of compound **66**.



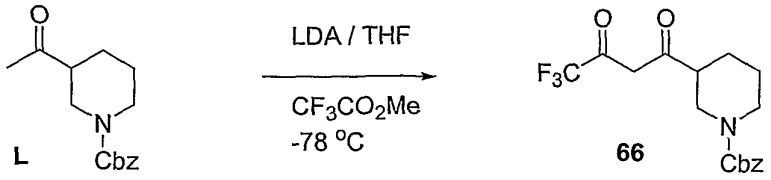

To a solution of acid **I** (2.0 g, 15.5 mmols) in 8.0 mL of dioxane was added benzyl chloroformate (3.1 g, 18.6 mmols) at room temperature followed by the addition of 8 mL of saturated aqueous $NaHCO_3$. The resulting mixture was vigorously stirred for 4 hours, the dioxane removed under reduced pressure, and the resulting solution diluted with $H_2O$. Extraction with $CH_2Cl_2$ was followed by drying the combined fractions over $Na_2SO_4$ and concentration under reduced pressure. The product **J** (3.3 g, 81%) was isolated as a colorless oil from the residual oil by column chromatography on silica (5-10% MeOH / $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$) δ: 7.36 (m, 5H), 5.13 (m, 2H), 4.19 (bm, 1H), 3.97 (m, 1H), 3.13 (bm, 1H), 2.94 (ddd, J = 3.0, 10.6, 13.6 Hz, 1H), 2.53 (bm, 1H), 2.09 (m, 1H), 1.72 (m, 2H), 1.51 (bm, 1H).



To a solution of acid **J** (3.3 g, 12.6 mmols) in 120 mL $CH_2Cl_2$:DMF (4:1, v/v) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (4.8 g, 25.2 mmols) and 4-*N,N*-dimethylaminopyridine (77 mg, 0.6 mmol). After stirring for 30 minutes *N,O*-dimethylhydroxylamine hydrochloride (1.2 g, 12.6 mmols) followed by triethylamine (1.3 g, 12.6 mmols). After stirring for 12 hours the solution was concentrated under reduced pressure and the residue dissolved in $CH_2Cl_2$ (200 mL). The solution was then washed with $H_2O$ and 1N aqueous HCl before being dried over $Na_2SO_4$ and concentrated under reduced pressure. The product **K** (3.2 g, 81%) was isolated as a pale yellow oil from the residual oil by column chromatography on silica (5-10% MeOH / $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$) δ: 7.35 (m, 5H), 5.13 (M, 2H), 4.20 (bm, 1H), 4.11 (m, 1H), 3.72 (s, 3H), 3.59, (s, 3H), 2.92 (m, 1H), 2.81 (m, 1H), 2.19 (m, 1H), 1.94 (m, 1H), 1.70 (m, 2H), 1.51 (m, 1H).



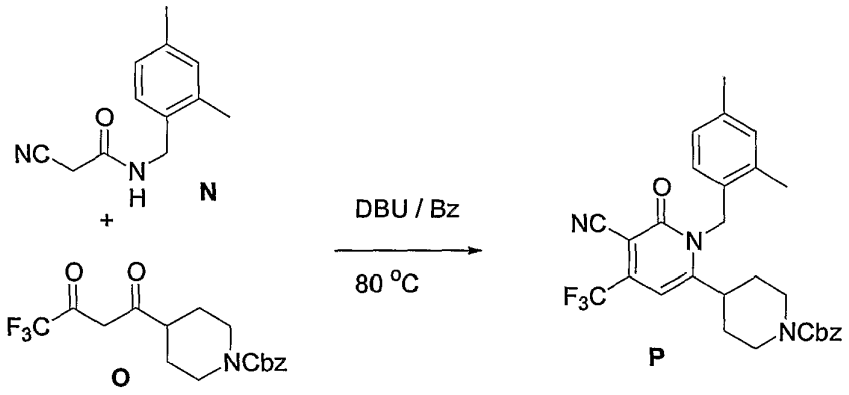

To a solution of amide **K** (600 mg, 2.0 mmols) in THF (20 mL) at 0 °C was added MeMgBr (1.2 mL, 2.2 mmols, 1.4 M in THF). After stirring for 1 hour, the reaction was quenched at 0 °C by the addition of 1N HCl in EtOH. The solution was diluted with $CH_2Cl_2$:$Et_2O$ (100 ml, v/v) and washed with saturated aqueous NaCl before being dried ($Na_2SO_4$) and concentrated under reduced pressure. The product **L** (257 mg, 50%) was isolated as a colorless oil from the residual oil by column chromatography on silica (10-50% EtOAc / hexanes). $^1H$ NMR ($CDCl_3$) δ: 7.37 (m, 5H), 5.15 (m, 2H), 4.22 (bm, 1H), 4.04 (bm, 1H), 3.02 (m, 1H), 2.88 (bm, 1H), 2.54 (bm, 1H), 2.19 (s, 3H), 2.04 (bm, 1H), 1.76 (m, 1H), 1.55 (m, 2H).



To a solution of ketone **L** (237 mg, 0.9 mmol) in 3.0 mL THF at -78 °C was added a solution of lithium diisopropylamide (0.45 mL, 0.9 mmol, 2.0M in THF). After stirring for 5 minutes ethyl trifluoromethylacetate (155 mg, 1.1 mmols) was added. Stirring for 2 hours at -78 °C was followed by warming to room temperature and the addition of EtOAc (50 mL). The resulting solution was washed with 10% aqueous $H_2SO_4$ and $H_2O$ before being dried with $Na_2SO_4$ and concentrated under reduced pressure. The product **66** (50 mg, 16%) was isolated from the residual oil by column chromatography on silica (10-50% EtOAc / hexanes). $^1$H NMR ($CDCl_3$) δ: 7.34 (m, 5H), 5.96 (s, 1H), 5.14 (m, 2H), 4.18 (bm, 1H), 4.07 (m, 1H), 3.01 (m, 1H), 2.89 (m, 1H), 2.68 (m, 1H), 2.52 (bm, 1H), 2.28 (m, 1H), 1.73 (m, 2H).

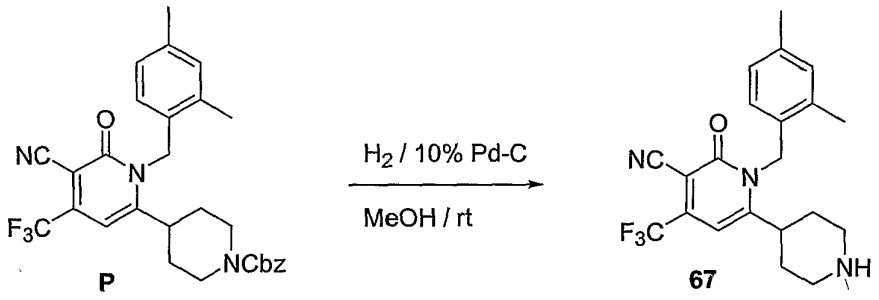
**Example 67**

This example illustrates the preparation of compound **67**.




A solution of amide **N** (81 mg, 0.4 mmol), diketone **O** (150 mg, 0.4 mmol), and DBU (30.4 mg, 0.2 mmol) in 2.0 mL benzene was heated to reflux for 12 hours. The solution was cooled to room temperature and concentrated under reduced pressure. The product **P** (118 mg, 58%) was isolated as a pale yellow solid from the residue by column chromatography on silica (10-50% EtOAc / hexanes). $^1$H NMR ($CDCl_3$) δ: 7.34 (m, 5H), 7.10 (d, J = 8.1 Hz, 1H), 7.01 (t, J = 13.4 Hz), 6.93 (d, J = 8.0 Hz), 6.35 (s, 1H), 5.35 (s, 2H), 5.10

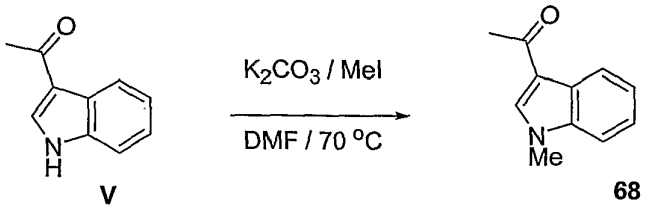
(s, 2H), 4.27 (bm, 2H), 2.68 (m, 1H), 2.60 (bm, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 1.63 (m, 2H), 1.57 (m, 2H).




To a solution of pyridone **P** (50 mg, 0.1 mmol) in 0.5 mL MeOH was added 10% Pd-C (5 mg, 10 wt%). The mixture was then stirred under $H_2$ (1 atm) at room temperature for 30 minutes. The flask was purged with $N_2$ and the mixture filtered through a pad of Celite using an EtOAc wash. The filtrate was concentrated under reduced pressure and the product **67** (20 mg, 51%) was isolated from the residual oil by column chromatography on silica (5-20% MeOH / $CH_2Cl_2$). $^1$H NMR ($CDCl_3$) δ: 7.10 (d, J = 7.6 Hz, 1H), 7.01 (t, J = 14.6 Hz, 1H), 6.93 (d, J = 7.3 Hz, 1H), 6.35 (s, 1H), 5.34 (m, 2H), 4.26 (bm, 2H), 2.65 (m, 1H), 2.51 (m, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 1.66 (m, 2H).

**Example 68**

This example illustrates the preparation of compound **68**.

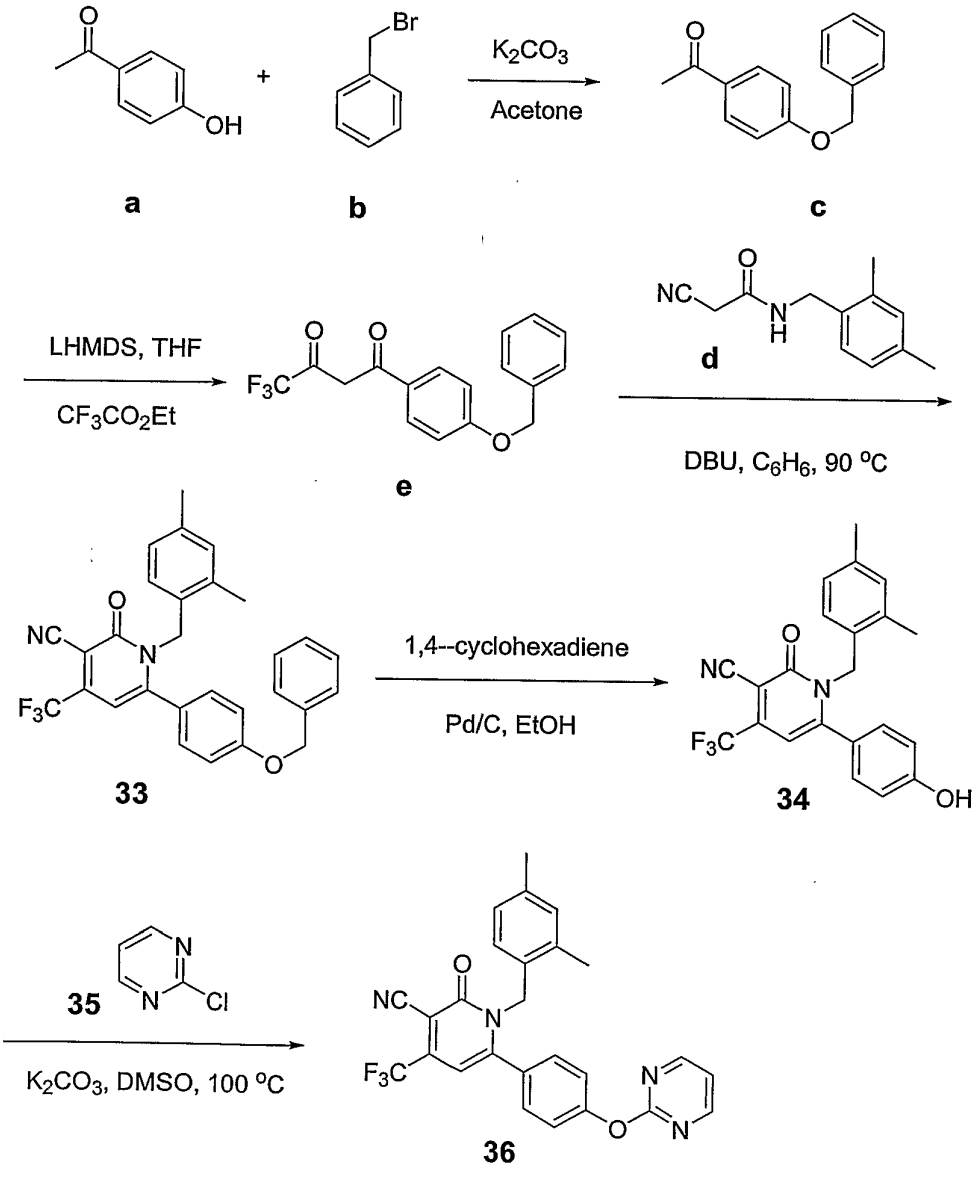



To a solution of indole **V** (0.5 g, 3.1 mmols) in 10 mL DMF was added MeI (483 mg, 3.4 mmols) and $K_2CO_3$ (1.3 g, 9.3 mmols). The resulting

mixture was heated to 70 °C for 15 hours, cooled to room temperature, and concentrated under reduced pressure. The product **68** (569 mg, 99%) was isolated as an off-white solid from the residual oil by column chromatography on silica (5-10% MeOH / $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$) □: 8.12 (m, 1H), 7.27 (s, 1H), 7.05-6.92 (m, 3H), 3.38 (s, 3H), 2.16 (s, 3H).

**Example 69**

This example illustrates the preparation of compound **69**.



To a solution of 4-hydroxyacetophenone **30** (6.81 g, 50 mmol) and benzyl bromide **23** (5.95 mL, 50 mmol) in acetone (100 mL) was added potassium carbonate (7.6 g, 55 mmol). The reaction mixture was stirred at ambient temperature under nitrogen atmosphere for overnight. The white solid was filtered off and the solvent was concentrated *in vacuo* to yield product **31** (11.8 g, 98% yield). The product was used for the next reaction without further purification.

The aryl benzyl ether **31**(11.14 g, 49.2 mmol) was dissolved in anhydrous THF (70 mL) and cooled to –78 °C under nitrogen atmosphere. A solution of lithium bis(trimethylsilyl)amide (49.2 mL, 1.0 M) in THF was added slowly. The reaction mixture was stirred at –20 °C under nitrogen atmosphere for 2 h. The reaction mixture was then cooled to –78 °C, and to it was added ethyl trifluoroacetate (8.78 mL, 73.8 mmol). The vigorously stirred solution was allowed to warm to ambient temperature overnight. The reaction mixture was poured into a mixture of 10% aq HCl and ice and extracted with chloroform three times. The chloroform extract was washed with water. The organic layer was separated and dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give crude product **32** (15.5 g, 98% yield). The product was used for the next reaction without purification.

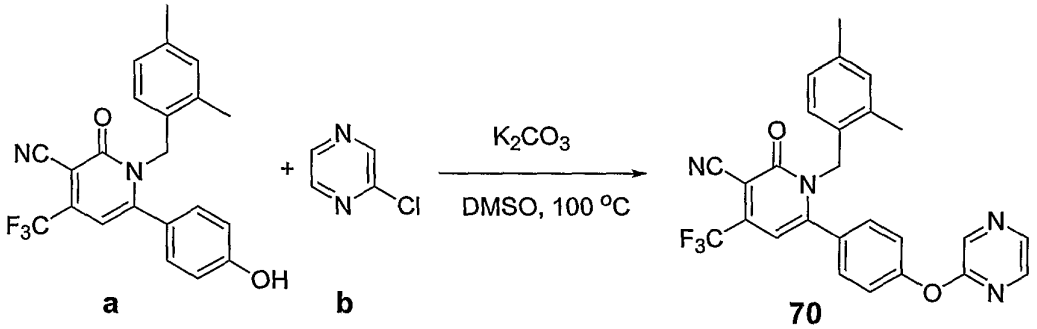
2,4-dimethylbenzyl cyanoacetamide **13** (2.02 g, 10 mmol) and diketone **32** (3.22 g, 10 mmol) were suspended in 25 mL of benzene. To the above reaction mixture was added DBU (0.75 mL, 5.0 mmol). The mixture was heated to reflux under nitrogen atmosphere for overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by column chromatography (20% ethyl acetate in hexane) to yield product **33** (3.2 g, 66% yield).

To a solution of **33** (2.84 g, 5.81 mmol) in anhydrous ethanol (90 mL) was added 2.85 g of 10% Pd/C and 1,4-cyclohexadiene (5.5 mL, 58.1 mmol). The mixture was stirred under nitrogen atmosphere for overnight. The solution was filtered through a pad of celite and the solvent was concentrated in vacuo to yield product **34** (2.20 g, 95%).

To a solution of **34** (100 mg, 0.25 mmol) and 2-chloropyrimidine **35** (29 mg, 0.25 mmol) in DMSO (2 mL) was added potassium carbonate (52 mg, 0.38 mmol). The reaction mixture in a sealed vial was stirred and heated to 100 °C overnight. After cooling off, the mixture was poured into water and extracted with chloroform. The chloroform extract was dried with anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (30 –60% EtOAc in hexane) to yield the product **36** (65 mg, 55% yield). $^1$H-NMR ($CDCl_3$): δ8.58 (d, J = 4.8 Hz, 2H), 7.21 (m, 3 H), 7.12 (m, 1 H), 6.95 (m, 1 H), 6.91 (s, 1 H), 6.63 (m, 1 H), 6.50 (s, 1 H), 5.15 (s, 2 H), 2.27 (s, 3 H), 1.97 (s, 3 H). MS (ES+): 477.1 (M+H).

Example 70

This example illustrates the preparation of compound **70**.




To a solution of **a** (71 mg, 0.18 mmol) and 2-chloropyrazine **b** (20 mg, 0.18 mmol) in DMSO (2 mL) was added potassium carbonate (37 mg, 0.27 mmol). The reaction mixture in a sealed vial was stirred and heated to 100 °C overnight. After cooling off, the mixture was poured into water and extracted with chloroform. The chloroform extract was dried with anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (25 –50% EtOAc in hexane) to yield the product **70** (48 mg, 57% yield). $^1$H-NMR ($CDCl_3$): δ8.49 (m, 1 H), 8.34 (m, 1 H), 8.11(m, 1 H), 7.19 (m, 4 H), 6.95 (m, 1 H), 6.92 (m, 1 H), 6.63 (m, 1 H), 6.49 (s, 1 H), 5.15 (s, 2 H), 2.28 (s, 3 H), 1.98 (s, 3 H). MS (ES+): 477.2 (M+H).

**Example 71**

FRET Coactivator assay

The FRET coactivator assay measures the ability of LXR ligands to promote protein-protein interactions between the ligand binding domain (LBD) of LXR and transcriptional coactivator proteins. The assay involves the use a recombinant Glutathione-S-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide sequence derived from the receptor interacting domain of a co-activator peptide such as the steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

In the presence of an agonist for the nuclear receptor, the peptide is recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the allophycocyanin. Upon excitation of the complex with light at 340 nm excitation energy absorbed by the europium chelate is transmitted to the allophycocyanin moiety resulting in emission at 665 nm. If the europium chelate is not brought in to close proximity to the allophycocyanin moiety there is little or no energy transfer and excitation of the europium chelate results in emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an indication of the strength of the protein-protein interaction.

**A. Required Materials:**

1. Partially purified recombinant protein comprising glutathione-S-transferase fused in frame to the LXR-ligand binding domain (comprising amino acids 188-447 of human LXR $\alpha$, or amino acids 198-461 of human LXR $\beta$).

2. Biotinylated peptide containing a SRC-1 LXXLL receptor interaction motif (B-SRC-1)

3. Anti-GST antibody conjugated to an Europium chelate (αGST-K) (From Wallac/PE Life Sciences Cat# AD0064)

4. Streptavidin linked allophycocyanin (SA-APC) (From Wallac/PE Life Sciences CAT# AD0059A)

5. 1x FRET Buffer: (20mM $KH_2PO_4/K_2HPO_4$ pH 7.3, 150mM NaCl, 2.5mM CHAPS, 2mM EDTA, 1mM DTT (add fresh))

6. 96 well or 384 well black multiwell plates (from LJL)

Stock Solutions:

0.5M $KH_2PO_4/K_2HPO_4$: pH 7.3

5M NaCl

80mM (5%) CHAPS

0.5M EDTA pH 8.0

1M DTT (keep at –20°C)

**B. Preparation of Screening Reagents:**

Prepare reaction mixture for the appropriate number of wells by combining the following reagents 5nM / well GST-hLXRαLBD, 5nM / well GST-hLXR βLBD, 5nM / well Anti-GST antibody (Eu), 12nM / well biotin-SRC-1 peptide, 12nM / well APC-SA adjust the volume to 10μL/well with 1x-FRET buffer.

**C. Procedure:**

Add 0.5μl of a 1mM stock compound (for approx. 10μM final concentration) or solvent to each well in a 96 well or 384 well black plate (LJL).

1. Add 10μl reaction mixture (prepared above) to each well of the multiwell plate.

2. Incubate covered or in the dark (the APC is light sensitive) at room temperature for 1-4hr. After this time if reactions are not read they can be stored at 4 degrees for several more hours without too much loss of signal.

3. Read the plate using an LJL Analyst, or similar instrument, using the following conditions:

Channel 1: Excitation is 330nm and emission is 615. This is for Eu chelate

Channel 2: Excitation is 330nm and emission is 665. This is for APC

For channel 1: Flashes per well = 100; Integration time = 1000μs; interval between flashes = 1x10ms; Delay after flash = 200μs

For channel 2: Flashes per well = 100; Integration time = 100μs; interval between flashes = 1x10ms; Delay after flashes = 65μs

**Example 72**

Scintillation proximity assay (SPA):

The SPA assay measures the radioactive signal generated by the binding of $^{3}$H-24, 25-epoxycholesterol to LXRα or LXRβ. The basis of the assay is the use of SPA beads containing a scintillant, such that when binding to the receptor brings the labeled ligand into proximity with the bead, the energy from the label stimulates the scintillant to emit light. The light is measured using a standard microplate scintillation reader. The ability of a ligand to bind to a receptor can be measured by assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor.

**A. Required Materials:**

1. Label: $^{3}$H-24, 25-epoxy-cholesterol (Amersham)

2. LXRα lysate: Baculovirus expressed LXRα/RXR heterodimer with RXR having a 6-HIS tag produced as a crude lysate

3. LXRβ lysate: Baculovirus expressed LXRβ/RXR heterodimer with RXR having a 6-HIS tag produced as a crude lysate

4. SPA beads: Ysi copper His-tag SPA beads (Amersham)

5. Plates: Non-binding surface 96-well plate (Corning)

6. Protein lysate dilution buffer: (20mM Tris-HCl pH 7.9, 500mM NaCl, 5mM Imidazole).

7. 2x SPA Buffer: (40mM $K_2HPO_4/KH_2PO_4$ pH7.3, 100mM NaCl, 0.05% Tween 20, 20% Glycerol, 4mM EDTA)

8. 2x SPA Buffer w/o EDTA: (40mM $K_2HPO_4/KH_2PO_4$ pH7.3, 100mM NaCl, 0.05% Tween 20, 20% Glycerol)

**A. Stock Solutions**

0.5M $K_2HPO_4/KH_2PO_4$ pH 7.3
0.5M EDTA pH 8.0
5M NaCl
10% Tween-20
Glycerol

**B. Preparation of Screening Reagents:**

1. [$^3$H] 24,25 Epoxycholesterol (EC) solution. For a single 384-well plate (or 400 wells), add 21μl [$^3$H] EC (specific activity 76.5Ci/mmol, concentration 3.2mCi/ml) in 4.4ml of 2x SPA buffer to a final concentration of 200nM. For each additional 384-well plate, add 19.1μl additional [$^3$H] EC and 4.0ml additional 2x SPA buffer. The final concentration of [$^3$H] EC in the well will be 50nM.
2. Dilute LXRα lysate with protein lysate dilution buffer. Make 1400μl of diluted LXRα lysate for a 384-well plate, (or 200 wells) and 1120μl of diluted LXRα lysate for each additional 384-well plate.

3. Diluted LXRβ lysate with protein lysate dilution buffer. Make 1400μl of diluted LXRβ lysate for 1 a 384-well plate, (or 200 wells) and 1120μl of diluted LXRβ lysate for each additional 384-well plate.
4. SPA bead solution. For 1 a 384-well plate (or 400 wells), mix 3.75ml of 2x SPA buffer w/o EDTA, 2.25ml of $H_2O$, and 1.5ml of Ysi His-tag SPA beads (Vortex well before taking). For each addition 384-well plate, mix additional 3.5ml of 2x SPA buffer w/o EDTA, 2.1ml of $H_2O$, and 1.4ml of Ysi His-tag SPA beads to the SPA bead solution.

**C. Procedure:**

1. Prepare appropriate dilutions of each compound and pipette into the appropriate wells of a multiwell plate.
2. Add 9.1μl of [3H] EC to each well of column 2-23 of the multiwell plate.
3. Add 5μl of diluted LXRα lysate to each well of column 2-23 on odd rows of the multiwell plate.
   Add 5ul of diluted LXRβ lysate to each well of column 2-23 on even rows of the multiwell plate.
4. Add 17.5μl of SPA bead solution to each well of column 2-23 of the multiwell plate.
5. Cover the plates with clear sealer. Place the plates in the MicroBeta. Incubate at room temperature for 1hr.
6. Count using program n ABASE 3H_384DPM. The setting for n ABASE 3H_384DPM is:
   Counting Mode: DPM
   Sample Type: SPA
   ParaLux Mode: low background
   Count time: 30sec.

Assays for LXRα and LXRβ were performed in the identical manner. The determined Ki represents the average of at least two independent dose response experiments. The binding affinity for each compound may be determined by non-linear regression analysis using the one site competition formula to determine the IC50 where:

$$Y=Bottom+\frac{(Top-Bottom)}{1+10^{X-LogIC50}}$$

The Ki is than calculated using the Cheng and Prusoff equation where:

$$Ki=\frac{IC50}{1+[Ligand]/Kd}$$

Ligand = 50nM EC and Kd = 200nM as determined by saturation binding

**Example 73**

Co-Transfection Assay

To measure the ability of compounds to activate or inhibit the transcriptional activity of LXR, in a cell based assay, the cotransfection assay may be used. It has been shown that LXR functions as a heterodimer with RXR. For the co-transfection assay, expression plasmids for LXR and RXR are introduced via transient transfection into mammalian cells along with a luciferase reporter plasmid that contains one copy of a DNA sequence that is bound by LXR-RXR heterodimers (LXRE; Willy, P. et al. 1995). Treatment of transfected cells with an LXR agonist increases the transcriptional activity of LXR, which is measured by an increase in luciferase activity. Similarly, LXR antagonist activity can be measured by determining the ability of a compound to competitively inhibit the activity of a LXR agonist.

**A. Required Materials**

1. CV-1 African Green Monkey Kidney Cells

2. Co-transfection Expression plasmids, CMX-hLXR, or CMX-hLXR , CMX-RXR, reporter (LXREx1-Tk-Luciferase), and control (CMX--Galactosidase expression vector).

3. Transfection reagent such as FuGENE6 (Roche).

4. 1x Cell lysis buffer (1 % Triton X 100 (JT Baker X200-07), 10% Glycerol (JT Baker M778-07), 5mM Ditriotreitol (Quantum Bioprobe DTT03; add fresh before lysing), 1mM EGTA (Ethylene Glycol-bis (B-Amino ethyl ether)-N,N,N',N'-Tetracetic Acid) (Sigma E-4378), 25mM Tricine (ICN 807420) pH 7.8

5. 1x Luciferase assay buffer (pH at 7.8) (0.73mM ATP , 22.3mM Tricine, 0.11mM EDTA 33.3mM DTT)

6. 1x Luciferrin/CoA (11 mM Luciferin, 3.05mM Coenzyme A, 10 mM HEPES

**B. Preparation of Screening Reagents**

1. CV-1 cells are prepared 24 hours prior to the experiment by plating them into T-175 flasks or 500cm$^2$ dishes in order to achieve 70-80% confluency on the day of the transfection. The number of cells to be transfected is determined by the number of plates to be screened. Each 384 well plate requires 1.92x10$^6$ cells or 5000 cells per well.
2. DNA Transfection Reagent is prepared by mixing the required plasmid DNAs with a cationic lipid transfection reagent such as DOTAP or FuGENE6 by following the instructions provided with the reagents. Optimal DNA amounts need to be determined empirically per cell line and size of vessel to be transfected.
3. Add 10-12mls media to the DNA Transfection Reagent and add this mixture to the cells after aspirating media from a T175 cm$^2$ flask.
4. Incubate at least 5 hours at 37 degrees to prepare screening cells.
5. Luciferase assay reagent is prepared by combining before use (per 10 ml):

10 ml 1x Luciferase assay buffer
0.54 mls of 1x Luciferrin/CoA
0.54 mls of 0.2 M Magnesium sulfate

1. C. Procedure

1. Prepare assay plates by dispensing 0.5μl of 1mM compound per well of a 384 well plate to achieve final compound concentration of 10μM and 1% DMSO.
2. Remove media from the screening cells, trypsinize, harvest cells by centrifugation, count the cells, and plate at 5000 cells per well in the 384 well assay plate prepared above in a volume of about 45μl.
3. Incubate assay plates containing both compounds and screening cells for 20 hours at 37 C degrees.
4. Carefully aspirate media from cells and ensure that cells are not lifted off.
5. Add lysis buffer (30μl/well) and incubate at least 30 minutes room temp.
6. Add luciferase assay buffer (30μl/well) and read assay plates on luminometer (PE Biosystems Northstar reader with on-board injectors, or equivalent).
7. Read plates immediately after addition of luciferase assay reagent.

The LXR/LXRE co-transfection assay can be used to establish the $EC_{50}/IC_{50}$ values for potency and percent activity or inhibition for efficacy. Efficacy defines the activity of a compound relative to a high control ((N-(3-((4-fluorophenyl)-(naphthalene-2-sulfonyl)-amino)propyl)-2,2-dimethylpropionamide)) or a low control (DMSO/vehicle). The dose response curves are generated from an 8 point curve with concentrations differing by ½ LOG units. Each point represents the average of 4 wells of data from a 384 well plate. The curve for the data is generated by using the equation:

Y = Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))

The $EC_{50}/IC_{50}$ is therefore defined as the concentration at which an agonist or antagonist elicits a response that is half way between the Top (maximum) and Bottom (baseline) values. The $EC_{50}/IC_{50}$ values represented are the averages of at least 3 independent experiments. The determination of the relative efficacy or %control for an agonist is by comparison to the

maximum response achieved by ((N-(3-((4-fluoro-phen-yl)-(naphthalene-2-sulfonyl)-amino)propyl)-2,2-dimethylpropionamide) that is measured individually in each dose response experiment.

For the antagonist assay, a LXR agonist can be added to each well of a 384 well plate to elicit a response. The %inhibition for each antagonist is therefore a measurement of the inhibition of the activity of the agonist. In this example 100% inhibition would indicate that the activity of a specific concentration of LXR agonist has been reduced to baseline levels, defined as the activity of the assay in the presence of DMSO only.

**Example 74**

In Vivo studies:

In order to evaluate direct regulation of key target genes by the compounds of the invention, animals are administered a single oral dose of the test compound and tissues collected at six or fifteen hours after dose. Male C57BL/6 mice (n=8) are dosed by oral gavage with vehicle or compound. At six and fifteen hours after the dose, animals are bled via the retro orbital sinus for plasma collection. Animals are then euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total cholesterol, HDL cholesterol and triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by LXR subtypes, LXR deficient mice ($LXR\alpha^{-/-}$ or $LXR\beta^{-/-}$) and C57BL/6 wild-type controls are used in this same protocol.

Plasma Lipid Evaluation:

To compare the effects of compounds on plasma cholesterol and triglycerides, animals are dosed with compound for one week and plasma lipid levels are monitored throughout the study. Male C57BL/6 mice (n=8) are dosed daily by oral gavage with vehicle or compound. Plasma samples are taken on day –1 (in order to group animals), day 1, 3, and 7. Samples are

collected three hours after the daily dose. On day 7 of the study, following plasma collection, animals are euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total cholesterol, HDL cholesterol and triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by LXR subtypes, LXR deficient mice (LXR$\alpha^{-/-}$ or LXR$\beta^{-/-}$) and C57BL/6 wild-type controls are used in this same protocol.

Cholesterol Absorption:

Evaluation of compounds to inhibit cholesterol absorption is done via measurement of labeled cholesterol in feces. Male A129 mice (n=7) are dosed daily by oral gavage with vehicle or compound for 7 days. On day 7 of the study, animals are administered [$^{14}$C]-cholesterol and [$^{3}$H]-sitostanol by oral gavage. Animals are individually housed on wire racks for the next 24 hours in order to collect feces. Feces are then dried and ground to a fine powder. Labeled cholesterol and sitostanol are extracted from the feces and ratios of the two are counted on a liquid scintillation counter in order to evaluate the amount of cholesterol absorbed by the individual animal.

