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(54) Benævnelse: **Antiinfektøse pyrimidiner og anvendelser heraf.**

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Description

FIELD OF THE INVENTION

5 **[0001]** This invention is directed to: (a) a crystalline form of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide or a crystalline form of a salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide; (b) compositions comprising such a crystalline form; (c) methods
10 for preparing such a crystalline form; (d) such a crystalline form for use in inhibiting replication of an RNA virus; and (e) a process for preparing a compound corresponding in structure to formula I-L0 as defined below.

BACKGROUND OF THE INVENTION

15

[0002] Hepatitis C is a blood-borne, infectious, viral disease that is caused by a hepatotropic virus called HCV. At least six different HCV genotypes (with several subtypes within each genotype) are known to date. In North America, HCV genotype 1a predominates, followed by HCV genotypes 1b, 2a, 2b, and 3a. In
20 the United States, HCV genotypes 1, 2, and 3 are the most common, with about 80% of the hepatitis C patients having HCV genotype 1. In Europe, HCV genotype 1b is predominant, followed by HCV genotypes 2a, 2b, 2c, and 3a. HCV genotypes 4 and 5 are found almost exclusively in Africa. As discussed below, the patient's HCV genotype is clinically important in determining the patient's
25 potential response to therapy and the required duration of such therapy.

[0003] An HCV infection can cause liver inflammation (hepatitis) that is often asymptomatic, but ensuing chronic hepatitis can result in cirrhosis of the liver (fibrotic scarring of the liver), liver cancer, and/or liver failure. The World Health
30 Organization estimates that about 170 million persons worldwide are chronically infected with HCV, and from about three to about four million persons are newly infected globally each year. According to the Centers for Disease Control and Prevention, about four million people in the United States are infected with

HCV. Co-infection with the human immunodeficiency virus (HIV) is common, and rates of HCV infection among HIV positive populations are higher.

[0004] There is a small chance of clearing the virus spontaneously, but the majority of patients with chronic hepatitis C will not clear it without treatment. Indications for treatment typically include proven HCV infection and persistent abnormal liver function tests. There are two treatment regimens that are primarily used to treat hepatitis C: monotherapy (using an interferon agent - either a "conventional" or longer-acting pegylated interferon) and combination therapy (using an interferon agent and ribavirin). Interferon, which is injected into the bloodstream, works by bolstering the immune response to HCV; and ribavirin, which is taken orally, is believed to work by preventing HCV replication. De Francesco et al in *Nature*, 463(18), 2005, pp953-960 and in *Antiviral Research*, 58 (2003), ppl-16 review a number of molecules that inhibit the NS3-4A serine protease and NS5B polymerase enzymes in HCV. In the second of these documents, ribavirin is exemplified as a nucleoside analogue that inhibits the NS5B polymerase enzyme in HCV. Taken alone, ribavirin does not effectively suppress HCV levels, but an interferon/ribavirin combination is more effective than interferon alone. Typically, hepatitis C is treated with a combination of pegylated interferon alpha and ribavirin for a period of 24 or 48 weeks, depending on the HCV genotype.

[0005] The goal of treatment is sustained viral response -- meaning that HCV is not measurable in the blood after therapy is completed. Following treatment with a combination of pegylated interferon alpha and ribavirin, sustained cure rates (sustained viral response) of about 75% or better occur in people with HCV genotypes 2 and 3 in 24 weeks of treatment, about 50% in those with HCV genotype 1 with 48 weeks of treatment, and about 65% in those with HCV genotype 4 in 48 weeks of treatment.

30

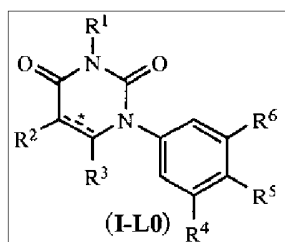
[0006] Treatment may be physically demanding, particularly for those with prior history of drug or alcohol abuse, because both interferon and ribavirin have numerous side effects. Common interferon-associated side effects include flu-like

symptoms, extreme fatigue, nausea, loss of appetite, thyroid problems, high blood sugar, hair loss, and skin reactions at the injection site. Possible serious interferon-associated side effects include psychoses (e.g., suicidal behavior), heart problems (e.g., heart attack, low blood pressure), other internal organ damage, blood problems (e.g., blood counts falling dangerously low), and new or
5 worsening autoimmune disease (e.g., rheumatoid arthritis). Ribavirin-associated side effects include anemia, fatigue, irritability, skin rash, nasal stuffiness, sinusitis, and cough. Ribavirin can also cause birth defects, so pregnancy in female patients and female partners of male patients must be avoided during treatment
10 and for six months afterward.

[0007] Some patients do not complete treatment because of the serious side effects discussed above; other patients (non-responders) continue to have measurable HCV levels despite treatment; and yet other patients (relapsers) "clear"
15 the virus during therapy, but the virus returns sometime after completion of the treatment regimen. Thus, there continues to be a need for alternative compounds, compositions, and compounds for use in methods of treatment (used either in combination with or in lieu of an interferon agent and/or ribavirin) to alleviate the symptoms of hepatitis C, thereby providing partial or complete relief.
20 This invention provides compounds (including salts thereof), compositions, and methods of treatment that generally address such a need.

SUMMARY OF THE INVENTION

25 **[0008]** This invention is directed to a process for preparing compounds that correspond in structure to formula **I-L0**:



[0009] In formula **I-L0**:

*

is selected from the group consisting of single carbon-carbon bond and double carbon-carbon bond;

R¹ is selected from the group consisting of hydrogen, methyl, and nitrogen-protecting group;

R² is selected from the group consisting of hydrogen, halo, hydroxy, methyl, cyclopropyl, and cyclobutyl;

R³ is selected from the group consisting of hydrogen, halo, oxo, and methyl;

R⁴ is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

(a) the amino, aminocarbonyl, and aminosulfonyl optionally are substituted with:

(1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl, or

(2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl, and

(b) the alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, and alkylsulfonyl, optionally are substituted with one or more substituents independently selected from the group consisting of halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

the amino optionally is substituted with:

(1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyl-oxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or

(2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl, and

(c) the carbocyclyl and heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

the amino optionally is substituted with:

(1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or

5 (2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl;

R^5 is selected from the group consisting of hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, carbocyclylsulfonyloxy, haloalkylsulfonyloxy, and halo;

10 R^6 is selected from the group consisting of fused 2-ring carbocyclyl and fused 2-ring heterocyclyl, wherein each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K ;

each R^E is independently selected from the group consisting of halo, nitro, hydroxy, oxo, carboxy, cyano, amino, imino, azido, and aldehydo, wherein:

15 the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl;

each R^F is independently selected from the group consisting of alkyl, alkenyl, and alkynyl, wherein:

20 each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

25 the amino, imino, aminosulfonyl, aminocarbonyl, carbocyclyl, and heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkylsulfonylamino, hydroxy, and alkyloxy,

30 wherein:

amino portion of the alkylsulfonylamino optionally is substituted with a substituent selected from the group consisting of alkyl, alkenyl, and alkynyl;

each R^G is independently selected from the group consisting of carbocyclyl and heterocyclyl, wherein:

each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl;

each R^H is independently selected from the group consisting of alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, alkenylsulfonyloxy, and alkynylsulfonyloxy, wherein:

each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl;

each R^I is independently selected from the group consisting of alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, aminocarbonyl, alkyloxycarbonyl, carbocyclylcarbonyl, and heterocyclylcarbonyl, wherein:

(a) the alkylcarbonyl, alkenylcarbonyl, and alkynylcarbonyl optionally are substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, and

(b) the aminocarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkyloxyalkyl, carbocyclyl, heterocyclyl, alkylsulfonyl, and alkylsulfonylamino, wherein:

5 the carbocyclyl and heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of halo, alkyl, and oxo;

each R^d is independently selected from the group consisting of carbocyclyl-sulfonylamino, heterocyclylsulfonylamino, alkylcarbonylamino, alkenylcarbonyl-
10 amino, alkynylcarbonylamino, alkyloxycarbonylamino, alkenyloxycarbonylami-
no, alkynyloxycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynyl-
sulfonylamino, aminocarbonylamino, alkyloxycarbonylaminoimino, alkylsulfonyl-
aminoimino, alkenylsulfonylaminoimino, and alkynylsulfonylaminoimino, where-
in:

15 (a) the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclyl-
alkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkenyl,
alkynyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkyloxycarbonyl, al-
kyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

20 (1) the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl
portion of the heterocyclylalkyl optionally are substituted with one or
more substituents independently selected from the group consisting
of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alky-
nyloxy, halo, nitro, cyano, azido, oxo, and amino, and

25 (2) the amino portion of the aminocarbonylalkyl optionally is substitu-
ted with one or two substituents independently selected from the
group consisting of alkyl, alkenyl, and alkynyl,

(b) the alkyl, alkenyl, and alkynyl portion of such substituents optionally is
substituted with one or more substituents independently selected from the
30 group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbo-
nyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, and alkynyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy;

- 5 **(c)** the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halo, nitro, cyano, azido, and amino, wherein:

the amino optionally is substituted with one or two substituents independently
10 selected from the group consisting of alkyl, alkenyl, and alkynyl; and
each R^K is independently selected from the group consisting of aminosulfonyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl, wherein:

- (a)** the alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl optionally are substituted with one or more substituents independently selected from the group
15 consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

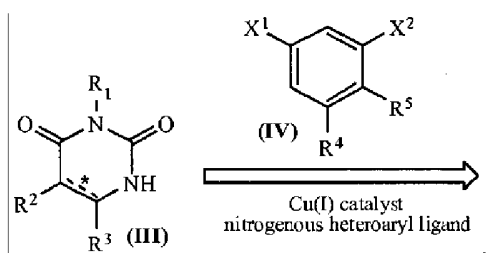
the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one
20 or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl; and

- (b)** the aminosulfonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl, wherein the process comprises reacting a compound of formula **III** with
25 a compound of formula **IV** in the presence of

(1) copper (I) salt catalyst and

(2) nitrogenous heteroaryl ligand,

wherein X^1 is halo; and X^2 is selected from the group consisting of chloro, bromo and iodo



[0010] This invention also is directed to a crystalline form of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide or a crystalline form of a salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0011] This invention also is directed to compositions (including pharmaceutical compositions) that comprise one or more crystalline forms of the invention, and, optionally, one or more additional therapeutic agents.

[0012] This invention also is directed to methods for preparing such crystalline forms.

[0013] This invention also is directed to such crystalline forms for use to, for example, inhibit replication of an RNA virus (including HCV), treat a disease treatable by inhibiting HCV ribonucleic acid (RNA) polymerase (including hepatitis C).

[0014] This invention also is directed to the use of such crystalline forms of the invention to prepare a medicament. The medicament optionally can comprise one or more additional therapeutic agents. In some embodiments, the medicament is useful for treating hepatitis C.

[0015] Further benefits of Applicants' invention will be apparent to one skilled in the art from reading this patent application.

BRIEF DESCRIPTION OF THE DRAWINGS**[0016]**

5 Figure 1 shows an illustrative PXRD pattern for the ethanol solvate of compound **IB-L0-2.3**.

Figure 2 shows an illustrative TGA profile of the ethanol solvate of compound **IB-L0-2.3**.

10 Figure 3 shows an illustrative PXRD pattern for the acetonitrile solvate of compound **IB-L0-2.3**.

Figure 4 shows an illustrative PXRD pattern for the ethyl acetate solvate of compound **IB-L0-2.3**.

15

Figure 5 shows an illustrative PXRD pattern for the 2-propanol solvate of compound **IB-L0-2.3**.

20 Figure 6 shows an illustrative PXRD pattern for the methanol solvate of compound **IB-L0-2.3**.

Figure 7 shows an illustrative PXRD pattern for the 1-propanol solvate of compound **IB-L0-2.3**.

25 Figure 8 shows an illustrative PXRD pattern for the solvent free crystalline compound **IB-L0-2.3**.

Figure 9 shows an illustrative PXRD pattern for the hydrate of compound **IB-L0-2.3**.

30

Figure 10 shows an illustrative PXRD pattern for the pattern A monosodium salt of compound **IB-L0-2.3**.

Figure 11 shows an illustrative TGA profile of the pattern A monosodium salt of compound **IB-L0-2.3**.

Figure 12 shows an illustrative PXRD pattern for the pattern B monosodium salt of compound **IB-L0-2.3**.

Figure 13 shows an illustrative TGA profile of the pattern B monosodium salt of compound **IB-L0-2.3**.

Figure 14 shows an illustrative PXRD pattern for the pattern C monosodium salt of compound **IB-L0-2.3**.

Figure 15 shows an illustrative PXRD pattern for the disodium salt of compound **IB-L0-2.3**.

Figure 16 shows an illustrative TGA profile of the disodium salt of compound **IB-L0-2.3**.

Figure 17 shows an illustrative PXRD pattern for the monopotassium salt of compound **IB-L0-2.3**.

Figure 18 shows an illustrative TGA profile of the monopotassium salt of compound **IB-L0-2.3**.

Figure 19 shows an illustrative PXRD pattern for the pattern A monocholine salt of compound **IB-L0-2.3**.

Figure 20 shows an illustrative TGA profile of the pattern A monocholine salt of compound **IB-L0-2.3**.

Figure 21 shows an illustrative PXRD pattern for the pattern B monocholine salt of compound **IB-L0-2.3**.

Figure 22 shows an illustrative TGA profile of the pattern B monocholine salt of compound **IB-L0-23**.

Figure 23 shows an illustrative PXRD pattern for the dicholine salt of compound
5 **IB-L0-2.3**.

DETAILED DESCRIPTION OF THE INVENTION

[0017] This detailed description is intended only to acquaint others skilled in the
10 art with Applicants' invention, its principles, and its practical application so that
others skilled in the art may adapt and apply the invention in its numerous
forms, as they may be best suited to the requirements of a particular use. This
description and its specific examples are intended for purposes of illustration
only.

15

A. Definitions.

[0018] The term "alkyl" (alone or in combination with another term(s)) means a
straight-or branched-chain saturated hydrocarbyl substituent typically containing
20 from 1 to about 20 carbon atoms, more typically from 1 to about 8 carbon
atoms, and even more typically from 1 to about 6 carbon atoms. Examples of
such substituents include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl,
sec-butyl, tert-butyl, pentyl, iso-amyl, and hexyl. As in this definition, throughout
this detailed description Applicants have provided illustrative examples. The
25 provision of such illustrative examples should not be interpreted as if the provi-
ded illustrative examples are the only options available to one skilled in the art.

[0019] The term "alkenyl" (alone or in combination with another term(s)) means
a straight- or branched-chain hydrocarbyl substituent containing one or more
30 double bonds and typically from 2 to about 20 carbon atoms, more typically
from about 2 to about 8 carbon atoms, and even more typically from about 2 to
about 6 carbon atoms. Examples of such substituents include ethenyl (vinyl), 2-

propenyl, 3-propenyl, 1,4-pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, and 3-butenyl.

[0020] The term "alkynyl" (alone or in combination with another term(s)) means
5 a straight- or branched-chain hydrocarbyl substituent containing one or more
triple bonds and typically from 2 to about 20 carbon atoms, more typically from
about 2 to about 8 carbon atoms, and even more typically from about 2 to about
6 carbon atoms. Examples of such substituents include ethynyl, 2-propynyl, 3-
propynyl, 2-butynyl, and 3-butynyl.

10

[0021] The term "carbocyclyl" (alone or in combination with another term(s))
means a saturated cyclic (*i.e.*, "cycloalkyl"), partially saturated cyclic (*i.e.*, "cyclo-
loalkenyl"), or completely unsaturated (*i.e.*, "aryl") hydrocarbyl substituent con-
taining from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound to-
15 gether to form the ring or rings of a cyclic substituent). A carbocyclyl may be a
single ring, which typically contains from 3 to 6 ring atoms. Examples of such
single-ring carbocyclyls include cyclopropyl (cyclopropanyl), cyclobutyl (cyclobu-
tanyl), cyclopentyl (cyclopentanyl), cyclopentenyl, cyclopentadienyl, cyclohexyl
(cyclohexanyl), cyclohexenyl, cyclohexadienyl, and phenyl. A carbocyclyl alter-
20 natively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydro-
naphthalenyl (tetralinyl), indenyl, indanyl (dihydroindenyl), anthracenyl, phenan-
threnyl, and decalinyl.