**Results of Examples 71, 72 and 73**

Most of the compounds disclosed herein and tested exhibited activity in at least one of the above assays ($EC_{50}$ or $IC_{50}$ less than 10 $\mu$m). Most showed activity at below 1 $\mu$M. Some showed activity below 100 nM. Representative data is shown in the Tables below. Ki's are determined in a scintillation proximity binding assay (Example 70). $EC_{50}$ and % efficacy are determined in a co-transfection assay (Example 71).

| Compound | Ki($\alpha$) $\mu$M | Ki($\beta$) $\mu$M | LXR$\alpha$/LXRE $EC_{50}$ ($\mu$M) |
|---|---|---|---|
| 1-Cyclohexylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile | 0.69 | 0.45 | 3.4 |
| 1-benzyl-3-cyano-6-(3-methoxyphenyl)-4-trifluoromethyl-1*H*-pyridin-2-one | 0.51 | 0.12 | 1.2 |
| 1-Benzyl-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile | 1.4 | 0.58 | 1.6 |
| 1-(5-Methyl-furan-2-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile | 0.36 | 0.23 | 0.58 |

| Compound | LXR$\alpha$/LXRE Eff (%) | LXR$\beta$/LXRE $EC_{50}$ ($\mu$M) | LXR$\beta$/LXRE Eff (%) |
|---|---|---|---|
| 1-Cyclohexylideneamino-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile | 90 | 4.3 | 72 |
| 1-benzyl-3-cyano-6-(3-methoxyphenyl)-4-trifluoromethyl-1*H*-pyridin-2-one | 78 | 0.84 | 79 |

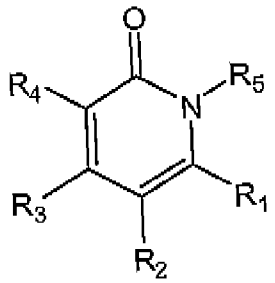
| Compound | LXR$\alpha$/LXRE Eff (%) | LXR$\beta$/LXRE $EC_{50}$ ($\mu$M) | LXR$\beta$/LXRE Eff (%) |
|---|---|---|---|
| 1-Benzyl-2-oxo-6-thiophen-2-yl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile | 56 | 1.8 | 82 |
| 1-(5-Methyl-furan-2-ylmethyl)-2-oxo-6-phenyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile | 91 | 0.81 | 93 |

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

2002351412 28 Apr 2010

**The claims defining the invention are as follows:**

1. A compound having formula I:



or a pharmaceutically acceptable derivative thereof, wherein

$R^1$ is selected from substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl and substituted or unsubstituted heterocyclylalkyl;

$R^2$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl;

$R^3$ and $R^4$ are selected from (i) or (ii) as follows:

(i) $R^3$ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkylaminocarbonyl or $C(J)OR^{30}$; and $R^4$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, halide, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, azide, $C(J)R^{30}$, $C(J)NR^{31}R^{32}$, $CH_2NR^{31}R^{32}$, $CH_2OR^{31}$, $CR^{30}=CR^{31}R^{32}$, $NO_2$, $NR^{31}R^{32}$;

(ii) $R^3$ and $R^4$, together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring, with the proviso that the heterocyclic ring has one oxo substituent;

$R^5$ is substituted or unsubstituted aralkyl or substituted or unsubstituted heteroaralkyl,- wherein $R^5$ is optionally substituted with one or more groups selected from alkyl, haloalkyl, halohydroxyalkyl, alkoxy, alkoxyalkoxyalkyl, alkoxyalkyl, aryl, halo, alkoxycarbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy,

hydroxyalkyl, heterocyclyl, heterocyclylalkyl, alkylcarbonyl, arylcarbonyl, alkylalkelenedioxy and dialkylalkelenedioxy;

$R^{30}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl;

$R^{31}$ and $R^{32}$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, or $C(J)R^{35}$; or $R^{31}$ and $R^{32}$ together with the atoms to which they are attached, form substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

J is O, S or $NR^{40}$;

$R^{35}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted arylalkylamino, or substituted or unsubstituted diarylamino;

$R^{40}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, alkylene, alkenylene, alkynylene, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl, and heteroaralkynyl moieties of $R^1$, $R^2$, and $R^3$, are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from $Q^1$, where $Q^1$ is halo, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, azide, hydroxy, oxo, thia, nitrile, nitro formyl, mercapto, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl,

diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, diaryl, hydroxyaryl, alkylaryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkylaralkyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylaryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, haloalkoxy, alkoxyaryloxy, alkylaryloxy, diaryloxy, alkylaryloxyalkyl, alkyldiaryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, heterocyclyloxy, alkoxyalkyl, alkoxyalkoxyalkyl, alkylheteroaryloxy, alkylcycloalkoxy, cycloalkyloxy, heterocyclyloxy, aralkoxy, haloaryloxy, heteroaryloxy, alkylheteroaryloxy, alkoxycarbonylheterocyclyloxy, alkylcarbonylaryloxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, alkoxyaryloxy, aralkoxycarbonyloxy, ureido, alkylureido, arylureido, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, haloalkylarylamino, arylamino, diarylamino, alkylarylamino, aralkylamino, alkylcarbonylamino, aralkylcarbonylamino, haloalkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylenedioxyalkyl, dialkylalkylenedioxyalkyl, alkylsulfonylamino, arylsulfonylamino, azido, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two $Q^1$ groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (i.e., $-O-(CH_2)_z-O-$), thioalkylenoxy (i.e., $-S-(CH_2)_z-O-$) or alkylenedithioxy(i.e., $-S-(CH_2)_z-S-$) where z is 1 or 2; and

each $Q^1$ is independently unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from $Q^2$, where $Q^2$ is halo, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, azide, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, amino,

hydroxyalkyl, hydroxyaryl, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, arylcarbonylalkyl,a minocarbonyl, alkoxy, aryloxy, aralkoxy, alkylenedioxy, amino, aminoalkyl, dialkylamino, arylamino, diarylamino, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, aralkylamino, alkoxycarbonylamino, arylcarbonylamino, alkylthio or arylthio.

2. The compound of claim 1, wherein $R^1$ is substituted or unsubstituted aryl.

3. The compound of claim 1, wherein $R^1$ is substituted or unsubstituted heteroaryl.

4. The compound of claim 1, wherein $R^1$ is substituted or unsubstituted heterocyclyl.

5. The compound of claim 1, wherein $R^1$ is substituted or unsubstituted cyclohexyl, substituted or unsubstituted cyclopentenyl, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted naphthyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted indanyl, substituted or unsubstituted benzofuryl, substituted or unsubstituted benzothiophenyl or substituted or unsubstituted indolyl, where the substituents are each independently selected from one or more $Q^1$.

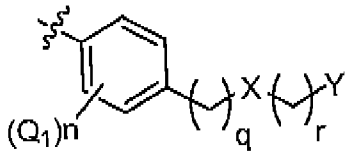
6. The compound of any one of claims 1-5, wherein $R^1$ is substituted or unsubstituted furyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted benzofuryl, substituted or unsubstituted benzothiophenyl or substituted or unsubstituted indolyl, where the substituents are each independently selected from one or more $Q^1$.

7. The compound of any one of claims 1-6, wherein $R^1$ is substituted with, in one embodiment one to five, in another embodiment one to three, in another embodiment one or two $Q^1$, where $Q^1$ is halo, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, azide, nitro, hydroxy, amino, hydroxyalkyl, hydroxyalkylaryloxy, hydroxyaryl, hydroxyalkylaryl, hydroxycarbonyl, haloalkyl, alkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkylaralkyl, alkylarylcarbonyl, heterocyclylcarbonyl, alkoxycarbonyl, alkoxycarbonylaryloxy, aryloxycarbonyl, heterocyclylcarbonylalkylaryl, aralkoxycarbonyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, alkylaryloxy, alkylaryloxyalkyl, alkyldiaryloxy, aryloxyalkoxy, aralkoxyaryloxy, alkylarylcycloalkyloxy, alkylheteroaryloxy, cycloalkyloxy, heterocyclyloxy, haloaryloxy, alkylcarbonylaryloxy, arylamino, alkylarylamino, aralkylamino, alkylcarbonylamino, alkylaminocarbonyl, haloalkylcarbonylamino, or arylthio; and each $Q^1$ is unsubstituted or further substituted with $Q^2$, which is hydrogen, alkyl, aryl, alkoxy, hydroxycarbonyl, alkoxycarbonyl, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, azide, halo, aryloxy, aralkoxy, haloalkyl, alkylthio, alkylamino, dialkylamino or hydroxy.

8. The compound any one of claims 1-7, wherein $R^1$ is substituted with one or more $Q^1$, which are independently selected from methyl, ethyl, trifluoromethyl, nitro, hydroxy, n-butyloxy, 3-(2-piperidinyl)ethoxy, methylcarbonylamino, ethylaminocarbonylamino, chloro, bromo, benzylamino, methylphenoxymethyl, trifluoromethylcarbonylamino, methoxycarbonyl, phenoxy, cyano, n-butoxy, benzoxy, 1-piperidinyl, methoxy, hydroxycarbonyl, tert-butoxycarbonylpiperazinylcarbonyl, hydroxymethyl, 1-piperidinylcarbonyl, phenyl, methylphenyl, dimethylamino, methylcarbonylamino, methoxyphenoxy, methylphenoxy, piperidinylmethyl, biphenoxy, benzoxycarbonyl, piperazinylcarbonyl, benzyl, phenylthio, chlorophenoxy, methylbenzyl, hydroxymethylphenoxy, ethoxycarbonylphenoxy, tertbutylmethylphenoxy, tertbutylbiphenoxy, ethylphenoxy, isopropylphenoxy, tertbutylphenoxy, -N,N-phenylmethylamino, 3-methylphenyl-1-amino, trifluoromethylphenoxy, ethylphenoxy, methylcarbonylphenoxy, tetrahydropyranyloxy, tetrahydronaphthoxy, hydroxycarbonylphenoxy, benzoxyphenoxy, cyclohexyloxy, indanyloxy, methoxycarbonylphenoxy, isopropylphenoxy, tert-butylphenoxy, N,N-dimethylaminophenoxy, methoxyphenoxy, cyanophenoxy, fluorophenoxy, benzoxyphenoxy, trifluoromethylphenoxy, bromophenoxy, 3,5-ditrifluoromethylphenoxy,

methylthiophenoxy, indolyl, tert-butoxycarbonyl-piperidinyloxy, hydroxyphenoxy, pyrimidinoxy and pyrazinoxy.

9. The compound of claim 1, wherein $R^1$ has formula II:




where, q and r are each independently an integer from 0 to 5, or from 0 to 3, or 0 or 1; n is an integer from 0 to 4, in one embodiment 0 to 2, in another embodiment 0 or 1; X is O, S or NR', where R' is alkyl, aryl or hydrogen; Y is alkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl.

10. The compound of claim 9, wherein X is O.

11. The compound of claim 1, wherein $R^1$ is cyclohexyl, 1-cyclopentenyl, indanyl, phenyl, 1-naphthyl, 2-naphthyl, 3-methylphenyl, 2-chlorophenyl, 4-chlorophenyl, 3-ethylphenyl, 3-trifluoromethylphenyl, 3-nitrophenyl, 3-hydroxyphenyl, 3-n-butoxyphenyl, 3-benzyloxyphenyl, 3-(2-piperidinyl)ethoxyphenyl, 3-methylcarbonyl-amino-phenyl, 3-ethylaminocarbonylaminophenyl, 2-methylphenyl, 2-methoxyphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 3-benzylaminophenyl, 3-(3-methyl)phenoxymethylphenyl, benzyl, 3-trifluoromethylcarbonylaminophenyl, 3,5-dimethylphenyl, 2-chloro-3-methylphenyl, phenylethyl, 4-butoxyphenyl, 4-methoxycarbonylphenyl, 4-phenoxyphenyl, 4-cyanophenyl, 4-benzoxyphenyl, 4-(1-piperidinyl)phenyl, 4-hydroxycarbonylphenyl, 4-(4-tert-butoxycarbonylpiperazin-1-ylcarbonyl)phenyl, 4-hydroxymethylphenyl, 4-(1-piperidinylcarbonyl)phenyl, 4-dimethylaminophenyl, 4-methylcarbonylaminophenyl, 4-nitrophenyl, 6-(1,2,3,4-tetrahydro)naphthyl, 4-(4-methoxyphenoxy)phenyl, 4-(2-methylphenoxy)phenyl, 4-(3-methylphenoxy)phenyl, 4-(4-methylphenoxy)phenyl, 4-(3-methoxyphenoxy)phenyl, 4-(1-piperidinylmethyl)phenyl, 4-(4-biphenoxy)phenyl, 3-(1-benzoxycarbonyl)-piperidinyl, 4-(1-piperazinylcarbonyl)phenyl, 5-(2-methyl-2,3-dihydro)benzofuryl, 4-benzylphenyl, 4-phenylthiophenyl, 4-(4-chlorophenoxy)-2-chlorophenyl, 4-(3-biphenoxy)phenyl, 4-(1-benzoxycarbonyl)-piperidinyl, 4-piperidinyl, 4-(1-(3-methylbenzyl))-piperidinyl, 4-(3-methyl-4-hydroxyphen-1-oxy)phenyl, 4-(2-methyl-4-hydroxyphenoxy)phenyl, 4-(4-ethoxycarbonylphenoxy)phenyl, 4-(2-methyl-4-

tertbutylphenoxy)phenyl, 4-(2-phenyl-4-tertbutylphenoxy)phenyl, 4-(3-ethylphenoxy)phenyl, 4-(3-isopropylphenoxy)phenyl, 4-(3-tertbutylphenoxy)phenyl, 4-(3,5-dimethylphenoxy)phenyl, 4-phenoxy-2-methylphenyl, 4-(2-methylphenoxy)-2-methylphenyl, 4-(2-methylphenoxy)-3-methylphenyl, 4-N-methyl-N-phenylaminophenyl, 4-(3-trifluoromethylphenoxy)phenyl, 4-(4-ethylphenoxy)phenyl, 4-(4-isopropylphenoxy)phenyl, 4-(4-tertbutylphenoxy)phenyl, 4-(3-methylcarbonylphenoxy)phenyl, 4-(3,4-dimethylphenoxy)phenyl, 4-(2-tetrahydropyranyloxy)phenyl, 4-(2-tetrahydropyranyloxy)-3-methylphenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 4-(4-methylphenoxy)-3-methylphenyl, 4-(2-ethylphenoxy)phenyl, 4-(2-isopropylphenoxy)phenyl, 4-(5,6,7,8-tetrahydronaphthyloxy)phenyl, 4-(3-hydroxycarbonylphenoxy)phenyl, 2-methyl-4-hydroxyphenyl, 4-phenoxy-2-hydroxyphenyl, 3-phenoxyphenyl, 4-(2,3,4-trimethylphenoxy)phenyl, 4-(4-benzyloxyphenoxy)phenyl, 4-(3-(methyl-3-indanyloxy)phenyl, 4-(2-methyl-5-benzothiazoloxy)phenyl, 4-cyclohexyloxyphenyl, 4-(3-methoxycarbonylphenoxy)phenyl, 4-(3-isopropylphenoxy)-3-methylphenyl, 4-tert-butyl-phenoxy-3-methylphenyl, 4-N,N-dimethylaminophenoxy-3-methylphenyl, 4-methoxy-phenoxy-3-methylphenyl, 3-methoxy-phenoxy-3-methylphenyl, 4-(3-methoxycarbonyl-phenoxy)-3-methylphenyl, 4-(3-cyanophenoxy)-3-methylphenyl, 4-(4-fluorophenoxy)-3-methylphenyl, 4-(4-benzoxy-phenoxy)-3-methylphenyl, 4-(3-benzoxy-phenoxy)-3-methylphenyl, 4-(2,5-dimethylphenoxy)-3-methylphenyl, 4-(2-chlorophenoxy)-3-methylphenyl, 4-(3-chlorophenoxy)-3-methylphenyl, 4-(2-trifluoromethylphenoxy)-3-methylphenyl, 4-(3-trifluoromethylphenoxy)-2-methylphenyl, 4-(3-bromophenoxy)-phenyl, 4-(4-bromophenoxy)-phenyl, 4-(3-benzyloxy-phenoxy)-phenyl, 4-(3-cyanophenoxy)-phenyl, 4-(4-cyanophenoxy)phenyl, 4-(2,4-dimethylphenoxy)-phenyl, 4-(3,5-trifluoromethylphenoxy)phenyl, 4-(4-methylthio-phenoxy)-phenyl, 4-(4-N,N-dimethylamino-phenoxy)-phenyl, 5-indolyloxyphenyl, 4-(1-tert-butoxycarbonyl-piperidin-4-oxy)-phenyl, 4-(4-hydroxyphenoxy)-phenyl, 4-(2-pyrimidinoxy)-phenyl, 4-(2-pyrazinoxy)-phenyl, 2-thienyl, 2-(5-chloro)thienyl, 2-(5-bromo)thienyl, 2-(5-phenyl)thienyl, 3-benzothiophenyl, 3-methyl-2-benzothiophenyl, 2-(5-(3-methylphenyl))-thienyl, 3-pyridinyl, 2-pyrazinyl, 4-(1-phenyl-5-methyl)pyrazolyl, 2-(1-methyl)pyrrolyl, 3-(1-methyl)indolyl, 3-(1-benzyloxycarbonyl)-piperidinyl, 4-(1-benzyloxycarbonyl)-piperidinyl, 4-piperidinyl, 4-(1-(3-methylbenzyl)-piperidinyl, 2-furyl, 2-(5-methyl)-furyl, 3-(2,5-dimethyl)-furyl, benzofuryl, 3-(2,4-dimethyl)-furyl, 2-(1,3-thiazolyl) or 5-(2,4-dimethyl)-1,3-thiazolyl.

12. The compound of any one of claims 1-11, wherein $R^2$ is alkyl or hydrogen.

13. The compound of any one of claims 1-12, wherein $R^3$ is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkoxycarbonyl or substituted or unsubstituted alkylaminocarbonyl, where the substituents are each independently selected from one or more $Q^1$.

14. The compound of any one of claims 1-13, wherein $R^3$ is substituted with one or more $Q^1$, which are independently selected from halo, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, azide, alkyl, alkoxy, alkoxycarbonyl and aryloxycarbonyl.

15. The compound of any one of claims 1-13, wherein $R^3$ is methyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, chlorodifluoromethyl, 1-(1-methoxy-1-fluoro)ethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethoxymethyl, methoxycarbonylmethyl or phenyl.

16. The compound of any one of claims 1-15, wherein $R^4$ is substituted or unsubstituted methyl, substituted or unsubstituted acetyl or cyano, where the substituents are each independently selected from one or more $Q^1$.

17. The compound of any one of claims 1-15, wherein $R^4$ is hydrogen, cyano, nitro, hydroxycarbonyl, trimethylsilylacetyl, acetyl, methylcarbonylaminomethyl, ethylcarbonylaminomethyl, n-propylcarbonylaminomethyl, isopropylcarbonylaminomethyl, n-octylcarbonylaminomethyl, phenylcarbonylaminomethyl, benzylcarbonylaminomethyl, phenylethylcarbonylaminomethyl, ethoxycabonylaminomethyl dimethylaminomethyl or aminomethyl.

18. The compound of any one of claims 1-15, wherein $R^3$ and $R^4$, together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclic ring, with the proviso that the heterocyclic ring has one oxo substituent.

19. The compound of any one of claims 1-18, wherein $R^5$ is substituted or unsubstituted aralkyl, where the substituents are each independently selected from one or more groups selected from alkyl, haloalkyl, halohydroxyalkyl, alkoxy, alkoxyalkoxyalkyl, alkoxyalkyl, aryl, halo, alkoxycarbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, alkylcarbonyl, arylcarbonyl, alkylalkelenedioxy, and dialkylalkelenedioxy.

20. The compound of any one of claims 1-18, wherein $R^5$ is substituted or unsubstituted heteroaralkyl, where the substituents are each independently selected from one or more groups selected from alkyl, haloalkyl, halohydroxyalkyl, alkoxy, alkoxyalkoxyalkyl, alkoxyalkyl, aryl, halo, alkoxycarbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, alkylcarbonyl, arylcarbonyl, alkylalkelenedioxy, and dialkylalkelenedioxy.

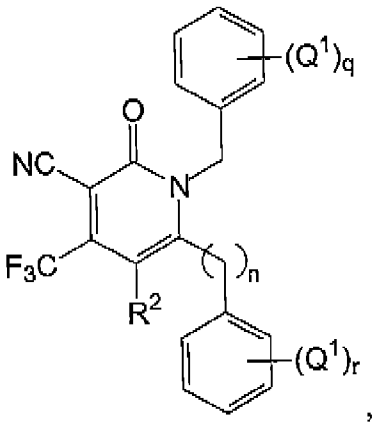
21. The compound of any one of claims 1-18, wherein $R^5$ is substituted or unsubstituted benzyl, substituted or unsubstituted 2-phenethyl, substituted or unsubstituted 1-phenethyl, substituted or unsubstituted 3-phenylpropyl, substituted or unsubstituted 3-pyridylmethyl, substituted or unsubstituted 4-pyridylmethyl, -substituted or unsubstituted thiazolylmethyl, substituted or unsubstituted oxazolylmethyl, where the substituents are each independently selected from one or more groups selected from alkyl, haloalkyl, halohydroxyalkyl, alkoxy, alkoxyalkoxyalkyl, alkoxyalkyl, aryl, halo, alkoxycarbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, alkylcarbonyl, arylcarbonyl, alkylalkelenedioxy, and dialkylalkelenedioxy.

22. The compound of any one of claims 1-18, wherein $R^5$ is substituted with one or more groups independently selected from alkyl, haloalkyl, halohydroxyalkyl, alkoxy, alkoxyalkoxyalkyl, alkoxyalkyl, aryl, halo, alkoxycarbonyl, alkylthio, aryloxy, haloalkoxy, aralkyl, heteroaryl, hydroxy, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, alkylcarbonyl, and arylcarbonyl.

23. The compound of any one of claims 1-18, wherein $R^5$ is 2,4-dimethylbenzyl, 4-isopropylbenzyl, 4-tert-butylbenzyl, 2,4,5-trifluorobenzyl, 1-naphthylmethyl, 4-methylbenzyl, 4-ethylbenzyl, -4-methylcarbonylbenzyl, benzyl, 4-(2-methyl)-thiazolylmethyl, 4-(2-phenyl)thiazolylmethyl, 3-methoxymethoxymethylbenzyl, 3-hydroxymethylbenzyl, 4-hydroxymethylbenzyl, 4-hydroxyethylbenzyl, 4-methoxymethylbenzyl, 4-(1-piperidinylmethyl)benzyl, 4-(2-ethyl)thiazolylmethyl, 4-(2-isopropyl)thiazolylmethyl, 4-(2-propyl)thiazolylmethyl, 4-(2-benzyl)thiazolylmethyl, 4-(2-methyl)oxazolylmethyl, 4-(2-ethyl)oxazolylmethyl, 4-(2-propyl)oxazolylmethyl, 4-(2-phenyl)oxazolylmethyl, 4-(2-benzyl)oxazolylmethyl, 4-n-propyloxymethylbenzyl, 2-(5-methyl)pyrazinylmethyl, 4-n-pentyloxymethylbenzyl, 4-n-octyloxymethylbenzyl, 3-ethoxymethylbenzyl, 3-n-butoxymethylbenzyl, 3-n-hexyloxymethylbenzyl, 3-n-octyloxymethylbenzyl, 2-methylbenzyl, 4-methylbenzyl, 3-methylbenzyl, phenylethyl, 4-(2,5-dimethyl)thiazolylmethyl, 4-(2-isopropyl-5-methyl)thiazolylmethyl, 4-(2-ethyl-5-methyl)thiazolylmethyl, 4-(2-methyl-5-ethyl)thiazolylmethyl, 4-(2,5-diethyl)thiazolylmethyl, 2-phenylethyl, 3-phenylpropyl, benzyl, 3-methylbenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-phenylbenzyl, 1-phenylethyl, 2-fluorobenzyl, 4-fluorobenzyl, 2,4-difluorobenzyl, 4-bromobenzyl, 4-methoxycarbonylbenzyl, 2-chlorobenzyl, 4-chlorobenzyl, 4-methylthiobenzyl, 4-phenoxybenzyl, 4-trifluoromethoxybenzyl, 3-pyridylmethyl or 4-pyridylmethyl.

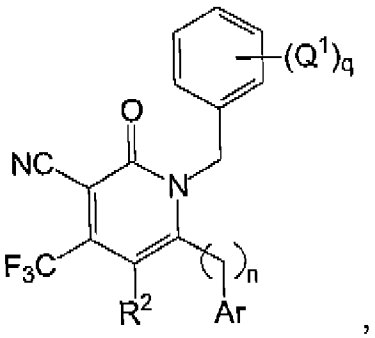
24. The compound of any one of claims 1-18, wherein $R^5$ is 4-(2-methyl)-thiazolylmethyl, 4-(2-phenyl)thiazolylmethyl, 4-(1-piperidinylmethyl)benzyl, 4-(2-ethyl)thiazolylmethyl, 4-(2-isopropyl)thiazolylmethyl, 4-(2-propyl)thiazolylmethyl, 4-(2-benzyl)thiazolylmethyl, 4-(2-methyl)oxazolylmethyl, 4-(2-ethyl)oxazolylmethyl, 4-(2-propyl)oxazolylmethyl, 4-(2-phenyl)oxazolylmethyl, 4-(2-benzyl)oxazolylmethyl, 4-(2-cyclohexyl)oxazolylmethyl, 2-(5-methyl)pyrazinylmethyl, 4-(2,5-dimethyl)thiazolylmethyl, 4-(2-isopropyl-5-methyl)thiazolylmethyl, 4-(2-ethyl-5-methyl)thiazolylmethyl, 4-(2-methyl-5-ethyl)thiazolylmethyl, 4-(2,5-diethyl)thiazolylmethyl, 3-pyridylmethyl or 4-pyridylmethyl.

25. The compound of claim 1 that has formula V:



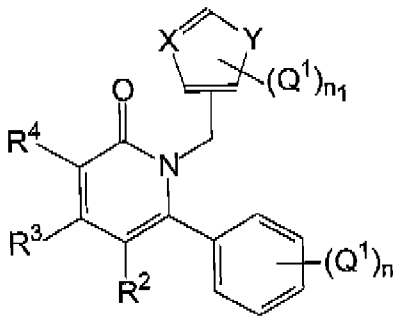
wherein n is an integer from 0 to 6 and q is an integer from 0 to 5.

26. The compound of claim 1 that has formula VII:



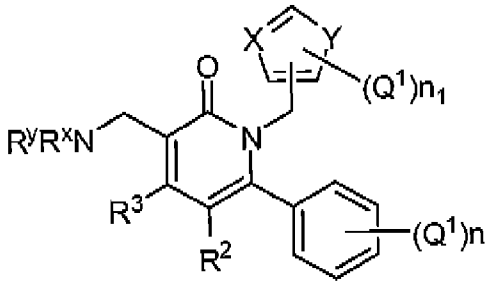
wherein n is an integer from 0 to 6 and q is an integer from 0 to 5.

27. The compound of claim 1 that has formula XI:



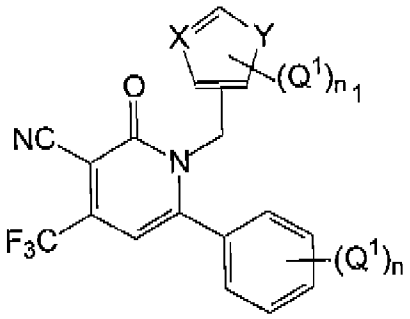
wherein n is an integer from 0 to 5; $n_1$ is an integer from 0 to 2; Y is selected from -CH=CH-, -C($Q^1$)=CH-, -C($Q^1$)=C($Q^1$)-, -CH=N-, -C($Q^1$)=N-, O, S and NR', where R' is hydrogen, alkyl or aryl and X is N or CH.

28. The compound of claim 1 that has formula XII:



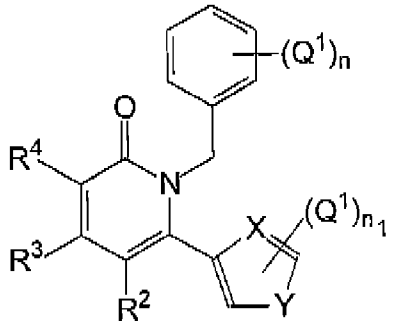
wherein n is an integer from 0 to 5; $n_1$ is an integer from 0 to 2; Y is selected from -CH=CH-, -C($Q^1$)=CH-, -C($Q^1$)=C($Q^1$)-, -CH=N-, -C($Q^1$)=N-, O, S and NR', where R' is hydrogen, alkyl or aryl and X is N or CH; $R^x$ and $R^y$ are each independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylcarbonyl, alkoxycarbonyl, and aralkoxycarbonyl.

29. The compound of claim 1 that has formula XIII:



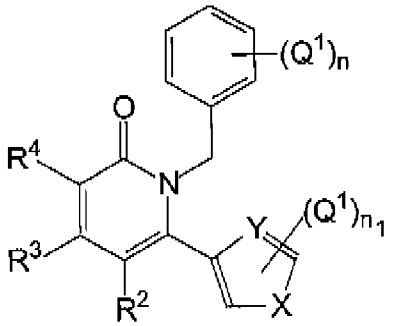
wherein n is an integer from 0 to 5; $n_1$ is an integer from 0 to 2; Y is selected from -CH=CH-, -C($Q^1$)=CH-, -C($Q^1$)=C($Q^1$)-, -CH=N-, -C($Q^1$)=N-, O, S and NR', where R' is hydrogen, alkyl or aryl and X is N or CH.

30. The compound of claim 1 that has formula XIV:



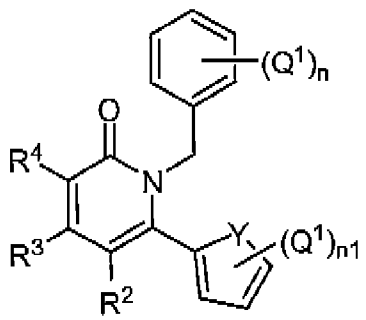
wherein n is an integer from 0 to 5; $n_1$ is an integer from 0 to 2; Y is selected from -CH=CH-, -C($Q^1$)=CH-, -C($Q^1$)=C($Q^1$)-, -CH=N-, -C($Q^1$)=N-, O, S and NR', where R' is hydrogen, alkyl or aryl and X is N.

31. The compound of claim 1 that has formula XVI:



wherein n is an integer from 0 to 5; $n_1$ is an integer from 0 to 2; Y is selected from -CH=CH-, -C($Q^1$)=CH-, -C($Q^1$)=C($Q^1$)-, -CH=N-, -C($Q^1$)=N-, O, S and NR', where R' is hydrogen, alkyl or aryl and X is N.

32. The compound of claim 1 that has formula XVII:



wherein n is an integer from 0 to 5; $n_1$ is an integer from 0 to 2; Y is selected from O, S and NR', where R' is hydrogen, alkyl or aryl.

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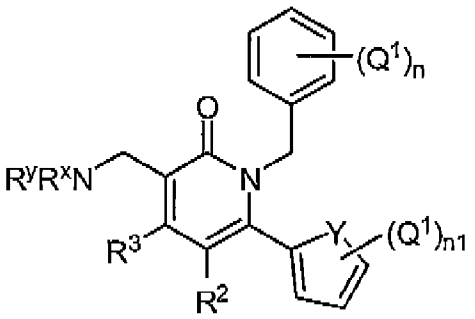
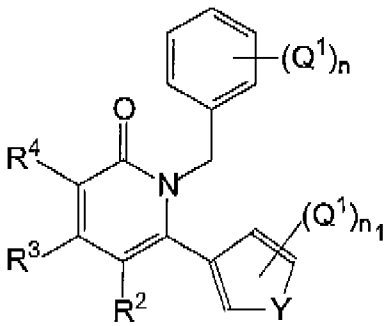
33. The compound of claim 1 that has formula XVIII:



wherein n is an integer from 0 to 5; $n_1$ is an integer from 0 to 2; Y is selected from O, S and NR', where R' is hydrogen, alkyl or aryl; and $R^x$ and $R^y$ are each independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylcarbonyl, alkoxycarbonyl, and aralkoxycarbonyl.

34. The compound of claim 1 that has formula XIX:



wherein n is an integer from 0 to 5; $n_1$ is an integer from 0 to 2; Y is selected from O, S and NR', where R' is hydrogen, alkyl or aryl.

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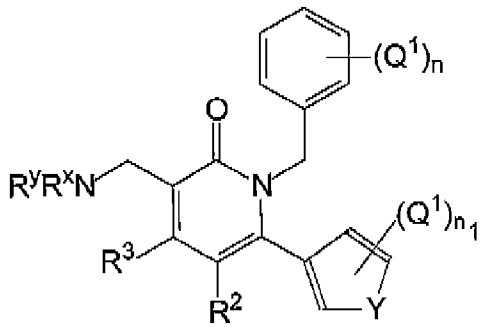
35. The compound of claim 1 that has formula XX:




wherein n is an integer from 0 to 5; $n_1$ is an integer from 0 to 2; Y is selected from O, S and NR', where R' is hydrogen, alkyl or aryl and $R^x$ and $R^y$ are each independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylcarbonyl, alkoxycarbonyl, and aralkoxycarbonyl.

36. A compound of claim 1 selected from Figure 1.

37. A pharmaceutical composition, comprising the compound of any one of claims 1-36, or a pharmaceutically acceptable derivative thereof, in a pharmaceutically acceptable carrier.

38. Use of a compound of any one of claims 1-36, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for treatment of a disease or disorder selected from hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

39. Use of a compound of any one of claims 1-36 or a pharmaceutically acceptable derivative thereof for reducing cholesterol levels in a subject in need thereof.

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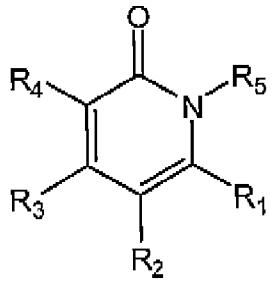
40. A method of treating a disease or disorder selected from hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1 to 36 or a pharmaceutically acceptable derivative thereof, or a composition according to claim 37.

41. A compound having formula I




or a pharmaceutically acceptable derivative thereof as defined in claim 1 and substantially as hereinbefore described with reference to any one of Examples 1 to 70.

**Dated 28 April, 2010**
**X-Ceptor Therapeutics, Inc.**

**Patent Attorneys for the Applicant/Nominated Person**
**SPRUSON & FERGUSON**

(2671877_1):KZA

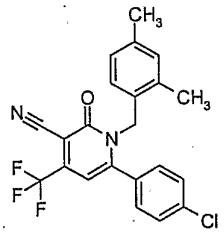
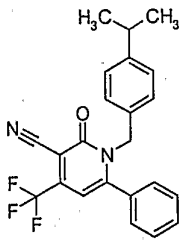
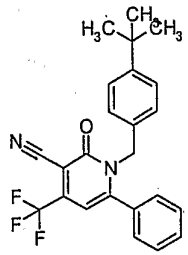
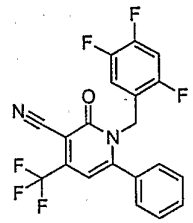
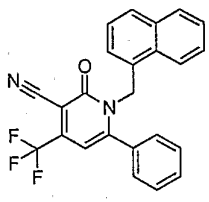
| Serial No. | Structure | Ki(a) | Ki(b) | EC50(a) | %Eff(a) | EC50(b) | %Eff(b) |
|---|---|---|---|---|---|---|---|
| 1 |  | B1 | B1 | III | B | III | B |
| 2 |  | D1 | D1 | IV | A | IV | B |
| 3 |  | NC | NC | NC | A | NC | A |
| 4 |  | A1 | A1 | III | B | III | B |
| 5 |  | B1 | B1 | IV | A | IV | B |

FIG. 1A

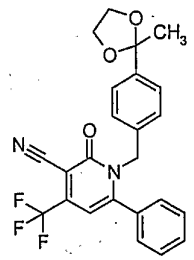
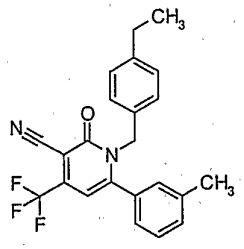
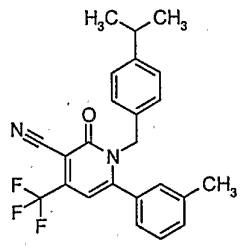
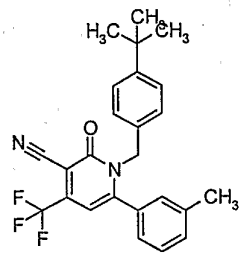
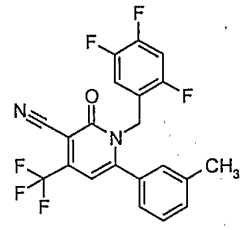
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 6 |  | NC | NC | NC | NC | NC | NC |
| 7 |  | B1 | B1 | III | B | III | B |
| 8 |  | D1 | D1 | III | A | IV | A |
| 9 |  | NC | NC | NC | NC | NC | NC |
| 10 |  | A1 | A1 | III | B | III | B |

FIG. 1B

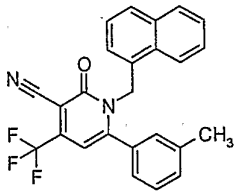
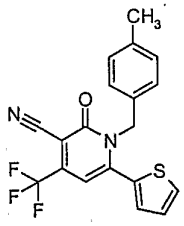
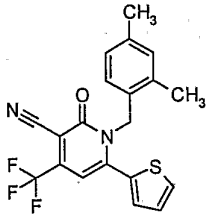
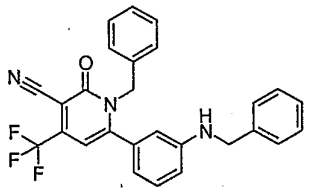
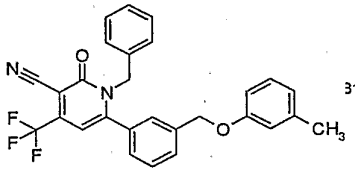
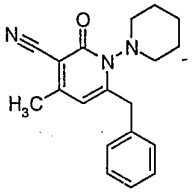
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 11 |  | B1 | B1 | III | B | IV | B |
| 12 |  | B1 | A1 | III | B | III | B |
| 13-1 |  | A1 | A1 | III | B | III | B |
| 13-2 | | A1 | A1 | III | B | III | C |
| 14 |  | C1 | B1 | III | B | III | B |
| 15 |  | 31 | B1 | IV | B | IV | B |
| 16 |  | NC | NC | NC | NC | NC | NC |

FIG. 1C

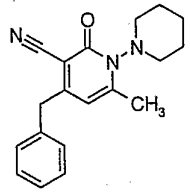
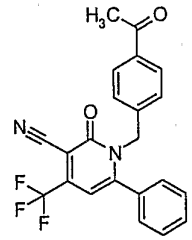
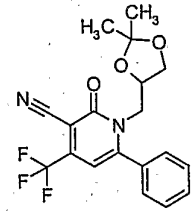
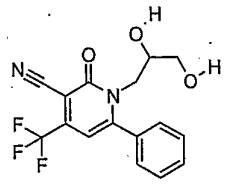
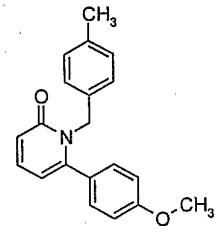
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 17 |  | D1 | NC | NC | NC | NC | NC |
| 18 |  | C1 | B1 | IV | B | IV | B |
| 19 |  | NC | D1 | III | A | NC | B |
| 20 |  | NC | NC | NC | NC | NC | NC |
| 21 |  | NC | NC | NC | NC | NC | NC |

FIG. 1D

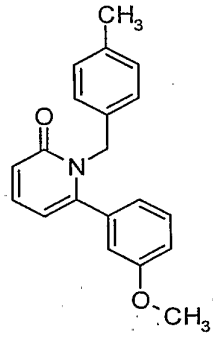
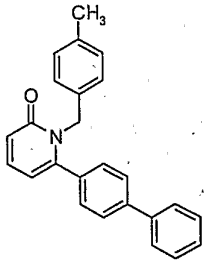
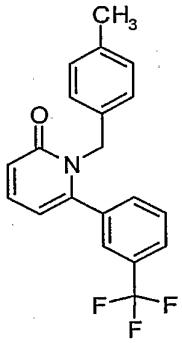
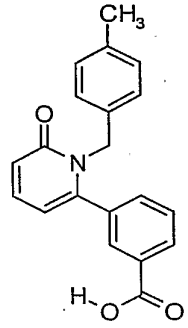
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 22 |  | NC | NC | NC | NC | NC | NC |
| 23 |  | NC | NC | NC | NC | NC | NC |
| 24 |  | NC | NC | NC | NC | NC | NC |
| 25 |  | NC | NC | NC | NC | NC | NC |

FIG. 1E

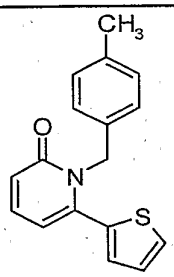
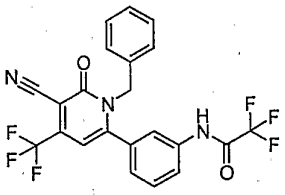
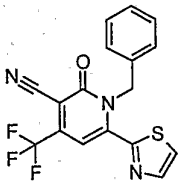
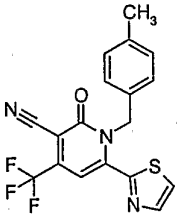
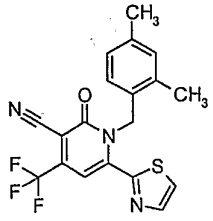
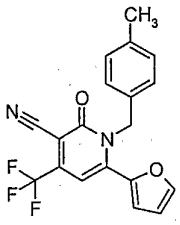
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 26 |  | NC | NC | NC | NC | NC | NC |
| 27 |  | B1 | B1 | IV | B | IV | C |
| 28 |  | C1 | B1 | IV | A | IV | A |
| 29 |  | B1 | A1 | III | B | III | C |
| 30-1 |  | B1 | A1 | III | B | III | D |
| 30-2 | | B1 | A1 | III | B | III | C |
| 31 |  | B1 | B1 | III | B | IV | C |

FIG. 1F

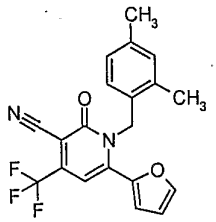
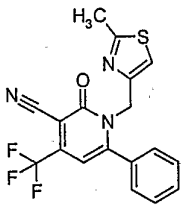
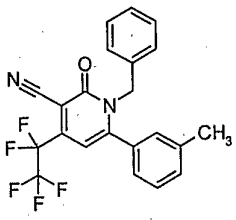
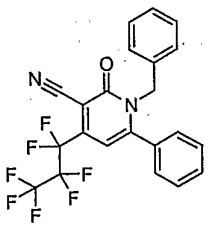
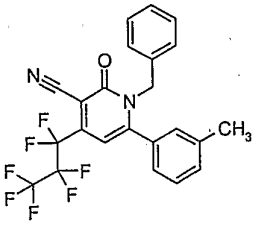
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 32-1 |  | B1 | B1 | III | A | III | B |
| 32-2 | | B1 | A1 | III | B | III | B |
| 33 |  | C1 | B1 | NC | B | IV | C |
| 34 |  | B1 | A1 | III | B | IV | B |
| 35 |  | D1 | B1 | IV | B | IV | B |
| 36 |  | B1 | B1 | IV | B | IV | B |

FIG. 1G

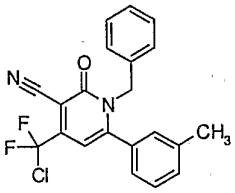
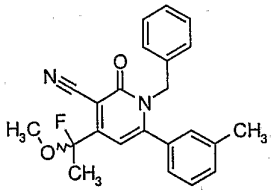
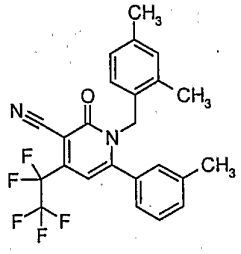
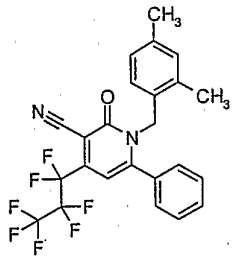
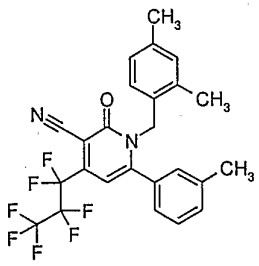
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 37 |  | B1 | A1 | III | B | III | C |
| 38 |  | D1 | C1 | IV | A | NC | B |
| 39 |  | A1 | A1 | III | A | III | B |
| 40 |  | B1 | B1 | III | B | III | B |
| 41 |  | B1 | B1 | III | B | III | B |

FIG. 1H

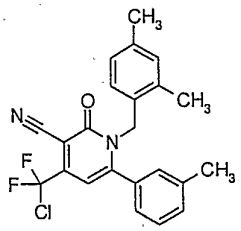
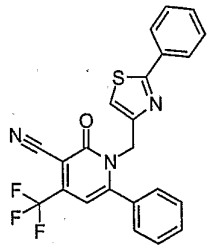
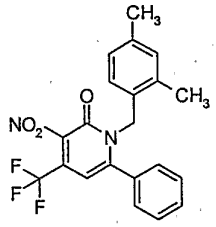
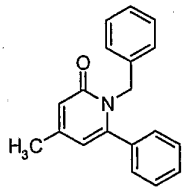
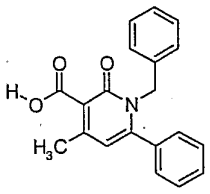
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 42 |  | A1 | A1 | III | B | III | B |
| 43 |  | NC | NC | IV | A | IV | A |
| 44 |  | NC | NC | NC | NC | NC | NC |
| 45 |  | NC | NC | NC | NC | NC | NC |
| 46 |  | NC | NC | NC | NC | NC | NC |

FIG. 1I

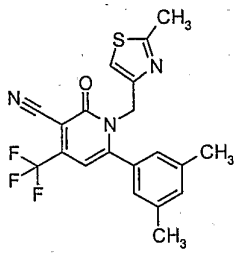
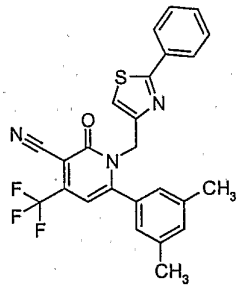
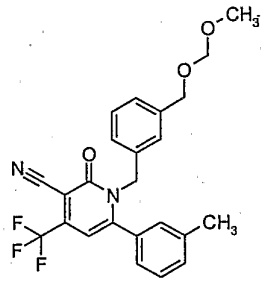
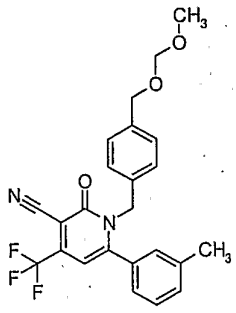
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 47 |  | B1 | B1 | IV | C | IV | C |
| 48 |  | B1 | B1 | IV | A | IV | B |
| 49 |  | NC | NC | NC | NC | NC | NC |
| 50 |  | NC | D1 | NC | NC | IV | A |

FIG. 1J

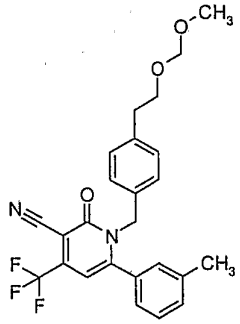
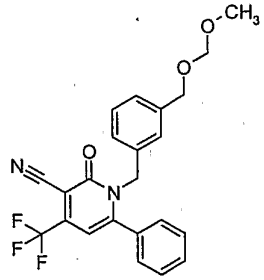
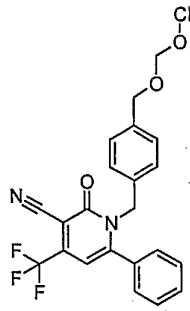
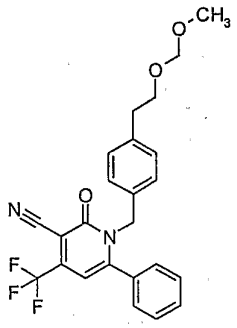
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 51 |  | NC | NC | NC | NC | IV | A |
| 52 |  | NC | NC | NC | NC | NC | NC |
| 53 |  | D1 | D1 | NC | NC | NC | NC |
| 54 |  | NC | NC | NC | NC | NC | NC |

FIG. 1K

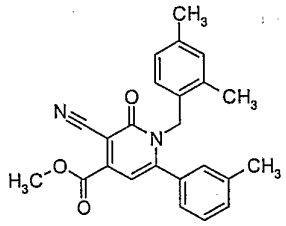
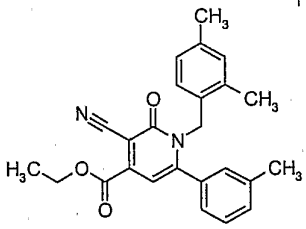
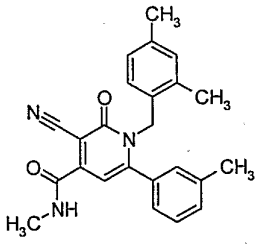
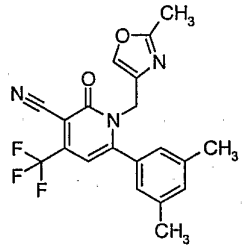
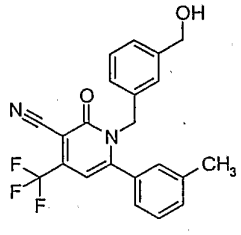
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 55 |  | D1 | D1 | IV | A | IV | A |
| 56 |  | C1 | B1 | NC | A | NC | B |
| 57 |  | D1 | D1 | NC | A | NC | A |
| 58 |  | C1 | B1 | IV | B | IV | B |
| 59 |  | NC | IV | NC | NC | NC | NC |

FIG. 1L

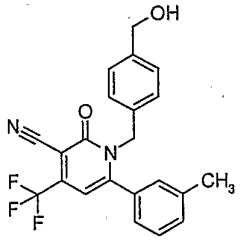
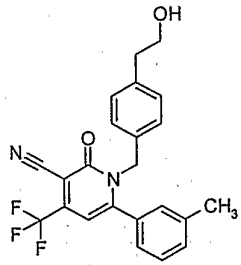
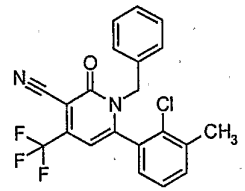
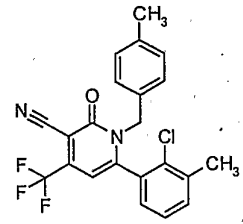
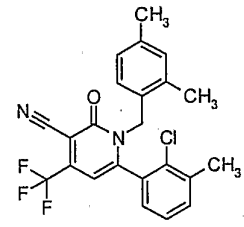
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 60 |  | D1 | D1 | NC | B | IV | B |
| 61 |  | NC | NC | NC | NC | NC | NC |
| 62 |  | B1 | A1 | III | C | III | C |
| 63 |  | A1 | A1 | III | C | III | B |
| 64 |  | B1 | A1 | III | B | III | B |

FIG. 1M

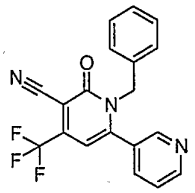
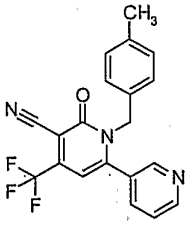
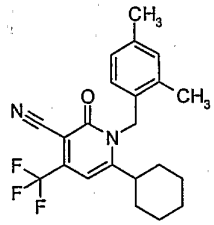
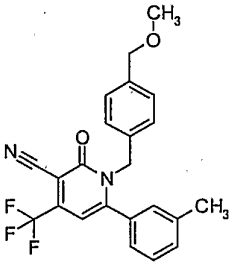
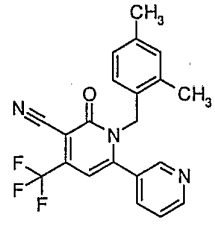
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 65 |  | NC | D1 | IV | A | IV | A |
| 66 |  | D1 | B1 | IV | B | IV | B |
| 67 |  | A1 | A1 | III | B | III | C |
| 68 |  | D1 | B1 | IV | A | IV | B |
| 69 |  | B1 | B1 | IV | B | III | B |

FIG. 1N

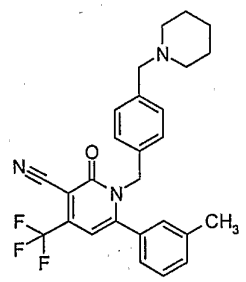
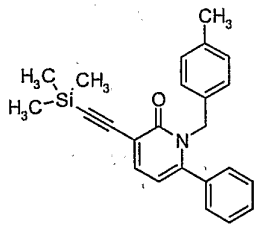
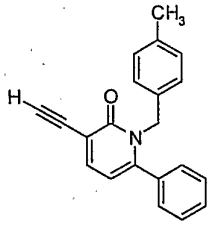
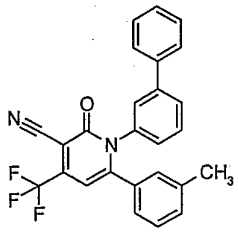
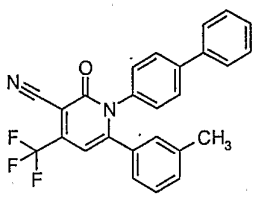
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 70 |  | D1 | D1 | NC | NC | NC | NC |
| 71 |  | NC | NC | NC | NC | NC | NC |
| 72 |  | NC | NC | NC | NC | NC | NC |
| 73 |  | D1 | B1 | IV | A | IV | B |
| 74 |  | D1 | D1 | NC | NC | IV | A |

FIG. 1O

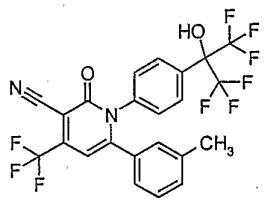
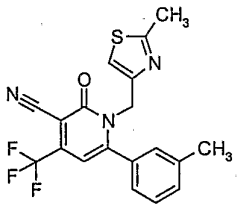
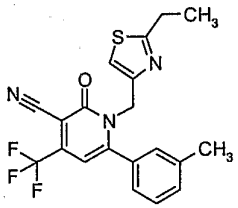
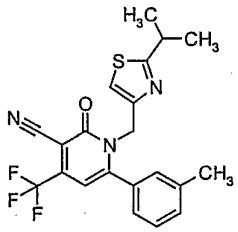
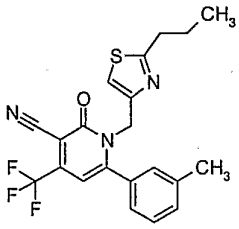
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 75 |  | D1 | D1 | IV | A | IV | B |
| 76 |  | B1 | B1 | IV | C | IV | C |
| 77 |  | B1 | A1 | III | C | IV | C |
| 78 |  | B1 | B1 | IV | B | IV | B |
| 79 |  | D1 | B1 | IV | B | IV | B |

FIG. 1P

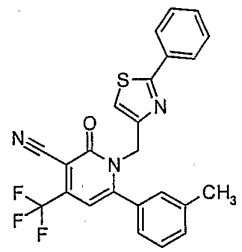
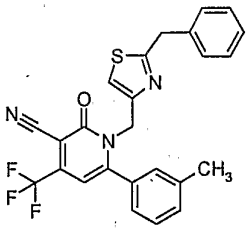
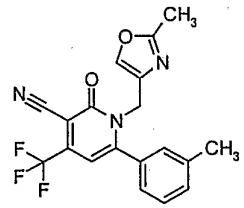
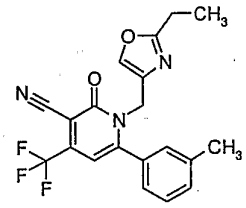
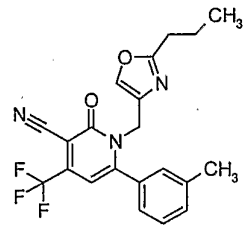
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 80 |  | NC | D1 | IV | A | IV | A |
| 81 |  | NC | NC | NC | NC | IV | A |
| 82 |  | C1 | B1 | IV | B | IV | B |
| 83 |  | B1 | B1 | IV | B | IV | B |
| 84 |  | D1 | C1 | IV | B | NC | B |

FIG. 1Q

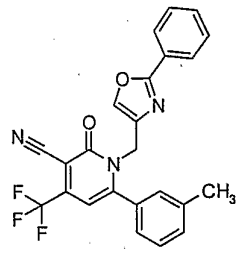
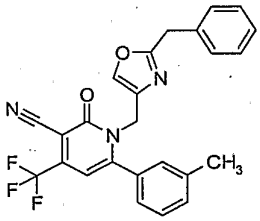
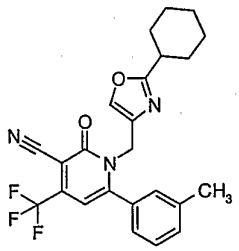
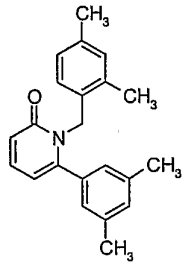
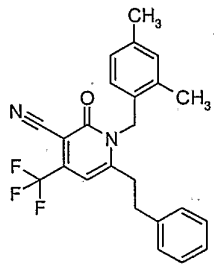
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 85 |  | NC | D1 | IV | A | IV | A |
| 86 |  | NC | D1 | NC | NC | NC | NC |
| 87 |  | NC | NC | NC | NC | NC | A |
| 88 |  | NC | NC | NC | NC | NC | NC |
| 89 |  | C1 | B1 | IV | A | IV | B |

FIG. 1R

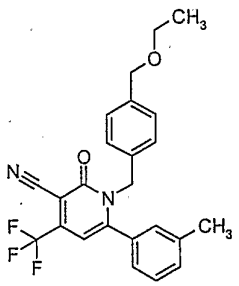
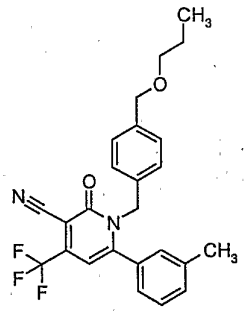
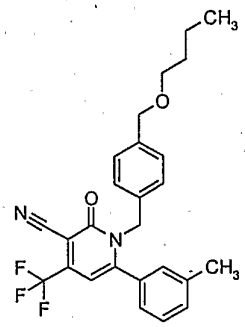
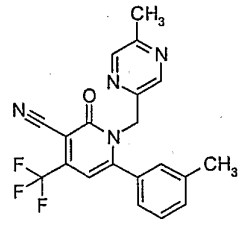
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 90 |  | NC | D1 | IV | A | IV | B |
| 91 |  | D1 | D1 | NC | NC | IV | A |
| 92 |  | D1 | D1 | IV | A | III | A |
| 93 |  | B1 | B1 | IV | C | IV | C |

FIG. 1S

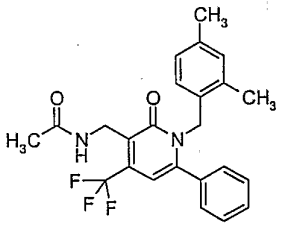
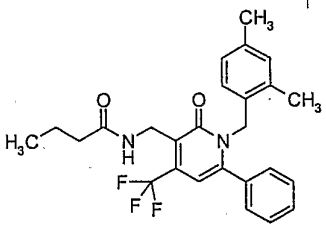
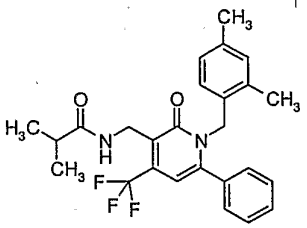
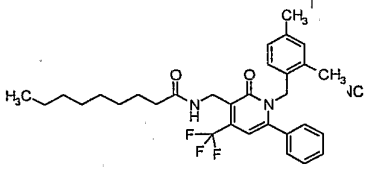
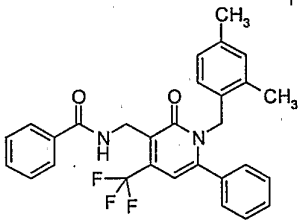
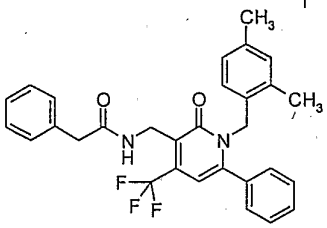
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 94 |  | D1 | C1 | IV | A | IV | B |
| 95 |  | D1 | D1 | NC | NC | NC | NC |
| 96 |  | D1 | D1 | NC | NC | NC | NC |
| 97 |  | D1 | D1 | NC | NC | NC | NC |
| 98 |  | D1 | D1 | IV | A | IV | B |
| 99 |  | D1 | D1 | NC | NC | NC | NC |

**FIG. 1T**

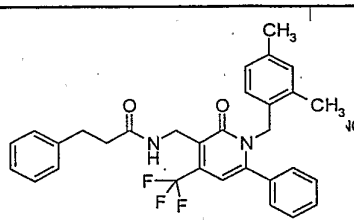
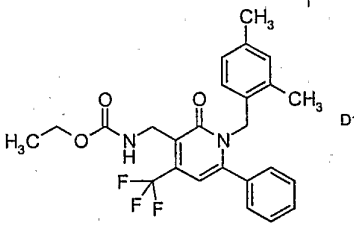
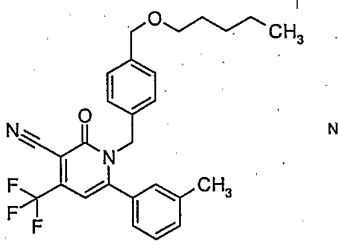
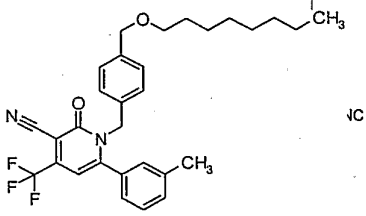
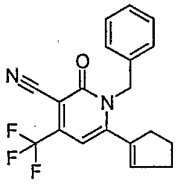
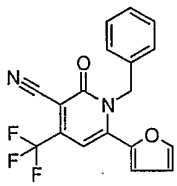
| | | | | | | |
|---|---|---|---|---|---|---|
| 100 |  | NC | NC | NC | NC | NC |
| 101 |  | D1 | B1 | IV | A | IV | B |
| 102 |  | NC | NC | NC | NC | NC | NC |
| 103 |  | NC | D1 | NC | NC | NC | NC |
| 104 |  | D1 | C1 | IV | A | IV | B |
| 105 |  | D1 | C1 | IV | A | IV | B |

FIG. 1U

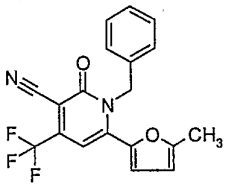
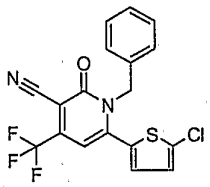
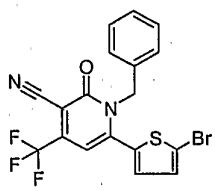
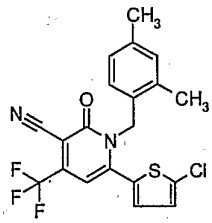
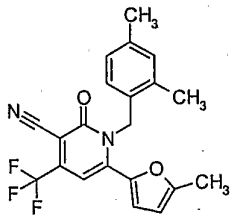
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 106 |  | D1 | B1 | IV | B | IV | C |
| 107 |  | D1 | D1 | IV | B | IV | B |
| 108 |  | D1 | D1 | NC | B | NC | B |
| 109-1 |  | B1 | B1 | III | B | III | C |
| 109-2 | | C1 | B1 | III | B | III | B |
| 110-1 |  | B1 | B1 | III | B | III | C |
| 110-2 | | B1 | A1 | III | B | III | C |

**FIG. 1V**

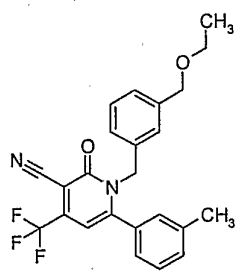
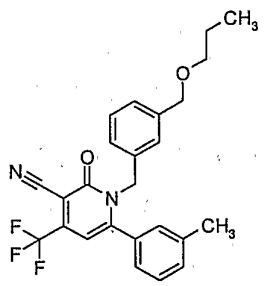
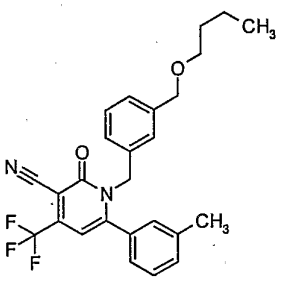
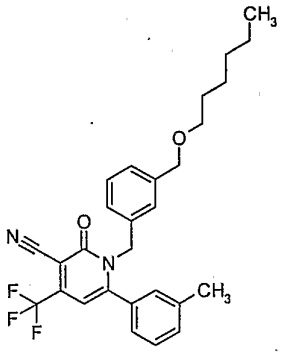
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 111 |  | NC | NC | NC | NC | NC | NC |
| 112 |  | D1 | D1 | NC | NC | NC | NC |
| 113 |  | D1 | D1 | NC | NC | NC | NC |
| 114 |  | NC | NC | NC | NC | NC | NC |

FIG. 1W

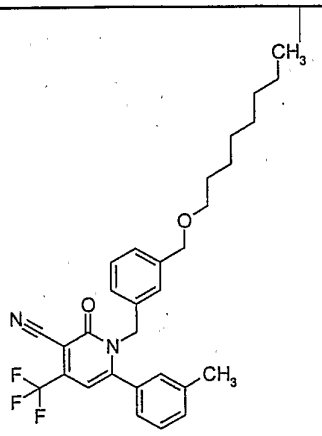
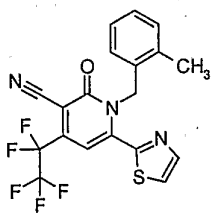
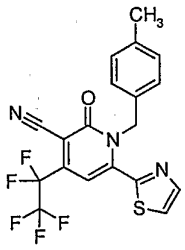
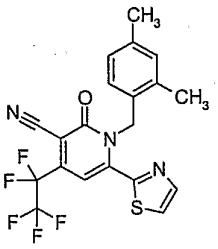
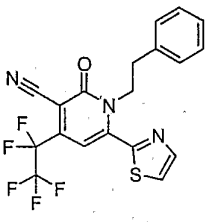
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 115 |  | NC | NC | NC | NC | NC | NC |
| 116 |  | B1 | A1 | III | B | III | C |
| 117 |  | B1 | B1 | III | B | III | C |
| 118 |  | B1 | A1 | III | B | III | C |
| 119 |  | D1 | D1 | IV | B | IV | C |

FIG. 1X

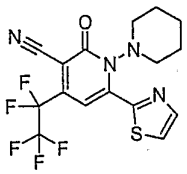
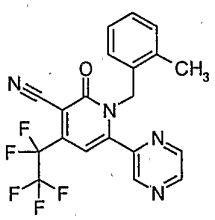
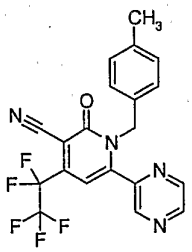
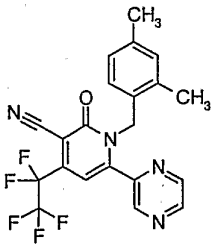
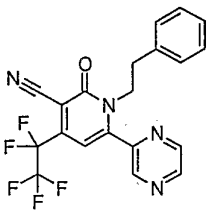
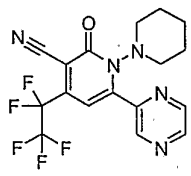
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 120 |  | D1 | D1 | NC | NC | NC | NC |
| 121 |  | B1 | A1 | IV | B | IV | C |
| 122 |  | B1 | B1 | IV | B | IV | C |
| 123-1 |  | B1 | A1 | III | B | III | C |
| 123-2 | | A1 | A1 | III | B | III | C |
| 124 |  | D1 | D1 | NC | B | IV | B |
| 125 |  | C | B1 | IV | B | IV | B |