[0022] The term "cycloalkyl" (alone or in combination with another term(s))
25 means a saturated cyclic hydrocarbyl substituent containing from 3 to 14 carbon
ring atoms. A cycloalkyl may be a single carbon ring, which typically contains
from 3 to 6 carbon ring atoms. Examples of single-ring cycloalkyls include cyclo-
propyl, cyclobutyl, cyclopentyl, and cyclohexyl. A cycloalkyl alternatively may be
2 or 3 carbon rings fused together, such as, decalinyl.

30

[0023] The term "aryl" (alone or in combination with another term(s)) means an
aromatic carbocyclyl containing from 6 to 14 carbon ring atoms. Examples of
aryls include phenyl, naphthalenyl, and indenyl.

[0024] In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl, alkenyl, alkynyl, or cycloalkyl) is indicated by the prefix "C_x-C_y", wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C₁-C₆-alkyl" refers to an alkyl substituent
5 containing from 1 to 6 carbon atoms. Illustrating further, C₃-C₆-cycloalkyl means a saturated hydrocarbyl ring containing from 3 to 6 carbon ring atoms.

[0025] The term "hydrogen" (alone or in combination with another term(s)) means a hydrogen radical, and may be depicted as -H.

10

[0026] The term "hydroxy" (alone or in combination with another term(s)) means -OH.

[0027] The term "nitro" (alone or in combination with another term(s)) means
15 -NO₂.

[0028] The term "cyano" (alone or in combination with another term(s)) means -CN, which also may be depicted as -C≡N.

[0029] The term "keto" (alone or in combination with another term(s)) means an
20 oxo radical, and may be depicted as =O.

[0030] The term "carboxy" (alone or in combination with another term(s)) means
-C(O)-OH.

25

[0031] The term "amino" (alone or in combination with another term(s)) means
-NH₂.

[0032] The term "imino" (alone or in combination with another term(s)) means
30 =NH.

[0033] The term "aminoimino" (alone or in combination with another term(s)) means =NNH₂.

[0034] The term "halogen" or "halo" (alone or in combination with another term(s)) means a fluorine radical (which may be depicted as -F), chlorine radical (which may be depicted as -Cl), bromine radical (which may be depicted as -Br), or iodine radical (which may be depicted as -I).

5

[0035] A substituent is "substitutable" if it comprises at least one carbon or nitrogen atom that is bonded to one or more hydrogen atoms. Thus, for example, hydrogen, halogen, and cyano do not fall within this definition. In addition, a sulfur atom in a heterocyclyl containing such atom is substitutable with one or two
10 oxo substituents.

[0036] If a substituent is described as being "substituted", a non-hydrogen radical is in the place of hydrogen radical on a carbon or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent in which
15 at least one non-hydrogen radical is in the place of a hydrogen radical on the alkyl substituent. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro radical, and difluoroalkyl is alkyl substituted with two fluoro radicals. It should be recognized that if there are more than one substitution on a substituent, each non-hydrogen radical may be identical or different (unless otherwise stated).

20

[0037] If a substituent is described as being "optionally substituted", the substituent may be either (1) not substituted or (2) substituted. If a substituent is described as being optionally substituted with up to a particular number of non-hydrogen radicals, that substituent may be either (1) not substituted; or (2) substituted by up to that particular number of non-hydrogen radicals or by up to the
25 maximum number of substitutable positions on the substituent, whichever is less. Thus, for example, if a substituent is described as a heteroaryl optionally substituted with up to 3 non-hydrogen radicals, then any heteroaryl with less than 3 substitutable positions would be optionally substituted by up to only as
30 many non-hydrogen radicals as the heteroaryl has substitutable positions. To illustrate, tetrazolyl (which has only one substitutable position) would be optionally substituted with up to one non-hydrogen radical. To illustrate further, if an amino nitrogen is described as being optionally substituted with up to 2 non-hy-

drogen radicals, then a primary amino nitrogen will be optionally substituted with up to 2 non-hydrogen radicals, whereas a secondary amino nitrogen will be optionally substituted with up to only 1 non-hydrogen radical.

- 5 **[0038]** This patent application uses the terms "substituent" and "radical" interchangeably.

- [0039]** The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen radicals.
- 10 For example, haloalkyl means an alkyl substituent in which at least one hydrogen radical is replaced with a halogen radical. Examples of haloalkyls include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, and 1,1,1-trifluoroethyl. It should be recognized that if a substituent is substituted by more than one halogen radical, those halogen radicals may be identical or different (unless otherwise stated).
- 15

- [0040]** The prefix "perhalo" indicates that every hydrogen radical on the substituent to which the prefix is attached is replaced with independently selected halogen radicals, i.e., each hydrogen radical on the substituent is replaced with a halogen radical. If all the halogen radicals are identical, the prefix typically will identify the halogen radical. Thus, for example, the term "perfluoro" means that every hydrogen radical on the substituent to which the prefix is attached is substituted with a fluorine radical. To illustrate, the term "perfluoroalkyl" means an alkyl substituent wherein a fluorine radical is in the place of each hydrogen radical.
- 20
- 25

[0041] The term "carbonyl" (alone or in combination with another term(s)) means -C(O)-.

- 30 **[0042]** The term "aminocarbonyl" (alone or in combination with another term(s)) means -C(O)-NH₂.

- [0043]** The term "oxy" (alone or in combination with another term(s)) means an ether substituent, and may be depicted as -O-.
- [0044]** The term "alkoxy" (alone or in combination with another term(s)) means
5 an alkylether substituent, i.e., -O-alkyl. Examples of such a substituent include methoxy (-O-CH₃), ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy.
- [0045]** The term "alkylcarbonyl" (alone or in combination with another term(s))
10 means -C(O)-alkyl.
- [0046]** The term "aminoalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-NH₂.
- [0047]** The term "alkoxycarbonyl" (alone or in combination with another term(s))
15 means -C(O)-O-alkyl.
- [0048]** The term "carbocyclylcarbonyl" (alone or in combination with another term(s)) means -C(O)-carbocyclyl.
20
- [0049]** Similarly, the term "heterocyclylcarbonyl" (alone or in combination with another term(s)) means -C(O)-heterocyclyl.
- [0050]** The term "carbocyclylalkylcarbonyl" (alone or in combination with an-
25 other term(s)) means -C(O)-alkyl-carbocyclyl.
- [0051]** Similarly, the term "heterocyclylalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-heterocyclyl.
- [0052]** The term "carbocyclyloxycarbonyl" (alone or in combination with another
30 term(s)) means -C(O)-O-carbocyclyl.

- [0053]** The term "carbocyclylalkoxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-alkyl-carbocyclyl.
- [0054]** The term "thio" or "thia" (alone or in combination with another term(s)) means a thiaether substituent, *i.e.*, an ether substituent wherein a divalent sulfur atom is in the place of the ether oxygen atom. Such a substituent may be depicted as -S-. This, for example, "alkyl-thio-alkyl" means alkyl-S-alkyl (alkyl-sulfanyl-alkyl).
- 5
- [0055]** The term "thiol" or "sulfhydryl" (alone or in combination with another term(s)) means a sulfhydryl substituent, and may be depicted as -SH.
- 10
- [0056]** The term "(thiocarbonyl)" (alone or in combination with another term(s)) means a carbonyl wherein the oxygen atom has been replaced with a sulfur. Such a substituent may be depicted as -C(S)-.
- 15
- [0057]** The term "sulfonyl" (alone or in combination with another term(s)) means -S(O)₂-.
- 20
- [0058]** The term "aminosulfonyl" (alone or in combination with another term(s)) means -S(O)₂-NH₂.
- [0059]** The term "sulfinyl" or "sulfoxido" (alone or in combination with another term(s)) means -S(O)-.
- 25
- [0060]** The term "heterocyclyl" (alone or in combination with another term(s)) means a saturated (*i.e.*, "heterocycloalkyl"), partially saturated (*i.e.*, "heterocycloalkenyl"), or completely unsaturated (*i.e.*, "heteroaryl") ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (*i.e.*, oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.
- 30

[0061] A heterocyclyl may be a single ring, which typically contains from 3 to 7 ring atoms, more typically from 3 to 6 ring atoms, and even more typically 5 to 6 ring atoms. Examples of single-ring heterocyclyls include furanyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl (thiofuranyl), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazoliny, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, oxazolyl, oxazolidinyl, isoxazolidinyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl (furazanyl), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathioly, oxathiolanyl, pyranyl, dihydropyranyl, thiopyranyl, tetrahydrothiopyranyl, pyridinyl (azinyl), piperidinyl, diazinyl (including pyridazinyl (1,2-diazinyl), pyrimidinyl (1,3-diazinyl), or pyrazinyl (1,4-diazinyl)), piperazinyl, triazinyl (including 1,3,5-triazinyl, 1,2,4-triazinyl, and 1,2,3-triazinyl)), oxazinyl (including 1,2-oxazinyl, 1,3-oxazinyl, or 1,4-oxazinyl)), oxathiazinyl (including 1,2,3-oxathiazinyl, 1,2,4-oxathiazinyl, 1,2,5-oxathiazinyl, or 1,2,6-oxathiazinyl)), oxadiazinyl (including 1,2,3-oxadiazinyl, 1,2,4-oxadiazinyl, 1,4,2-oxadiazinyl, or 1,3,5-oxadiazinyl)), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

20

[0062] A heterocyclyl alternatively may be 2 or 3 rings fused together, such as, for example, indolizinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl. Other examples of fused-ring heterocyclyls include benzo-fused heterocyclyls, such as indolyl, isoindolyl (isobenzazolyl, pseudoisoindolyl), indoleninyl (pseudoindolyl), isoindazolyl (benzpyrazolyl), benzaziny (including quinolinyl (1-benzaziny) or isoquinolinyl (2-benzaziny)), phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl (including cinnolinyl (1,2-benzodiazinyl) or quinazolinyl (1,3-benzodiazinyl)), benzopyranyl (including chromanyl or isochromanyl), benzoxazinyl (including 1,3,2-benzoxazinyl, 1,4,2-benzoxazinyl, 2,3,1-benzoxazinyl, or 3,1,4-benzoxazinyl), and benzisoxazinyl (including 1,2-benzisoxazinyl or 1,4-benzisoxazinyl).

30

[0063] The term "2-fused ring" heterocyclyl (alone or in combination with another term(s)) means a saturated, partially saturated, or aryl heterocyclyl containing 2 fused rings. Examples of 2-fused-ring heterocyclyls include indoliziny, quinoliziny, puriny, naphthyridiny, pteridiny, indoly, isoindoly, indoleniny, isoindazolyl, phthalaziny, quinoxaliny, quinazoliny, benzodiaziny, benzopyrany, benzothiopyrany, benzoxazolyl, anthranily, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofurany, isobenzofurany, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxaziny, and tetrahydroisoquinoliny.

10 **[0064]** The term "heteroaryl" (alone or in combination with another term(s)) means an aromatic heterocyclyl containing from 5 to 14 ring atoms. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, pyridaziny, and 1,3,5-, 1,2,4- or 1,2,3-triaziny; 5-membered ring substituents such as imidazyl, furany, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 15 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofurany, benzisoxazolyl, benzoxazolyl, puriny, and anthranily; and 6/6-membered fused rings such as benzopyrany, quinoliny, isoquinoliny, cinnoliny, quinazoliny, and benzoxaziny.

20

[0065] A prefix attached to a multi-component substituent only applies to the first component. To illustrate, the term "alkylcycloalkyl" contains two components: alkyl and cycloalkyl. Thus, the C₁-C₆-prefix on C₁-C₆-alkylcycloalkyl means that the alkyl component of the alkylcycloalkyl contains from 1 to 6 carbon atoms; the C₁-C₆-prefix does not describe the cycloalkyl component. To illustrate further, the prefix "halo" on haloalkoxyalkyl indicates that only the alkoxy component of the alkoxyalkyl substituent is substituted with one or more halogen radicals. If halogen substitution may alternatively or additionally occur on the alkyl component, the substituent would instead be described as "halogen-substituted alkoxyalkyl" rather than "haloalkoxyalkyl." And finally, if the halogen substitution may only occur on the alkyl component, the substituent would instead be described as "alkoxyhaloalkyl."

30

[0066] If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

- 5 **[0067]** When words are used to describe a substituent, the rightmost-described component of the substituent is the component that has the free valence.

[0068] When a chemical formula is used to describe a substituent, the dash on the left side of the formula: indicates the portion of the substituent that has the
10 free valence.

[0069] When a chemical formula is used to describe a linking element between two other elements of a depicted chemical structure, the leftmost dash of the substituent indicates the portion of the substituent that is bound to the left ele-
15 ment in the depicted structure. The rightmost dash, on the other hand, indicates the portion of the substituent that is bound to the right element in the depicted structure. To illustrate, if the depicted chemical structure is X-L-Y and L is described as -C(O)-N(H)-, then the chemical would be X-C(O)-N(H)-Y.

- 20 **[0070]** With reference to the use of the words "comprise" or "comprises" or "comprising" in this patent application (including the claims), Applicants note that unless the context requires otherwise, those words are used on the basis and clear understanding that they are to be interpreted inclusively, rather than exclusively, and that Applicants intend each of those words to be so interpreted
25 in construing this patent application, including the claims below.

[0071] ChemDraw software has been used to generate the compound names in this patent application.

- 30 **[0072]** The term "amorphous" as applied to a compound refers to a solid-state in which the compound molecules are present in a disordered arrangement and do not form a distinguishable crystal lattice or unit cell. When subjected to X-ray

powder diffraction, an amorphous compound does not produce any characteristic crystalline peaks.

5 **[0073]** The term "crystalline form" as applied to a compound refers to a solid-state in which the compound molecules are arranged to form a distinguishable crystal lattice (i) comprising distinguishable unit cells, and (ii) yielding diffraction pattern peaks when subjected to X-ray radiation.

10 **[0074]** The term "purity", unless otherwise qualified, means the chemical purity of a compound according to conventional HPLC assay.

[0075] The term "phase purity" means the solid-state purity of a compound with regard to a particular crystalline or amorphous form of the compound as determined by X-ray powder diffraction analytical methods.

15

[0076] The term "phase pure" refers to purity with respect to other solid-state forms of the compound, and does not necessarily imply a high degree of chemical purity with respect to other compounds.

20 **[0077]** The term "PXRD" means X-ray powder diffraction.

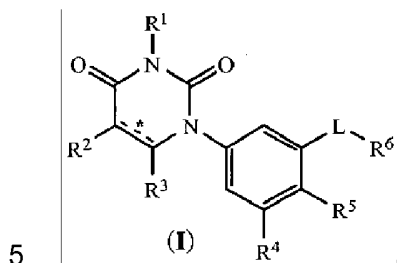
[0078] The term "TGA" means thermogravimetric analysis.

[0079] The term "DSC" means differential scanning calorimetry.

25

B. Compounds.

[0080] This invention is directed, in part, to a process for preparing compounds that are phenyl-uracil derivatives that correspond in structure to formula I:



[0081] In these compounds,



is selected from the group consisting of single carbon-carbon bond and double carbon-carbon bond.