FIG. 1Y

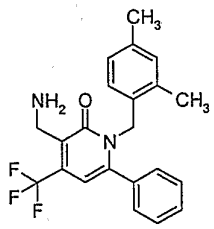
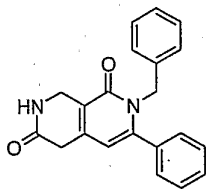
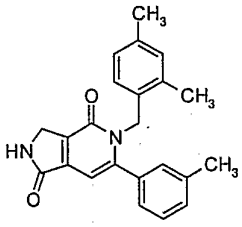
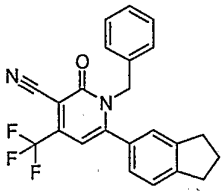
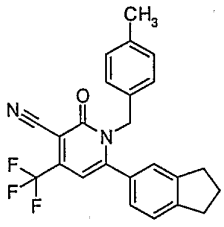
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 126 |  | C | B1 | IV | B | IV | C |
| 127 |  | NC | NC | NC | NC | NC | NC |
| 128 |  | NC | NC | NC | NC | NC | NC |
| 129 |  | B1 | B1 | III | B | III | B |
| 130 |  | B1 | A1 | III | B | III | C |

FIG. 1Z

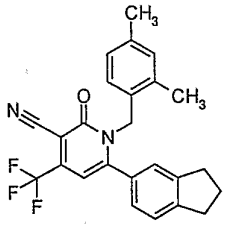
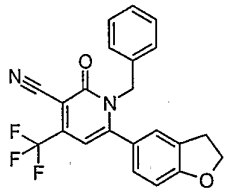
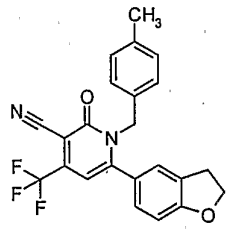
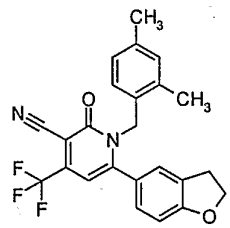
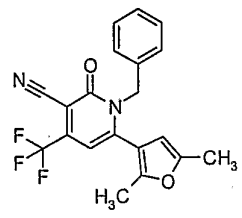
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 131 |  | B1 | A1 | III | C | III | C |
| 132 |  | C | B1 | III | A | III | A |
| 133 |  | B1 | A1 | III | C | II | C |
| 134 |  | B1 | A1 | III | B | III | B |
| 135 |  | B1 | B1 | IV | B | III | C |

FIG. 1AA

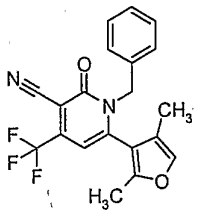
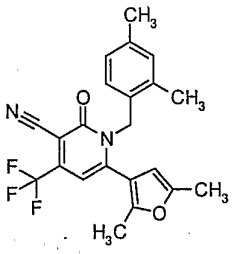
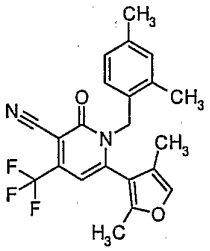
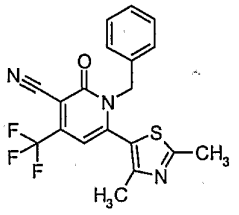
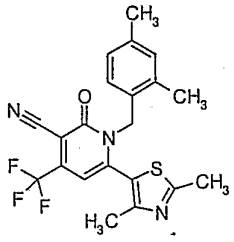
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 136 |  | D1 | D1 | IV | A | NC | A |
| 137 |  | A1 | A1 | II | B | II | C |
| 138 |  | D1 | D1 | IV | A | IV | B |
| 139 |  | D1 | D1 | IV | A | NC | NC |
| 140 |  | D1 | D1 | IV | B | IV | B |

**FIG. 1AB**

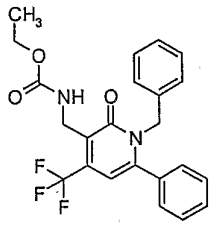
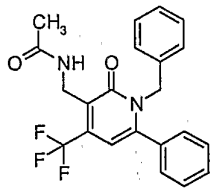
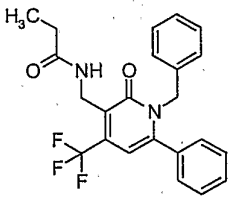
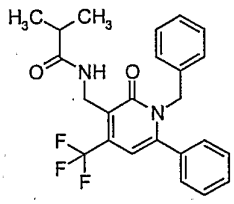
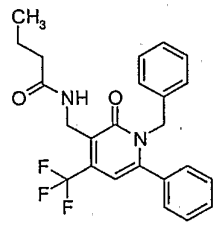
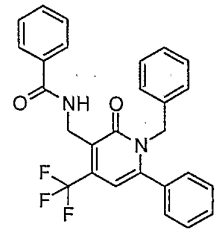
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 141 |  | NC | D1 | NC | NC | IV | A |
| 142 |  | NC | NC | NC | NC | IV | A |
| 143 |  | D1 | NC | NC | NC | IV | A |
| 144 |  | NC | D1 | NC | NC | IV | A |
| 145 |  | NC | NC | NC | NC | NC | NC |
| 146 |  | D1 | D1 | NC | NC | NC | NC |

FIG. 1AC

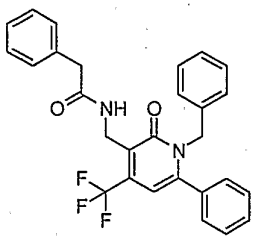
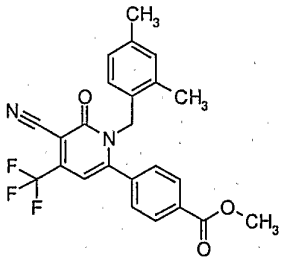
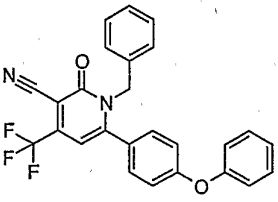
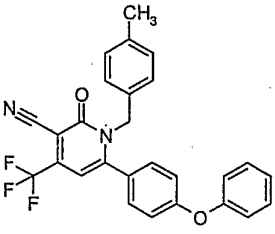
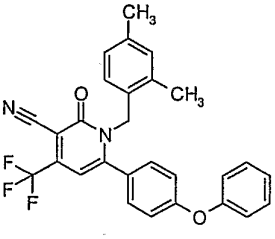
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 147 |  | D1 | D1 | NC | NC | IV | A |
| 148 |  | B1 | B1 | IV | B | IV | B |
| 149 |  | A1 | A1 | III | B | II | C |
| 150 |  | NC | NC | II | C | II | C |
| 151 |  | A1 | A1 | II | C | II | C |

FIG. 1AD

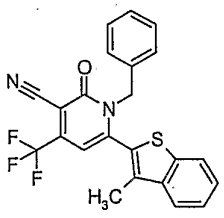
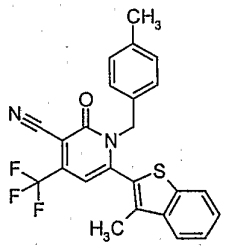
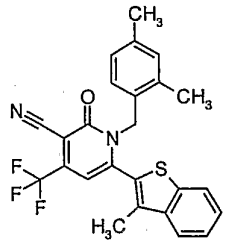
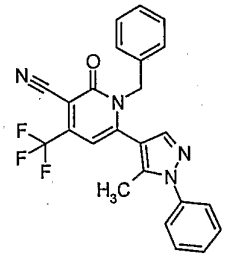
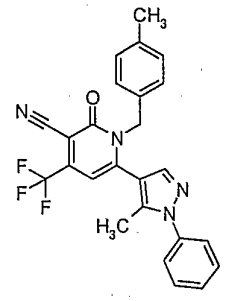
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 152 |  | C | C1 | IV | A | IV | A |
| 153 |  | B1 | B1 | III | B | III | B |
| 154 |  | B1 | B1 | III | B | III | B |
| 155 |  | D1 | C | IV | B | IV | B |
| 156 |  | B1 | A1 | III | B | III | C |

FIG. 1AE

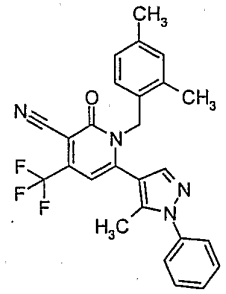
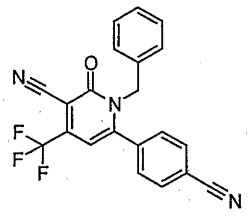
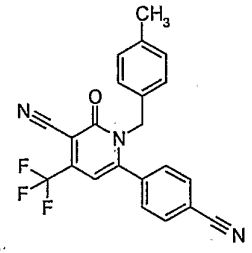
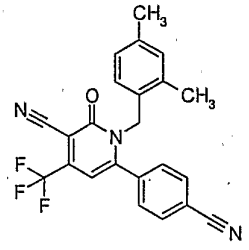
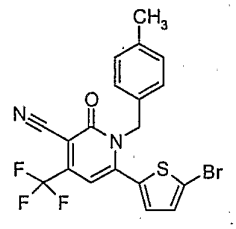
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 157 |  | A1 | A1 | III | B | III | C |
| 158 |  | D1 | D1 | IV | A | IV | B |
| 159 |  | B1 | B1 | IV | B | IV | C |
| 160 |  | B1 | A1 | III | B | III | C |
| 161 |  | B1 | B1 | III | B | III | A |

FIG. 1AF

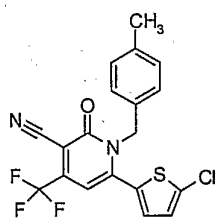
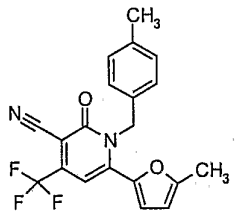
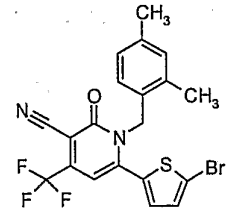
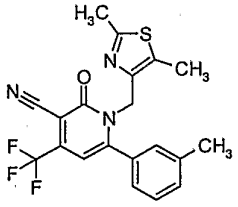
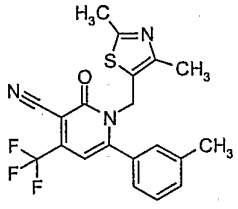
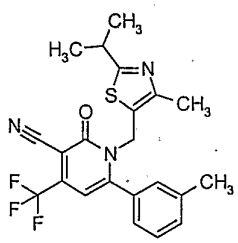
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 162 |  | B1 | B1 | III | C | III | B |
| 163 |  | B1 | A1 | III | B | III | B |
| 164 |  | D1 | D1 | III | B | III | B |
| 165 |  | B1 | A1 | III | B | III | B |
| 166 |  | C1 | C1 | IV | B | IV | A |
| 167 |  | D1 | D1 | IV | A | NC | NC |

FIG. 1AG

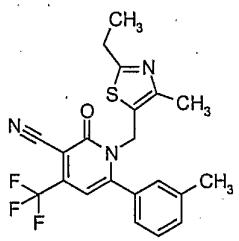
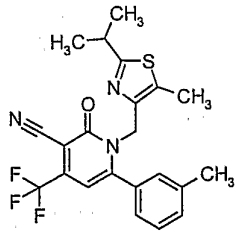
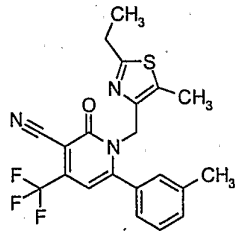
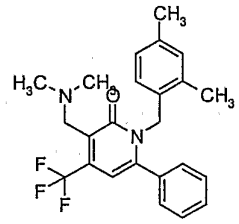
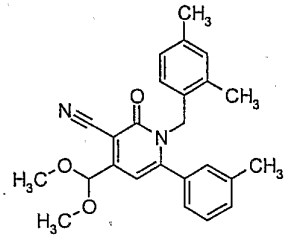
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 168 |  | C1 | C1 | IV | B | IV | A |
| 169 |  | B1 | B1 | III | B | III | B |
| 170 |  | B1 | A1 | III | B | III | B |
| 171 |  | B1 | B1 | III | B | III | B |
| 172 |  | A1 | A1 | III | B | III | B |

FIG. 1AH

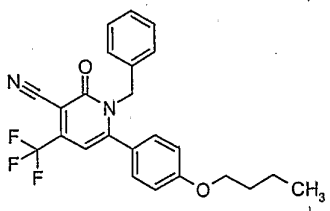
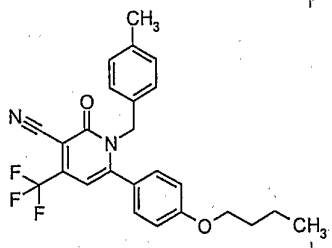
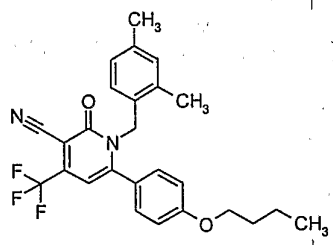
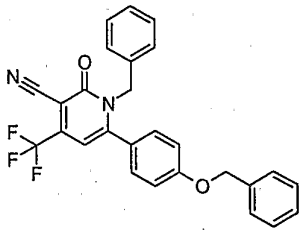
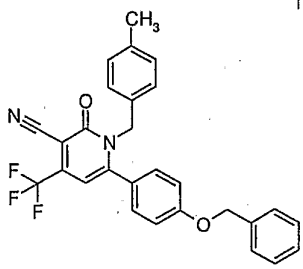
| | | | | | | |
|---|---|---|---|---|---|---|
| 173 |  | C | B1 | III | B | III | B |
| 174 |  | B1 | B1 | III | B | III | B |
| 175 |  | B1 | A1 | III | B | II | B |
| 176 |  | C1 | B1 | II | A | III | B |
| 177 |  | B1 | B1 | III | B | III | B |

FIG. 1AI

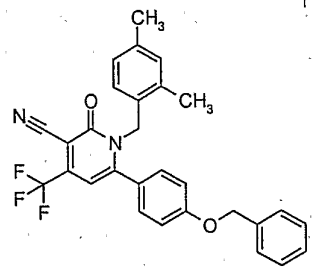
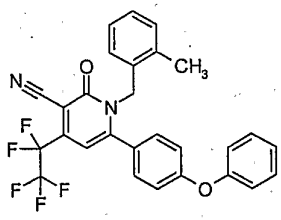
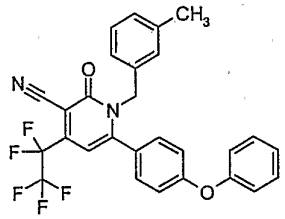
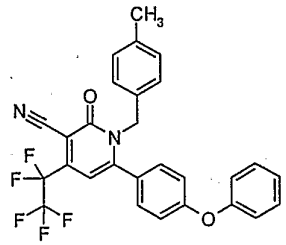
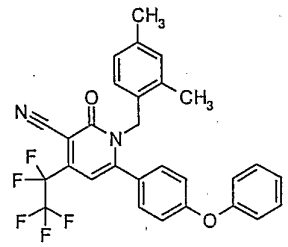
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 178 |  | B1 | A1 | III | B | III | B |
| 179 |  | A1 | A1 | II | B | III | C |
| 180 |  | A1 | A1 | II | C | IV | C |
| 181 |  | A1 | A1 | II | B | II | C |
| 182 |  | A1 | A1 | II | B | II | C |

FIG. 1AJ

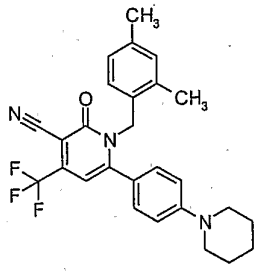
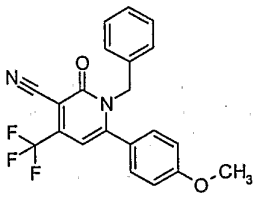
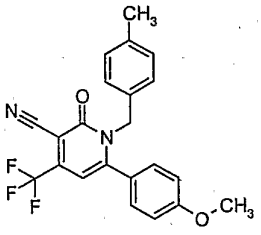
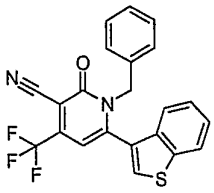
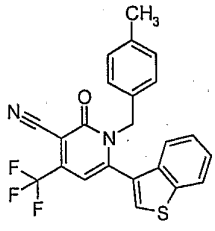
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 183-1 |  | A1 | A1 | II | B | II | C |
| 183-2 | | A1 | A1 | II | B | II | C |
| 184 |  | C1 | B1 | IV | B | IV | C |
| 185 |  | B1 | A1 | III | B | III | C |
| 186 |  | C1 | B1 | III | B | III | B |
| 187 |  | B1 | A1 | III | B | III | C |

FIG. 1AK

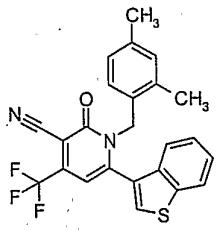
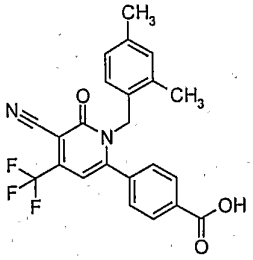
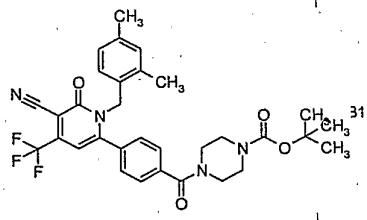
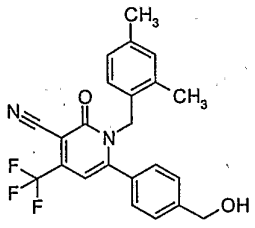
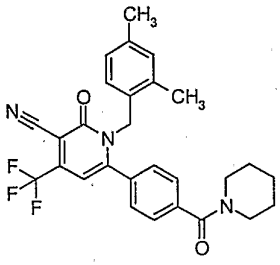
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 188 |  | B1 | A1 | III | B | III | C |
| 189 |  | D1 | D1 | NC | B | NC | NC |
| 190 |  | B1 | | III | B | IV | D |
| 191 |  | B1 | A1 | III | B | III | C |
| 192 |  | B1 | B1 | III | B | IV | D |

FIG. 1AL

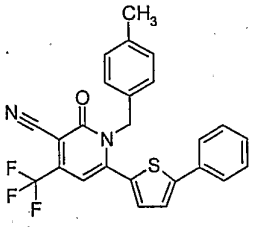
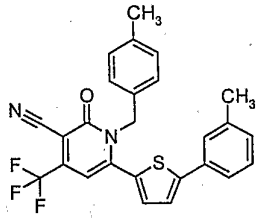
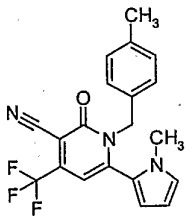
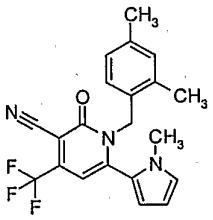
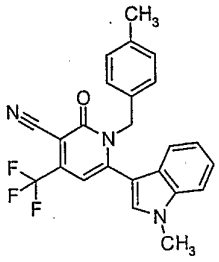
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 193 |  | C1 | B1 | III | B | III | C |
| 194 |  | C1 | B1 | III | B | III | C |
| 195 |  | B1 | B1 | III | B | III | C |
| 196 |  | B1 | A1 | III | C | III | D |
| 197 |  | D1 | B1 | III | B | III | C |

FIG. 1AM

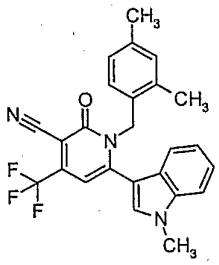
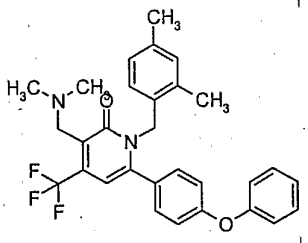
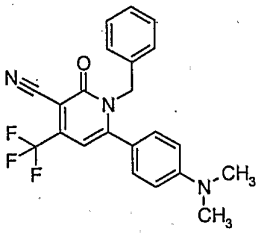
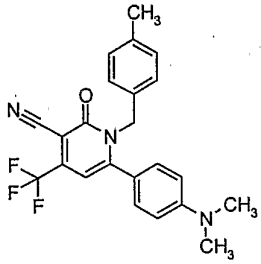
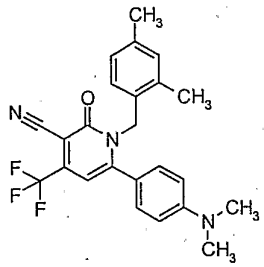
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 198 |  | D1 | D1 | IV | B | IV | B |
| 199 |  | A1 | A1 | III | B | III | C |
| 200 |  | D1 | C1 | IV | A | III | A |
| 201 |  | B1 | B1 | III | B | III | B |
| 202 |  | B1 | A1 | III | B | III | C |

FIG. 1AN

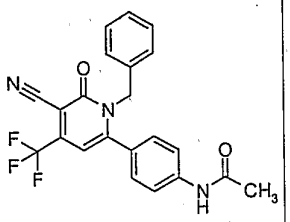
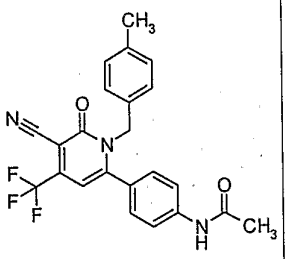
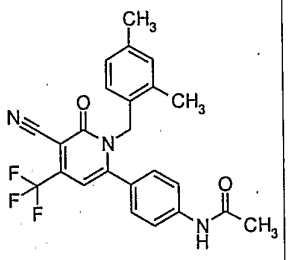
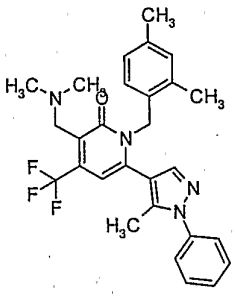
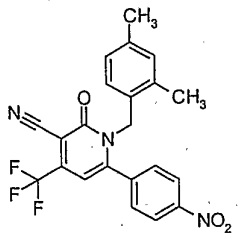
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 203 |  | D1 | D1 | IV | A | NC | NC |
| 204 |  | D1 | D1 | IV | B | IV | B |
| 205 |  | C1 | C1 | III | B | IV | B |
| 206 |  | C1 | B1 | IV | C | NC | D |
| 207 |  | C1 | B1 | IV | B | IV | C |

FIG. 1AO

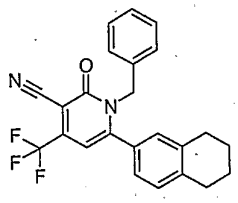
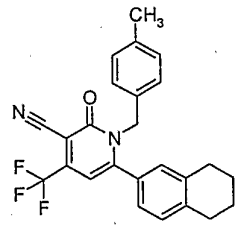
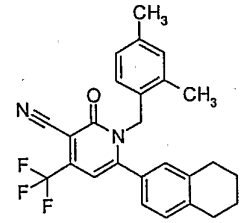
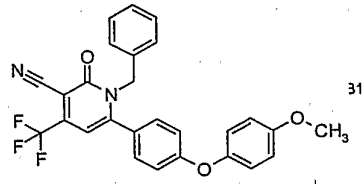
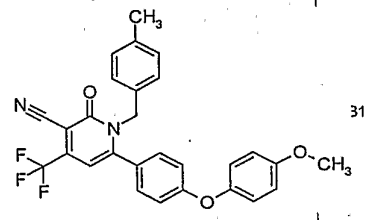
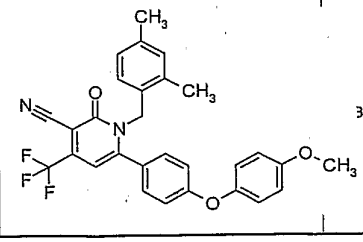
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 208 |  | B1 | B1 | III | A | III | B |
| 209 |  | B1 | A1 | III | B | III | C |
| 210 |  | B1 | B1 | III | B | III | C |
| 211 |  | 31 | B1 | III | C | III | C |
| 212 |  | 31 | A1 | III | C | III | C |
| 213 |  | 31 | A1 | II | C | II | D |

FIG. 1AP

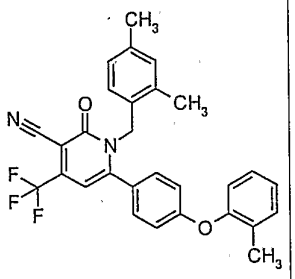
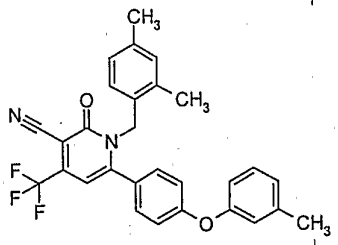
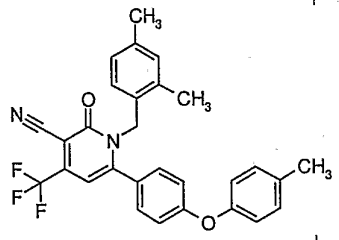
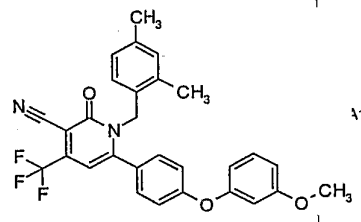
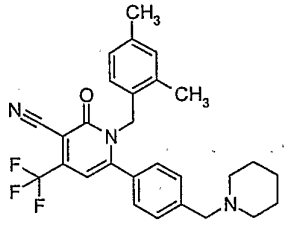
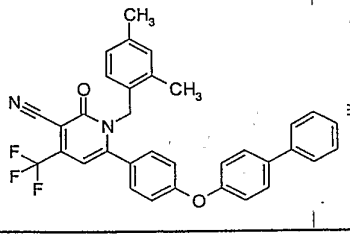
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 214 |  | A1 | A1 | II | B | II | C |
| 215 |  | A1 | A1 | II | C | II | D |
| 216 |  | A1 | A1 | III | C | II | C |
| 217 |  | A1 | A1 | II | C | II | C |
| 218 |  | B1 | B1 | IV | B | IV | B |
| 219 |  | B1 | B1 | II | B | II | B |

FIG. 1AQ

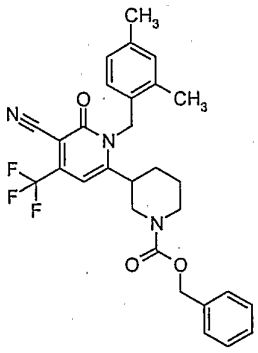
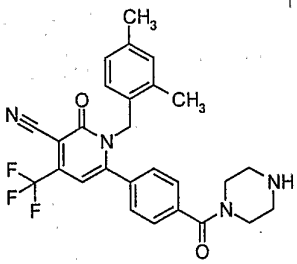
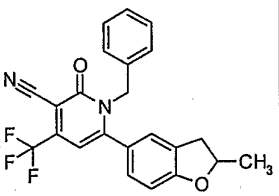
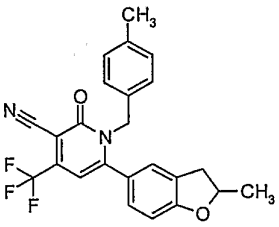
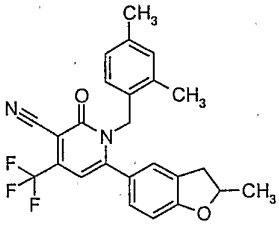
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 220 |  | B1 | A1 | III | B | III | B |
| 221 |  | D1 | D1 | NC | B | IV | B |
| 222 |  | C1 | B1 | III | A | NC | C |
| 223 |  | B1 | A1 | III | B | III | B |
| 224 |  | A1 | A1 | III | B | III | B |

FIG. 1AR

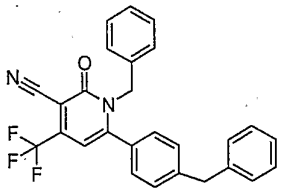
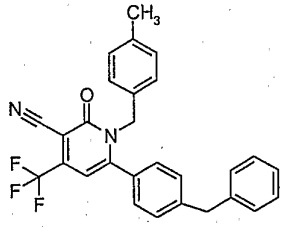
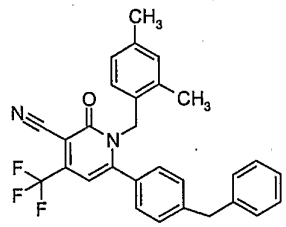
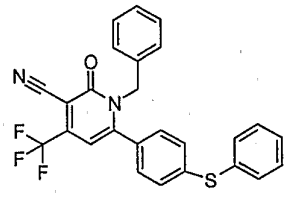
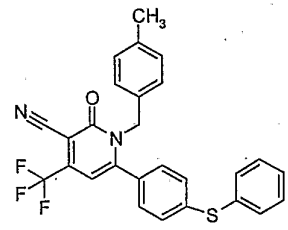
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 225 |  | D1 | B1 | IV | A | III | B |
| 226 |  | B1 | B1 | III | B | III | B |
| 227 |  | B1 | A1 | III | B | III | B |
| 228 |  | C1 | B1 | IV | B | III | B |
| 229 |  | B1 | B1 | III | B | III | C |

FIG. 1AS

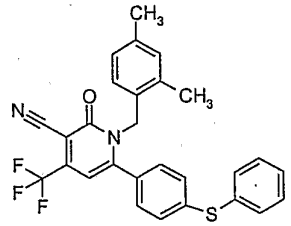
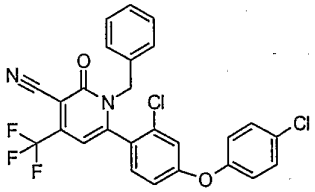
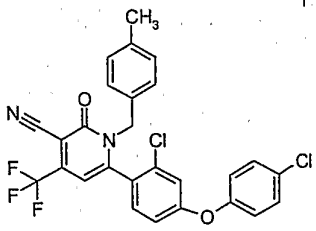
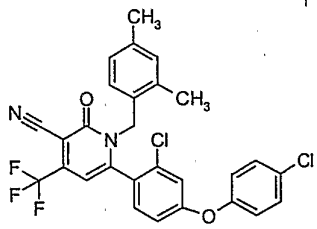
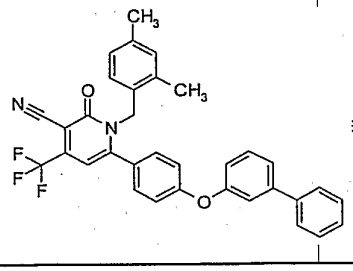
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 230 |  | B1 | A1 | III | B | III | C |
| 231 |  | B1 | B1 | III | B | III | C |
| 232 |  | A1 | A1 | III | B | III | C |
| 233 |  | B1 | A1 | II | B | II | C |
| 234 |  | 31 | A1 | III | B | NC | C |

FIG. 1AT

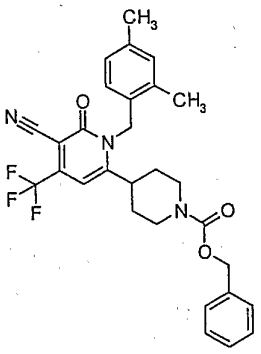
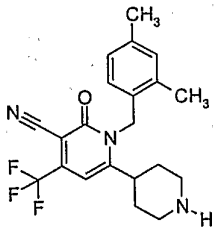
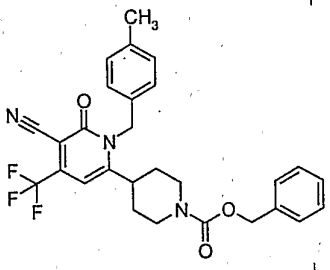
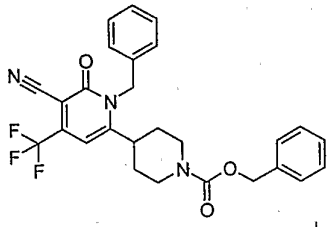
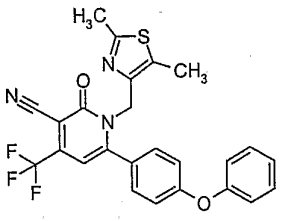
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 235 |  | D1 | D1 | IV | A | NC | A |
| 236 |  | NC | NC | NC | NC | NC | NC |
| 237-1 |  | D1 | D1 | IV | A | IV | B |
| 237-2 | | D1 | C1 | IV | A | IV | B |
| 238 |  | NC | NC | NC | A | NC | B |
| 239 |  | B1 | B1 | III | B | III | B |

FIG. 1AU

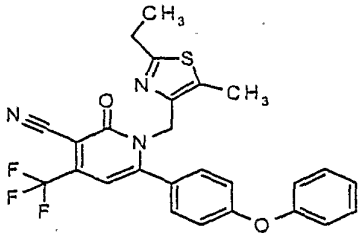
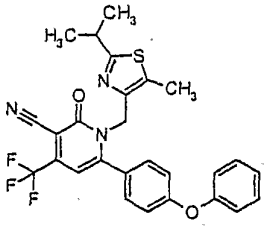
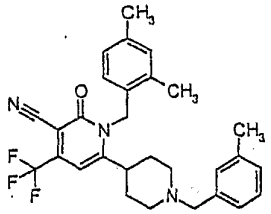
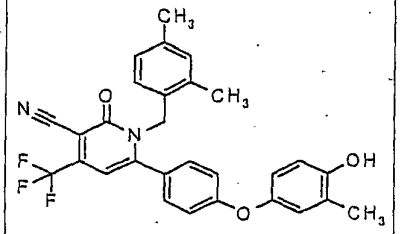
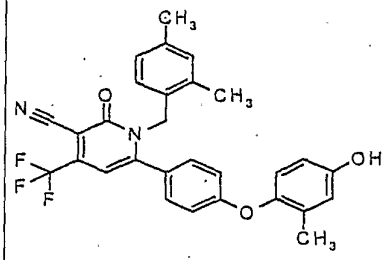
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 240 |  | B1 | B1 | III | B | III | C |
| 241 |  | D1 | C1 | III | B | IV | B |
| 242 |  | B1 | B1 | NC | B | III | B |
| 243 |  | A1 | A1 | II | B | II | C |
| 244 |  | A1 | A1 | I | B | I | C |