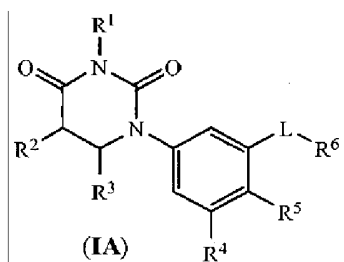
10

[0082] In some embodiments,



is a single carbon-carbon bond. In these embodiments, the compounds of formula I correspond in structure to the following formula (*i.e.*, formula IA):

15

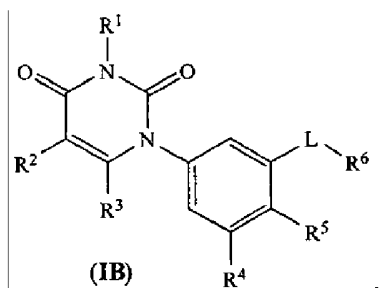


[0083] In other embodiments,



is a double carbon-carbon bond. In these embodiments, the compounds of formula I correspond in structure to the following formula (*i.e.*, formula IB):

20



B1. Substituent R^1 .

- 5 [0084] R^1 is selected from the group consisting of hydrogen, methyl, and nitrogen-protecting group.

[0085] In some embodiments, R^1 is hydrogen.

- 10 [0086] In some embodiments, R^1 is methyl.

[0087] In some embodiments, R^1 is selected from the group consisting of hydrogen and methyl.

- 15 [0088] In some embodiments, R^1 is a nitrogen-protecting group. In these embodiments, the compounds are useful as intermediates for the preparation of compounds of formula I. Nitrogen-protecting groups suitable for preparing compounds of formula I are known to those skilled in the art.

20 **B2. Substituent R^2 .**

[0089] R^2 is selected from the group consisting of hydrogen, halo, hydroxy, methyl, cyclopropyl, and cyclobutyl.

- 25 [0090] In some embodiments, R^2 is hydrogen.

[0091] In some embodiments, R^2 is halo. In some such embodiments, R^2 is selected from the group consisting of fluoro and chloro. In other such embodi-

ments, R^2 is fluoro. In yet other such embodiments, R^2 is chloro. In yet other such embodiments, R^2 is bromo. In further such embodiments, R^2 is iodo.

[0092] In some embodiments, R^2 is hydroxy.

5

[0093] In some embodiments, R^2 is methyl.

[0094] In some embodiments, R^2 is cyclopropyl.

10 **[0095]** In some embodiments, R^2 is cyclobutyl.

[0096] In some embodiments, R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, and halo. In some such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, fluoro, and chloro. In other
15 such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, and fluoro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, and chloro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, and bromo. In further such embodiments, R^2 is selected from the group
20 consisting of hydrogen, methyl, hydroxy, and iodo.

[0097] In some embodiments, R^2 is selected from the group consisting of hydrogen, methyl, and halo. In some such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, fluoro, and chloro. In other such embodi-
25 ments, R^2 is selected from the group consisting of hydrogen, methyl, and fluoro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, and chloro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, and bromo. In further such embodi-
ments, R^2 is selected from the group consisting of hydrogen, methyl, and iodo.

30

[0098] In some embodiments, R^2 is selected from the group consisting of hydrogen and halo. In some such embodiments, R^2 is selected from the group consisting of hydrogen, fluoro, and chloro. In other such embodiments, R^2 is se-

lected from the group consisting of hydrogen and fluoro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen and chloro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen and bromo. In further such embodiments, R^2 is selected from the group
5 consisting of hydrogen and iodo.

B3. Substituent R^3 .

[0099] R^3 is selected from the group consisting of hydrogen, halo, oxo, and methyl. In some such embodiments, R^3 is selected from the group consisting of
10 hydrogen, fluoro, oxo, and methyl. In other such embodiments, R^3 is selected from the group consisting of hydrogen, chloro, oxo, and methyl. In yet other such embodiments, R^3 is selected from the group consisting of hydrogen, bromo, oxo, and methyl. In yet other such embodiments, R^3 is selected from the
15 group consisting of hydrogen, iodo, oxo, and methyl.

[0100] In some embodiments, R^3 is selected from the group consisting of hydrogen, halo, and oxo. In some such embodiments, R^3 is selected from the group consisting of hydrogen, fluoro, and oxo. In other such embodiments, R^3 is selected
20 from the group consisting of hydrogen, chloro, and oxo. In yet other such embodiments, R^3 is selected from the group consisting of hydrogen, bromo, and oxo. In yet other such embodiments, R^3 is selected from the group consisting of hydrogen, iodo, and oxo.

25 **[0101]** In some embodiments, R^3 is selected from the group consisting of hydrogen and methyl.

[0102] In some embodiments, R^3 is hydrogen.

30 **[0103]** In some embodiments, R^3 is methyl.

[0104] In some embodiments, R^3 is oxo.

[0105] In some embodiments, R^3 is halo. In some such embodiments, R^3 is fluoro. In other such embodiments, R^3 is chloro. In yet other such embodiments, R^3 is bromo. In further such embodiments, R^3 is iodo.

5 ***B⁴. Substituent R⁴.***

[0106] R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

10 (a) the amino, aminocarbonyl, and aminosulfonyl optionally are substituted with:

(1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl, or

15 (2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl,

(b) the alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, and alkylsulfonyl, optionally are substituted with one or more substituents independently selected from the group consisting of halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

20 the amino optionally is substituted with:

(1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyl-oxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or

25 (2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl, and

(c) the carbocyclyl and heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

30 the amino optionally is substituted with:

(1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyl-

oxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or

(2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

5

[0107] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

10 the amino, aminocarbonyl, and aminosulfonyl optionally are substituted with:

(1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl, or

(2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

15

[0108] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

20 the alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, and alkylsulfonyl, optionally are substituted with one or more substituents independently selected from the group consisting of halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

the amino optionally is substituted with:

25 (1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or

(2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

30

[0109] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, ami-

no, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

the carbocyclyl and heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

the amino optionally is substituted with:

- (1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or
- (2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

[0110] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

(a) the amino, aminocarbonyl, and aminosulfonyl optionally are substituted with:

- (1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl, or,
- (2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl; and

(b) the alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyl, carbocyclyl, and heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, carbocyclyl, and heterocyclyl, wherein the amino optionally is substituted with:

- (1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or,

(2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

[0111] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

the amino, aminocarbonyl, and aminosulfonyl optionally are substituted with:

- (1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl, or,
- (2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

[0112] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

the alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyl, carbocyclyl, and heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, carbocyclyl, and heterocyclyl, wherein the amino optionally is substituted with:

- (1) one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or,
- (2) two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

[0113] In some embodiments, R^4 is selected from the group consisting of halo, C_1 - C_4 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, amino, C_1 - C_4 -alkylsulfonyl, C_3 - C_6 -carbocyclyl, and 5-6-membered heterocyclyl, wherein:

(a) the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl,

(b) the C₁-C₄-alkyl, C₂-C₄-alkenyl, and C₂-C₄-alkynyl optionally are substituted with one or more substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyloxy, and trimethylsilyl, and

(c) the C₃-C₆-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, and amino, wherein:

10 the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl.

[0114] In some embodiments, R⁴ is selected from the group consisting of C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, amino, C₁-C₄-alkylsulfonyl, C₃-C₆-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

(a) the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl,

(b) the C₁-C₄-alkyl, C₂-C₄-alkenyl, and C₂-C₄-alkynyl optionally are substituted with one or more substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyloxy, and trimethylsilyl, and

(c) the C₃-C₆-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, and amino, wherein:

25 the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl.

[0115] In some embodiments, R⁴ is selected from the group consisting of halo, C₁-C₄-alkyl, C₃-C₆-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

30 (a) the C₁-C₄-alkyl optionally is substituted with up to three substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyloxy, and trimethylsilyl, and

(b) the C₃-C₆-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, halo, and alkylsulfonylamino.

5 [0116] In some embodiments, R⁴ is selected from the group consisting of halo, C₁-C₄-alkyl, C₃-C₆-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

(a) the C₁-C₄-alkyl optionally is substituted with one or two substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyl-oxy, and trimethylsilyl, and

10 (b) the C₃-C₆-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with a substituent selected from the group consisting of alkyl, halo, and alkylsulfonylamino.

[0117] In some embodiments, R⁴ is selected from the group consisting of C₁-C₄-
15 alkyl, C₃-C₆-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

(a) the C₁-C₄-alkyl optionally is substituted with up to three substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyl-oxy, and trimethylsilyl, and

20 (b) the C₃-C₆-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, halo, and alkylsulfonylamino.

[0118] In some embodiments, R⁴ is selected from the group consisting of halo, tert-butyl, C₃-C₆-carbocyclyl, and 5-6-membered heterocyclyl, wherein:
25 the C₃-C₆-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with a substituent selected from the group consisting of alkyl, halo, and alkylsulfonylamino.

[0119] In some embodiments, R⁴ is selected from the group consisting of tert-
30 butyl, C₃-C₆-carbocyclyl, and 5-6-membered heterocyclyl, wherein:
the C₃-C₆-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with a substituent selected from the group consisting of alkyl, halo, and alkylsulfonylamino.

[0120] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, haloalkyl, carboxyalkyl, hydroxyalkyl, alkyloxyalkyl, trimethylsilylalkynyl, alkylcarbocyclyl, carbocyclyl, alkylheterocyclyl, heterocyclyl, halocarbocyclyl, alkylsulfonylamino, and alkylsulfonyl.

5

[0121] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl.

- 10 **[0122]** In some embodiments, R^4 is selected from the group consisting of halo, C_1 - C_4 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, amino, C_1 - C_4 -alkylsulfonyl, C_3 - C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In some such embodiment, R^4 is selected from the group consisting of halo, C_1 - C_4 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, amino, C_1 - C_4 -alkylsulfonyl, C_6 -carbocyclyl, and 5-6-membered heterocyclyl.
- 15 In other such embodiment, R^4 is selected from the group consisting of halo, C_1 - C_4 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, amino, C_1 - C_4 -alkylsulfonyl, phenyl, and 5-6-membered heteroaryl.

- [0123]** In some embodiments, R^4 is selected from the group consisting of C_1 - C_4 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, amino, C_1 - C_4 -alkylsulfonyl, C_3 - C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In some such embodiment, R^4 is selected from the group consisting of C_1 - C_4 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, amino, C_1 - C_4 -alkylsulfonyl, C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiment, R^4 is selected from the group consisting of C_1 - C_4 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, amino, C_1 - C_4 -alkylsulfonyl, phenyl, and 5-6-membered heteroaryl.
- 20
- 25

- [0124]** In some embodiments, R^4 is selected from the group consisting of halo, C_1 - C_4 -alkyl, C_3 - C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In some such
- 30
- embodiments, R^4 is selected from the group consisting of halo, C_1 - C_4 -alkyl, C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiments, R^4 is selected from the group consisting of halo, C_1 - C_4 -alkyl, phenyl, and 5-6-membered heteroaryl.

[0125] In some embodiments, R^4 is selected from the group consisting of C_1 - C_4 -alkyl, C_3 - C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In some such embodiments, R^4 is selected from the group consisting of C_1 - C_4 -alkyl, C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiments, R^4 is selected from the group consisting of C_1 - C_4 -alkyl, phenyl, and 5-6-membered heteroaryl.

[0126] In some embodiments, R^4 is selected from the group consisting of halo, tert-butyl, C_3 - C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In some such embodiments, R^4 is selected from the group consisting of halo, tert-butyl, C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiments, R^4 is selected from the group consisting of halo, tert-butyl, phenyl, and 5-6-membered heteroaryl.

[0127] In some embodiments, R^4 is selected from the group consisting of tert-butyl, C_3 - C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In some such embodiments, R^4 is selected from the group consisting of tert-butyl, C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiments, R^4 is selected from the group consisting of tert-butyl, phenyl, and 5-6-membered heteroaryl.

[0128] In some embodiments, R^4 is selected from the group consisting of C_3 - C_6 -carbocyclyl and 5-6-membered heterocyclyl. In some such embodiments, R^4 is selected from the group consisting of C_6 -carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiments, R^4 is selected from the group consisting of phenyl and 5-6-membered heteroaryl.

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[0129] Suitable carbocyclyls for the above embodiments include, for example, cyclopropyl and phenyl.

[0130] Suitable heterocyclyls for the above embodiments include, for example, furanyl, thienyl, and pyridinyl.

30

[0131] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, and alkyloxy.

[0132] In some embodiments, R^4 is alkyl.

[0133] In some embodiments, R^4 is tert-butyl.

5 **B5. Substituent R^5 .**

[0134] R^5 is selected from the group consisting of hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, carbocyclisulfonyloxy, haloalkylsulfonyloxy, and halo.

10

[0135] In some embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and halo. In some such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and fluoro. In other such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and fluoro. In yet other such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and chloro. In yet other such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and bromo. In further such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and iodo.

20

[0136] In some embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and halo. In some such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and fluoro. In other such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and chloro. In yet other such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and bromo. In further such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and iodo.

25

[0137] In some embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, and alkyloxy. In some such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and ethoxy.

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[0138] In some embodiments, R^5 is hydrogen.

[0139] In some embodiments, R^5 is hydroxy.

5 [0140] In some embodiments, R^5 is alkyloxy.

[0141] In some embodiments, R^5 is methoxy.

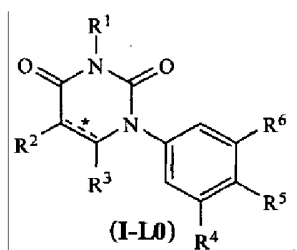
[0142] In some embodiments, R^5 is ethoxy.

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B6. Substituent L.

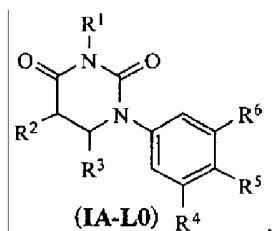
[0143] L is a bond, and the compounds of formula I correspond in structure to formula I-L0:

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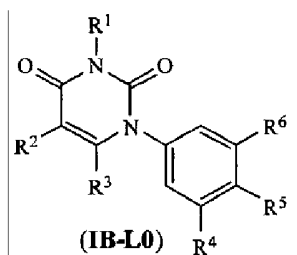


[0144] In some such embodiments, the compounds correspond in structure to the following formula (*i.e.*, formula IA-L0):

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[0145] In other such embodiments, the compounds correspond in structure to the following formula (*i.e.*, formula IB-L0):



[0146] B7. Substituent R^6 .

- 5 **[0147]** In some embodiments, R^6 is selected from the group consisting of fused 2-ring carbocyclyl and fused 2-ring heterocyclyl, wherein each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K .
- 10 **[0148]** In some such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are not substituted.
- [0149]** In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with a substituent selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In some such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with a substituent selected from the group consisting of R^E , R^F , R^I , R^J , and R^K . In other such embodiments, fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with a substituent selected from the group consisting of R^E , R^F , and R^J . In yet other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with a substituent selected from the group consisting of R^F and R^J . In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with R^J .
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- 25 **[0150]** In yet other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with two substituents independently selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In some such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with two substituents independently selected from the group consisting of

R^E , R^F , R^I , R^J , and R^K . In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with two substituents independently selected from the group consisting of R^E , R^F , and R^J . In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted
5 with two substituents independently selected from the group consisting of R^F and R^J .

[0151] In further such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with three substituents independently selected
10 from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In some such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with three substituents independently selected from the group consisting of R^E , R^F , R^I , R^J , and R^K . In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with three substituents inde-
15 pendently selected from the group consisting of R^E , R^F , and R^J . In further such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with three substituents independently selected from the group consisting of R^F and R^J .

[0152] In further such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with one, two, or three substituents independently selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In some such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with one, two, or three substituents independently selected
25 from the group consisting of R^E , R^F , R^I , R^J , and R^K . In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with one, two, or three substituents independently selected from the group consisting of R^E , R^F , and R^J . In further such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with one, two, or three substituents independently selected from the group consisting of R^F and R^J .
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[0153] In some embodiments, R^G is fused 2-ring carbocyclyl optionally substituted with one or more substituents independently selected from the group con-

sisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In some such embodiments, the fused 2-ring carbocyclyl is not substituted. In other such embodiments, the fused 2-ring carbocyclyl is substituted with a substituent selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In yet other such embodiments, the fused 2-ring carbocyclyl is substituted with two substituents independently selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In further such embodiments, the fused 2-ring carbocyclyl is substituted with three substituents independently selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In further such embodiments, the fused 2-ring carbocyclyl is substituted with one, two, or three substituents independently selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K .

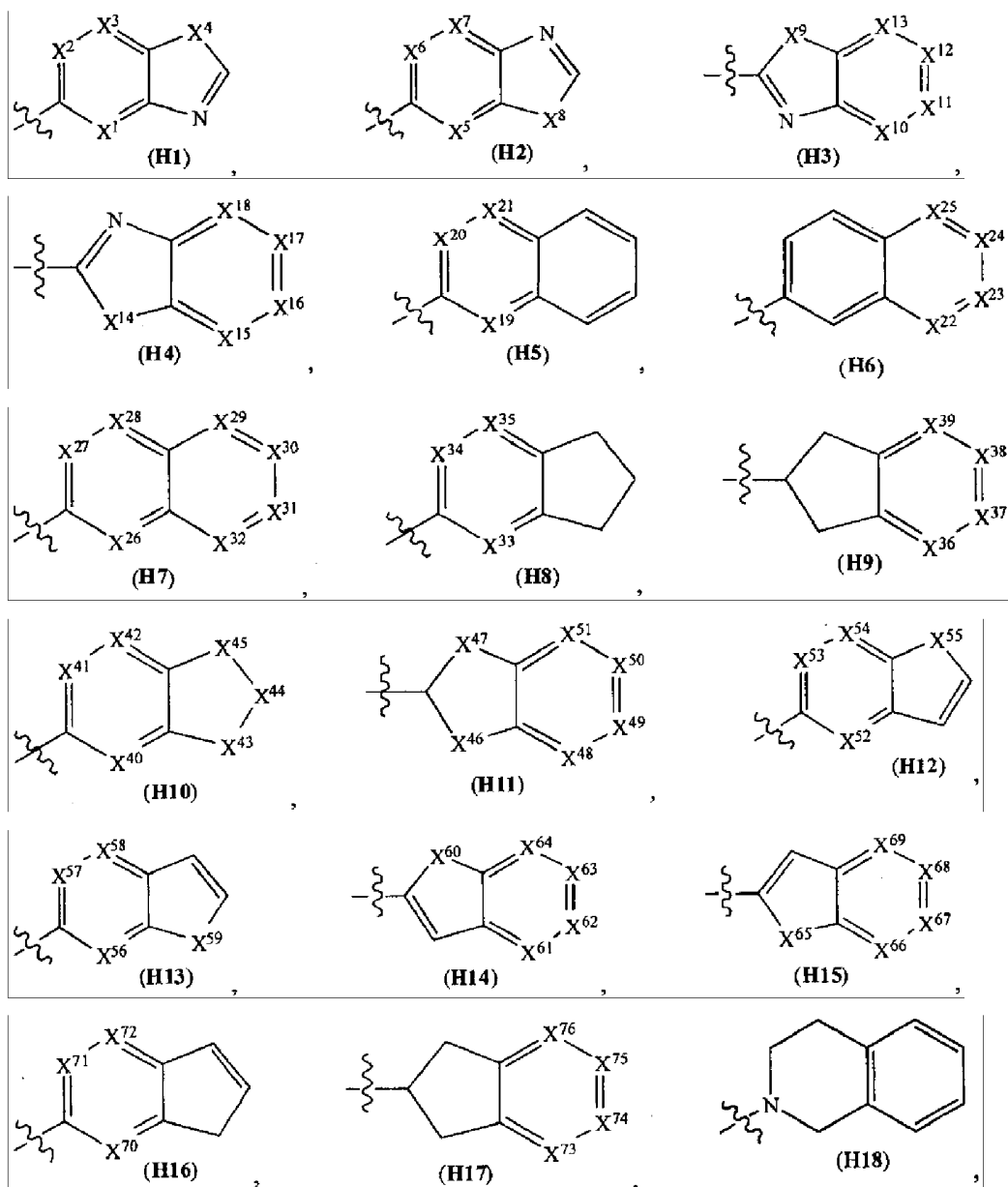
[0154] In some embodiments, R^6 is fused 2-ring heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In some such embodiments, the fused 2-ring heterocyclyl is not substituted. In other such embodiments, the fused 2-ring heterocyclyl is substituted with a substituent selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In yet other such embodiments, the fused 2-ring heterocyclyl is substituted with two substituents independently selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In further such embodiments, the fused 2-ring heterocyclyl is substituted with three substituents independently selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K . In further such embodiments, the fused 2-ring heterocyclyl is substituted with one, two, or three substituents independently selected from the group consisting of R^E , R^F , R^G , R^H , R^I , R^J , and R^K .

[0155] In some of the above embodiments, the optionally substituted fused 2-ring carbocyclyl is selected from the group consisting of naphthalenyl, dihydronaphthalenyl, tetrahydronaphthalenyl, hexahydronaphthalenyl, octahydronaphthalenyl, decahydronaphthalenyl, indenyl, dihydroindenyl, hexahydroindenyl, octahydroindenyl, pentalenyl, octahydropentalenyl, and hexahydropentalenyl. In some such embodiments, the optionally substituted fused 2-ring carbocyclyl is selected from the group consisting of naphthalenyl and dihydroindenyl. In some

such embodiments, the optionally substituted fused 2-ring carbocyclyl is naphthalenyl. In other such embodiments, the optionally substituted fused 2-ring carbocyclyl is dihydroindenyl. In further such embodiments, the optionally substituted fused 2-ring carbocyclyl is indenyl.

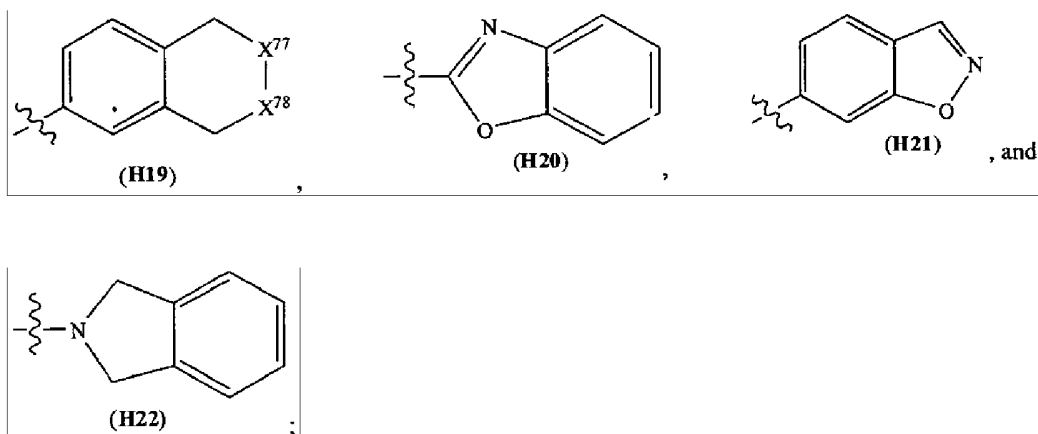
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[0156] In some of the above embodiments, the optionally substituted fused 2-ring heterocyclyl is selected from the group consisting of



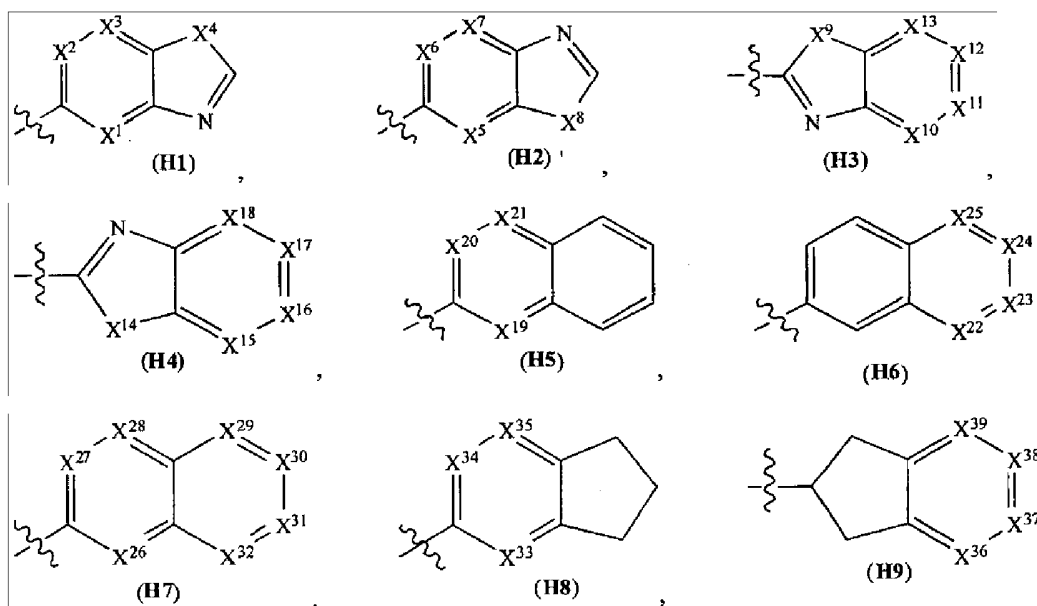
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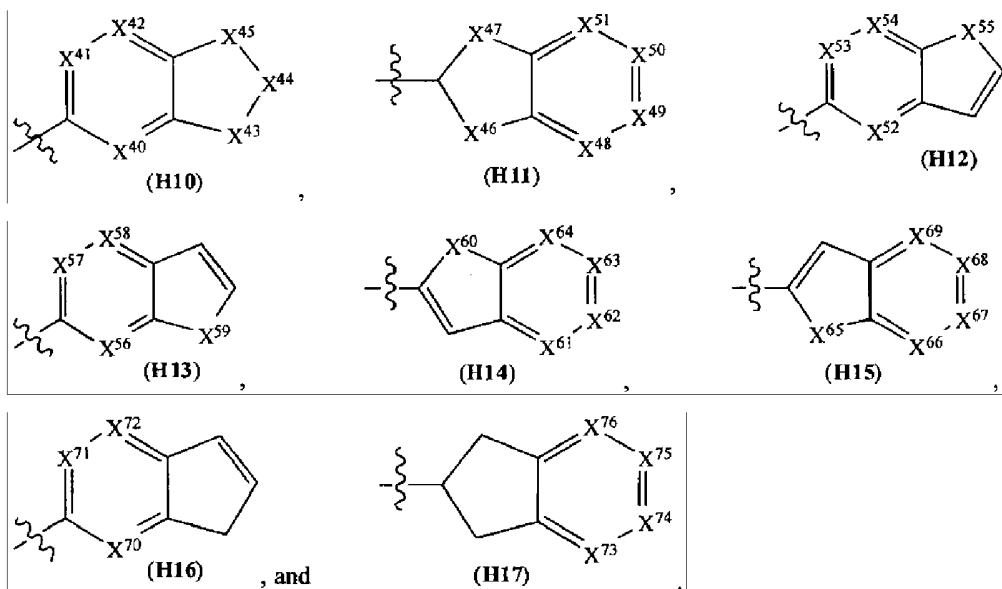


- X^1 , X^2 , and X^3 are independently selected from the group consisting of N and C(H);
- 5 X^4 is selected from the group consisting of N(H), O, and S;
- X^5 , X^6 , and X^7 are independently selected from the group consisting of N and C(H);
- X^8 is selected from the group consisting of N(H), O, and S;
- 10 X^9 is selected from the group consisting of N(H), O, and S;
- X^{10} , X^{11} , X^{12} and X^{13} are independently selected from the group consisting of N and C(H);
- X^{14} is selected from the group consisting of N(H), O, and S;
- X^{15} , X^{16} , X^{17} , and X^{18} are independently selected from the group consisting of N and C(H);
- 15 one or more of X^{19} , X^{20} , and X^{21} is N, and the remaining one(s) is/are C(H);
- one or more of X^{22} , X^{23} , X^{24} , and X^{25} is N, and the remaining one(s) is/are C(H);
- one or more of X^{26} , X^{27} , and X^{28} is N, and the remaining one(s) is/are C(H);
- one or more of X^{29} , X^{30} , X^{31} , and X^{32} is N, and the remaining one(s) is/are C(H);
- 20 one or more of X^{33} , X^{34} , and X^{35} is N, and the remaining one(s) is/are C(H);
- one or more of X^{36} , X^{37} , X^{38} , and X^{39} is N, and the remaining one(s) is/are C(H);
- X^{40} , X^{41} , and X^{42} are independently selected from the group consisting of N and C(H);
- one of X^{43} , X^{44} , and X^{45} is selected from the group consisting of N(H), O, and S,
- 25 and the remaining two are C(H)₂;
- one of X^{46} and X^{47} is selected from the group consisting of N(H), O, and S, and the other one is C(H)₂;

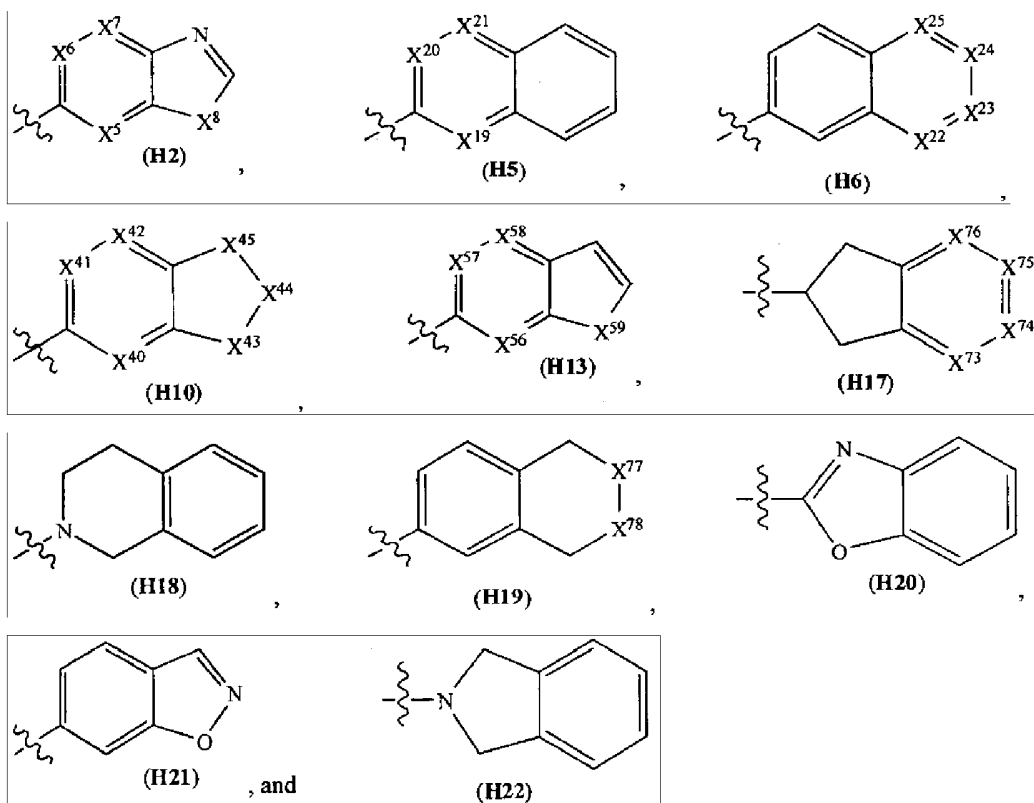
- X^{48} , X^{49} , X^{50} , and X^{51} are independently selected from the group consisting of N and C(H);
- X^{52} , X^{53} , and X^{54} are independently selected from the group consisting of N and C(H);
- 5 X^{55} is selected from the group consisting of N(H), O, and S;
- X^{56} , X^{57} , and X^{58} are independently selected from the group consisting of N and C(H);
- X^{59} is selected from the group consisting of N(H), O, and S;
- X^{60} is selected from the group consisting of N(H), O, and S;
- 10 X^{61} , X^{62} , X^{63} , and X^{64} are independently selected from the group consisting of N and C(H);
- X^{65} is selected from the group consisting of N(H), O, and S;
- X^{66} , X^{67} , X^{68} , and X^{69} are independently selected from the group consisting of N and C(H);
- 15 one or more of X^{70} , X^{71} , and X^{72} is N, and the remaining one(s) is/are C(H);
- one or more of X^{73} , X^{74} , X^{75} , and X^{76} is N, and the remaining one(s) is/are C(H);
- and
- one of X^{77} and X^{78} is N(H), and the remaining one is C(H)₂.
- 20 **[0157]** In some of the above embodiments, the optionally substituted fused 2-ring heterocyclyl is selected from the group consisting of



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- 5 [0158] In some of the above embodiments, the optionally substituted fused 2-ring heterocyclyl is selected from the group consisting of:



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[0159] In some of the above embodiments, X^1 , X^2 , and X^3 are C(H).