FIG. 1AV

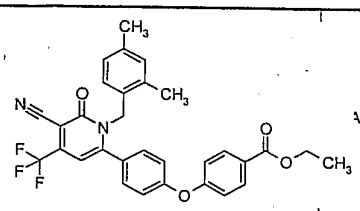
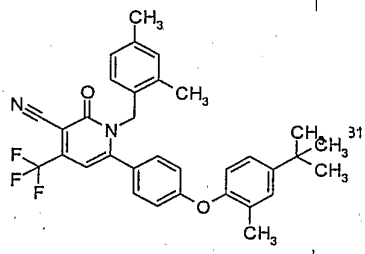
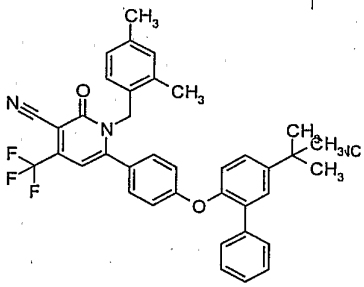
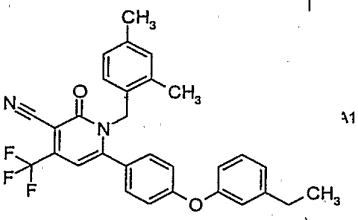
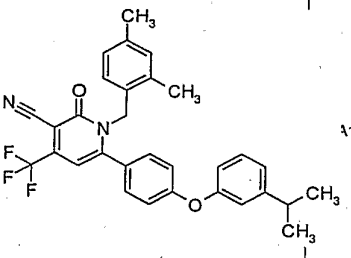
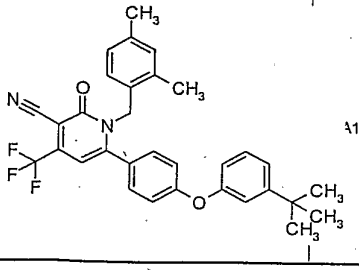
| | | | | | | |
|---|---|---|---|---|---|---|
| 245 |  | A1 | A1 | II | B | II | C |
| 246 |  | A1 | A1 | III | B | III | C |
| 247 |  | NC | NC | NC | NC | IV | A |
| 248 |  | A1 | A1 | I | B | II | C |
| 249 |  | A1 | A1 | II | C | II | C |
| 250 |  | A1 | A1 | II | C | II | C |

FIG. AW

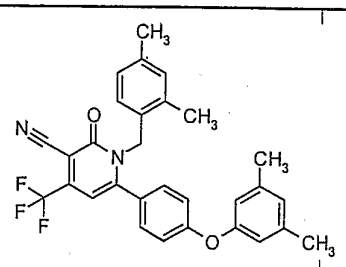
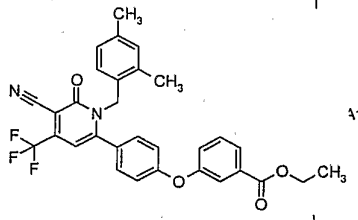
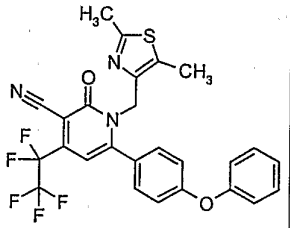
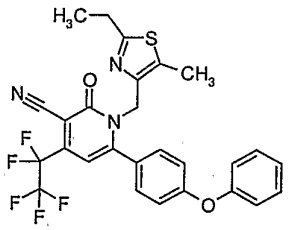
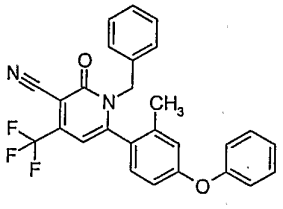
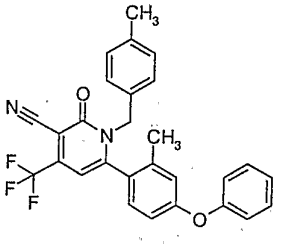
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 251 |  | A1 | A1 | I | C | I | D |
| 252 |  | A1 | A1 | II | B | II | C |
| 253 |  | B1 | B1 | III | B | III | C |
| 254 |  | B1 | B1 | III | B | III | C |
| 255 |  | B1 | A1 | II | B | II | B |
| 256 |  | A1 | A1 | II | B | II | D |

FIG. AX

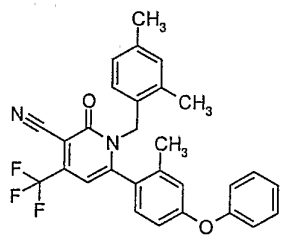
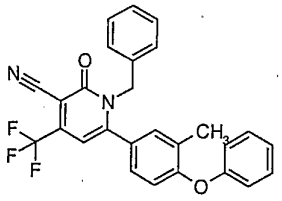
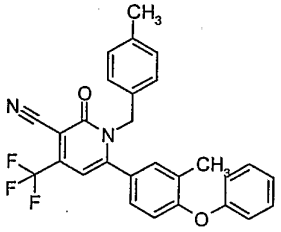
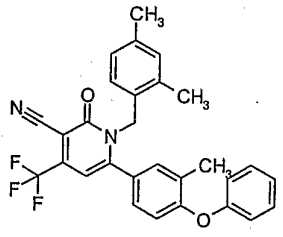
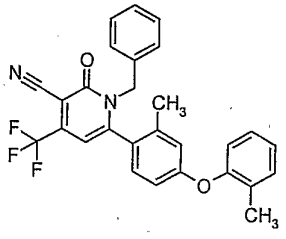
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 257 |  | A1 | A1 | II | B | II | C |
| 258 |  | B1 | B1 | III | B | III | C |
| 259 |  | A1 | A1 | II | B | II | C |
| 260 |  | A1 | A1 | II | C | II | C |
| 261 |  | A1 | A1 | II | C | II | C |

FIG. AY

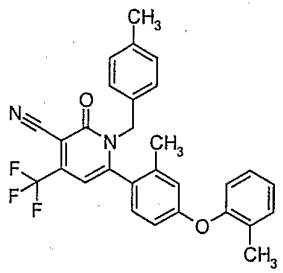
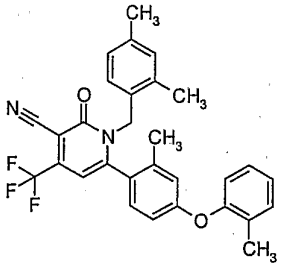
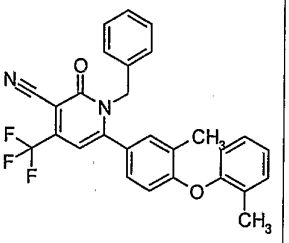
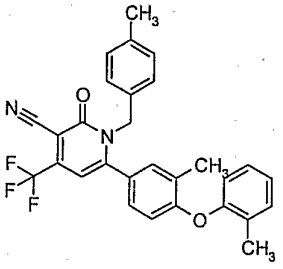
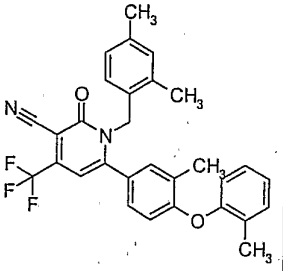
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 262 |  | A1 | A1 | II | B | II | C |
| 263 |  | B1 | A1 | II | B | II | C |
| 264 |  | A1 | A1 | II | B | II | B |
| 265 |  | B1 | A1 | II | B | II | B |
| 266 |  | A1 | A1 | II | B | II | B |

FIG. AZ

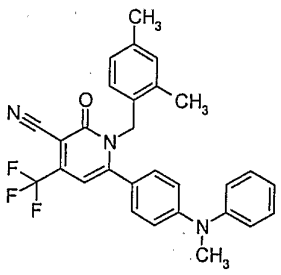
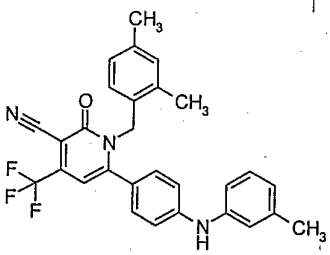
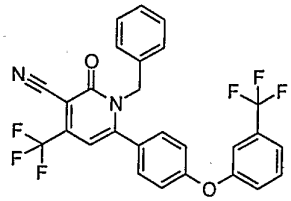
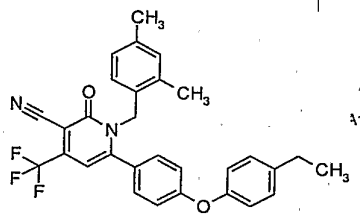
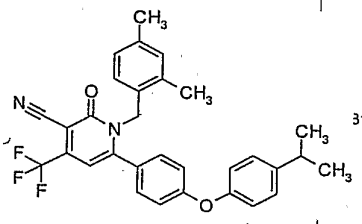
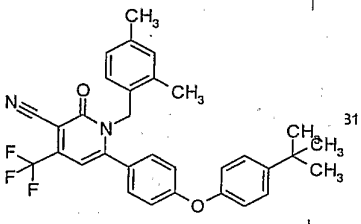
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 267 |  | B1 | A1 | III | B | III | B |
| 268 |  | A1 | A1 | II | C | II | C |
| 269 |  | B1 | A1 | III | B | II | C |
| 270 |  | A1 | A1 | II | C | II | C |
| 271 |  | 31 | A1 | II | C | II | C |
| 272 |  | 31 | B1 | III | B | III | C |

FIG. 1BA

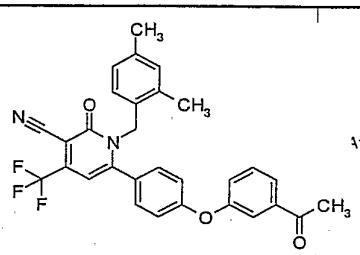
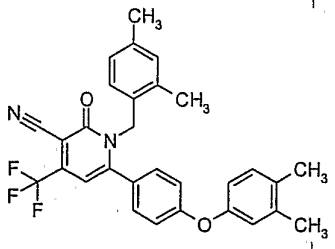
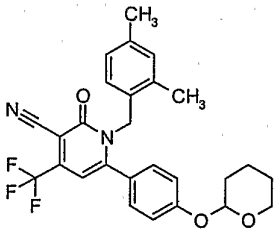
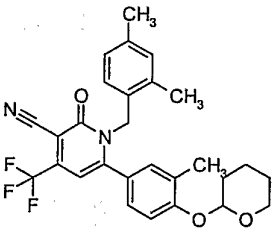
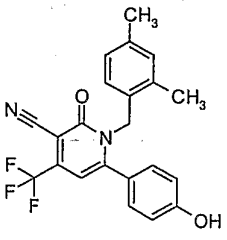
| | | | | | | |
|---|---|---|---|---|---|---|
| 273 |  | A1 | A1 | II | B | II | C |
| 274 |  | A1 | A1 | II | B | II | C |
| 275 |  | A1 | B1 | II | B | III | B |
| 276 |  | A1 | A1 | III | B | III | B |
| 277 |  | B1 | A1 | III | B | III | B |

FIG. 1BB

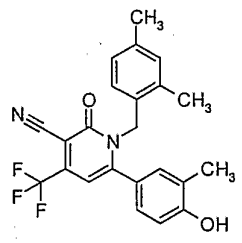
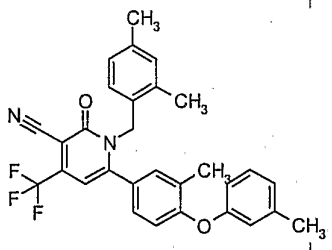
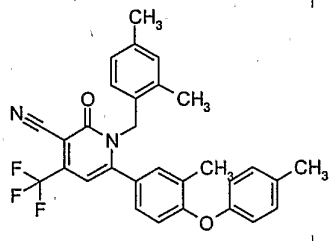
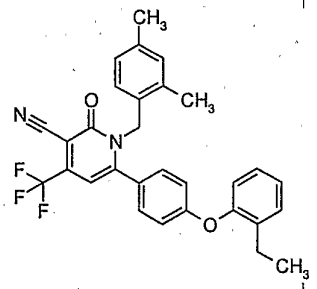
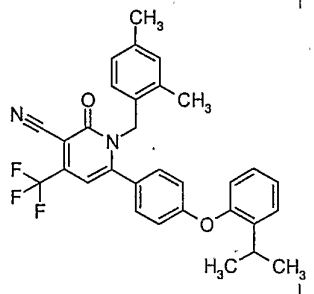
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 278 |  | B1 | B1 | III | B | III | B |
| 279 |  | A1 | A1 | II | B | II | B |
| 280 |  | B1 | B1 | III | B | III | B |
| 281 |  | A1 | A1 | II | B | II | B |
| 282 |  | A1 | A1 | II | B | II | B |

FIG. 1BC

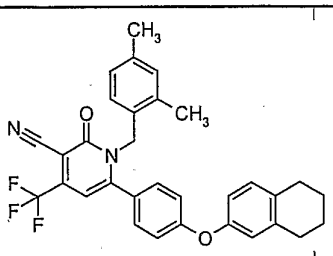
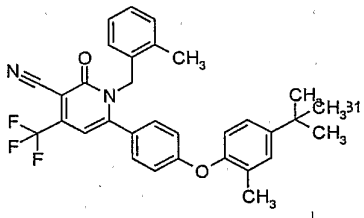
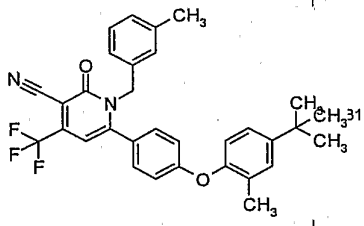
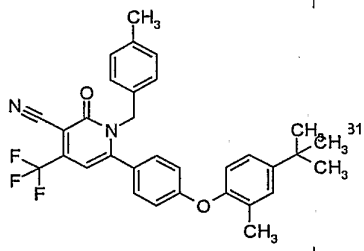
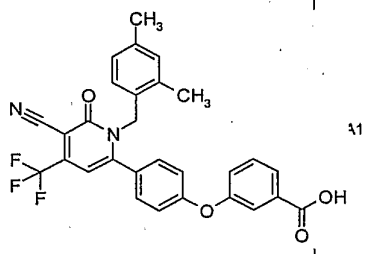
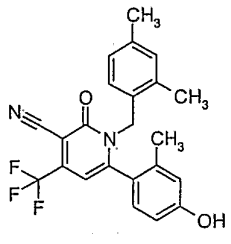
| | | | | | | |
|---|---|---|---|---|---|---|
| 283 |  | A1 | A1 | II | B | II | B |
| 284 |  | B1 | III | B | III | C |
| 285 |  | B1 | III | B | III | B |
| 286 |  | A1 | III | B | III | C |
| 287 |  | A1 | III | B | III | B |
| 288 |  | A1 | III | B | III | B |

FIG. 1BD

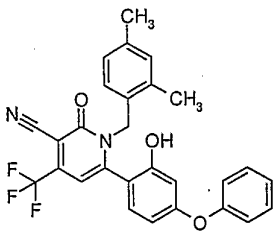
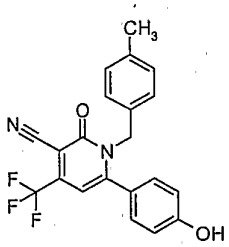
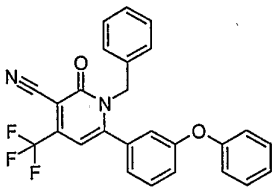
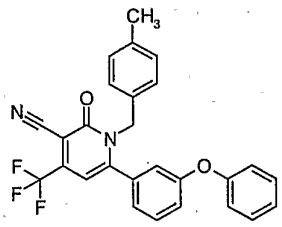
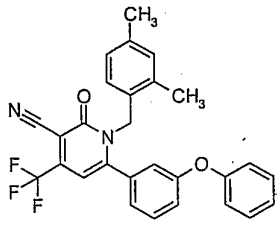
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 289 |  | A1 | B1 | III | B | III | B |
| 290 |  | B1 | B1 | III | B | III | B |
| 291 |  | B1 | A1 | III | B | III | B |
| 292 |  | B1 | A1 | III | B | III | B |
| 293 |  | A1 | A1 | II | B | II | B |

FIG. 1BE

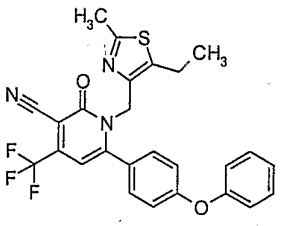
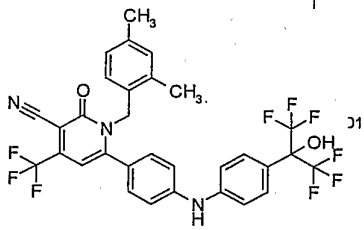
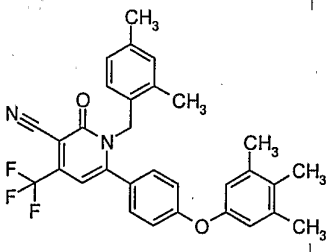
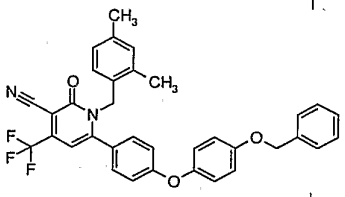
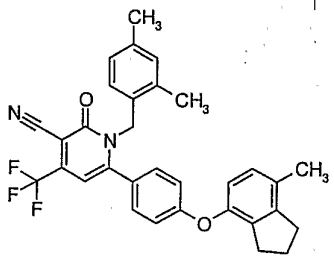
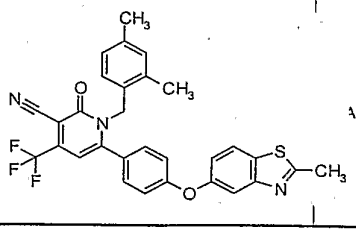
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 294 |  | B1 | B1 | III | B | III | B |
| 295 |  | C1 | C1 | II | B | II | B |
| 296 |  | A1 | A1 | II | B | II | C |
| 297 |  | B1 | B1 | II | C | II | C |
| 298 |  | A1 | A1 | II | B | II | C |
| 299 |  | A1 | B1 | II | B | II | B |

FIG. 1BF

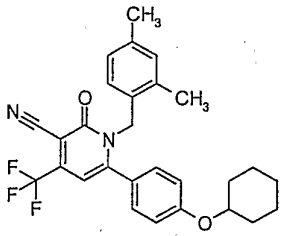
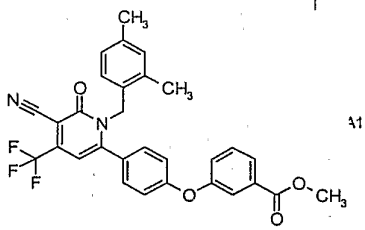
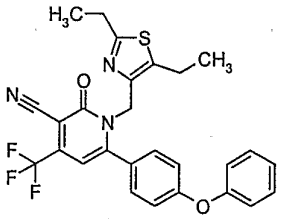
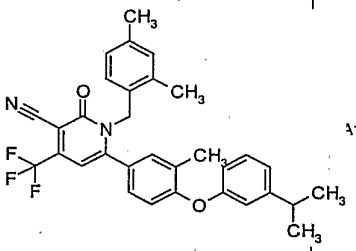
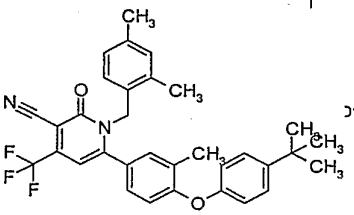
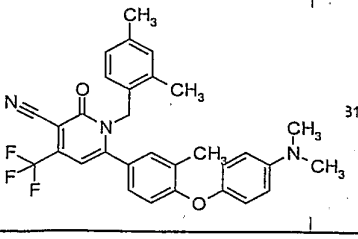
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 300 |  | B1 | B1 | II | B | II | B |
| 301 |  | A1 | A1 | II | B | II | C |
| 302 |  | B1 | B1 | III | B | III | B |
| 303 |  | A1 | A1 | II | B | II | B |
| 304 |  | B1 | B1 | III | B | III | C |
| 305 |  | A1 | A1 | II | B | II | C |

FIG. 1BG

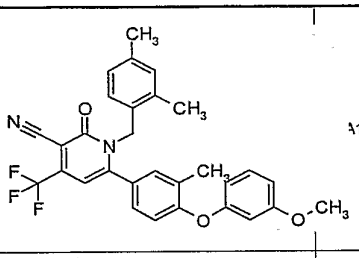
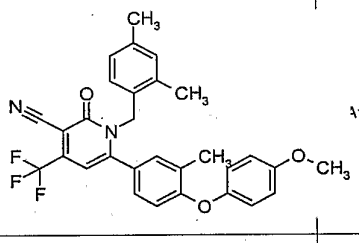
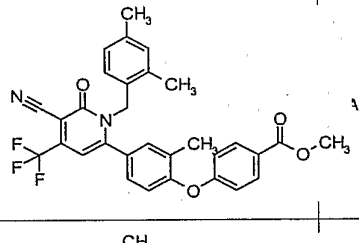
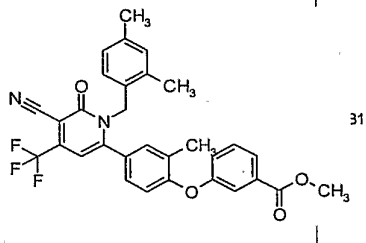
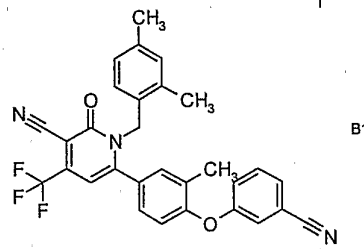
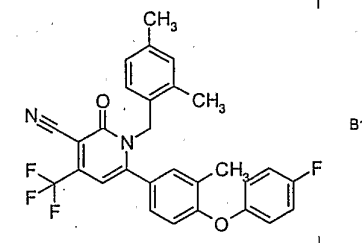
| | | | | | | |
|---|---|---|---|---|---|---|
| 306 |  | A1 | A1 | II | B | II | C |
| 307 |  | A1 | A1 | III | B | III | C |
| 308 |  | A1 | A1 | III | B | III | C |
| 309 |  | B1 | A1 | III | B | III | C |
| 310 |  | B1 | B1 | III | B | III | C |
| 311 |  | B1 | A1 | III | B | II | C |

FIG. 1BH

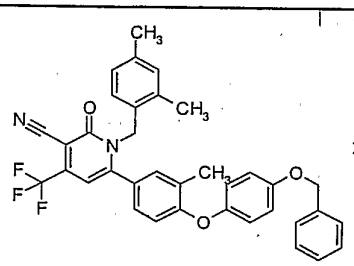
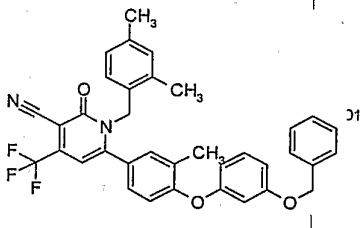
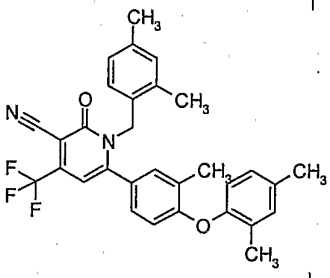
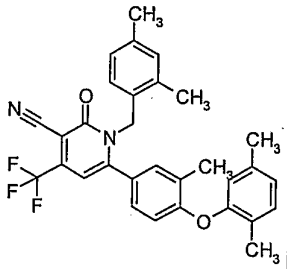
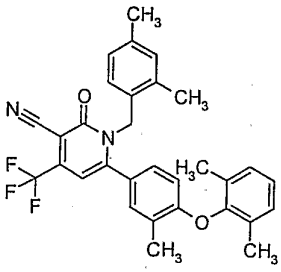
| | | | | | | |
|---|---|---|---|---|---|---|
| 312 |  | C1 | C1 | II | C | II | D |
| 313 |  | C1 | C1 | III | B | III | C |
| 314 |  | B1 | A1 | III | B | II | C |
| 315 |  | A1 | A1 | II | B | II | C |
| 316 |  | B1 | B1 | III | B | III | B |

FIG. 1BI

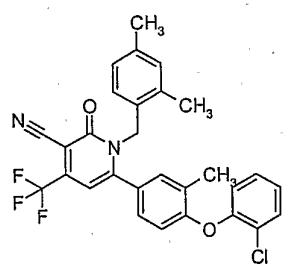
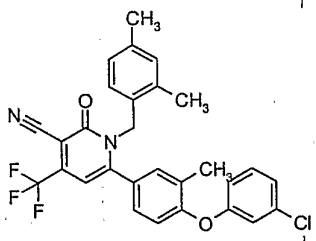
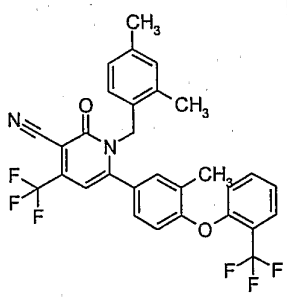
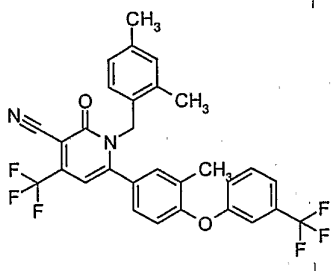
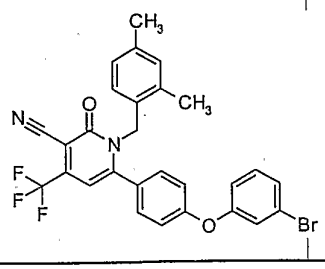
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 317 |  | A1 | A1 | II | B | II | C |
| 318 |  | A1 | A1 | II | B | II | C |
| 319 |  | A1 | A1 | II | B | II | C |
| 320 |  | A1 | A1 | II | B | II | C |
| 321 |  | A1 | A1 | II | B | II | D |

FIG. 1BJ

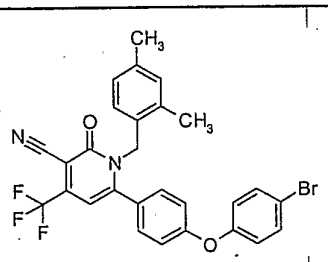
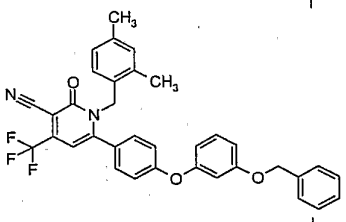
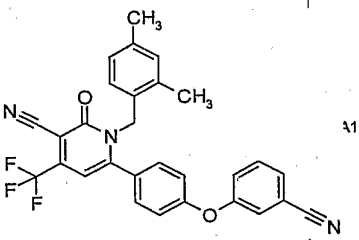
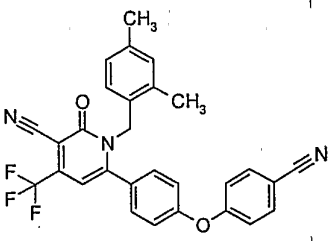
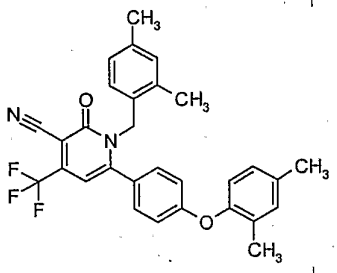
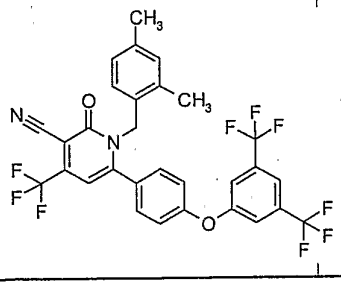
| | | | | | | |
|---|---|---|---|---|---|---|
| 322 |  | A1 | A1 | III | B | III | C |
| 323 |  | 31 | B1 | II | B | II | C |
| 324 |  | 31 | A1 | II | B | II | D |
| 325 |  | B1 | B1 | III | B | III | C |
| 326 |  | A1 | A1 | II | B | II | C |
| 327 |  | B1 | A1 | II | B | II | D |

FIG. 1BK

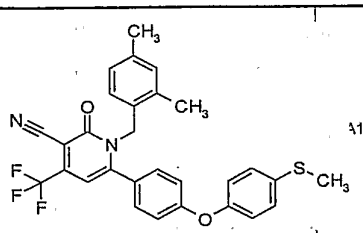
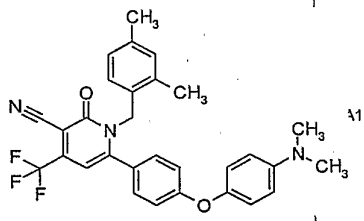
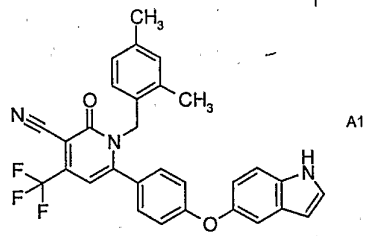
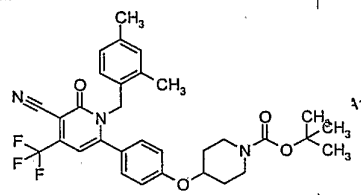
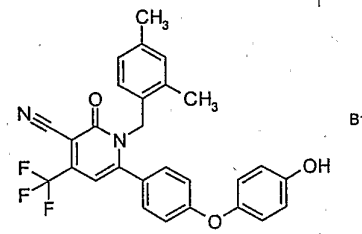
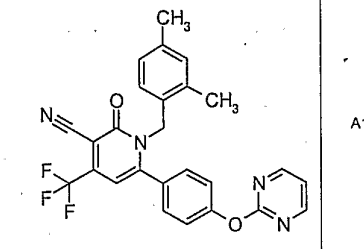
| | | | | | | |
|---|---|---|---|---|---|---|
| 328 |  | A1 | A1 | II | B | II | C |
| 329 |  | A1 | A1 | II | B | II | C |
| 330 |  | A1 | A1 | I | C | I | D |
| 331 |  | A1 | A1 | II | B | II | B |
| 332 |  | B1 | A1 | II | C | II | C |
| 333 |  | A1 | A1 | II | B | II | C |

FIG. 1BL

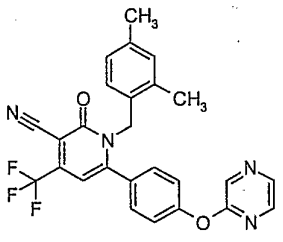
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 334 |  | A1 | A1 | II | C | II | C |

FIG. 1BM

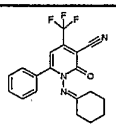
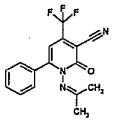
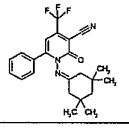
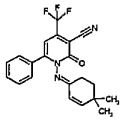
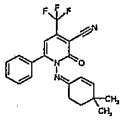
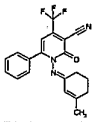
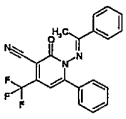
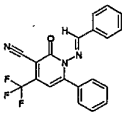
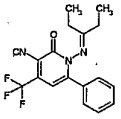
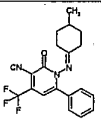
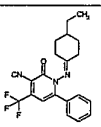
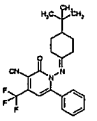
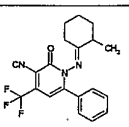
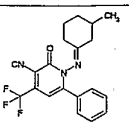
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 335 |  | B1 | B1 | IV | B | IV | NC |
| 336 |  | D1 | D1 | NC | A | NC | NC |
| 337 |  | NC | NC | NC | A | NC | NC |
| 338 |  | NC | NC | NC | A | NC | NC |
| 339 |  | NC | NC | NC | A | NC | NC |
| 340 |  | NC | D1 | NC | A | NC | NC |
| 341 |  | D1 | D1 | NC | A | NC | NC |
| 342 |  | NC | NC | NC | A | NC | NC |
| 343 |  | D1 | D1 | IV | B | NC | NC |
| 344 |  | D1 | D1 | IV | A | NC | NC |
| 345 |  | D1 | D1 | IV | A | NC | NC |
| 346 |  | NC | NC | NC | A | NC | NC |
| 347 |  | D1 | B1 | IV | B | NC | NC |
| 348 |  | D1 | D1 | IV | A | NC | NC |

FIG. 1BN

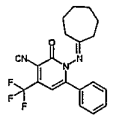
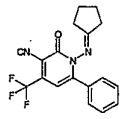
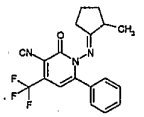
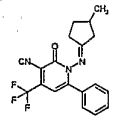
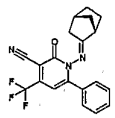
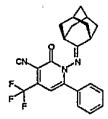
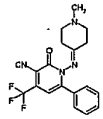
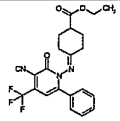
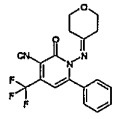
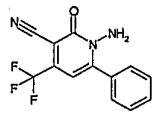
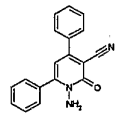
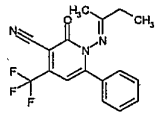
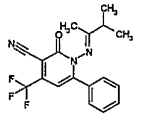
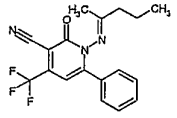
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 349 |  | D1 | B1 | IV | B | NC | NC |
| 350 |  | D1 | D1 | NC | A | NC | NC |
| 351 |  | D1 | C1 | IV | B | NC | NC |
| 352 |  | D1 | D1 | IV | A | NC | NC |
| 353 |  | D1 | D1 | IV | B | NC | NC |
| 354 |  | D1 | D1 | NC | A | NC | NC |
| 355 |  | NC | D1 | NC | A | NC | NC |
| 356 |  | NC | NC | NC | A | NC | NC |
| 357 |  | D1 | D1 | NC | A | NC | NC |
| 358 |  | NC | NC | NC | A | NC | NC |
| 359 |  | NC | NC | NC | A | NC | NC |
| 360 |  | D1 | D1 | IV | A | NC | NC |
| 361 |  | C1 | B1 | IV | B | NC | NC |
| 362 |  | D1 | D1 | NC | B | NC | NC |

FIG. 1BO

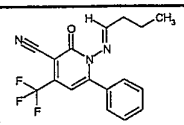
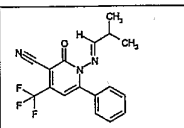
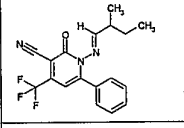
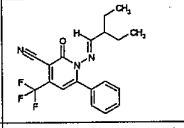
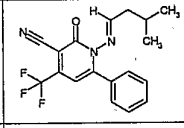
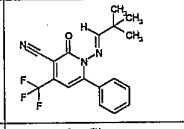
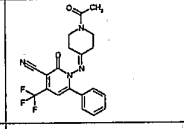
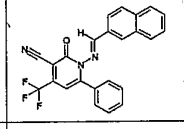
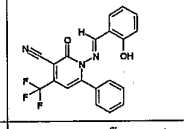
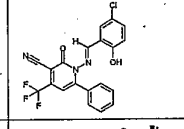
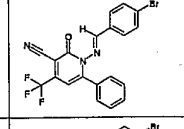
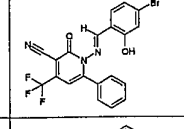
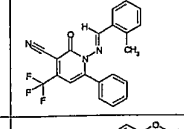
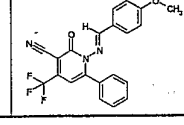
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 363 |  | NC | D1 | NC | A | NC | NC |
| 364 |  | D1 | D1 | NC | A | NC | NC |
| 365 |  | D1 | D1 | NC | A | NC | NC |
| 366 |  | NC | NC | NC | A | NC | NC |
| 367 |  | D1 | D1 | NC | A | NC | NC |
| 368 |  | NC | NC | NC | A | NC | NC |
| 369 |  | NC | NC | NC | A | NC | NC |
| 370 |  | NC | D1 | NC | A | NC | NC |
| 371 |  | NC | D1 | NC | A | NC | NC |
| 372 |  | NC | NC | NC | A | NC | NC |
| 373 |  | NC | D1 | NC | A | NC | NC |
| 374 |  | NC | NC | NC | A | NC | NC |
| 375 |  | NC | NC | NC | A | NC | NC |
| 376 |  | NC | NC | NC | A | NC | NC |

FIG. 1BP

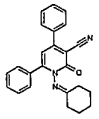
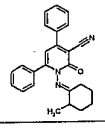
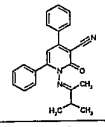
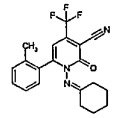
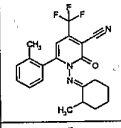
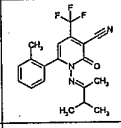
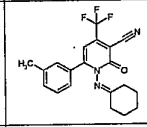
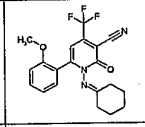
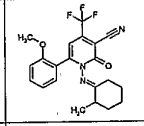
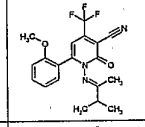
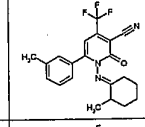
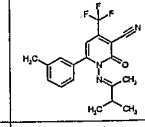
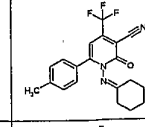
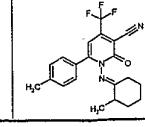
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 377 |  | NC | NC | NC | A | NC | NC |
| 378 |  | NC | NC | NC | A | NC | NC |
| 379 |  | NC | NC | NC | A | NC | NC |
| 380 |  | C1 | D1 | IV | A | NC | NC |
| 381 |  | D1 | C1 | NC | A | NC | NC |
| 382 |  | D1 | D1 | IV | A | NC | NC |
| 383 |  | B1 | B1 | IV | B | NC | NC |
| 384 |  | C1 | D1 | IV | A | NC | NC |
| 385 |  | D1 | D1 | NC | A | NC | NC |
| 386 |  | D1 | D1 | IV | A | NC | NC |
| 387 |  | B1 | B1 | IV | A | NC | NC |
| 388 |  | B1 | B1 | IV | B | NC | NC |
| 389 |  | B1 | B1 | IV | B | NC | NC |
| 390 |  | C1 | B1 | IV | A | NC | NC |

FIG. 1BQ

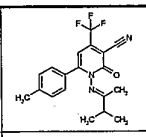
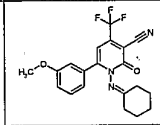
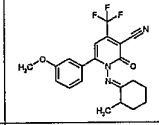
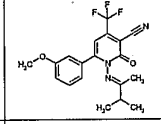
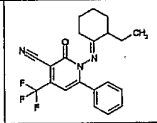
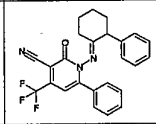
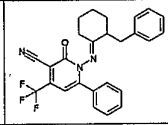
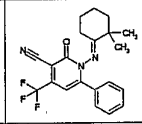
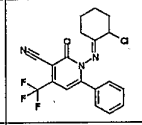
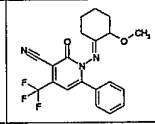
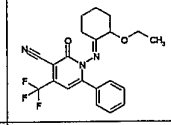
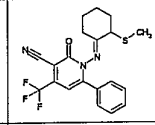
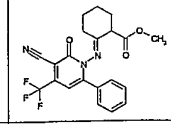
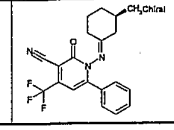
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 391 |  | C1 | C1 | IV | A | NC | NC |
| 392 |  | B1 | B1 | IV | B | NC | NC |
| 393 |  | D1 | B1 | IV | B | III | B |
| 394 |  | C1 | B1 | IV | B | NC | NC |
| 395 |  | D1 | D1 | IV | A | NC | NC |
| 396 |  | NC | NC | NC | A | NC | NC |
| 397 |  | NC | NC | NC | A | NC | NC |
| 398 |  | D1 | C1 | IV | A | IV | NC |
| 399 |  | C1 | B1 | III | B | IV | NC |
| 400 |  | NC | NC | NC | A | NC | A |
| 401 |  | NC | NC | NC | A | NC | NC |
| 402 |  | NC | D1 | IV | A | NC | NC |
| 403 |  | NC | NC | NC | A | NC | NC |
| 404 |  | NC | D1 | IV | A | NC | NC |

FIG. 1BR

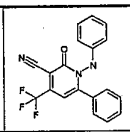
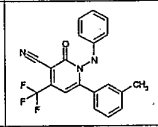
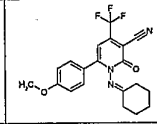
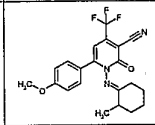
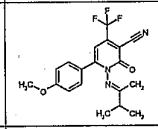
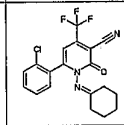
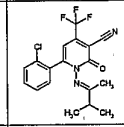
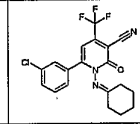
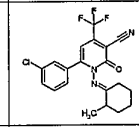
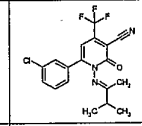
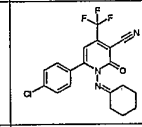
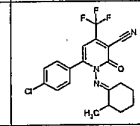
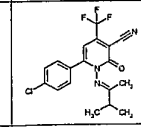
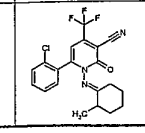
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 405 |  | NC | D1 | NC | A | NC | NC |
| 406 |  | NC | D1 | IV | A | NC | NC |
| 407 |  | D1 | C1 | IV | C | IV | NC |
| 408 |  | D1 | C1 | IV | B | IV | NC |
| 409 |  | D1 | D1 | IV | B | IV | NC |
| 410 |  | B1 | B1 | III | B | IV | NC |
| 411 |  | B1 | B1 | III | B | IV | NC |
| 412 |  | C1 | B1 | III | B | IV | NC |
| 413 |  | C1 | B1 | III | A | IV | NC |
| 414 |  | C1 | B1 | IV | B | IV | NC |
| 415 |  | C1 | C1 | IV | B | IV | NC |
| 416 |  | NC | D1 | IV | A | IV | NC |
| 417 |  | D1 | D1 | IV | B | IV | NC |
| 418 |  | C1 | B1 | IV | A | IV | B |

FIG. 1BS

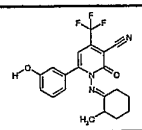
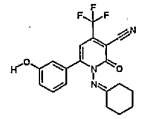
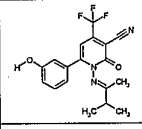
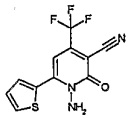
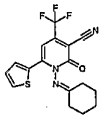
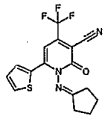
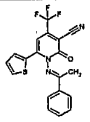
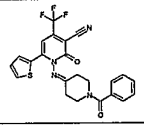
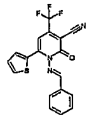
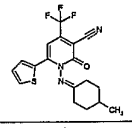
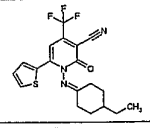
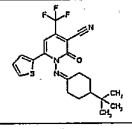
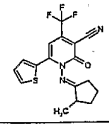
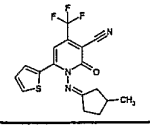
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 419 |  | D1 | C1 | IV | A | IV | B |
| 420 |  | D1 | C1 | IV | A | IV | B |
| 421 |  | D1 | D1 | IV | A | NC | NC |
| 422 |  | NC | NC | NC | A | NC | NC |
| 423 |  | D1 | D1 | IV | A | NC | NC |
| 424 |  | NC | NC | NC | A | NC | NC |
| 425 |  | NC | NC | NC | A | NC | NC |
| 426 |  | NC | NC | NC | A | NC | NC |
| 427 |  | NC | NC | III | A | NC | NC |
| 428 |  | D1 | D1 | NC | A | NC | NC |
| 429 |  | D1 | D1 | NC | A | NC | NC |
| 430 |  | NC | NC | NC | NC | NC | NC |
| 431 |  | D1 | D1 | NC | NC | NC | NC |
| 432 |  | NC | NC | NC | NC | NC | NC |

FIG. 1BT

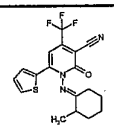
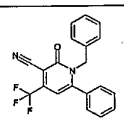
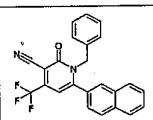
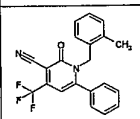
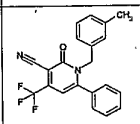
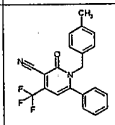
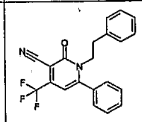
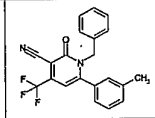
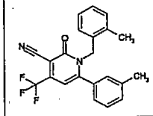
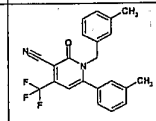
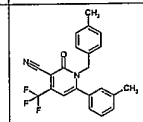
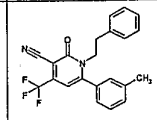
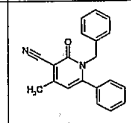
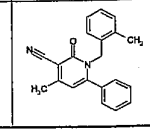
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 433 |  | D1 | D1 | III | A | NC | NC |
| 434 |  | B1 | B1 | IV | B | IV | B |
| 435 |  | D1 | C1 | IV | A | NC | NC |
| 436 |  | B1 | A1 | IV | B | III | B |
| 437 |  | B1 | A1 | III | A | III | B |
| 438 |  | B1 | A1 | III | C | III | B |
| 439 |  | B1 | B1 | IV | B | III | B |
| 440 |  | B1 | B1 | III | B | III | B |
| 441 |  | B1 | A1 | III | B | III | B |
| 442 |  | B1 | B1 | III | B | III | B |
| 443 |  | B1 | A1 | III | C | III | B |
| 444 |  | B1 | B1 | IV | B | IV | A |
| 445 |  | NC | D1 | NC | A | NC | NC |
| 446 |  | D1 | B1 | IV | A | NC | NC |

FIG. 1BU

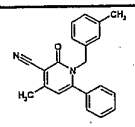
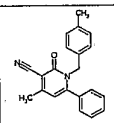
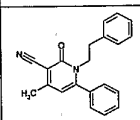
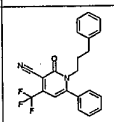
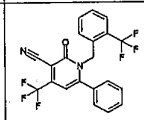
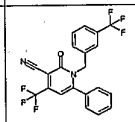
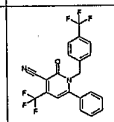
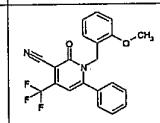
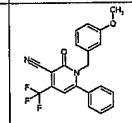
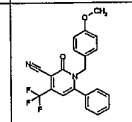
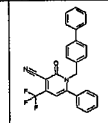
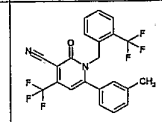
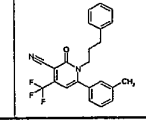
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 447 |  | D1 | D1 | NC | NC | NC | A |
| 448 |  | D1 | B1 | IV | B | NC | NC |
| 449 |  | D1 | D1 | NC | NC | NC | A |
| 450 |  | D1 | C1 | IV | B | IV | B |
| 451 |  | B1 | B1 | IV | B | IV | B |
| 452 |  | C1 | B1 | IV | B | IV | B |
| 453 |  | D1 | C1 | IV | A | IV | B |
| 454 |  | B1 | B1 | IV | B | IV | B |
| 455 |  | B1 | B1 | IV | B | IV | B |
| 456 |  | B1 | B1 | IV | B | IV | B |
| 457 |  | NC | NC | NC | A | NC | A |
| 458 |  | B1 | B1 | III | B | III | B |
| 459 |  | D1 | D1 | IV | A | IV | A |

FIG. 1BV

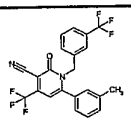
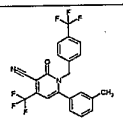
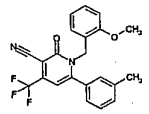
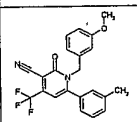
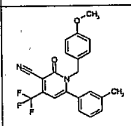
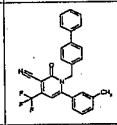
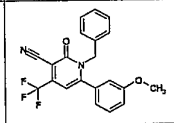
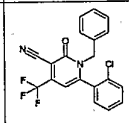
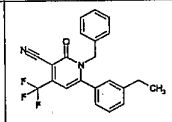
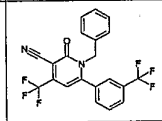
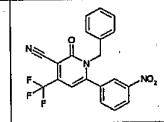
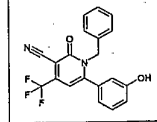
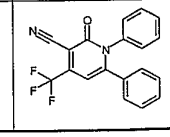
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 460 |  | C1 | B1 | III | B | III | B |
| 461 |  | D1 | D1 | IV | A | IV | B |
| 462 |  | B1 | B1 | III | B | IV | B |
| 463 |  | B1 | B1 | III | B | III | B |
| 464 |  | B1 | B1 | III | B | III | C |
| 465 |  | D1 | NC | NC | A | IV | A |
| 466 |  | B1 | B1 | IV | B | III | B |
| 467 |  | B1 | B1 | III | B | III | B |
| 468 |  | B1 | A1 | III | B | III | B |
| 469 |  | D1 | C1 | IV | A | IV | B |
| 470 |  | D1 | C1 | IV | A | IV | B |
| 471 |  | D1 | B1 | IV | B | IV | B |
| 472 |  | B1 | B1 | IV | B | IV | B |

FIG. 1BW

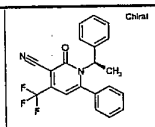
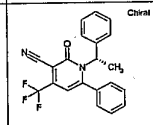
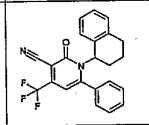
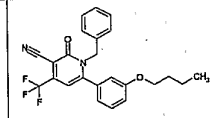
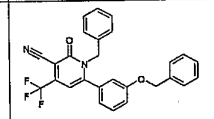
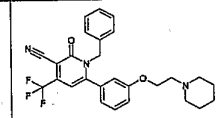
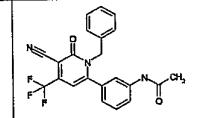
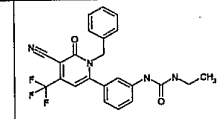
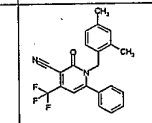
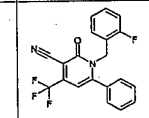
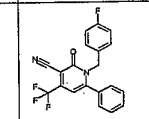
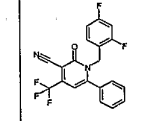
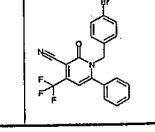
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 473 |  | D1 | C1 | IV | A | IV | B |
| 474 |  | D1 | C1 | IV | B | IV | B |
| 475 |  | D1 | C1 | IV | A | IV | B |
| 476 |  | D1 | C1 | IV | A | III | A |
| 477 |  | B1 | B1 | III | A | III | B |
| 478 |  | NC | D1 | NC | A | NC | A |
| 479 |  | D1 | B1 | IV | B | IV | C |
| 480 |  | D1 | D1 | NC | A | IV | B |
| 481 |  | B1 | A1 | III | C | III | B |
| 482 |  | B1 | A1 | III | B | III | B |
| 483 |  | B1 | B1 | IV | C | III | B |
| 484 |  | B1 | A1 | III | B | III | B |
| 485 |  | B1 | B1 | III | B | III | B |

FIG. 1BX

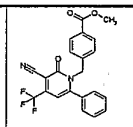
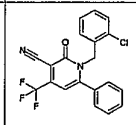
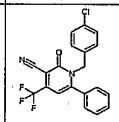
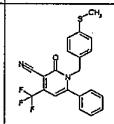
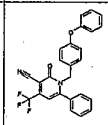
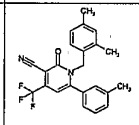
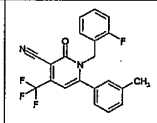
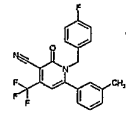
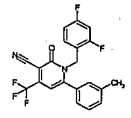
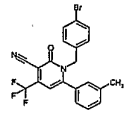
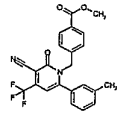
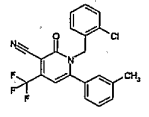
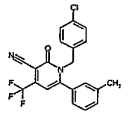
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 486 |  | C1 | B1 | IV | B | IV | B |
| 487 |  | B1 | B1 | III | C | III | C |
| 488 |  | B1 | A1 | III | B | III | B |
| 489 |  | C1 | B1 | IV | B | III | B |
| 490 |  | NC | D1 | NC | A | NC | A |
| 491 |  | A1 | A1 | III | C | II | B |
| 492 |  | B1 | A1 | III | B | III | B |
| 493 |  | B1 | A1 | III | B | III | B |
| 494 |  | B1 | A1 | III | B | III | B |
| 495 |  | B1 | B1 | III | C | III | B |
| 496 |  | B1 | B1 | III | C | III | B |
| 497 |  | B1 | A1 | III | B | III | B |
| 498 |  | B1 | A1 | III | C | III | B |

FIG. 1BY

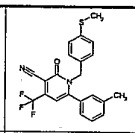
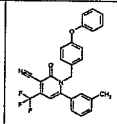
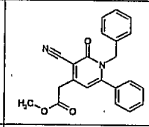
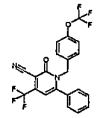
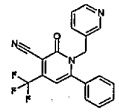
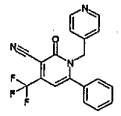
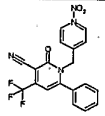
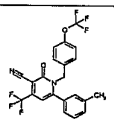
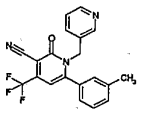
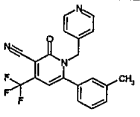
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 499 |  | B1 | B1 | III | B | III | B |
| 500 |  | NC | NC | NC | A | NC | A |
| 501 |  | NC | NC | NC | A | NC | A |
| 502 |  | D1 | D1 | IV | A | III | A |
| 503 |  | NC | D1 | IV | A | IV | B |
| 504 |  | NC | NC | NC | A | NC | A |
| 505 |  | B1 | A1 | III | B | III | C |
| 506 |  | D1 | D1 | IV | A | III | B |
| 507 |  | D1 | D1 | III | B | III | B |
| 508 |  | NC | NC | NC | A | NC | A |

FIG. 1BZ

SEQUENCE LISTING

<110> X-Ceptor Therapeutics, Inc.
Bayne Christopher D.
Johnson Alan T.
Lu Shao-Po
Mohan Raju
Griffith Ronald C.

<120> Modulators Of LXR

<130> 38205-3005PC

<140> Unassigned
<141> Herewith

<150> 60/342,707
<151> 2001-12-21

<160> 18

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 1528
<212> DNA
<213> Homo Sapien

<220>
<221> CDS
<222> (36)...(1379)

<300>
<308> GeneBank Nm_005693
<309> 2002-05-14

<400> 1

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cagtgccttg gtaatgacca gggctccaga aagag atg tcc ttg tgg ctg ggg     53
                                       Met Ser Leu Trp Leu Gly
                                        1               5

gcc cct gtg cct gac att cct cct gac tct gcg gtg gag ctg tgg aag   101
Ala Pro Val Pro Asp Ile Pro Pro Asp Ser Ala Val Glu Leu Trp Lys
            10                  15                  20

cca ggc gca cag gat gca agc agc cag gcc cag gga ggc agc agc tgc   149
Pro Gly Ala Gln Asp Ala Ser Ser Gln Ala Gln Gly Gly Ser Ser Cys
        25                  30                  35

atc ctc aga gag gaa gcc agg atg ccc cac tct gct ggg ggt act gca   197
Ile Leu Arg Glu Glu Ala Arg Met Pro His Ser Ala Gly Gly Thr Ala
    40                  45                  50

ggg gtg ggg ctg gag gct gca gag ccc aca gcc ctg ctc acc agg gca   245
Gly Val Gly Leu Glu Ala Ala Glu Pro Thr Ala Leu Leu Thr Arg Ala
55                  60                  65                  70

gag ccc cct tca gaa ccc aca gag atc cgt cca caa aag cgg aaa aag   293
Glu Pro Pro Ser Glu Pro Thr Glu Ile Arg Pro Gln Lys Arg Lys Lys
                75                  80                  85

ggg cca gcc ccc aaa atg ctg ggg aac gag cta tgc agc gtg tgt ggg   341
Gly Pro Ala Pro Lys Met Leu Gly Asn Glu Leu Cys Ser Val Cys Gly
            90                  95                  100
```

```
gac aag gcc tcg ggc ttc cac tac aat gtt ctg agc tgc gag ggc tgc   389
Asp Lys Ala Ser Gly Phe His Tyr Asn Val Leu Ser Cys Glu Gly Cys
        105                 110                 115

aag gga ttc ttc cgc cgc agc gtc atc aag gga gcg cac tac atc tgc   437
Lys Gly Phe Phe Arg Arg Ser Val Ile Lys Gly Ala His Tyr Ile Cys
    120                 125                 130

cac agt ggc ggc cac tgc ccc atg gac acc tac atg cgt cgc aag tgc   485
His Ser Gly Gly His Cys Pro Met Asp Thr Tyr Met Arg Arg Lys Cys
135                 140                 145                 150

cag gag tgt cgg ctt cgc aaa tgc cgt cag gct ggc atg cgg gag gag   533
Gln Glu Cys Arg Leu Arg Lys Cys Arg Gln Ala Gly Met Arg Glu Glu
                155                 160                 165

tgt gtc ctg tca gaa gaa cag atc cgc ctg aag aaa ctg aag cgg caa   581
Cys Val Leu Ser Glu Glu Gln Ile Arg Leu Lys Lys Leu Lys Arg Gln
            170                 175                 180

gag gag gaa cag gct cat gcc aca tcc ttg ccc ccc agg cgt tcc tca   629
Glu Glu Glu Gln Ala His Ala Thr Ser Leu Pro Pro Arg Arg Ser Ser
        185                 190                 195

ccc ccc caa atc ctg ccc cag ctc agc ccg gaa caa ctg ggc atg atc   677
Pro Pro Gln Ile Leu Pro Gln Leu Ser Pro Glu Gln Leu Gly Met Ile
    200                 205                 210

gag aag ctc gtc gct gcc cag caa cag tgt aac cgg cgc tcc ttt tct   725
Glu Lys Leu Val Ala Ala Gln Gln Gln Cys Asn Arg Arg Ser Phe Ser
215                 220                 225                 230

gac cgg ctt cga gtc acg cct tgg ccc atg gca cca gat ccc cat agc   773
Asp Arg Leu Arg Val Thr Pro Trp Pro Met Ala Pro Asp Pro His Ser
                235                 240                 245

cgg gag gcc cgt cag cag cgc ttt gcc cac ttc act gag ctg gcc atc   821
Arg Glu Ala Arg Gln Gln Arg Phe Ala His Phe Thr Glu Leu Ala Ile
            250                 255                 260

gtc tct gtg cag gag ata gtt gac ttt gct aaa cag cta ccc ggc ttc   869
Val Ser Val Gln Glu Ile Val Asp Phe Ala Lys Gln Leu Pro Gly Phe
        265                 270                 275

ctg cag ctc agc cgg gag gac cag att gcc ctg ctg aag acc tct gcg   917
Leu Gln Leu Ser Arg Glu Asp Gln Ile Ala Leu Leu Lys Thr Ser Ala
    280                 285                 290

atc gag gtg atg ctt ctg gag aca tct cgg agg tac aac cct ggg agt   965
Ile Glu Val Met Leu Leu Glu Thr Ser Arg Arg Tyr Asn Pro Gly Ser
295                 300                 305                 310

gag agt atc acc ttc ctc aag gat ttc agt tat aac cgg gaa gac ttt   1013
Glu Ser Ile Thr Phe Leu Lys Asp Phe Ser Tyr Asn Arg Glu Asp Phe
                315                 320                 325

gcc aaa gca ggg ctg caa gtg gaa ttc atc aac ccc atc ttc gag ttc   1061
Ala Lys Ala Gly Leu Gln Val Glu Phe Ile Asn Pro Ile Phe Glu Phe
            330                 335                 340

tcc agg gcc atg aat gag ctg caa ctc aat gat gcc gag ttt gcc ttg   1109
Ser Arg Ala Met Asn Glu Leu Gln Leu Asn Asp Ala Glu Phe Ala Leu
        345                 350                 355