[0160] In some of the above embodiments, X^5 , X^6 , and X^7 are C(H).

- [0161] In some of the above embodiments, X^{10} , X^{11} , X^{12} , and X^{13} are C(H).
- [0162] In some of the above embodiments, X^{15} , X^{16} , X^{17} , and X^{18} are C(H).
- 5 [0163] In some of the above embodiments, one of X^{19} , X^{20} , and X^{21} is N.
- [0164] In some of the above embodiments, one of X^{22} , X^{23} , X^{24} , and X^{15} is N.
- [0165] In some of the above embodiments, one of X^{26} , X^{27} , and X^{28} is N, and
10 one of X^{29} , X^{30} , X^{31} , and X^{32} is N.
- [0166] In some of the above embodiments, X^{40} , X^{41} , and X^{42} are C(H).
- [0167] In some of the above embodiments, X^{48} , X^{49} , X^{50} , and X^{51} are C(H).
15
- [0168] In some of the above embodiments, X^{52} , X^{53} , and X^{54} are C(H).
- [0169] In some of the above embodiments, X^{56} , X^{57} , and X^{58} are C(H).
- 20 [0170] In some of the above embodiments, X^{61} , X^{62} , X^{63} , and X^{64} are C(H).
- [0171] In some of the above embodiments, X^{66} , X^{67} , X^{68} , and X^{69} are C(H).
- [0172] In some of the above embodiments, one or more of X^{70} , X^{71} , and X^{72} is
25 N, and the remaining one(s) is/are C(H).
- [0173] In some of the above embodiments, one or more of X^{73} , X^{74} , X^{75} , and
 X^{76} is N, and the remaining one(s) is/are C(H).
- 30 **B8. Substituent R^E .**
- [0174] Each R^E is independently selected from the group consisting of halo, ni-
tro, hydroxy, oxo, carboxy, cyano, amino, imino, azido, and aldehydo, wherein

the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl.

5 **[0175]** In some embodiment, each R^E is independently selected from the group consisting of halo, nitro, hydroxy, oxo, carboxy, amino, imino, and aldehydo, wherein the amino optionally is substituted with one or two independently selected alkyl.

10 **[0176]** In some embodiment, each R^E is independently selected from the group consisting of halo, nitro, hydroxy, oxo, carboxy, amino, imino, aldehydo, and alkylamino.

15 **[0177]** In some embodiment, each R^E is independently selected from the group consisting of chloro, fluoro, nitro, hydroxy, oxo, carboxy, amino, imino, aldehydo, and alkylamino.

[0178] In some embodiment, each R^E is independently selected from the group consisting of halo, nitro, hydroxy, oxo, carboxy, cyano, amino, imino, and azido. In some such embodiments, each R^E is halo. In other such embodiments, each
20 R^E is nitro. In yet other such embodiments, each R^E is hydroxy. In yet other such embodiments, each R^E is oxo. In yet other such embodiments, each R^E is carboxy. In yet other such embodiments, each R^E is cyano. In yet other such embodiments, each R^E is amino. In further such embodiments, each R^E is imino. In yet further such embodiments, each R^E is and azido.

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[0179] In some embodiments, each R^E is independently selected from the group consisting of halo, nitro, hydroxy, oxo, carboxy, cyano, amino, and imino.

B9. Substituent R^F .

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[0180] Each R^F is independently selected from the group consisting of alkyl, alkenyl, and alkynyl, wherein:

each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, 5 alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, imino, aminosulfonyl, aminocarbonyl, carbocyclyl, and heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, 10 alkynylsulfonyl, alkylsulfonylamino, hydroxy, and alkyloxy, wherein:

amino portion of the alkylsulfonylamino optionally is substituted with a substituent selected from the group consisting of alkyl, alkenyl, and alkynyl.

15 **[0181]** In some embodiment, each R^F is independently selected from the group consisting of alkyl, alkenyl, and alkynyl, wherein:

each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein: 20

the amino, imino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, and alkylsulfonylamino, wherein: 25

amino portion of the alkylsulfonylamino optionally is substituted with a substituent selected from the group consisting of alkyl, alkenyl, and alkynyl.

30 **[0182]** In some of the above embodiments, each R^F is independently selected from the group consisting of the alkyl, alkynyl, and alkenyl, wherein such substituents are not substituted.

[0183] In some embodiments, each R^F is independently selected from the group consisting of alkyl, alkenyl, and alkynyl, wherein:
each such substituent optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:
5 the amino, imino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkylsulfonyl, and alkylsulfonylamino,
10 wherein:
amino portion of the alkylsulfonylamino optionally is substituted with alkyl.

[0184] In some embodiments, each R^F is an independently selected alkyl optionally substituted with a substituent selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:
15 the amino, imino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkylsulfonyl, and alkylsulfonylamino, wherein:
20 amino portion of the alkylsulfonylamino optionally is substituted with alkyl.

[0185] In some embodiments, each R^F is an independently selected alkyl optionally substituted with a substituent selected from the group consisting of carboxy, halo, amino, imino, and aminosulfonyl, wherein:
25 the amino, imino, and aminosulfonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkylsulfonyl, and alkylsulfonylamino.

[0186] In some embodiments, each R^F is an independently selected alkyl optionally substituted with amino, wherein the amino optionally is substituted with alkylsulfonyl.
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[0187] In some embodiments, each R^F is an independently selected alkyl substituted with amino, wherein the amino is substituted with alkylsulfonyl. In some such embodiments, each R^F is methylsulfonylaminomethyl.

- 5 [0188] In some embodiments, each R^F is independently selected from the group consisting of alkyl, alkenyl, and alkynyl, wherein:
each such substituent optionally is substituted with one, two, or three substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, 10 alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl.

- [0189] In some embodiments, each R^F is independently selected alkyl substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl.

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B10. Substituent R^G .

- [0190] Each R^G is independently selected from the group consisting of carbocyclyl and heterocyclyl, wherein:
25 each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, 30 cyano, and aminocarbonyl, wherein:
the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl.

[0191] In some of the above embodiments, each R^G is independently selected from the group consisting of carbocyclyl and heterocyclyl, wherein such substituents are not substituted.

- 5 **[0192]** In some embodiments, each R^G is independently selected from the group consisting of carbocyclyl and heterocyclyl, wherein:
each such substituent optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy,
10 carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:
the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl and alkylsulfonyl.

- 15 **[0193]** In some of the above embodiments, the carbocyclyl is C₃-C₆-carbocyclyl.

[0194] In some of the above embodiments, the heterocyclyl is 5-6-membered heterocyclyl.

20 **B11. Substituent R^H .**

[0195] Each R^H is independently selected from the group consisting of alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, alkenylsulfonyloxy, and alkynylsulfonyloxy, wherein:

- 25 each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl,
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the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl.

[0196] In some of the above embodiments, each R^H is independently selected from the group consisting of alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, alkenylsulfonyloxy, and alkynylsulfonyloxy, wherein such substituents are not substituted.

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[0197] In some embodiments, each R^H is independently selected from the group consisting of alkyloxy and alkylsulfonyloxy, wherein:

each such substituent optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

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the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl and alkylsulfonyl.

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[0198] In some embodiments, each R^H is independently selected from the group consisting of alkyloxy and alkylsulfonyloxy, wherein:

each such substituent optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, cyano, and aminocarbonyl, wherein:

20

the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl and alkylsulfonyl.

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[0199] In some embodiments, each R^H is independently selected from the group consisting of alkyloxy and alkylsulfonyloxy, wherein:

each such substituent optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, cyano, and aminocarbonyl.

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[0200] In some embodiments, each R^H is independently selected alkyloxy.

[0201] In some embodiments, each R^H is independently selected alkylsulfonyloxy.

B12. Substituent R^I .

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[0202] Each R^I is independently selected from the group consisting of alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, aminocarbonyl, alkyloxy carbonyl, carbocyclylcarbonyl, and heterocyclylcarbonyl, wherein:

10 (a) the alkylcarbonyl, alkenylcarbonyl, and alkynylcarbonyl optionally are substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, amino-sulfonyl, alkyloxy carbonyl, alkenyloxy carbonyl, alkynyloxy carbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, and

15 (b) the aminocarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkyloxyalkyl, carbocyclyl, heterocyclyl, alkylsulfonyl, and alkylsulfonylamino, wherein:

20 the carbocyclyl and heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of halo, alkyl, and oxo.

[0203] In some embodiments, each R^I is independently selected from the group consisting of alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, aminocarbonyl, alkyloxy carbonyl, carbocyclylcarbonyl, and heterocyclylcarbonyl, wherein such substituents are not substituted.

[0204] In some embodiments, each R^I is independently selected from the group consisting of alkylcarbonyl, aminocarbonyl, alkyloxy carbonyl, carbocyclylcarbonyl, and heterocyclylcarbonyl, wherein:

30 (a) the alkylcarbonyl optionally is substituted with a substituent selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxy carbonyl, alkylcarbonyloxy, alkyloxy, and aminocarbonyl, and

(b) the aminocarbonyl optionally is substituted with a substituent selected from the group consisting of alkyl, alkyloxyalkyl, alkylsulfonyl, and alkylsulfonylamino.

5 [0205] In some embodiments, each R^1 is independently selected from the group consisting of alkylcarbonyl and aminocarbonyl, wherein:

the aminocarbonyl optionally is substituted with a substituent selected from the group consisting of alkyl, alkyloxyalkyl, alkylsulfonyl, and alkylsulfonylamino.

10 [0206] In some embodiment, each R^1 is independently selected from the group consisting of alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, and aminocarbonyl, wherein:

(a) the alkylcarbonyl, alkenylcarbonyl, and alkynylcarbonyl optionally are substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, amino-

15 sulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, and

(b) the aminocarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,

20 and alkylsulfonylamino.

[0207] In some of the above embodiments, each R^1 is independently selected from the group consisting of alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl,

25 and aminocarbonyl, wherein such substituents are not substituted.

[0208] In some embodiments, each R^1 is independently selected from the group consisting of alkylcarbonyl and aminocarbonyl, wherein:

(a) the alkylcarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo,

30 amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, and

(b) the aminocarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkylsulfonylamino.

5 **[0209]** In some embodiments, each R^1 is independently selected from the group consisting of alkylcarbonyl and aminocarbonyl, wherein:

(a) the alkylcarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyl-
10 oxy, cyano, and aminocarbonyl, and

(b) the aminocarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkylsulfonylamino.

15 **[0210]** In some embodiments, each R^1 is independently selected from the group consisting of alkylcarbonyl and aminocarbonyl, wherein:

the alkylcarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl.
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[0211] In some embodiments, each R^1 is independently selected alkylcarbonyl.

[0212] In some embodiments, each R^1 is independently selected aminocarbonyl.
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[0213] *B13. Substituent R^j .*

[0214] Each R^j is independently selected from the group consisting of carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, alkyloxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, aminocarbonylamino, alkyloxycarbonylaminoimino, alkylsul-
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fonylaminoimino, alkenylsulfonylaminoimino, and alkynylsulfonylaminoimino, wherein:

(a) the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclyl-alkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkenyl, alkynyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

(1) the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alky-nyloxy, halo, nitro, cyano, azido, oxo, and amino, and

(2) the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,

(b) the alkyl, alkenyl, and alkynyl portion of such substituents optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, and alkynyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy;

(c) the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halo, nitro, cyano, azido, and amino, wherein:

the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl.

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[0215] In some embodiment, each R^J is independently selected from the group consisting of carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, alkyloxycarbonylamino,

alkenyloxycarbonylamino, alkynyloxycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, aminocarbonylamino, alkylsulfonylaminoimino, alkenylsulfonylaminoimino, and alkynylsulfonylaminoimino, wherein:

5 (a) the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclalkyl, heterocyclalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkenyl, alkynyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

10 (1) the carbocycl portion of the carbocyclalkyl and the heterocycl portion of the heterocyclalkyl optionally are substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkyloxy, halo, nitro, cyano, azido, oxo, and amino, and

15 (2) the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,

(b) the alkyl, alkenyl, and alkynyl portion of such substituents optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocycl, heterocycl, and cyano, wherein:

20 the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, and alkyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy;

25 (c) the carbocycl and heterocycl portions of such substituents optionally are substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkyloxy, halo, nitro, cyano, azido, and amino, wherein:

30 the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl; and

[0216] In some of the above embodiments, each R^J is independently selected from the group consisting of carbocyclsulfonylamino, heterocyclsulfonylami-

no, alkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, alkyloxy-carbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, aminocarbonylamino, alkylsulfonylaminoimino, alkenylsulfonylaminoimino, and alkynylsulfonylamino-
5 imino, wherein such substituents are not substituted.

[0217] In some embodiments, each R^J is independently selected from the group consisting of carbocyclisulfonylamino, heterocyclisulfonylamino, alkylcarbonylamino, alkyloxycarbonylamino, alkylsulfonylamino, aminocarbonylamino, and
10 alkylsulfonylaminoimino, wherein:

(a) the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and
15 alkylsulfonyl, wherein:

(1) the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino,
20 and

(2) the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,

(b) the alkyl portion of such substituents optionally is substituted with one or
25 two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

30 the alkyl optionally is substituted with one or more hydroxy;

(c) the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or two substituents independently selected from the

group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, and amino, wherein:

the amino optionally is substituted with one or two substituents independently selected alkyl.

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[0218] In some embodiments, each R^J is independently selected from the group consisting of carbocyclisulfonylamino, heterocyclisulfonylamino, alkylsulfonylamino, and alkylsulfonylaminoimino, wherein:

(a) the amino portion of such substituents optionally is substituted with a
10 substituent independently selected from the group consisting of carbocyclyl-alkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

(1) the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl
15 portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and

(2) the amino portion of the aminocarbonylalkyl optionally is substituted
20 ted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,

(b) the alkyl portion of such substituents optionally is substituted with one or
two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyl-
25 oxy, carbocyclyl, heterocyclyl, and cyano, wherein:

the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy;

(c) the carbocyclyl and heterocyclyl portions of such substituents optionally
30 are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, and amino, wherein:

the amino optionally is substituted with one or two substituents independently selected alkyl.

[0219] In some embodiments, each R^J is independently selected from the group
5 consisting of carbocyclisulfonylamino, heterocyclisulfonylamino, alkylsulfonyl-
amino, and alkylsulfonylaminoimino, wherein:

the amino portion of such substituents optionally is substituted with a substitu-
ent independently selected from the group consisting of carbocyclylalkyl, hete-
rocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyl-
10 oxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl,
wherein:

(1) the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl por-
tion of the heterocyclylalkyl optionally are substituted with one or two sub-
stituents independently selected from the group consisting of alkyl, carboxy,
15 hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and

(2) the amino portion of the aminocarbonylalkyl optionally is substituted with
one or two substituents independently selected from the group consisting of
alkyl, alkenyl, and alkynyl.

[0220] In some embodiments, each R^J is independently selected from the group
20 consisting of carbocyclisulfonylamino, heterocyclisulfonylamino, alkylsulfonyl-
amino, and alkylsulfonylaminoimino, wherein:

the alkyl portion of the alkylsulfonylamino and alkylsulfonylaminoimino optionally
is substituted with one or two substituents independently selected from the
25 group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyl-
oxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

the amino optionally is substituted with one or two substituents independently
selected from the group consisting of alkyl and alkyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy.

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[0221] In some embodiments, each R^J is independently selected from the group
consisting of carbocyclisulfonylamino, heterocyclisulfonylamino, alkylsulfonyl-
amino, and alkylsulfonylaminoimino, wherein:

the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, and amino.

- 5 **[0222]** In some embodiments, each R^d is independently selected from the group consisting of carbocyclylsulfonylamino and heterocyclylsulfonylamino, wherein: the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, and amino.

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[0223] In some embodiments, each R^d is independently selected from the group consisting of alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, and alkylsulfonylaminoimino, wherein:

- (a) the amino portion of such substituents optionally is substituted with a
15 substituent independently selected from the group consisting of carbocyclyl-alkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

- (1) the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl
20 portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and

- (2) the amino portion of the aminocarbonylalkyl optionally is substituted
25 ted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,

- (b) the alkyl, alkenyl, and alkynyl portion of such substituents optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

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the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy.

[0224] In some embodiments, each R^J is an independently selected alkylsulfonylamino, wherein:

5 (a) the amino portion of the alkylsulfonylamino optionally is substituted with a substituent independently selected from the group consisting of carbocyclalkyl, heterocyclalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

10 (1) the carbocycl portion of the carbocyclalkyl and the heterocycl portion of the heterocyclalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and

15 (2) the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,

(b) the alkyl portion of the alkylsulfonylamino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxy, alkylcarbonyloxy, hydroxy, alkyloxy, carbocycl, heterocycl, and cyano, wherein:

20 the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:
the alkyl optionally is substituted with one or more hydroxy.

[0225] In some embodiments, each R^J is an independently selected alkylsulfonylamino, wherein:

25 the amino portion of the alkylsulfonylamino optionally is substituted with a substituent independently selected from the group consisting of carbocyclalkyl, heterocyclalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

30 (1) the carbocycl portion of the carbocyclalkyl and the heterocycl portion of the heterocyclalkyl optionally are substituted with one or two sub-

stituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and
(2) the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of
5 alkyl, alkenyl, and alkynyl.

[0226] In some embodiments, each R^i is an independently selected alkylsulfonylamino, wherein:
the amino portion of the alkylsulfonylamino optionally is substituted with a sub-
10 stituent independently selected from the group consisting of carbocyclalkyl, heterocyclalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl.

15 **[0227]** In some embodiments, each R^j is an independently selected alkylsulfonylamino, wherein:
the alkyl portion of the alkylsulfonylamino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocycl, heterocycl, and cyano, wherein:
20 the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:
the alkyl optionally is substituted with one or more hydroxy.

25 **[0228]** In some embodiments, each R^j is an independently selected alkylsulfonylamino, wherein:
the alkyl portion of the alkylsulfonylamino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocycl, heterocycl, and cyano.
30

[0229] In some embodiments, each R^j is an independently selected alkylsulfonylamino. In some such embodiments, each R^j is methylsulfonylamino.

[0230] In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino, wherein:

(a) the amino portion of the alkylsulfonylaminoimino optionally is substituted with a substituent independently selected from the group consisting of carbocyclalkyl, heterocyclalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, 5 alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxy carbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

(1) the carbocycl portion of the carbocyclalkyl and the heterocycl portion of the heterocyclalkyl optionally are substituted with one or 10 two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and

(2) the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the 15 group consisting of alkyl, alkenyl, and alkynyl,

(b) the alkyl portion of the alkylsulfonylaminoimino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxy carbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocycl, heterocycl, and cyano, wherein:

20 the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:
the alkyl optionally is substituted with one or more hydroxy.

[0231] In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino, wherein:

25 the amino portion of the alkylsulfonylaminoimino optionally is substituted with a substituent independently selected from the group consisting of carbocyclalkyl, heterocyclalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxy carbonyl, alkyloxyalkyloxy carbonyl, alkylcarbonyloxyalkyl, and alkyl- 30 sulfonyl, wherein:

(1) the carbocycl portion of the carbocyclalkyl and the heterocycl portion of the heterocyclalkyl optionally are substituted with one or two sub-

stituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and
(2) the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of
5 alkyl, alkenyl, and alkynyl.

[0232] In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino, wherein:
the amino portion of the alkylsulfonylaminoimino optionally is substituted with a
10 substituent independently selected from the group consisting of carbocyclyl-alkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl.

15 **[0233]** In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino, wherein:
the alkyl portion of the alkylsulfonylaminoimino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy,
20 carbocyclyl, heterocyclyl, and cyano, wherein:
the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:
the alkyl optionally is substituted with one or more hydroxy.

25 **[0234]** In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino, wherein:
the alkyl portion of the alkylsulfonylaminoimino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy,
30 carbocyclyl, heterocyclyl, and cyano.

[0235] In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino. In some such embodiments, each R^J is methylsulfonylaminoimino.

- 5 [0236] In some embodiments, each R^J is independently selected from the group consisting of alkylcarbonylamino and alkyloxycarbonylamino, wherein:
the alkyl portion of such substituents optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl,
10 heterocyclyl, and cyano.

B14. Substituent R^K .

[0237] Each R^K is independently selected from the group consisting of amino-
15 sulfonyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl, wherein:

- (a) the alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl optionally are substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy,
20 alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl; and

- 25 (b) the aminosulfonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl.

[0238] In some of the above embodiments, each R^K is independently selected
30 from the group consisting of aminosulfonyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl, wherein such substituents are not substituted.

[0239] In some embodiments, each R^K is independently selected from the group consisting of aminosulfonyl and alkylsulfonyl, wherein:

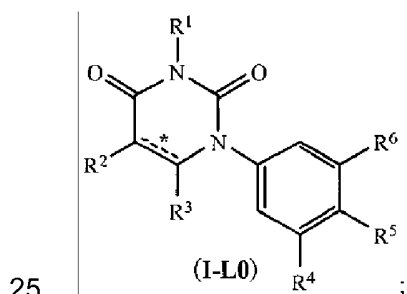
- (a) the alkylsulfonyl optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyl-oxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl; and
- (b) the aminosulfonyl optionally is substituted with one or two substituents independently selected alkyl.

[0240] In some embodiments, each R^K is independently selected from the group consisting of aminosulfonyl and alkylsulfonyl.

C. Embodiments of Compounds of Formula I.

[0241] Various embodiments of substituents R^1 , R^2 , R^3 , R^4 , R^5 , L , R^A , R^B , R^C , R^D , R^E , R^F , R^G , R^H , R^I , R^J , and R^K have been discussed above. These substituent embodiments can be combined to form various embodiments of compounds of formula I. All embodiments of compounds of formula I formed by combining the substituent embodiments discussed above are within the scope of Applicants' process invention, and some illustrative embodiments of the compounds of formula I are provided below.

[0242] In some embodiments, the compounds of formula I correspond in structure to formula I-L0:



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is selected from the group consisting of single carbon-carbon bond and double carbon-carbon bond;

- R^1 is selected from the group consisting of hydrogen and methyl;
- R^2 is selected from the group consisting of hydrogen and halo
- R^3 is selected from the group consisting of hydrogen and halo;
- R^4 is selected from the group consisting of C₁-C₄-alkyl, C₃-C₆-carbocyclyl, and
- 5 5-6-membered heterocyclyl, wherein:
- (a) the C₁-C₄-alkyl optionally is substituted with up to three substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyloxy, and trimethylsilyl, and
- (b) the C₃-C₆-carbocyclyl and 5-6-membered heterocyclyl optionally are
- 10 substituted with one or two substituents independently selected from the group consisting of alkyl, halo, and alkylsulfonylamino;
- R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and halo;
- R^6 is selected from the group consisting of fused 2-ring heterocyclyl and fused
- 15 2-ring carbocyclyl, wherein each such substituent is substituted with one, two, or three substituents independently selected from the group consisting of R^E , R^F , R^I , R^J , and R^K ;
- each R^E is independently selected from the group consisting of chloro, fluoro, nitro, hydroxy, oxo, carboxy, amino, imino, aldehydo, and alkylamino;
- 20 each R^F is an independently selected alkyl optionally substituted with a substituent selected from the group consisting of carboxy, halo, amino, imino, and aminosulfonyl, wherein:
- the amino, imino, and aminosulfonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkylsul-
- 25 fonyl, and alkylsulfonylamino;
- each R^I is independently selected from the group consisting of alkylcarbonyl and aminocarbonyl, wherein:
- the aminocarbonyl optionally is substituted with a substituent selected from the group consisting of alkyl, alkyloxyalkyl, alkylsulfonyl, and alkylsulfonylamino;
- 30 each R^J is independently selected from the group consisting of alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, and alkylsulfonylaminoimino, wherein:

(a) the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclalkyl, heterocyclalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

(1) the carbocycl portion of the carbocyclalkyl and the heterocycl portion of the heterocyclalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and

(2) the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,

(b) the alkyl, alkenyl, and alkynyl portion of such substituents optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocycl, heterocycl, and cyano, wherein:

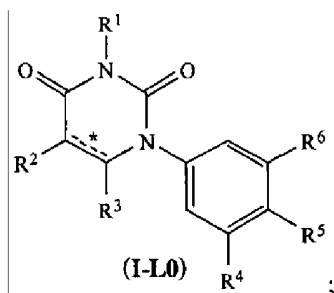
the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy; and each R^K is independently selected from the group consisting of aminosulfonyl and alkylsulfonyl, wherein:

(a) the alkylsulfonyl optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocycl, heterocycl, cyano, and aminocarbonyl; and

(b) the aminosulfonyl optionally is substituted with one or two substituents independently selected alkyl.

[0243] In some embodiments, the compounds of formula I correspond in structure to formula I-L0:



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is selected from the group consisting of single carbon-carbon bond and double carbon-carbon bond;

5 R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and halo

R^3 is hydrogen;

R^4 is tert-butyl;

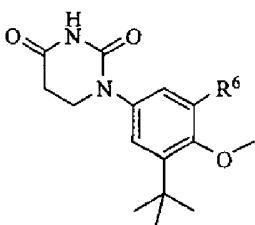
10 R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and halo;

R^6 is a fused 2-ring carbocyclyl selected from the group consisting of naphthalenyl, dihydronaphthalenyl, tetrahydronaphthalenyl, hexahydronaphthalenyl, octahydronaphthalenyl, decahydronaphthalenyl, indenyl, dihydroindenyl, hexahydroindenyl, octahydroindenyl, pentalenyl, octahydropentalenyl, and hexahydropentalenyl, wherein each such substituent is substituted with a substituent selected from the group consisting of R^F and R^J ;

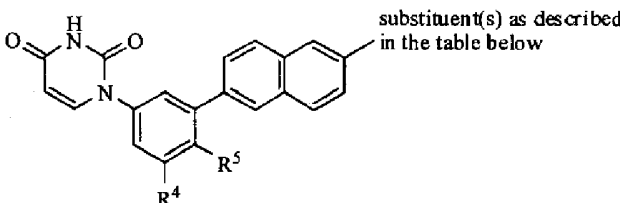
R^F is alkylsulfonylaminoalkyl; and

R^J is alkylsulfonylamino.

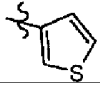
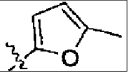

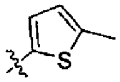
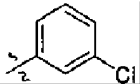
20 **[0244]** Examples of compounds of formula I (and salts thereof) are shown in Tables 1-9 below. The synthesis examples below provide step-by-step preparation instructions for some of these compounds. The remaining compounds were prepared utilizing the general method-of-preparation discussion, specific synthesis examples below, and/or the discussion throughout this application.

TABLE 1


compound	R ⁶	
	ring/ring structure	substituent(s)
IA-L0-2.1	benzimidazol-2-yl	-5-N(H)S(O) ₂ CH ₃
IA-L0-2.2	benzthiazol-2-yl	-6-N(H)S(O) ₂ CH ₃
IA-L0-2.3	benzthiazol-2-yl	---
IA-L0-2.4	benzthiazol-2-yl	-5-N(H)S(O) ₂ CH ₃
IA-L0-2.5	benzoxazol-2-yl	-6-N(H)S(O) ₂ CH ₃
IA-L0-2.6	benzoxazol-2-yl	-6-NO ₂
IA-L0-2.7	benzoxazol-2-yl	-5-NO ₂
IA-L0-2.8	benzoxazol-2-yl	-5-N(H)S(O) ₂ CH ₃
IA-L0-2.9	naphthalen-2-yl	-6-N(H)S(O) ₂ CH ₃
IA-L0-2.10	benzimidazol-2-yl	-5-N[S(O) ₂ CH ₃] ₂

TABLE 2


compound	R ⁴	R ⁵	substituent(s)
IB-L0-2.1	-C(CH ₃) ₃	-OCH ₃	-H
IB-L0-2.2	-C(CH ₃) ₃	-OCH ₃	-OCH ₃
IB-L0-2.3	-C(CH ₃) ₃	-OCH ₃	-N(H)S(O) ₂ CH ₃
IB-L0-2.8	-C(CH ₃) ₃	-H	-N(H)S(O) ₂ CH ₃
IB-L0-2.14	-C(CH ₃) ₃	-Cl	-N(H)S(O) ₂ CH ₃

IB-L0-2.23	$-\text{C}(\text{CH}_3)_3$	$-\text{OC}(\text{H})_2\text{CH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.52	$-\text{C}(\text{CH}_3)_2\text{C}(\text{H})_2\text{C}(\text{H})_3$	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.53		$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.54	$-\text{C}(\text{CH}_3)_2\text{C}(\text{H})_2\text{OH}$	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.56	$-\text{CF}_3$	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.57	$-\text{I}$	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.58		$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.59	furan-2-yl	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.60	$-\text{C}(\text{F})_2\text{CF}_3$	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.61		$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.64	furan-3-yl	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.66	$-\text{C}(\text{CH}_3)_2\text{C}(\text{H})_2\text{OCH}_3$	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.68	$-\text{S}(\text{O})_2\text{CH}_3$	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.69	$-\text{Br}$	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.70	$-\text{C}(\text{CH}_3)_2\text{C}(\text{O})\text{OCH}_3$	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.71	phenyl	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.72	$-\text{C}(\text{O})\text{OCH}_3$	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.73		$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.74		$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.75	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$	$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$
IB-L0-2.76		$-\text{OCH}_3$	$-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$

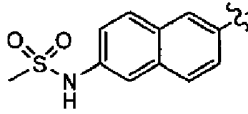
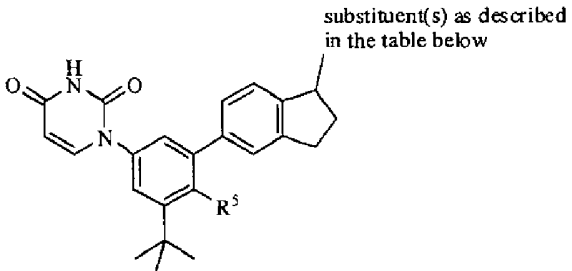
			
IB-L0-2.77	-C(CH ₃) ₂ C(O)OH	-OCH ₃	-N(H)S(O) ₂ CH ₃
IB-L0-2.78	-C≡CSi(CH ₃) ₃	-OCH ₃	-N(H)S(O) ₂ CH ₃

TABLE 3

		
compound	R ⁵	substituent(s)
IB-L0-2.4	-OCH ₃	=NN(H)S(O) ₂ CH ₃
IB-L0-2.7	-H	=NN(H)S(O) ₂ CH ₃
IB-L0-2.9	-OCH ₃	(S) -C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.10	-OCH ₃	(R) -F and -C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.12	-OCH ₃	-F and -C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.15	-OCH ₃	(R) -C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.17	-OCH ₃	-C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.20	-OCH ₃	(S) -F and -C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.22	-OCH ₃	(S) -C(CH ₃) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.24	-OCH ₃	=NN(H)C(O)OCH ₃
IB-L0-2.25	-OCH ₃	-CH ₃ and -C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.29	-OCH ₃	-C(CH ₃) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.31	-OCH ₃	-N(H)N(O) ₂ CH ₃
IB-L0-2.34	-OCH ₃	-C(O)N(H)S(O) ₂ CH ₃
IB-L0-2.36	-OCH ₃	-OH
IB-L0-2.37	-OCH ₃	(R) -C(CH ₃) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.44	-OCH ₃	-N(H)S(O) ₂ CH ₃