ctc att gct atc agc atc ttc tct gca gac cgg ccc aac gtg cag gac   1157
Leu Ile Ala Ile Ser Ile Phe Ser Ala Asp Arg Pro Asn Val Gln Asp
    360                 365                 370
```

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cag ctc cag gtg gag agg ctg cag cac aca tat gtg gaa gcc ctg cat  1205
Gln Leu Gln Val Glu Arg Leu Gln His Thr Tyr Val Glu Ala Leu His
375                 380                 385                 390

gcc tac gtc tcc atc cac cat ccc cat gac cga ctg atg ttc cca cgg  1253
Ala Tyr Val Ser Ile His His Pro His Asp Arg Leu Met Phe Pro Arg
                395                 400                 405

atg cta atg aaa ctg gtg agc ctc cgg acc ctg agc agc gtc cac tca  1301
Met Leu Met Lys Leu Val Ser Leu Arg Thr Leu Ser Ser Val His Ser
            410                 415                 420

gag caa gtg ttt gca ctg cgt ctg cag gac aaa aag ctc cca ccg ctg  1349
Glu Gln Val Phe Ala Leu Arg Leu Gln Asp Lys Lys Leu Pro Pro Leu
        425                 430                 435

ctc tct gag atc tgg gat gtg cac gaa tga ctgttctgtc cccatatttt    1399
Leu Ser Glu Ile Trp Asp Val His Glu  *
    440                 445

ctgttttctt ggccggatgg ctgaggcctg gtggctgcct cctagaagtg gaacagactg 1459
agaagggcaa acattcctgg gagctgggca aggagatcct cccgtggcat taaaagagag 1519
tcaaagggt                                                        1528

<210> 2
<211> 447
<212> PRT
<213> Homo Sapien

<400> 2
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Ala Val Glu Leu Trp Lys Pro Gly Ala Gln Asp Ala Ser Ser Gln Ala
            20                  25                  30
Gln Gly Gly Ser Ser Cys Ile Leu Arg Glu Glu Ala Arg Met Pro His
        35                  40                  45
Ser Ala Gly Gly Thr Ala Gly Val Gly Leu Glu Ala Ala Glu Pro Thr
    50                  55                  60
Ala Leu Leu Thr Arg Ala Glu Pro Pro Ser Glu Pro Thr Glu Ile Arg
65                  70                  75                  80
Pro Gln Lys Arg Lys Lys Gly Pro Ala Pro Lys Met Leu Gly Asn Glu
                85                  90                  95
Leu Cys Ser Val Cys Gly Asp Lys Ala Ser Gly Phe His Tyr Asn Val
            100                 105                 110
Leu Ser Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Val Ile Lys
        115                 120                 125
Gly Ala His Tyr Ile Cys His Ser Gly Gly His Cys Pro Met Asp Thr
    130                 135                 140
Tyr Met Arg Arg Lys Cys Gln Glu Cys Arg Leu Arg Lys Cys Arg Gln
145                 150                 155                 160
Ala Gly Met Arg Glu Glu Cys Val Leu Ser Glu Glu Gln Ile Arg Leu
                165                 170                 175
Lys Lys Leu Lys Arg Gln Glu Glu Glu Gln Ala His Ala Thr Ser Leu
            180                 185                 190
Pro Pro Arg Arg Ser Ser Pro Pro Gln Ile Leu Pro Gln Leu Ser Pro
        195                 200                 205
Glu Gln Leu Gly Met Ile Glu Lys Leu Val Ala Ala Gln Gln Gln Cys
    210                 215                 220
Asn Arg Arg Ser Phe Ser Asp Arg Leu Arg Val Thr Pro Trp Pro Met
225                 230                 235                 240
Ala Pro Asp Pro His Ser Arg Glu Ala Arg Gln Gln Arg Phe Ala His
                245                 250                 255
Phe Thr Glu Leu Ala Ile Val Ser Val Gln Glu Ile Val Asp Phe Ala
            260                 265                 270
Lys Gln Leu Pro Gly Phe Leu Gln Leu Ser Arg Glu Asp Gln Ile Ala
        275                 280                 285
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Leu Leu Lys Thr Ser Ala Ile Glu Val Met Leu Leu Glu Thr Ser Arg
    290                 295                 300
Arg Tyr Asn Pro Gly Ser Glu Ser Ile Thr Phe Leu Lys Asp Phe Ser
305                 310                 315                 320
Tyr Asn Arg Glu Asp Phe Ala Lys Ala Gly Leu Gln Val Glu Phe Ile
                325                 330                 335
Asn Pro Ile Phe Glu Phe Ser Arg Ala Met Asn Glu Leu Gln Leu Asn
            340                 345                 350
Asp Ala Glu Phe Ala Leu Leu Ile Ala Ile Ser Ile Phe Ser Ala Asp
        355                 360                 365
Arg Pro Asn Val Gln Asp Gln Leu Gln Val Glu Arg Leu Gln His Thr
    370                 375                 380
Tyr Val Glu Ala Leu His Ala Tyr Val Ser Ile His His Pro His Asp
385                 390                 395                 400
Arg Leu Met Phe Pro Arg Met Leu Met Lys Leu Val Ser Leu Arg Thr
                405                 410                 415
Leu Ser Ser Val His Ser Glu Gln Val Phe Ala Leu Arg Leu Gln Asp
            420                 425                 430
Lys Lys Leu Pro Pro Leu Leu Ser Glu Ile Trp Asp Val His Glu
        435                 440                 445


<210> 3
<211> 1815
<212> DNA
<213> Homo Sapien

<220>
<221> CDS
<222> (56)...(1438)

<300>
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<309> 2002-08-01

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                                                               1

tcc tct cct acc acg agt tcc ctg gat acc ccc ctg cct gga aat ggc  106
Ser Ser Pro Thr Thr Ser Ser Leu Asp Thr Pro Leu Pro Gly Asn Gly
             5                  10                  15

ccc cct cag cct ggc gcc cct tct tct tca ccc act gta aag gag gag  154
Pro Pro Gln Pro Gly Ala Pro Ser Ser Ser Pro Thr Val Lys Glu Glu
         20                  25                  30

ggt ccg gag ccg tgg ccc ggg ggt ccg gac cct gat gtc cca ggc act  202
Gly Pro Glu Pro Trp Pro Gly Gly Pro Asp Pro Asp Val Pro Gly Thr
     35                  40                  45

gat gag gcc agc tca gcc tgc agc aca gac tgg gtc atc cca gat ccc  250
Asp Glu Ala Ser Ser Ala Cys Ser Thr Asp Trp Val Ile Pro Asp Pro
 50                  55                  60                  65

gaa gag gaa cca gag cgc aag cga aag aag ggc cca gcc ccg aag atg  298
Glu Glu Glu Pro Glu Arg Lys Arg Lys Lys Gly Pro Ala Pro Lys Met
                 70                  75                  80

ctg ggc cac gag ctt tgc cgt gtc tgt ggg gac aag gcc tcc ggc ttc  346
Leu Gly His Glu Leu Cys Arg Val Cys Gly Asp Lys Ala Ser Gly Phe
             85                  90                  95

cac tac aac gtg ctc agc tgc gaa ggc tgc aag ggc ttc ttc cgg cgc  394
His Tyr Asn Val Leu Ser Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg
        100                 105                 110
```

```
agt gtg gtc cgt ggt ggg gcc agg cgc tat gcc tgc cgg ggt ggc gga   442
Ser Val Val Arg Gly Gly Ala Arg Arg Tyr Ala Cys Arg Gly Gly Gly
    115                 120                 125

acc tgc cag atg gac gct ttc atg cgg cgc aag tgc cag cag tgc cgg   490
Thr Cys Gln Met Asp Ala Phe Met Arg Arg Lys Cys Gln Gln Cys Arg
130                 135                 140                 145

ctg cgc aag tgc aag gag gca ggg atg agg gag cag tgc gtc ctt tct   538
Leu Arg Lys Cys Lys Glu Ala Gly Met Arg Glu Gln Cys Val Leu Ser
                150                 155                 160

gaa gaa cag atc cgg aag aag aag att cgg aaa cag cag cag gag tca   586
Glu Glu Gln Ile Arg Lys Lys Lys Ile Arg Lys Gln Gln Gln Glu Ser
            165                 170                 175

cag tca cag tcg cag tca cct gtg ggg ccg cag ggc agc agc agc tca   634
Gln Ser Gln Ser Gln Ser Pro Val Gly Pro Gln Gly Ser Ser Ser Ser
        180                 185                 190

gcc tct ggg cct ggg gct tcc cct ggt gga tct gag gca ggc agc cag   682
Ala Ser Gly Pro Gly Ala Ser Pro Gly Gly Ser Glu Ala Gly Ser Gln
    195                 200                 205

ggc tcc ggg gaa ggc gag ggt gtc cag cta aca gcg gct caa gaa cta   730
Gly Ser Gly Glu Gly Glu Gly Val Gln Leu Thr Ala Ala Gln Glu Leu
210                 215                 220                 225

atg atc cag cag ttg gtg gcg gcc caa ctg cag tgc aac aaa cgc tcc   778
Met Ile Gln Gln Leu Val Ala Ala Gln Leu Gln Cys Asn Lys Arg Ser
                230                 235                 240

ttc tcc gac cag ccc aaa gtc acg ccc tgg ccc ctg ggc gca gac ccc   826
Phe Ser Asp Gln Pro Lys Val Thr Pro Trp Pro Leu Gly Ala Asp Pro
            245                 250                 255

cag tcc cga gat gcc cgc cag caa cgc ttt gcc cac ttc acg gag ctg   874
Gln Ser Arg Asp Ala Arg Gln Gln Arg Phe Ala His Phe Thr Glu Leu
        260                 265                 270

gcc atc atc tca gtc cag gag atc gtg gac ttc gct aag caa gtg cct   922
Ala Ile Ile Ser Val Gln Glu Ile Val Asp Phe Ala Lys Gln Val Pro
    275                 280                 285

ggt ttc ctg cag ctg ggc cgg gag gac cag atc gcc ctc ctg aag gca   970
Gly Phe Leu Gln Leu Gly Arg Glu Asp Gln Ile Ala Leu Leu Lys Ala
290                 295                 300                 305

tcc act atc gag atc atg ctg cta gag aca gcc agg cgc tac aac cac  1018
Ser Thr Ile Glu Ile Met Leu Leu Glu Thr Ala Arg Arg Tyr Asn His
                310                 315                 320

gag aca gag tgt atc acc ttc ttg aag gac ttc acc tac agc aag gac  1066
Glu Thr Glu Cys Ile Thr Phe Leu Lys Asp Phe Thr Tyr Ser Lys Asp
            325                 330                 335

gac ttc cac cgt gca ggc ctg cag gtg gag ttc atc aac ccc atc ttc  1114
Asp Phe His Arg Ala Gly Leu Gln Val Glu Phe Ile Asn Pro Ile Phe
        340                 345                 350

gag ttc tcg cgg gcc atg cgg cgg ctg ggc ctg gac gac gct gag tac  1162
Glu Phe Ser Arg Ala Met Arg Arg Leu Gly Leu Asp Asp Ala Glu Tyr
    355                 360                 365

gcc ctg ctc atc gcc atc aac atc ttc tcg gcc gac cgg ccc aac gtg  1210
Ala Leu Leu Ile Ala Ile Asn Ile Phe Ser Ala Asp Arg Pro Asn Val
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370                 375                 380                 385

cag gag ccg ggc cgc gtg gag gcg ttg cag cag ccc tac gtg gag gcg   1258
Gln Glu Pro Gly Arg Val Glu Ala Leu Gln Gln Pro Tyr Val Glu Ala
                390                 395                 400

ctg ctg tcc tac acg cgc atc aag agg ccg cag gac cag ctg cgc ttc   1306
Leu Leu Ser Tyr Thr Arg Ile Lys Arg Pro Gln Asp Gln Leu Arg Phe
            405                 410                 415

ccg cgc atg ctc atg aag ctg gtg agc ctg cgc acg ctg agc tct gtg   1354
Pro Arg Met Leu Met Lys Leu Val Ser Leu Arg Thr Leu Ser Ser Val
        420                 425                 430

cac tcg gag cag gtc ttc gcc ttg cgg ctc cag gac aag aag ctg ccg   1402
His Ser Glu Gln Val Phe Ala Leu Arg Leu Gln Asp Lys Lys Leu Pro
    435                 440                 445

cct ctg ctg tcg gag atc tgg gac gtc cac gag tga ggggctggcc        1448
Pro Leu Leu Ser Glu Ile Trp Asp Val His Glu  *
450                 455                 460

acccagcccc acagccttgc ctgaccaccc tccagcagat agacgccggc acccttcct 1508
cttcctaggg tggaaggggc cctgggccga gcctgtagac ctatcggctc tcatcccttg 1568
ggataagccc cagtccaggt ccaggaggct ccctccctgc ccagcgagtc ttccagaagg 1628
ggtgaaaggg ttgcaggtcc cgaccactga cccttcccgg ctgccctccc tccccagctt 1688
acacctcaag cccagcacgc agtgcacctt gaacagaggg aggggaggac ccatggctct 1748
ccccctagc ccgggagacc agggccttcc tcttcctctg cttttattta ataaaaacta 1808
aaaacag                                                          1815
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<210> 4
<211> 460
<212> PRT
<213> Homo Sapien

<400> 4

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Met Ser Ser Pro Thr Thr Ser Ser Leu Asp Thr Pro Leu Pro Gly Asn
 1               5                  10                  15
Gly Pro Pro Gln Pro Gly Ala Pro Ser Ser Ser Pro Thr Val Lys Glu
            20                  25                  30
Glu Gly Pro Glu Pro Trp Pro Gly Gly Pro Asp Pro Asp Val Pro Gly
        35                  40                  45
Thr Asp Glu Ala Ser Ser Ala Cys Ser Thr Asp Trp Val Ile Pro Asp
    50                  55                  60
Pro Glu Glu Glu Pro Glu Arg Lys Arg Lys Lys Gly Pro Ala Pro Lys
65                  70                  75                  80
Met Leu Gly His Glu Leu Cys Arg Val Cys Gly Asp Lys Ala Ser Gly
                85                  90                  95
Phe His Tyr Asn Val Leu Ser Cys Glu Gly Cys Lys Gly Phe Phe Arg
            100                 105                 110
Arg Ser Val Val Arg Gly Gly Ala Arg Arg Tyr Ala Cys Arg Gly Gly
        115                 120                 125
Gly Thr Cys Gln Met Asp Ala Phe Met Arg Arg Lys Cys Gln Gln Cys
    130                 135                 140
Arg Leu Arg Lys Cys Lys Glu Ala Gly Met Arg Glu Gln Cys Val Leu
145                 150                 155                 160
Ser Glu Glu Gln Ile Arg Lys Lys Lys Ile Arg Lys Gln Gln Gln Glu
                165                 170                 175
Ser Gln Ser Gln Ser Gln Ser Pro Val Gly Pro Gln Gly Ser Ser Ser
            180                 185                 190
Ser Ala Ser Gly Pro Gly Ala Ser Pro Gly Gly Ser Glu Ala Gly Ser
        195                 200                 205
Gln Gly Ser Gly Glu Gly Glu Gly Val Gln Leu Thr Ala Ala Gln Glu
    210                 215                 220
Leu Met Ile Gln Gln Leu Val Ala Ala Gln Leu Gln Cys Asn Lys Arg
225                 230                 235                 240
Ser Phe Ser Asp Gln Pro Lys Val Thr Pro Trp Pro Leu Gly Ala Asp
```

```
                245                 250                 255
Pro Gln Ser Arg Asp Ala Arg Gln Gln Arg Phe Ala His Phe Thr Glu
            260                 265                 270
Leu Ala Ile Ile Ser Val Gln Glu Ile Val Asp Phe Ala Lys Gln Val
        275                 280                 285
Pro Gly Phe Leu Gln Leu Gly Arg Glu Asp Gln Ile Ala Leu Leu Lys
    290                 295                 300
Ala Ser Thr Ile Glu Ile Met Leu Leu Glu Thr Ala Arg Arg Tyr Asn
305                 310                 315                 320
His Glu Thr Glu Cys Ile Thr Phe Leu Lys Asp Phe Thr Tyr Ser Lys
                325                 330                 335
Asp Asp Phe His Arg Ala Gly Leu Gln Val Glu Phe Ile Asn Pro Ile
            340                 345                 350
Phe Glu Phe Ser Arg Ala Met Arg Arg Leu Gly Leu Asp Asp Ala Glu
        355                 360                 365
Tyr Ala Leu Leu Ile Ala Ile Asn Ile Phe Ser Ala Asp Arg Pro Asn
    370                 375                 380
Val Gln Glu Pro Gly Arg Val Glu Ala Leu Gln Gln Pro Tyr Val Glu
385                 390                 395                 400
Ala Leu Leu Ser Tyr Thr Arg Ile Lys Arg Pro Gln Asp Gln Leu Arg
                405                 410                 415
Phe Pro Arg Met Leu Met Lys Leu Val Ser Leu Arg Thr Leu Ser Ser
            420                 425                 430
Val His Ser Glu Gln Val Phe Ala Leu Arg Leu Gln Asp Lys Lys Leu
        435                 440                 445
Pro Pro Leu Leu Ser Glu Ile Trp Asp Val His Glu
    450                 455                 460
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<210> 5
<211> 2070
<212> DNA
<213> Rattus norvegicus

<220>
<221> CDS
<222> (172)...(1581)

<300>
<308> GeneBank U18374
<309> 1995-06-21

<400> 5

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atcctctcag ggccttggac gtctctgacc caaaacaatc caaggttctt atttgaagac 120
caccatccca gaagcacatt ctcgagttga aaagttggag tggtgttcga a atg aat  177
                                                        Met Asn
                                                         1

ctg att ggg ccc tcc cat tta caa gcc acg gac gag ttt gct ctt tct   225
Leu Ile Gly Pro Ser His Leu Gln Ala Thr Asp Glu Phe Ala Leu Ser
 5                   10                  15

gaa aac tta ttt gga gtg cta aca gag cac gcg gca ggt cct ctg ggg   273
Glu Asn Leu Phe Gly Val Leu Thr Glu His Ala Ala Gly Pro Leu Gly
     20                  25                  30

cag aat ctg gac ttg gaa tcg tac tcc cca tac aac aat gtg cag ttt   321
Gln Asn Leu Asp Leu Glu Ser Tyr Ser Pro Tyr Asn Asn Val Gln Phe
 35                  40                  45                  50

cct caa gtt cag cca cag atc tcc tcc tcg tcc tat tat tcc aac ctg   369
Pro Gln Val Gln Pro Gln Ile Ser Ser Ser Ser Tyr Tyr Ser Asn Leu
                 55                  60                  65

ggt ttc tac ccg caa caa ccg gaa gac tgg tac tct cct gga ctc tat   417
Gly Phe Tyr Pro Gln Gln Pro Glu Asp Trp Tyr Ser Pro Gly Leu Tyr
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                70                  75                  80

gaa ctc agg cga atg ccc act gag agt gtg tac cag gga gag act gag   465
Glu Leu Arg Arg Met Pro Thr Glu Ser Val Tyr Gln Gly Glu Thr Glu
        85                  90                  95

gta tcc gag atg cct gtg aca aag aag ccg cga atg gcc gcc tca tcg   513
Val Ser Glu Met Pro Val Thr Lys Lys Pro Arg Met Ala Ala Ser Ser
    100                 105                 110

gcg gga aga ata aaa ggg gat gag ctg tgt gtg gtc tgc gga gac agg   561
Ala Gly Arg Ile Lys Gly Asp Glu Leu Cys Val Val Cys Gly Asp Arg
115                 120                 125                 130

gcc tct ggg tac cat tac aac gcg ctc acc tgc gag ggc tgc aaa ggt   609
Ala Ser Gly Tyr His Tyr Asn Ala Leu Thr Cys Glu Gly Cys Lys Gly
                135                 140                 145

ttc ttc cga aga agc atc acc aaa aac gcc gtg tac aag tgt aag aac   657
Phe Phe Arg Arg Ser Ile Thr Lys Asn Ala Val Tyr Lys Cys Lys Asn
            150                 155                 160

ggg ggc aac tgc gtg atg gat atg tac atg cgt cgg aag tgc cag gat   705
Gly Gly Asn Cys Val Met Asp Met Tyr Met Arg Arg Lys Cys Gln Asp
        165                 170                 175

tgc cgg cta agg aag tgc aga gag atg gga atg ttg gct gaa tgt ttg   753
Cys Arg Leu Arg Lys Cys Arg Glu Met Gly Met Leu Ala Glu Cys Leu
    180                 185                 190

tta act gaa att cag tgt aaa tct aaa cgg cta agg aaa aat gtg aag   801
Leu Thr Glu Ile Gln Cys Lys Ser Lys Arg Leu Arg Lys Asn Val Lys
195                 200                 205                 210

cag cat gcg gat cag aca gtg aat gag gac agc gaa ggg cgt gac ttg   849
Gln His Ala Asp Gln Thr Val Asn Glu Asp Ser Glu Gly Arg Asp Leu
                215                 220                 225

cgg caa gtg acc tcc acg acc aag cta tgc agg gag aaa act gaa ctc   897
Arg Gln Val Thr Ser Thr Thr Lys Leu Cys Arg Glu Lys Thr Glu Leu
            230                 235                 240

act gta gac cag cag acc ctc ctg gat tat att atg gac tca tac agc   945
Thr Val Asp Gln Gln Thr Leu Leu Asp Tyr Ile Met Asp Ser Tyr Ser
        245                 250                 255

aaa cag aga atg cca cag gag atc aca aat aaa atc tta aaa gaa gaa   993
Lys Gln Arg Met Pro Gln Glu Ile Thr Asn Lys Ile Leu Lys Glu Glu
    260                 265                 270

ttt agt gca gaa gaa aat ttt ctc ata tta aca gaa atg gct acc agt   1041
Phe Ser Ala Glu Glu Asn Phe Leu Ile Leu Thr Glu Met Ala Thr Ser
275                 280                 285                 290

cac gta cag att ctc gta gaa ttc aca aaa aga ctt cca ggg ttt cag   1089
His Val Gln Ile Leu Val Glu Phe Thr Lys Arg Leu Pro Gly Phe Gln
                295                 300                 305

aca ctg gac cac gaa gac cag att gct ttg ctc aaa ggg tcc gca gtc   1137
Thr Leu Asp His Glu Asp Gln Ile Ala Leu Leu Lys Gly Ser Ala Val
            310                 315                 320

gag gcc atg ttc ctt cgt tca gcg gag att ttc aat aag aaa ctt cct   1185
Glu Ala Met Phe Leu Arg Ser Ala Glu Ile Phe Asn Lys Lys Leu Pro
        325                 330                 335

gcc gga cac gca gac ctg ttg gaa gaa aga att cga aag agc ggc atc   1233
```

```
Ala Gly His Ala Asp Leu Leu Glu Glu Arg Ile Arg Lys Ser Gly Ile
    340                 345                 350

tcc gat gag tac ata acc ccg atg ttt agt ttc tat aaa agt gtc ggg  1281
Ser Asp Glu Tyr Ile Thr Pro Met Phe Ser Phe Tyr Lys Ser Val Gly
355                 360                 365                 370

gag ctg aaa atg acc cag gaa gag tac gct ctg ctc aca gca att gtc  1329
Glu Leu Lys Met Thr Gln Glu Glu Tyr Ala Leu Leu Thr Ala Ile Val
                375                 380                 385

atc ctc tct cca gac aga caa tac ata aag gat aga gag gca gtg gag  1377
Ile Leu Ser Pro Asp Arg Gln Tyr Ile Lys Asp Arg Glu Ala Val Glu
            390                 395                 400

aag ctt cag gag cct ctg ctc gat gtc cta caa aaa ctc tgc aag atc  1425
Lys Leu Gln Glu Pro Leu Leu Asp Val Leu Gln Lys Leu Cys Lys Ile
        405                 410                 415

tac cag ccc gag aac cct cag cat ttc gcc tgc ctc ctg ggt cgc ctg  1473
Tyr Gln Pro Glu Asn Pro Gln His Phe Ala Cys Leu Leu Gly Arg Leu
    420                 425                 430

aca gaa ctc cgg aca ttc aac cat cac cac gct gag atg ctg atg tct  1521
Thr Glu Leu Arg Thr Phe Asn His His His Ala Glu Met Leu Met Ser
435                 440                 445                 450

tgg agg gtg aat gac cac aag ttc acc ccg ctc ctc tgt gag atc tgg  1569
Trp Arg Val Asn Asp His Lys Phe Thr Pro Leu Leu Cys Glu Ile Trp
                455                 460                 465

gat gtg cag tga aggacacggg gagaggctag ctccttgtcc tcctcagagc      1621
Asp Val Gln  *


agcaacctgg tattggactt cccttctttt catttgtacc aggtctcact caagaatctc 1681
aatgaatatt tatgtggcaa ttatacaatt cccacaactg taaatacagg ctccatagaa 1741
ttgcttcccc tacactgtat tttacaaggc ttcgggaaac cccactgaca cgccctttt 1801
gcctcattaa atcaattgtt acttcaattt tgtcaactga gctagggacc gcctcgtttt 1861
atcctccatg cggcaacatt atatatatat atattttatc aaatagctgt tttctcttcc 1921
ttttttttt ttttttttt cggagctggg gactgaaccc agggccttgc gcttgctagg 1981
caagcgctct accactgagc taaatcccca acccctatta aatagctgtt ttcaactgag 2041
acaataaact gaacgtaatg ccaagagaa                                   2070

<210> 6
<211> 469
<212> PRT
<213> Rattus norvegicus

<400> 6
Met Asn Leu Ile Gly Pro Ser His Leu Gln Ala Thr Asp Glu Phe Ala
 1               5                  10                  15
Leu Ser Glu Asn Leu Phe Gly Val Leu Thr Glu His Ala Ala Gly Pro
            20                  25                  30
Leu Gly Gln Asn Leu Asp Leu Glu Ser Tyr Ser Pro Tyr Asn Asn Val
        35                  40                  45
Gln Phe Pro Gln Val Gln Pro Gln Ile Ser Ser Ser Ser Tyr Tyr Ser
    50                  55                  60
Asn Leu Gly Phe Tyr Pro Gln Gln Pro Glu Asp Trp Tyr Ser Pro Gly
65                  70                  75                  80
Leu Tyr Glu Leu Arg Arg Met Pro Thr Glu Ser Val Tyr Gln Gly Glu
                85                  90                  95
Thr Glu Val Ser Glu Met Pro Val Thr Lys Lys Pro Arg Met Ala Ala
            100                 105                 110
Ser Ser Ala Gly Arg Ile Lys Gly Asp Glu Leu Cys Val Val Cys Gly
        115                 120                 125
Asp Arg Ala Ser Gly Tyr His Tyr Asn Ala Leu Thr Cys Glu Gly Cys
```

```
    130                 135                 140
Lys Gly Phe Phe Arg Arg Ser Ile Thr Lys Asn Ala Val Tyr Lys Cys
145                 150                 155                 160
Lys Asn Gly Gly Asn Cys Val Met Asp Met Tyr Met Arg Arg Lys Cys
                165                 170                 175
Gln Asp Cys Arg Leu Arg Lys Cys Arg Glu Met Gly Met Leu Ala Glu
            180                 185                 190
Cys Leu Leu Thr Glu Ile Gln Cys Lys Ser Lys Arg Leu Arg Lys Asn
        195                 200                 205
Val Lys Gln His Ala Asp Gln Thr Val Asn Glu Asp Ser Glu Gly Arg
    210                 215                 220
Asp Leu Arg Gln Val Thr Ser Thr Thr Lys Leu Cys Arg Glu Lys Thr
225                 230                 235                 240
Glu Leu Thr Val Asp Gln Gln Thr Leu Leu Asp Tyr Ile Met Asp Ser
                245                 250                 255
Tyr Ser Lys Gln Arg Met Pro Gln Glu Ile Thr Asn Lys Ile Leu Lys
            260                 265                 270
Glu Glu Phe Ser Ala Glu Glu Asn Phe Leu Ile Leu Thr Glu Met Ala
        275                 280                 285
Thr Ser His Val Gln Ile Leu Val Glu Phe Thr Lys Arg Leu Pro Gly
    290                 295                 300
Phe Gln Thr Leu Asp His Glu Asp Gln Ile Ala Leu Leu Lys Gly Ser
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Ala Val Glu Ala Met Phe Leu Arg Ser Ala Glu Ile Phe Asn Lys Lys
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Leu Pro Ala Gly His Ala Asp Leu Leu Glu Glu Arg Ile Arg Lys Ser
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Gly Ile Ser Asp Glu Tyr Ile Thr Pro Met Phe Ser Phe Tyr Lys Ser
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Val Gly Glu Leu Lys Met Thr Gln Glu Glu Tyr Ala Leu Leu Thr Ala
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Ile Val Ile Leu Ser Pro Asp Arg Gln Tyr Ile Lys Asp Arg Glu Ala
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Val Glu Lys Leu Gln Glu Pro Leu Leu Asp Val Leu Gln Lys Leu Cys
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Lys Ile Tyr Gln Pro Glu Asn Pro Gln His Phe Ala Cys Leu Leu Gly
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Arg Leu Thr Glu Leu Arg Thr Phe Asn His His His Ala Glu Met Leu
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Glu Phe Ser Phe Ser Glu Asn Leu Phe Gly Val Leu Thr Glu Gln Val
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gca ggt cct ctg gga cag aac ctg gaa gtg gaa cca tac tcg caa tac   500
Ala Gly Pro Leu Gly Gln Asn Leu Glu Val Glu Pro Tyr Ser Gln Tyr
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agc aat gtt cag ttt ccc caa gtt caa cca cag att tcc tcg tca tcc   548
Ser Asn Val Gln Phe Pro Gln Val Gln Pro Gln Ile Ser Ser Ser Ser
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tat tat tcc aac ctg ggt ttc tac ccc cag cag cct gaa gag tgg tac   596
Tyr Tyr Ser Asn Leu Gly Phe Tyr Pro Gln Gln Pro Glu Glu Trp Tyr
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Ser Pro Gly Ile Tyr Glu Leu Arg Arg Met Pro Ala Glu Thr Leu Tyr
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cag gga gaa act gag gta gca gag atg cct gta aca aag aag ccc cgc   692
Gln Gly Glu Thr Glu Val Ala Glu Met Pro Val Thr Lys Lys Pro Arg
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Met Gly Ala Ser Ala Gly Arg Ile Lys Gly Asp Glu Leu Cys Val Val
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Ala Glu Cys Leu Leu Thr Glu Ile Gln Cys Lys Ser Lys Arg Leu Arg
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Gly Arg Asp Leu Arg Gln Val Thr Ser Thr Thr Lys Ser Cys Arg Glu
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aaa act gaa ctc acc cca gat caa cag act ctt cta cat ttt att atg   1124
Lys Thr Glu Leu Thr Pro Asp Gln Gln Thr Leu Leu His Phe Ile Met
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atg gca acc aat cat gta cag gtt ctt gta gaa ttc aca aaa aag cta   1268
Met Ala Thr Asn His Val Gln Val Leu Val Glu Phe Thr Lys Lys Leu
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aaa agt att ggg gaa ctg aaa atg act caa gag gag tat gct ctg ctt   1508
Lys Ser Ile Gly Glu Leu Lys Met Thr Gln Glu Glu Tyr Ala Leu Leu
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aca gca att gtt atc ctg tct cca gat aga caa tac ata aag gat aga   1556
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Cys Glu Ile Trp Asp Val Gln  *
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Glu Gly Arg Asp Leu Arg Gln Val Thr Ser Thr Thr Lys Ser Cys Arg
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Glu Lys Thr Glu Leu Thr Pro Asp Gln Gln Thr Leu Leu His Phe Ile
245 250 255
Met Asp Ser Tyr Asn Lys Gln Arg Met Pro Gln Glu Ile Thr Asn Lys
260 265 270
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Glu Met Ala Thr Asn His Val Gln Val Leu Val Glu Phe Thr Lys Lys
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Tyr Lys Ser Ile Gly Glu Leu Lys Met Thr Gln Glu Glu Tyr Ala Leu
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385 390 395 400
Arg Glu Ala Val Glu Lys Leu Gln Glu Pro Leu Leu Asp Val Leu Gln
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Val Asn Ser Ser Leu Thr Ser Pro Thr Gly Arg Gly Ser Met Ala Ala
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Pro Ser Leu His Pro Ser Leu Gly Pro Gly Ile Gly Ser Pro Gly Gln
35 40 45

ctg cat tct ccc atc agc acc ctg agc tcc ccc atc aac ggc atg ggc 254
Leu His Ser Pro Ile Ser Thr Leu Ser Ser Pro Ile Asn Gly Met Gly
50 55 60

ccg cct ttc tcg gtc atc agc tcc ccc atg ggc ccc cac tcc atg tcg 302
Pro Pro Phe Ser Val Ile Ser Ser Pro Met Gly Pro His Ser Met Ser
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Met Ala Ser Phe Thr Lys His Ile Cys Ala Ile Cys Gly Asp Arg Ser
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gca gcc gac aaa cag ctt ttc acc ctg gtg gag tgg gcc aag cgg atc   926
Ala Ala Asp Lys Gln Leu Phe Thr Leu Val Glu Trp Ala Lys Arg Ile
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cca cac ttc tca gag ctg ccc ctg gac gac cag gtc atc ctg ctg cgg   974
Pro His Phe Ser Glu Leu Pro Leu Asp Asp Gln Val Ile Leu Leu Arg
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Ala Gly Trp Asn Glu Leu Leu Ile Ala Ser Phe Ser His Arg Ser Ile
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gcc gtg aag gac ggg atc ctc ctg gcc acc ggg ctg cac gtc cac cgg   1070
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aac agc gcc cac agc gca ggg gtg ggc gcc atc ttt gac agg gtg ctg   1118
Asn Ser Ala His Ser Ala Gly Val Gly Ala Ile Phe Asp Arg Val Leu
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acg gag ctt gtg tcc aag atg cgg gac atg cag atg gac aag acg gag   1166
Thr Glu Leu Val Ser Lys Met Arg Asp Met Gln Met Asp Lys Thr Glu
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Leu Ser Asn Pro Ala Glu Val Glu Ala Leu Arg Glu Lys Val Tyr Ala
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Ser Leu Glu Ala Tyr Cys Lys His Lys Tyr Pro Glu Gln Pro Gly Arg
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Leu His Pro Ser Leu Gly Pro Gly Ile Gly Ser Pro Gly Gln Leu His
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Ser Pro Ile Ser Thr Leu Ser Ser Pro Ile Asn Gly Met Gly Pro Pro
    50                  55                  60
Phe Ser Val Ile Ser Ser Pro Met Gly Pro His Ser Met Ser Val Pro
65                  70                  75                  80
Thr Thr Pro Thr Leu Gly Phe Ser Thr Gly Ser Pro Gln Leu Ser Ser
                85                  90                  95
Pro Met Asn Pro Val Ser Ser Ser Glu Asp Ile Lys Pro Pro Leu Gly
            100                 105                 110
Leu Asn Gly Val Leu Lys Val Pro Ala His Pro Ser Gly Asn Met Ala
        115                 120                 125
Ser Phe Thr Lys His Ile Cys Ala Ile Cys Gly Asp Arg Ser Ser Gly
    130                 135                 140
Lys His Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys Gly Phe Phe Lys
145                 150                 155                 160
Arg Thr Val Arg Lys Asp Leu Thr Tyr Thr Cys Arg Asp Asn Lys Asp
                165                 170                 175
Cys Leu Ile Asp Lys Arg Gln Arg Asn Arg Cys Gln Tyr Cys Arg Tyr
            180                 185                 190
Gln Lys Cys Leu Ala Met Gly Met Lys Arg Glu Ala Val Gln Glu Glu