IB-L0-2.50	-OCH ₃	=O
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TABLE 4

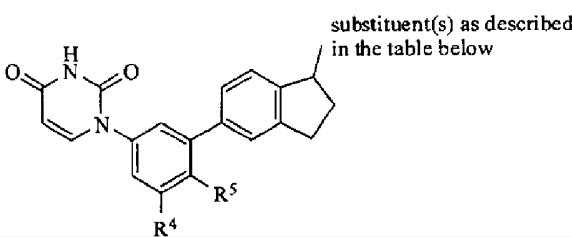
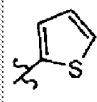
			
compound	R ⁴	R ⁵	substituent(s)
IB-L0-2.51		-OCH ₃	=NN(H)S(O) ₂ CH ₃
IB-L0-2.55	furan-2-yl	-OCH ₃	=NN(H)S(O) ₂ CH ₃

TABLE 5

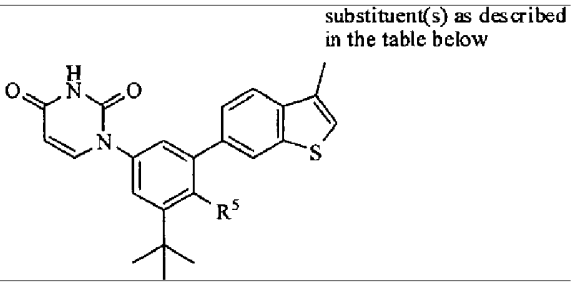
		
compound	R ⁵	substituent(s)
IB-L0-2.11	-OCH ₃	C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.21	-OCH ₃	-C(H) ₂ N(CH ₃)S(O) ₂ CH ₃
IB-L0-2.35	-Cl	-C(H) ₂ N(H)S(O) ₂ CH ₃

TABLE 6

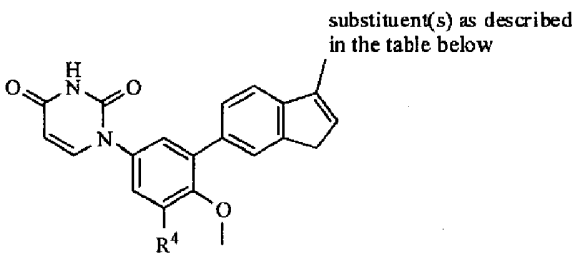


		
compound	R ⁴	substituent(s)
IB-L0-2.13	-C(CH ₃) ₃	-C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.16	-C(CH ₃) ₃	-C(H) ₂ N(CH ₃)S(O) ₂ CH ₃
IB-L0-2.41	-C(CH ₃) ₃	-C(CH ₃) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.62		-C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.63		-C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.65	furan-2-yl	-C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.67	furan-3-yl	-C(H) ₂ N(H)S(O) ₂ CH ₃

TABLE 7

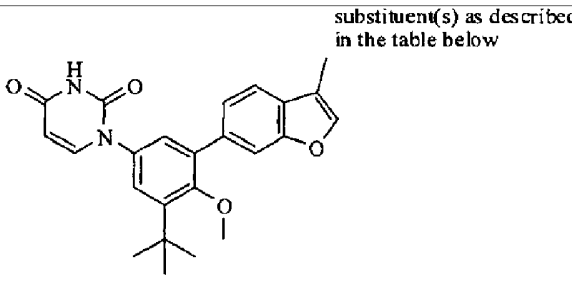
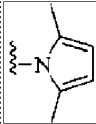
	
compound	substituent(s)
IB-L0-2.18	-C(H) ₂ N(H)S(O) ₂ CH ₃
IB-L0-2.42	-CH ₃

TABLE 8

compound	substituent(s)
IB-L0-2.27	-NH ₂
IB-L0-2.28	-N(H)S(O) ₂ CH ₃
IB-L0-233	-H
IB-L0-238	-Cl
IB-L0-239	-NH ₂
IB-L0-2.46	-N(H)C(H) ₂ C(H) ₂ CH ₃
IB-L0-2.47	
IB-L0-2.49	-N(H)C(O)CH ₃

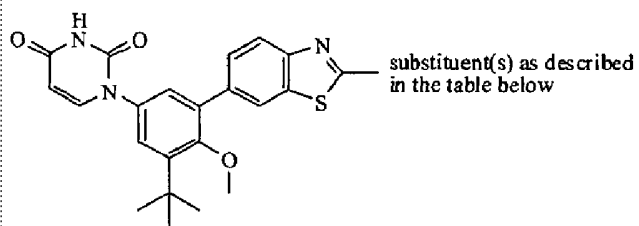
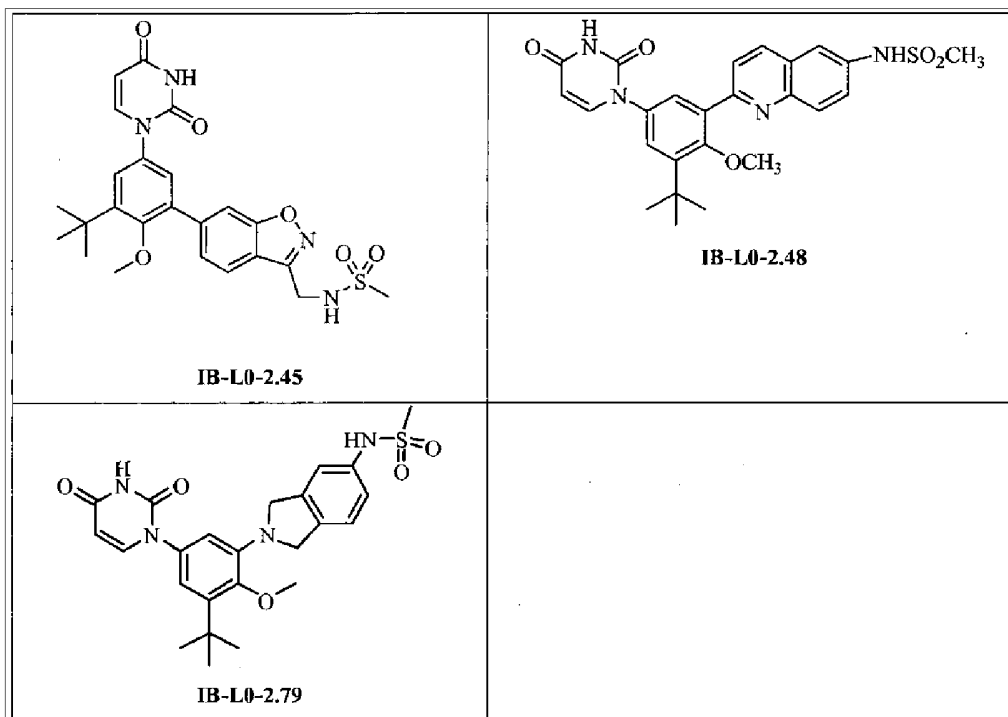


TABLE 9

<p>IB-L0-2.5</p>	<p>IB-L0-2.6</p>
<p>IB-L0-2.19</p>	<p>IB-L0-2.26</p>
<p>IB-L0-2.30</p>	<p>IB-L0-2.32</p>
<p>IB-L0-2.40</p>	<p>IB-L0-2.43</p>



D. Isomers.

5

[0245] This invention also is directed, in part, to a process for preparing all isomers of the compounds of formula I (and their salts) (*i.e.*, structural and stereoisomers). Structural isomers include chain and position isomers. Stereoisomers include E/Z isomers (*i.e.*, isomers with regard to one or more double bonds), enantiomers (*i.e.*, stereo- isomers that have opposite configurations at all stereogenic centers), and diastereoisomers (*i.e.*, stereo- isomers that have the same configuration at one or more stereogenic centers, but differ at other stereogenic centers).

15 **E. Salts.**

[0246] This invention also is directed, in part, to a process for preparing all salts of the compounds of formula I. A salt of a compound may be advantageous due to one or more of the salt's properties, such as, for example, enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubili-

20

ty in water or other solvents. Where a salt is intended to be administered to a patient (as opposed to, for example, being in use in an *in vitro* context), the salt preferably is pharmaceutically acceptable and/or physiologically compatible. The term "pharmaceutically acceptable" is used adjectivally in this patent application to mean that the modified noun is appropriate for use as a pharmaceutical product or as a part of a pharmaceutical product. Pharmaceutically acceptable salts include salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. In general, these salts typically may be prepared by conventional means by reacting, for example, the appropriate acid or base with a compound of the invention.

[0247] Pharmaceutically acceptable acid addition salts of the compounds of formula I can be prepared from an inorganic or organic acid. Examples of often suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids. Specific examples of often suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), ethanesulfonate, benzenesulfonate, pantothenate, 2-hydroxyethanesulfonate, sulfanilate, cyclohexylaminosulfonate, alginic acid, beta-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, bisulfate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, oxalate, palmoate, pectinate, 2-naphthalesulfonate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

[0248] Pharmaceutically acceptable base addition salts of the compounds of formula I include, for example, metallic salts and organic salts. Preferred metallic salts include alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts, and other physiologically acceptable metal salts. Such salts may be made

from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. Preferred organic salts can be made from amines, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl (C₁-C₆) halides (*e.g.*, methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

10

[0249] In some embodiments, the salt is sodium salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydro-pyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

15 **[0250]** In some embodiments, the salt is monosodium salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0251] In some embodiments, the salt is disodium salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydro-pyrimidin-1(2H)-yl)-2-methoxyphenyl)aphthalen-2-yl)methanesulfonamide.

20 **[0252]** In some embodiments, the salt is potassium salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydro-pyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)-
25 methanesulfonamide.

[0253] In some embodiments, the salt is monopotassium salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

30

[0254] In some embodiments, the salt is choline salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydro-pyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0255] In some embodiments, the salt is monocholine salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)-methanesulfonamide.

5 **F. Purity.**

[0256] Compounds of formula I (and salts thereof) with any level of purity (including pure and substantially pure) are within the scope of Applicants' invention. The term "substantially pure" in reference to a compound/salt/isomer, means
10 that the preparation/composition containing the compound/salt/isomer contains more than about 85% by weight of the compound/salt/isomer, preferably more than about 90% by weight of the compound/salt/isomer, preferably more than about 95% by weight of the compound/salt/isomer, preferably more than about 97% by weight of the compound/salt/isomer, and preferably more than about
15 99% by weight of the compound/salt/isomer.

G. Crystalline Forms of Some Specific Compounds and Salts of The Invention.

20 **G1. Crystalline Forms of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.3).**

[0257] This invention also relates, in part, to crystalline forms of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound **IB-L0-2.3**), namely the solvate, hydrate, and solvent-free crystalline forms discussed below.

G1A. IB-L0-2.3 Solvates.

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[0258] This invention also relates, in part, to an ethanol solvate of compound **IB-L0-2.3**.

[0259] In some embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.3 ± 0.2 , 9.7 ± 0.2 , 10.6 ± 0.2 , 13.6 ± 0.2 , 17.2 ± 0.2 , 19.2 ± 0.2 , 22.7 ± 0.2 , 26.9 ± 0.2 , and 29.4 ± 0.2 degrees two theta (2θ). In some such embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.3 ± 0.2 , 9.7 ± 0.2 , 10.6 ± 0.2 , 13.6 ± 0.2 , 17.2 ± 0.2 , 19.2 ± 0.2 , 22.7 ± 0.2 , 26.9 ± 0.2 , and 29.4 ± 0.2 degrees 2θ . In other such embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.3 ± 0.2 , 9.7 ± 0.2 , 10.6 ± 0.2 , 13.6 ± 0.2 , 17.2 ± 0.2 , 19.2 ± 0.2 , 22.7 ± 0.2 , 26.9 ± 0.2 , and 29.4 ± 0.2 degrees 2θ .

[0260] In some embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.3 ± 0.2 , 9.7 ± 0.2 , 10.0 ± 0.2 , 10.6 ± 0.2 , 13.6 ± 0.2 , 17.2 ± 0.2 , 17.5 ± 0.2 , 19.2 ± 0.2 , 19.4 ± 0.2 , 22.7 ± 0.2 , 26.9 ± 0.2 , and 29.4 ± 0.2 degrees 2θ . In some such embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.3 ± 0.2 , 9.7 ± 0.2 , 10.0 ± 0.2 , 10.6 ± 0.2 , 13.6 ± 0.2 , 17.2 ± 0.2 , 17.5 ± 0.2 , 19.2 ± 0.2 , 19.4 ± 0.2 , 22.7 ± 0.2 , 26.9 ± 0.2 , and 29.4 ± 0.2 degrees 2θ . In other embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.3 ± 0.2 , 9.7 ± 0.2 , 10.0 ± 0.2 , 10.6 ± 0.2 , 13.6 ± 0.2 , 17.2 ± 0.2 , 17.5 ± 0.2 , 19.2 ± 0.2 , 19.4 ± 0.2 , 22.7 ± 0.2 , 26.9 ± 0.2 , and 29.4 ± 0.2 degrees 2θ .

25

[0261] In some embodiments, the ethanol solvate has an X-ray powder diffraction pattern substantially as shown in Figure 1. The 2θ values for the peaks in Figure 1 (and their intensities) are as follows: 8.25 (54), 9.67 (74), 9.92 (63), 10.59 (21), 13.64 (49), 17.25 (40), 17.51 (20), 19.19 (66), 19.43 (100), 22.75 (19), 26.92 (25), and 29.39 (18).

30

[0262] This invention also relates, in part, to an acetonitrile solvate of compound **IB-L0-2.3**.

[0263] In some embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.3 ± 0.2 , 8.3 ± 0.2 , 9.7 ± 0.2 , 10.5 ± 0.2 , 13.8 ± 0.2 , 17.2 ± 0.2 , 19.1 ± 0.2 , and 19.5 ± 0.2 degrees 2θ . In some such embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.3 ± 0.2 , 8.3 ± 0.2 , 9.7 ± 0.2 , 10.5 ± 0.2 , 13.8 ± 0.2 , 17.2 ± 0.2 , 19.1 ± 0.2 , and 19.5 ± 0.2 degrees 2θ . In other such embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.3 ± 0.2 , 8.3 ± 0.2 , 9.7 ± 0.2 , 10.5 ± 0.2 , 13.8 ± 0.2 , 17.2 ± 0.2 , 19.1 ± 0.2 , and 19.5 ± 0.2 degrees 2θ .

[0264] In some embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.3 ± 0.2 , 8.3 ± 0.2 , 9.7 ± 0.2 , 10.5 ± 0.2 , 13.8 ± 0.2 , 17.2 ± 0.2 , 17.7 ± 0.2 , 19.1 ± 0.2 , 19.5 ± 0.2 , 22.0 ± 0.2 , 22.8 ± 0.2 , and 27.2 ± 0.2 degrees 2θ . In some such embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.3 ± 0.2 , 8.3 ± 0.2 , 9.7 ± 0.2 , 10.5 ± 0.2 , 13.8 ± 0.2 , 17.2 ± 0.2 , 17.7 ± 0.2 , 19.1 ± 0.2 , 19.5 ± 0.2 , 22.0 ± 0.2 , 22.8 ± 0.2 , and 27.2 ± 0.2 degrees 2θ . In other such embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.3 ± 0.2 , 8.3 ± 0.2 , 9.7 ± 0.2 , 10.5 ± 0.2 , 13.8 ± 0.2 , 17.2 ± 0.2 , 17.7 ± 0.2 , 19.1 ± 0.2 , 19.5 ± 0.2 , 22.0 ± 0.2 , 22.8 ± 0.2 , and 27.2 ± 0.2 degrees 2θ .