        195                 200                 205
Arg Gln Arg Gly Lys Asp Arg Asn Glu Asn Glu Val Glu Ser Thr Ser
    210                 215                 220
Ser Ala Asn Glu Asp Met Pro Val Glu Arg Ile Leu Glu Ala Glu Leu
225                 230                 235                 240
Ala Val Glu Pro Lys Thr Glu Thr Tyr Val Glu Ala Asn Met Gly Leu
                245                 250                 255
Asn Pro Ser Ser Pro Asn Asp Pro Val Thr Asn Ile Cys Gln Ala Ala
            260                 265                 270
Asp Lys Gln Leu Phe Thr Leu Val Glu Trp Ala Lys Arg Ile Pro His
        275                 280                 285
Phe Ser Glu Leu Pro Leu Asp Asp Gln Val Ile Leu Leu Arg Ala Gly
    290                 295                 300
Trp Asn Glu Leu Leu Ile Ala Ser Phe Ser His Arg Ser Ile Ala Val
305                 310                 315                 320
Lys Asp Gly Ile Leu Leu Ala Thr Gly Leu His Val His Arg Asn Ser
                325                 330                 335
Ala His Ser Ala Gly Val Gly Ala Ile Phe Asp Arg Val Leu Thr Glu
            340                 345                 350
Leu Val Ser Lys Met Arg Asp Met Gln Met Asp Lys Thr Glu Leu Gly
        355                 360                 365
Cys Leu Arg Ala Ile Val Leu Phe Asn Pro Asp Ser Lys Gly Leu Ser
    370                 375                 380
Asn Pro Ala Glu Val Glu Ala Leu Arg Glu Lys Val Tyr Ala Ser Leu
385                 390                 395                 400
Glu Ala Tyr Cys Lys His Lys Tyr Pro Glu Gln Pro Gly Arg Phe Ala
                405                 410                 415
Lys Leu Leu Leu Arg Leu Pro Ala Leu Arg Ser Ile Gly Leu Lys Cys
            420                 425                 430
Leu Glu His Leu Phe Phe Phe Lys Leu Ile Gly Asp Thr Pro Ile Asp
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Thr Phe Leu Met Glu Met Leu Glu Ala Pro His Gln Met Thr
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atcacagctt agcgctctgt ggcctgcctg gccacatcca tccaac atg gtg gac 175
Met Val Asp
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Thr Glu Ser Pro Ile Cys Pro Leu Ser Pro Leu Glu Ala Asp Asp Leu
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gaa agt ccc tta tct gaa gaa ttc tta caa gaa atg gga aac att caa 271
Glu Ser Pro Leu Ser Glu Glu Phe Leu Gln Glu Met Gly Asn Ile Gln
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gag att tct cag tcc atc ggt gag gag agc tct gga agc ttt ggt ttt 319
Glu Ile Ser Gln Ser Ile Gly Glu Glu Ser Ser Gly Ser Phe Gly Phe
40 45 50

gca gac tac cag tac tta gga agc tgt ccg ggc tcc gag ggc tct gtc 367
Ala Asp Tyr Gln Tyr Leu Gly Ser Cys Pro Gly Ser Glu Gly Ser Val
55 60 65

atc aca gac acc ctc tct cca cgt tcc agc cct tcc tca gtc agc tgc 415
Ile Thr Asp Thr Leu Ser Pro Arg Ser Ser Pro Ser Ser Val Ser Cys
70 75 80

ccc gtg atc ccc gcc agc acg gac gag tcc ccc ggc agt gcc ctg aac 463
Pro Val Ile Pro Ala Ser Thr Asp Glu Ser Pro Gly Ser Ala Leu Asn
85 90 95

atc gag tgt cga ata tgt ggg gac aag gcc tca ggg tac cac tac gga 511
Ile Glu Cys Arg Ile Cys Gly Asp Lys Ala Ser Gly Tyr His Tyr Gly
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gtt cac gca tgt gaa ggc tgt aag ggc ttc ttt cgg cga act att cgg 559
Val His Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Thr Ile Arg
120 125 130

ctg aag ctg gtg tac gac aag tgt gat cgg agc tgc aag att cag aag 607
Leu Lys Leu Val Tyr Asp Lys Cys Asp Arg Ser Cys Lys Ile Gln Lys
135 140 145

aag aac cgg aac aaa tgc cag tac tgc cgt ttt cac aag tgc ctg tct 655
Lys Asn Arg Asn Lys Cys Gln Tyr Cys Arg Phe His Lys Cys Leu Ser
150 155 160

gtc ggg atg tca cac aat gca att cgc ttt gga aga atg cca aga tct 703
Val Gly Met Ser His Asn Ala Ile Arg Phe Gly Arg Met Pro Arg Ser
165 170 175

gaa aaa gca aaa ctg aaa gca gaa att ctt acc tgt gaa cac gac ctg 751
Glu Lys Ala Lys Leu Lys Ala Glu Ile Leu Thr Cys Glu His Asp Leu
180 185 190 195

aaa gat tcg gaa act gca gac ctc aaa tct ctg ggc aag aga atc cac 799
Lys Asp Ser Glu Thr Ala Asp Leu Lys Ser Leu Gly Lys Arg Ile His
200 205 210

gaa gcc tac ctg aag aac ttc aac atg aac aag gtc aag gcc cgg gtc 847

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ata ctc gcg gga aag acc agc aac aac ccg cct ttt gtc ata cat gac   895
Ile Leu Ala Gly Lys Thr Ser Asn Asn Pro Pro Phe Val Ile His Asp
        230                 235                 240

atg gag acc ttg tgt atg gcc gag aag acg ctt gtg gcc aag atg gtg   943
Met Glu Thr Leu Cys Met Ala Glu Lys Thr Leu Val Ala Lys Met Val
    245                 250                 255

gcc aac ggc gtc gaa gac aaa gag gca gag gtc cga ttc ttc cac tgc   991
Ala Asn Gly Val Glu Asp Lys Glu Ala Glu Val Arg Phe Phe His Cys
260                 265                 270                 275

tgc cag tgc atg tcc gtg gag acc gtc acg gag ctc aca gaa ttt gcc  1039
Cys Gln Cys Met Ser Val Glu Thr Val Thr Glu Leu Thr Glu Phe Ala
                280                 285                 290

aag gct atc cca ggc ttt gca aac ttg gac ttg aac gac caa gtc acc  1087
Lys Ala Ile Pro Gly Phe Ala Asn Leu Asp Leu Asn Asp Gln Val Thr
            295                 300                 305

ttg cta aag tac ggt gtg tat gaa gcc atc ttc acg atg ctg tcc tcc  1135
Leu Leu Lys Tyr Gly Val Tyr Glu Ala Ile Phe Thr Met Leu Ser Ser
        310                 315                 320

ttg atg aac aaa gac ggg atg ctg atc gcg tac ggc aat ggc ttt atc  1183
Leu Met Asn Lys Asp Gly Met Leu Ile Ala Tyr Gly Asn Gly Phe Ile
    325                 330                 335

aca cgc gag ttc ctt aag aac ctg agg aag ccg ttc tgt gac atc atg  1231
Thr Arg Glu Phe Leu Lys Asn Leu Arg Lys Pro Phe Cys Asp Ile Met
340                 345                 350                 355

gaa ccc aag ttt gac ttc gct atg aag ttc aat gcc tta gaa ctg gat  1279
Glu Pro Lys Phe Asp Phe Ala Met Lys Phe Asn Ala Leu Glu Leu Asp
                360                 365                 370

gac agt gac att tcc ctg ttt gtg gct gct ata att tgc tgt gga gat  1327
Asp Ser Asp Ile Ser Leu Phe Val Ala Ala Ile Ile Cys Cys Gly Asp
            375                 380                 385

cgg cct ggc ctt cta aac ata ggc tac att gag aag ttg cag gag ggg  1375
Arg Pro Gly Leu Leu Asn Ile Gly Tyr Ile Glu Lys Leu Gln Glu Gly
        390                 395                 400

att gtg cac gtg ctt aag ctc cac ctg cag agc aac cat cca gat gac  1423
Ile Val His Val Leu Lys Leu His Leu Gln Ser Asn His Pro Asp Asp
    405                 410                 415

acc ttc ctc ttc cca aag ctc ctt caa aaa atg gtg gac ctt cgg cag  1471
Thr Phe Leu Phe Pro Lys Leu Leu Gln Lys Met Val Asp Leu Arg Gln
420                 425                 430                 435

ctg gtc acg gag cat gcg cag ctc gta cag gtc atc aag aag acc gag  1519
Leu Val Thr Glu His Ala Gln Leu Val Gln Val Ile Lys Lys Thr Glu
                440                 445                 450

tcc gac gca gcg ctg cac cca ctg ttg caa gag atc tac aga gac atg  1567
Ser Asp Ala Ala Leu His Pro Leu Leu Gln Glu Ile Tyr Arg Asp Met
            455                 460                 465

tac tga tctttcctga gatggcaggc cattaccact gttcagggac ctccgaggcc  1623
Tyr  *
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tgaagagggc tgagcgtagg taatgcgggc tctccccaca tcctttctga atgggcactt 1743
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35 40 45
Phe Gly Phe Ala Asp Tyr Gln Tyr Leu Gly Ser Cys Pro Gly Ser Glu
50 55 60
Gly Ser Val Ile Thr Asp Thr Leu Ser Pro Arg Ser Ser Pro Ser Ser
65 70 75 80
Val Ser Cys Pro Val Ile Pro Ala Ser Thr Asp Glu Ser Pro Gly Ser
85 90 95
Ala Leu Asn Ile Glu Cys Arg Ile Cys Gly Asp Lys Ala Ser Gly Tyr
100 105 110
His Tyr Gly Val His Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg
115 120 125
Thr Ile Arg Leu Lys Leu Val Tyr Asp Lys Cys Asp Arg Ser Cys Lys
130 135 140
Ile Gln Lys Lys Asn Arg Asn Lys Cys Gln Tyr Cys Arg Phe His Lys
145 150 155 160
Cys Leu Ser Val Gly Met Ser His Asn Ala Ile Arg Phe Gly Arg Met
165 170 175
Pro Arg Ser Glu Lys Ala Lys Leu Lys Ala Glu Ile Leu Thr Cys Glu
180 185 190
His Asp Leu Lys Asp Ser Glu Thr Ala Asp Leu Lys Ser Leu Gly Lys
195 200 205
Arg Ile His Glu Ala Tyr Leu Lys Asn Phe Asn Met Asn Lys Val Lys
210 215 220
Ala Arg Val Ile Leu Ala Gly Lys Thr Ser Asn Asn Pro Pro Phe Val
225 230 235 240
Ile His Asp Met Glu Thr Leu Cys Met Ala Glu Lys Thr Leu Val Ala
245 250 255
Lys Met Val Ala Asn Gly Val Glu Asp Lys Glu Ala Glu Val Arg Phe
260 265 270
Phe His Cys Cys Gln Cys Met Ser Val Glu Thr Val Thr Glu Leu Thr
275 280 285
Glu Phe Ala Lys Ala Ile Pro Gly Phe Ala Asn Leu Asp Leu Asn Asp
290 295 300
Gln Val Thr Leu Leu Lys Tyr Gly Val Tyr Glu Ala Ile Phe Thr Met
305 310 315 320
Leu Ser Ser Leu Met Asn Lys Asp Gly Met Leu Ile Ala Tyr Gly Asn
325 330 335
Gly Phe Ile Thr Arg Glu Phe Leu Lys Asn Leu Arg Lys Pro Phe Cys
340 345 350
Asp Ile Met Glu Pro Lys Phe Asp Phe Ala Met Lys Phe Asn Ala Leu
355 360 365
Glu Leu Asp Asp Ser Asp Ile Ser Leu Phe Val Ala Ala Ile Ile Cys
370 375 380
Cys Gly Asp Arg Pro Gly Leu Leu Asn Ile Gly Tyr Ile Glu Lys Leu
385 390 395 400
Gln Glu Gly Ile Val His Val Leu Lys Leu His Leu Gln Ser Asn His
405 410 415

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Pro Asp Asp Thr Phe Leu Phe Pro Lys Leu Leu Gln Lys Met Val Asp
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Leu Arg Gln Leu Val Thr Glu His Ala Gln Leu Val Gln Val Ile Lys
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Lys Thr Glu Ser Asp Ala Ala Leu His Pro Leu Leu Gln Glu Ile Tyr
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gag gaa gtg gcc atg ggt gac gga gcc ccg gag ctc aat ggg gga cca   96
Glu Glu Val Ala Met Gly Asp Gly Ala Pro Glu Leu Asn Gly Gly Pro
             20                  25                  30

gaa cac acg ctt cct tcc agc agc tgt gca gac ctc tcc cag aat tcc   144
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         35                  40                  45

tcc cct tcc tcc ctg ctg gac cag ctg cag atg ggc tgt gat ggg gcc   192
Ser Pro Ser Ser Leu Leu Asp Gln Leu Gln Met Gly Cys Asp Gly Ala
     50                  55                  60

tca ggc ggc agc ctc aac atg gaa tgt cgg gtg tgc ggg gac aag gcc   240
Ser Gly Gly Ser Leu Asn Met Glu Cys Arg Val Cys Gly Asp Lys Ala
 65                  70                  75                  80

tcg ggc ttc cac tac ggg gtc cac gcg tgc gag ggg tgc aag ggc ttc   288
Ser Gly Phe His Tyr Gly Val His Ala Cys Glu Gly Cys Lys Gly Phe
                 85                  90                  95

ttc cgc cgg aca atc cgc atg aag ctc gag tat gag aag tgc gat cgg   336
Phe Arg Arg Thr Ile Arg Met Lys Leu Glu Tyr Glu Lys Cys Asp Arg
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atc tgc aag atc cag aag aag aac cgc aac aag tgt cag tac tgc cgc   384
Ile Cys Lys Ile Gln Lys Lys Asn Arg Asn Lys Cys Gln Tyr Cys Arg
        115                 120                 125

ttc cag aag tgc ctg gca ctc ggc atg tcg cac aac gct atc cgc ttt   432
Phe Gln Lys Cys Leu Ala Leu Gly Met Ser His Asn Ala Ile Arg Phe
    130                 135                 140

gga cgg atg ccg gac ggc gag aag agg aag ctg gtg gcg ggg ctg act   480
Gly Arg Met Pro Asp Gly Glu Lys Arg Lys Leu Val Ala Gly Leu Thr
145                 150                 155                 160

gcc agc gag ggg tgc cag cac aac ccc cag ctg gcc gac ctg aag gcc   528
Ala Ser Glu Gly Cys Gln His Asn Pro Gln Leu Ala Asp Leu Lys Ala
                165                 170                 175
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ttc tct aag cac atc tac aac gcc tac ctg aaa aac ttc aac atg acc   576
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            180                 185                 190

aaa aag aag gcc cgg agc atc ctc acc ggc aag tcc agc cac aac gca   624
Lys Lys Lys Ala Arg Ser Ile Leu Thr Gly Lys Ser Ser His Asn Ala
        195                 200                 205

ccc ttt gtc atc cac gac atc gag aca ctg tgg cag gca gag aag ggc   672
Pro Phe Val Ile His Asp Ile Glu Thr Leu Trp Gln Ala Glu Lys Gly
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ctg gtg tgg aaa cag ctg gtg aac ggg ctg ccg ccc tac aac gag atc   720
Leu Val Trp Lys Gln Leu Val Asn Gly Leu Pro Pro Tyr Asn Glu Ile
225                 230                 235                 240

agt gtg cac gtg ttc tac cgc tgc cag tcc acc aca gtg gag aca gtc   768
Ser Val His Val Phe Tyr Arg Cys Gln Ser Thr Thr Val Glu Thr Val
                245                 250                 255

cga gag ctc acc gag ttc gcc aag aac atc ccc aac ttc agc agc ctc   816
Arg Glu Leu Thr Glu Phe Ala Lys Asn Ile Pro Asn Phe Ser Ser Leu
            260                 265                 270

ttc ctc aat gac cag gtg acc ctc ctc aag tat ggc gtg cac gag gcc   864
Phe Leu Asn Asp Gln Val Thr Leu Leu Lys Tyr Gly Val His Glu Ala
        275                 280                 285

atc ttt gcc atg ctg gcc tcc atc gtc aac aaa gac ggg ctg ctg gtg   912
Ile Phe Ala Met Leu Ala Ser Ile Val Asn Lys Asp Gly Leu Leu Val
    290                 295                 300

gcc aac ggc agt ggc ttc gtc acc cac gag ttc ttg cga agt ctc cgc   960
Ala Asn Gly Ser Gly Phe Val Thr His Glu Phe Leu Arg Ser Leu Arg
305                 310                 315                 320

aag ccc ttc agt gac atc att gag ccc aag ttc gag ttt gct gtc aag  1008
Lys Pro Phe Ser Asp Ile Ile Glu Pro Lys Phe Glu Phe Ala Val Lys
                325                 330                 335

ttc aat gcg ctg gag ctc gat gac agt gac ctg gcg ctc ttc atc gcg  1056
Phe Asn Ala Leu Glu Leu Asp Asp Ser Asp Leu Ala Leu Phe Ile Ala
            340                 345                 350

gcc atc att ctg tgt gga gac cgg cca ggc ctc atg aat gtg ccc cag  1104
Ala Ile Ile Leu Cys Gly Asp Arg Pro Gly Leu Met Asn Val Pro Gln
        355                 360                 365

gta gaa gcc atc cag gac acc att ctg cgg gct cta gaa ttc cat ctg  1152
Val Glu Ala Ile Gln Asp Thr Ile Leu Arg Ala Leu Glu Phe His Leu
    370                 375                 380

cag gtc aac cac cct gac agc cag tac ctc ttc ccc aag ctg ctg cag  1200
Gln Val Asn His Pro Asp Ser Gln Tyr Leu Phe Pro Lys Leu Leu Gln
385                 390                 395                 400

aag atg gca gac ctg cgg cag ctg gtc act gag cat gcc cag atg atg  1248
Lys Met Ala Asp Leu Arg Gln Leu Val Thr Glu His Ala Gln Met Met
                405                 410                 415

cag tgg cta aag aag acg gag agt gag acc ttg ctg cac ccc ctg ctc  1296
Gln Trp Leu Lys Lys Thr Glu Ser Glu Thr Leu Leu His Pro Leu Leu
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435 440

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            20                  25                  30
Glu His Thr Leu Pro Ser Ser Ser Cys Ala Asp Leu Ser Gln Asn Ser
        35                  40                  45
Ser Pro Ser Ser Leu Leu Asp Gln Leu Gln Met Gly Cys Asp Gly Ala
    50                  55                  60
Ser Gly Gly Ser Leu Asn Met Glu Cys Arg Val Cys Gly Asp Lys Ala
65                  70                  75                  80
Ser Gly Phe His Tyr Gly Val His Ala Cys Glu Gly Cys Lys Gly Phe
                85                  90                  95
Phe Arg Arg Thr Ile Arg Met Lys Leu Glu Tyr Glu Lys Cys Asp Arg
            100                 105                 110
Ile Cys Lys Ile Gln Lys Lys Asn Arg Asn Lys Cys Gln Tyr Cys Arg
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Phe Gln Lys Cys Leu Ala Leu Gly Met Ser His Asn Ala Ile Arg Phe
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Gly Arg Met Pro Asp Gly Glu Lys Arg Lys Leu Val Ala Gly Leu Thr
145                 150                 155                 160
Ala Ser Glu Gly Cys Gln His Asn Pro Gln Leu Ala Asp Leu Lys Ala
                165                 170                 175
Phe Ser Lys His Ile Tyr Asn Ala Tyr Leu Lys Asn Phe Asn Met Thr
            180                 185                 190
Lys Lys Lys Ala Arg Ser Ile Leu Thr Gly Lys Ser Ser His Asn Ala
        195                 200                 205
Pro Phe Val Ile His Asp Ile Glu Thr Leu Trp Gln Ala Glu Lys Gly
    210                 215                 220
Leu Val Trp Lys Gln Leu Val Asn Gly Leu Pro Pro Tyr Asn Glu Ile
225                 230                 235                 240
Ser Val His Val Phe Tyr Arg Cys Gln Ser Thr Thr Val Glu Thr Val
                245                 250                 255
Arg Glu Leu Thr Glu Phe Ala Lys Asn Ile Pro Asn Phe Ser Ser Leu
            260                 265                 270
Phe Leu Asn Asp Gln Val Thr Leu Leu Lys Tyr Gly Val His Glu Ala
        275                 280                 285
Ile Phe Ala Met Leu Ala Ser Ile Val Asn Lys Asp Gly Leu Leu Val
    290                 295                 300
Ala Asn Gly Ser Gly Phe Val Thr His Glu Phe Leu Arg Ser Leu Arg
305                 310                 315                 320
Lys Pro Phe Ser Asp Ile Ile Glu Pro Lys Phe Glu Phe Ala Val Lys
                325                 330                 335
Phe Asn Ala Leu Glu Leu Asp Asp Ser Asp Leu Ala Leu Phe Ile Ala
            340                 345                 350
Ala Ile Ile Leu Cys Gly Asp Arg Pro Gly Leu Met Asn Val Pro Gln
        355                 360                 365
Val Glu Ala Ile Gln Asp Thr Ile Leu Arg Ala Leu Glu Phe His Leu
    370                 375                 380
Gln Val Asn His Pro Asp Ser Gln Tyr Leu Phe Pro Lys Leu Leu Gln
385                 390                 395                 400
Lys Met Ala Asp Leu Arg Gln Leu Val Thr Glu His Ala Gln Met Met
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Met Tyr
1

gga aat tat tct cac ttc atg aag ttt ccc gca ggc tat gga ggc tcc 345
Gly Asn Tyr Ser His Phe Met Lys Phe Pro Ala Gly Tyr Gly Gly Ser
5 10 15

cct ggc cac act ggc tct aca tcc atg agc cca tca gca gcc ttg tcc 393
Pro Gly His Thr Gly Ser Thr Ser Met Ser Pro Ser Ala Ala Leu Ser
20 25 30

aca ggg aag cca atg gac agc cac ccc agc tac aca gat acc cca gtg 441
Thr Gly Lys Pro Met Asp Ser His Pro Ser Tyr Thr Asp Thr Pro Val
35 40 45 50

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Ser Ala Pro Arg Thr Leu Ser Ala Val Gly Thr Pro Leu Asn Ala Leu
55 60 65

ggc tct cca tat cga gtc atc acc tct gcc atg ggc cca ccc tca gga 537
Gly Ser Pro Tyr Arg Val Ile Thr Ser Ala Met Gly Pro Pro Ser Gly
70 75 80

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Ala Leu Ala Ala Pro Pro Gly Ile Asn Leu Val Ala Pro Pro Ser Ser
85 90 95

cag cta aat gtg gtc aac agt gtc agc agt tca gag gac atc aag ccc 633
Gln Leu Asn Val Val Asn Ser Val Ser Ser Ser Glu Asp Ile Lys Pro
100 105 110

tta cca ggg ctt ccc ggg att gga aac atg aac tac cca tcc acc agc 681
Leu Pro Gly Leu Pro Gly Ile Gly Asn Met Asn Tyr Pro Ser Thr Ser
115 120 125 130

ccc gga tct ctg gtt aaa cac atc tgt gcc atc tgt gga gac aga tcc 729
Pro Gly Ser Leu Val Lys His Ile Cys Ala Ile Cys Gly Asp Arg Ser
135 140 145

tca gga aag cac tac ggg gta tac agt tgt gaa ggc tgc aaa ggg ttc 777
Ser Gly Lys His Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys Gly Phe
150 155 160

ttc aag agg acg ata agg aag gac ctc atc tac acg tgt cgg gat aat 825
Phe Lys Arg Thr Ile Arg Lys Asp Leu Ile Tyr Thr Cys Arg Asp Asn
165 170 175

aaa gac tgc ctc att gac aag cgt cag cgc aac cgc tgc cag tac tgt 873

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195                 200                 205                 210

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                215                 220                 225

gct acc agt ggt cat gaa gac atg cct gtg gag agg att cta gaa gct   1017
Ala Thr Ser Gly His Glu Asp Met Pro Val Glu Arg Ile Leu Glu Ala
            230                 235                 240

gaa ctt gct gtt gaa cca aag aca gaa tcc tat ggt gac atg aat atg   1065
Glu Leu Ala Val Glu Pro Lys Thr Glu Ser Tyr Gly Asp Met Asn Met
        245                 250                 255

gag aac tcg aca aat gac cct gtt acc aac ata tgt cat gct gct gac   1113
Glu Asn Ser Thr Asn Asp Pro Val Thr Asn Ile Cys His Ala Ala Asp
    260                 265                 270

aag cag ctt ttc acc ctc gtt gaa tgg gcc aag cgt att ccc cac ttc   1161
Lys Gln Leu Phe Thr Leu Val Glu Trp Ala Lys Arg Ile Pro His Phe
275                 280                 285                 290

tct gac ctc acc ttg gag gac cag gtc att ttg ctt cgg gca ggg tgg   1209
Ser Asp Leu Thr Leu Glu Asp Gln Val Ile Leu Leu Arg Ala Gly Trp
                295                 300                 305

aat gaa ttg ctg att gcc tct ttc tcc cac cgc tca gtt tcc gtg cag   1257
Asn Glu Leu Leu Ile Ala Ser Phe Ser His Arg Ser Val Ser Val Gln
            310                 315                 320

gat ggc atc ctt ctg gcc acg ggt tta cat gtc cac cgg agc agt gcc   1305
Asp Gly Ile Leu Leu Ala Thr Gly Leu His Val His Arg Ser Ser Ala
        325                 330                 335

cac agt gct ggg gtc ggc tcc atc ttt gac aga gtc cta act gag ctg   1353
His Ser Ala Gly Val Gly Ser Ile Phe Asp Arg Val Leu Thr Glu Leu
    340                 345                 350

gtt tcc aaa atg aaa gac atg cag atg gac aag tcg gaa ctg gga tgc   1401
Val Ser Lys Met Lys Asp Met Gln Met Asp Lys Ser Glu Leu Gly Cys
355                 360                 365                 370

ctg cga gcc att gta ctc ttt aac cca gat gcc aag ggc ctg tcc aac   1449
Leu Arg Ala Ile Val Leu Phe Asn Pro Asp Ala Lys Gly Leu Ser Asn
                375                 380                 385

ccc tct gag gtg gag act ctg cga gag aag gtt tat gcc acc ctt gag   1497
Pro Ser Glu Val Glu Thr Leu Arg Glu Lys Val Tyr Ala Thr Leu Glu
            390                 395                 400

gcc tac acc aag cag aag tat ccg gaa cag cca ggc agg ttt gcc aag   1545
Ala Tyr Thr Lys Gln Lys Tyr Pro Glu Gln Pro Gly Arg Phe Ala Lys
        405                 410                 415

ctg ctg ctg cgc ctc cca gct ctg cgt tcc att ggc ttg aaa tgc ctg   1593
Leu Leu Leu Arg Leu Pro Ala Leu Arg Ser Ile Gly Leu Lys Cys Leu
    420                 425                 430

gag cac ctc ttc ttc ttc aag ctc atc ggg gac acc ccc att gac acc   1641
Glu His Leu Phe Phe Phe Lys Leu Ile Gly Asp Thr Pro Ile Asp Thr
435                 440                 445                 450
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ttc ctc atg gag atg ttg gag acc ccg ctg cag atc acc tga 1683
Phe Leu Met Glu Met Leu Glu Thr Pro Leu Gln Ile Thr *
455 460

gccccaccag ccacagcctc cccacccagg atgacccctg ggcaggtgtg tgtggacccc 1743
caccctgcac tttcctccac ctcccaccct gacccccttc ctgtccccaa aatgtgatgc 1803
ttataataaa gaaaaccttt ctac 1827

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<211> 463
<212> PRT
<213> Homo Sapien

<400> 16
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20 25 30
Leu Ser Thr Gly Lys Pro Met Asp Ser His Pro Ser Tyr Thr Asp Thr
35 40 45
Pro Val Ser Ala Pro Arg Thr Leu Ser Ala Val Gly Thr Pro Leu Asn
50 55 60
Ala Leu Gly Ser Pro Tyr Arg Val Ile Thr Ser Ala Met Gly Pro Pro
65 70 75 80
Ser Gly Ala Leu Ala Ala Pro Pro Gly Ile Asn Leu Val Ala Pro Pro
85 90 95
Ser Ser Gln Leu Asn Val Val Asn Ser Val Ser Ser Ser Glu Asp Ile
100 105 110
Lys Pro Leu Pro Gly Leu Pro Gly Ile Gly Asn Met Asn Tyr Pro Ser
115 120 125
Thr Ser Pro Gly Ser Leu Val Lys His Ile Cys Ala Ile Cys Gly Asp
130 135 140
Arg Ser Ser Gly Lys His Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys
145 150 155 160
Gly Phe Phe Lys Arg Thr Ile Arg Lys Asp Leu Ile Tyr Thr Cys Arg
165 170 175
Asp Asn Lys Asp Cys Leu Ile Asp Lys Arg Gln Arg Asn Arg Cys Gln
180 185 190
Tyr Cys Arg Tyr Gln Lys Cys Leu Val Met Gly Met Lys Arg Glu Ala
195 200 205
Val Gln Glu Glu Arg Gln Arg Ser Arg Glu Arg Ala Glu Ser Glu Ala
210 215 220
Glu Cys Ala Thr Ser Gly His Glu Asp Met Pro Val Glu Arg Ile Leu
225 230 235 240
Glu Ala Glu Leu Ala Val Glu Pro Lys Thr Glu Ser Tyr Gly Asp Met
245 250 255
Asn Met Glu Asn Ser Thr Asn Asp Pro Val Thr Asn Ile Cys His Ala
260 265 270
Ala Asp Lys Gln Leu Phe Thr Leu Val Glu Trp Ala Lys Arg Ile Pro
275 280 285
His Phe Ser Asp Leu Thr Leu Glu Asp Gln Val Ile Leu Leu Arg Ala
290 295 300
Gly Trp Asn Glu Leu Leu Ile Ala Ser Phe Ser His Arg Ser Val Ser
305 310 315 320
Val Gln Asp Gly Ile Leu Leu Ala Thr Gly Leu His Val His Arg Ser
325 330 335
Ser Ala His Ser Ala Gly Val Gly Ser Ile Phe Asp Arg Val Leu Thr
340 345 350
Glu Leu Val Ser Lys Met Lys Asp Met Gln Met Asp Lys Ser Glu Leu
355 360 365
Gly Cys Leu Arg Ala Ile Val Leu Phe Asn Pro Asp Ala Lys Gly Leu
370 375 380
Ser Asn Pro Ser Glu Val Glu Thr Leu Arg Glu Lys Val Tyr Ala Thr
385 390 395 400
Leu Glu Ala Tyr Thr Lys Gln Lys Tyr Pro Glu Gln Pro Gly Arg Phe
405 410 415
Ala Lys Leu Leu Leu Arg Leu Pro Ala Leu Arg Ser Ile Gly Leu Lys

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            420                 425                 430
Cys Leu Glu His Leu Phe Phe Phe Lys Leu Ile Gly Asp Thr Pro Ile
        435                 440                 445
Asp Thr Phe Leu Met Glu Met Leu Glu Thr Pro Leu Gln Ile Thr
    450                 455                 460
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<210> 17
<211> 1330
<212> DNA
<213> Homo Sapien

<220>
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<300>
<308> GeneBank XM_042579
<309> 2002-02-06

<400> 17

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gaatgtgcat tgcagggcct tgcttagtgg taggga atg att tcc atc act tct   114
                                          Met Ile Ser Ile Thr Ser
                                           1               5

gtg aca ttc tgc ttc cca ata agt ctt cct gtg act tcc cta ttt ccc   162
Val Thr Phe Cys Phe Pro Ile Ser Leu Pro Val Thr Ser Leu Phe Pro
            10                  15                  20

cca tcc cag att aac tca aca gtg tca ctc cct ggg ggt ggg tct ggc   210
Pro Ser Gln Ile Asn Ser Thr Val Ser Leu Pro Gly Gly Gly Ser Gly
        25                  30                  35

ccc cct gaa gat gtg aag cca cca gtc tta ggg gtc cgg ggc ctg cac   258
Pro Pro Glu Asp Val Lys Pro Pro Val Leu Gly Val Arg Gly Leu His
    40                  45                  50

tgt cca ccc cct cca ggt ggc cct ggg gct ggc aaa cgg cta tgt gca   306
Cys Pro Pro Pro Pro Gly Gly Pro Gly Ala Gly Lys Arg Leu Cys Ala
55                  60                  65                  70

atc tgc ggg gac aga agc tca ggc aaa cac tac ggg gtt tac agc tgt   354
Ile Cys Gly Asp Arg Ser Ser Gly Lys His Tyr Gly Val Tyr Ser Cys
                75                  80                  85

gag ggt tgc aag ggc ttc ttc aaa cgc acc atc cgc aaa gac ctt aca   402
Glu Gly Cys Lys Gly Phe Phe Lys Arg Thr Ile Arg Lys Asp Leu Thr
            90                  95                  100

tac tct tgc cgg gac aac aaa gac tgc aca gtg gac aag cgc cag cgg   450
Tyr Ser Cys Arg Asp Asn Lys Asp Cys Thr Val Asp Lys Arg Gln Arg
        105                 110                 115

aac cgc tgt cag tac tgc cgc tat cag aag tgc ctg gcc act ggc atg   498
Asn Arg Cys Gln Tyr Cys Arg Tyr Gln Lys Cys Leu Ala Thr Gly Met
    120                 125                 130

aag agg gag gcg gta cag gag gag cgt cag cgg gga aag gac aag gat   546
Lys Arg Glu Ala Val Gln Glu Glu Arg Gln Arg Gly Lys Asp Lys Asp
135                 140                 145                 150

ggg gat ggg gag ggg gct ggg gga gcc ccc gag gag atg cct gtg gac   594
Gly Asp Gly Glu Gly Ala Gly Gly Ala Pro Glu Glu Met Pro Val Asp
                155                 160                 165

agg atc ctg gag gca gag ctt gct gtg gaa cag aag agt gac cag ggc   642
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Arg Ile Leu Glu Ala Glu Leu Ala Val Glu Gln Lys Ser Asp Gln Gly
            170                 175                 180

gtt gag ggt cct ggg gga acc ggg ggt agc ggc agc agc gtg agt gtt   690
Val Glu Gly Pro Gly Gly Thr Gly Gly Ser Gly Ser Ser Val Ser Val
        185                 190                 195

ggg gtc aat cca ctc tcc ttc gtg atg ggg gtt ggg gga ggc agt cta   738
Gly Val Asn Pro Leu Ser Phe Val Met Gly Val Gly Gly Gly Ser Leu
    200                 205                 210

ggt ctg ttc tac atc ccc tcc ccc tcc ttt ccc ctc ata acc ttc cta   786
Gly Leu Phe Tyr Ile Pro Ser Pro Ser Phe Pro Leu Ile Thr Phe Leu
215                 220                 225                 230

aca cta ctt ggg act gga ggt gct gcc aaa caa ggt ctt tca aac atc   834
Thr Leu Leu Gly Thr Gly Gly Ala Ala Lys Gln Gly Leu Ser Asn Ile
                235                 240                 245

tga ggtggatgtg atagctcctt ctgtctccac tccccaaaca acccactggc        887
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agaaccatag gcatgtccca aataaataat tgtttgcact aatgccagaa gagaagactc 947
acttacaggg attggtttgg atggggctca caggaagact atatgtaagg agggggtgtc 1007
aaaagcctct tacaaggggg ctcccagcat atctcaaaat cttccataac tcttaccccc 1067
gtcccctgca gccaaatgac cctgtgacta acatctgtca ggcagctgac aaacagctat 1127
tcacgcttgt tgagtgggcg aagaggatcc cacacttttc ctccttgcct ctggatgatc 1187
aggtcatatt gctgcgggca ggtcagtgac cttggatccc tttgacttct tgacatttga 1247
ccccctctttg acttcccgat ctttagtgac cccagtggcc ttaccttgcg tacccaggga 1307
gccaaacttg ctgacctcgc cac                                        1330

<210> 18
<211> 246
<212> PRT
<213> Homo Sapien

<400> 18

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Met Ile Ser Ile Thr Ser Val Thr Phe Cys Phe Pro Ile Ser Leu Pro
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Val Thr Ser Leu Phe Pro Pro Ser Gln Ile Asn Ser Thr Val Ser Leu
            20                  25                  30
Pro Gly Gly Gly Ser Gly Pro Pro Glu Asp Val Lys Pro Pro Val Leu
        35                  40                  45
Gly Val Arg Gly Leu His Cys Pro Pro Pro Pro Gly Gly Pro Gly Ala
    50                  55                  60
Gly Lys Arg Leu Cys Ala Ile Cys Gly Asp Arg Ser Ser Gly Lys His
65                  70                  75                  80
Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys Gly Phe Phe Lys Arg Thr
                85                  90                  95
Ile Arg Lys Asp Leu Thr Tyr Ser Cys Arg Asp Asn Lys Asp Cys Thr
            100                 105                 110
Val Asp Lys Arg Gln Arg Asn Arg Cys Gln Tyr Cys Arg Tyr Gln Lys
        115                 120                 125
Cys Leu Ala Thr Gly Met Lys Arg Glu Ala Val Gln Glu Glu Arg Gln
    130                 135                 140
Arg Gly Lys Asp Lys Asp Gly Asp Gly Glu Gly Ala Gly Gly Ala Pro
145                 150                 155                 160
Glu Glu Met Pro Val Asp Arg Ile Leu Glu Ala Glu Leu Ala Val Glu
                165                 170                 175
Gln Lys Ser Asp Gln Gly Val Glu Gly Pro Gly Gly Thr Gly Gly Ser
            180                 185                 190
Gly Ser Ser Val Ser Val Gly Val Asn Pro Leu Ser Phe Val Met Gly
        195                 200                 205
Val Gly Gly Gly Ser Leu Gly Leu Phe Tyr Ile Pro Ser Pro Ser Phe
    210                 215                 220
Pro Leu Ile Thr Phe Leu Thr Leu Leu Gly Thr Gly Gly Ala Ala Lys
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225 230 235 240
Gln Gly Leu Ser Asn Ile
245