[0265] In some embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern substantially as shown in Figure 3. The 2θ values for the peaks in Figure 3 (and their intensities) are as follows: 5.27 (14), 8.29 (33), 9.72 (100), 10.53 (20), 13.77 (67), 17.25 (38), 17.69 (17), 19.05 (63), 19.47 (58), 22.05 (19), 22.75 (16), and 27.17 (21).

[0266] This invention also relates, in part, to an ethyl acetate solvate of compound **IB-L0-2.3**.

[0267] In some embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 7.9 ± 0.2 , 9.3 ± 0.2 , 9.7 ± 0.2 , 10.6 ± 0.2 , 18.7 ± 0.2 , 38.5 ± 0.2 , and 44.7 ± 0.2 degrees 2θ . In some such embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 7.9 ± 0.2 , 9.3 ± 0.2 , 9.7 ± 0.2 , 10.6 ± 0.2 , 18.7 ± 0.2 , 38.5 ± 0.2 , and 44.7 ± 0.2 degrees 2θ . In other such embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 7.9 ± 0.2 , 9.3 ± 0.2 , 9.7 ± 0.2 , 10.6 ± 0.2 , 18.7 ± 0.2 , 38.5 ± 0.2 , and 44.7 ± 0.2 degrees 2θ .

[0268] In some embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 7.9 ± 0.2 , 9.3 ± 0.2 , 9.7 ± 0.2 , 10.6 ± 0.2 , 13.7 ± 0.2 , 17.4 ± 0.2 , 18.7 ± 0.2 , 21.7 ± 0.2 , 22.0 ± 0.2 , 28.2 ± 0.2 , 38.5 ± 0.2 , and 44.7 ± 0.2 degrees 2θ . In some such embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 7.9 ± 0.2 , 9.3 ± 0.2 , 9.7 ± 0.2 , 10.6 ± 0.2 , 13.7 ± 0.2 , 17.4 ± 0.2 , 18.7 ± 0.2 , 21.7 ± 0.2 , 22.0 ± 0.2 , 28.2 ± 0.2 , 38.5 ± 0.2 , and 44.7 ± 0.2 degrees 2θ . In other such embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 7.9 ± 0.2 , 9.3 ± 0.2 , 9.7 ± 0.2 , 10.6 ± 0.2 , 13.7 ± 0.2 , 17.4 ± 0.2 , 18.7 ± 0.2 , 21.7 ± 0.2 , 22.0 ± 0.2 , 28.2 ± 0.2 , 38.5 ± 0.2 , and 44.7 ± 0.2 degrees 2θ .

[0269] In some embodiments, the ethyl acetate has an X-ray powder diffraction pattern substantially as shown in Figure 4. The 2θ values for the peaks in Figure 4 (and their intensities) are as follows: 7.94 (24), 9.33 (26), 9.72 (13), 10.58 (23), 13.71 (19), 17.40 (28), 18.72 (44), 21.69 (8), 22.04 (10), 28.23 (8), 38.45 (100), and 44.66 (95).

[0270] This invention also relates, in part, to a 2-propanol solvate of compound **IB-L0-2.3**.

[0271] In some embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 16.3 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 19.4 ± 0.2 , 21.6 ± 0.2 , and 22.5 ± 0.2 degrees 2θ . In some such embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 16.3 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 19.4 ± 0.2 , 21.6 ± 0.2 , and 22.5 ± 0.2 degrees 2θ . In other such embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 16.3 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 19.4 ± 0.2 , 21.6 ± 0.2 , and 22.5 ± 0.2 degrees 2θ .

[0272] In some embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 16.3 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 19.4 ± 0.2 , 21.6 ± 0.2 , 22.5 ± 0.2 , 23.8 ± 0.2 , 26.0 ± 0.2 , and 28.0 ± 0.2 degrees 2θ . In some such embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 16.3 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 19.4 ± 0.2 , 21.6 ± 0.2 , 22.5 ± 0.2 , 23.8 ± 0.2 , 26.0 ± 0.2 , and 28.0 ± 0.2 degrees 2θ . In other such embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 16.3 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 19.4 ± 0.2 , 21.6 ± 0.2 , 22.5 ± 0.2 , 23.8 ± 0.2 , 26.0 ± 0.2 , and 28.0 ± 0.2 degrees 2θ .

25

[0273] In some embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern substantially as shown in Figure 5. The 2θ values for the peaks in Figure 5 (and their intensities) are as follows: 8.18 (32), 9.26 (100), 10.12 (81), 16.28 (93), 18.11 (30), 18.59 (63), 19.40 (67), 21.57 (60), 22.51 (31), 23.82 (29), 25.94 (24), and 28.05 (29).

30

[0274] This invention also relates, in part, to a methanol solvate of compound **IB-L0-2.3**.

[0275] In some embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.4 ± 0.2 , 9.7 ± 0.2 , 10.1 ± 0.2 , 13.8 ± 0.2 , 17.4 ± 0.2 , 19.3 ± 0.2 , and 19.6 ± 0.2 degrees 2θ . In some such embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.4 ± 0.2 , 9.7 ± 0.2 , 10.1 ± 0.2 , 13.8 ± 0.2 , 17.4 ± 0.2 , 19.3 ± 0.2 , and 19.6 ± 0.2 degrees 2θ . In other such embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.4 ± 0.2 , 9.7 ± 0.2 , 10.1 ± 0.2 , 13.8 ± 0.2 , 17.4 ± 0.2 , 19.3 ± 0.2 , and 19.6 ± 0.2 degrees 2θ .

[0276] In some embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.4 ± 0.2 , 9.7 ± 0.2 , 10.1 ± 0.2 , 13.5 ± 0.2 , 13.8 ± 0.2 , 17.4 ± 0.2 , 19.3 ± 0.2 , 19.6 ± 0.2 , and 27.1 ± 0.2 degrees 2θ . In some such embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.4 ± 0.2 , 9.7 ± 0.2 , 10.1 ± 0.2 , 13.5 ± 0.2 , 13.8 ± 0.2 , 17.4 ± 0.2 , 19.3 ± 0.2 , 19.6 ± 0.2 , and 27.1 ± 0.2 degrees 2θ . In other such embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.4 ± 0.2 , 9.7 ± 0.2 , 10.1 ± 0.2 , 13.5 ± 0.2 , 13.8 ± 0.2 , 17.4 ± 0.2 , 19.3 ± 0.2 , 19.6 ± 0.2 , and 27.1 ± 0.2 degrees 2θ .

[0277] In some embodiments, the methanol solvate has an X-ray powder diffraction pattern substantially as shown in Figure 6. The 2θ values for the peaks in Figure 6 (and their intensities) are as follows: 8.36 (48), 9.74 (65), 10.05 (74), 13.55 (24), 13.79 (69), 17.40 (32), 19.30 (80), 19.58 (100), and 27.08 (24).

[0278] This invention also relates, in part, to a 1-propanol solvate of compound **IB-L0-2.3**.

[0279] In some embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consi-

sting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 15.7 ± 0.2 , 16.2 ± 0.2 , 18.4 ± 0.2 , 19.3 ± 0.2 , 21.6 ± 0.2 , and 22.8 ± 0.2 degrees 2θ . In some such embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 15.7 ± 0.2 , 16.2 ± 0.2 , 18.4 ± 0.2 , 19.3 ± 0.2 , 21.6 ± 0.2 , and 22.8 ± 0.2 degrees 2θ . In other such
5 embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 15.7 ± 0.2 , 16.2 ± 0.2 , 18.4 ± 0.2 , 19.3 ± 0.2 , 21.6 ± 0.2 , and 22.8 ± 0.2 degrees 2θ .

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[0280] In some embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 10.5 ± 0.2 , 15.7 ± 0.2 , 16.2 ± 0.2 , 18.4 ± 0.2 , 18.6 ± 0.2 , 19.3 ± 0.2 , 21.0 ± 0.2 , 21.6 ± 0.2 , and 22.8 ± 0.2 degrees 2θ . In some such
15 embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 10.5 ± 0.2 , 15.7 ± 0.2 , 16.2 ± 0.2 , 18.4 ± 0.2 , 18.6 ± 0.2 , 19.3 ± 0.2 , 21.0 ± 0.2 , 21.6 ± 0.2 , and 22.8 ± 0.2 degrees 2θ . In other such embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising five or
20 more peaks selected from the group consisting of 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 10.5 ± 0.2 , 15.7 ± 0.2 , 16.2 ± 0.2 , 18.4 ± 0.2 , 18.6 ± 0.2 , 19.3 ± 0.2 , 21.0 ± 0.2 , 21.6 ± 0.2 , and 22.8 ± 0.2 degrees 2θ .

[0281] In some embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern substantially as shown in Figure 7. The 2θ values for the peaks in Figure 7 (and their intensities) are as follows: 8.15 (27), 9.26 (87), 10.08 (84), 10.47 (62), 15.73 (40), 16.24 (100), 18.37 (41), 18.59 (49), 19.33 (50), 20.97 (28), 21.65 (71), and 22.81 (44).

[0282] This invention also relates, in part, to a process for preparing the above solvates by suspending compound **IB-L0-2.3** in the corresponding solvent.

30

GIB. Solvent Free IB-L0-2.3.

[0283] This invention also relates, in part, to a solvent free crystalline form of compound **IB-L0-2.3**.

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[0284] In some embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 6.2 ± 0.2 , 7.9 ± 0.2 , 9.9 ± 0.2 , 16.2 ± 0.2 , and 18.3 ± 0.2 degrees two theta (2θ). In some such embodiments, the solvent free compound **IB-L0-**
10 **2.3** has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 6.2 ± 0.2 , 7.9 ± 0.2 , 9.9 ± 0.2 , 16.2 ± 0.2 , and 18.3 ± 0.2 degrees 2θ . In other such embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 6.2 ± 0.2 , 7.9 ± 0.2 , 9.9 ± 0.2 , 16.2 ± 0.2 , and
15 18.3 ± 0.2 degrees 2θ .

[0285] In some embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 6.2 ± 0.2 , 7.9 ± 0.2 , 9.9 ± 0.2 , 10.1 ± 0.2 , 14.9 ± 0.2 , 16.2 ± 0.2 ,
20 18.3 ± 0.2 , 19.8 ± 0.2 , and 26.5 ± 0.2 degrees 2θ . In some such embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 6.2 ± 0.2 , 7.9 ± 0.2 , 9.9 ± 0.2 , 10.1 ± 0.2 , 14.9 ± 0.2 , 16.2 ± 0.2 , 18.3 ± 0.2 , 19.8 ± 0.2 , and 26.5 ± 0.2 degrees 2θ . In other such embodiments, the solvent free compound
25 **IB-L0-2.3** has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 6.2 ± 0.2 , 7.9 ± 0.2 , 9.9 ± 0.2 , 10.1 ± 0.2 , 14.9 ± 0.2 , 16.2 ± 0.2 , 18.3 ± 0.2 , 19.8 ± 0.2 , and 26.5 ± 0.2 degrees 2θ . In yet other such embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising eight or more peaks selected from the group consisting of 6.2 ± 0.2 , 7.9 ± 0.2 , 9.9 ± 0.2 , 10.1 ± 0.2 , 14.9 ± 0.2 , 16.2 ± 0.2 , 18.3 ± 0.2 ,
30 19.8 ± 0.2 , and 26.5 ± 0.2 degrees 2θ .

[0286] In some embodiments, the solvent free compound **IB-L0-2.3** has an X-

ray powder diffraction pattern substantially as shown in Figure 8. The 2θ values for the peaks in Figure 8 (and their intensities) are as follows: 6.20 (36), 7.85 (66), 9.89 (61), 10.12 (75), 14.87 (27), 16.19 (89), 18.32 (100), 19.82 (77), and 26.53 (34).

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[0287] This invention also relates, in part, to a process for preparing the solvent free crystalline form of compound **IB-L0-2.3** by desolvating one of **IB-L0-2.3** solvates discussed above. A solvate can be desolvated by heating the solvate solid for about 10min at $\sim 125^{\circ}\text{C}$.

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G1C. IB-L0-2.3 Hydrate.

[0288] This invention also relates, in part, to a hydrate of compound **IB-L0-2.3**.

15 **[0289]** In some embodiments, the hydrate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 6.4 ± 0.2 , 12.9 ± 0.2 , 17.9 ± 0.2 , and 18.9 ± 0.2 degrees 2θ . In some such embodiments, the hydrate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 6.4 ± 0.2 , 12.9 ± 0.2 , 17.9 ± 0.2 ,
20 and 18.9 ± 0.2 degrees 2θ .

[0290] In some embodiments, the hydrate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 6.4 ± 0.2 , 12.9 ± 0.2 , 17.5 ± 0.2 , 17.9 ± 0.2 , 18.9 ± 0.2 , and 24.4 ± 0.2 degrees 2θ . In
25 some such embodiments, the hydrate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 6.4 ± 0.2 , 12.9 ± 0.2 , 17.5 ± 0.2 , 17.9 ± 0.2 , 18.9 ± 0.2 , and 24.4 ± 0.2 degrees 2θ . In other such
embodiments, the hydrate has an X-ray powder diffraction pattern comprising
30 five or more peaks selected from the group consisting of 6.4 ± 0.2 , 12.9 ± 0.2 , 17.5 ± 0.2 , 17.9 ± 0.2 , 18.9 ± 0.2 , and 24.4 ± 0.2 degrees 2θ .

[0291] In some embodiments, the hydrate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of

6.4±0.2, 12.7±0.2, 12.9±0.2, 14.1±0.2, 15.7±0.2, 17.2±0.2, 17.5±0.2, 17.9±0.2, 18.9±0.2, 21.2±0.2, 24.4±0.2, and 25.0±0.2 degrees 2θ. In some such embodiments, the hydrate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 6.4±0.2, 12.7±0.2, 12.9±0.2, 14.1±0.2, 15.7±0.2, 17.2±0.2, 17.5±0.2, 17.9±0.2, 18.9±0.2, 21.2±0.2, 24.4±0.2, and 25.0±0.2 degrees 2θ. In other such embodiments, the hydrate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 6.4±0.2, 12.7±0.2, 12.9±0.2, 14.1±0.2, 15.7±0.2, 17.2±0.2, 17.5±0.2, 17.9±0.2, 18.9±0.2, 21.2±0.2, 24.4±0.2, and 25.0±0.2 degrees 2θ.

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[0292] In some embodiments, the hydrate has an X-ray powder diffraction pattern substantially as shown in Figure 9. The 2θ values for the peaks in Figure 9 (and their intensities) are as follows: 6.42 (60), 12.71 (33), 12.89 (58), 14.05 (17), 15.68 (18), 17.22 (44), 17.53 (100), 17.86 (51), 18.87 (77), 21.25 (17), 24.35 (28), and 24.95 (20).

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[0293] This invention also relates, in part, to a process for preparing the hydrate by suspending the above-described solvent free crystalline compound in water. The hydrate was prepared by suspending 300mg of the solvent free crystalline compound in 2ml of water at 45°C for four days.

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G2. Crystalline Forms of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, Monosodium Salt.

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[0294] This invention also relates, in part, to crystalline forms of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, monosodium salt, namely the pattern A, pattern B, and pattern C crystalline forms discussed below.

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[0295] This invention relates, in part, to a pattern A crystalline monosodium salt.

[0296] In some embodiments, the pattern A monosodium salt has an X-ray

powder diffraction pattern comprising one or more peaks selected from the group consisting of 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 , 15.6 ± 0.2 , 18.6 ± 0.2 , 22.8 ± 0.2 , and 23.9 ± 0.2 degrees 2θ . In some such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising three or more
5 peaks selected from the group consisting of 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 , 15.6 ± 0.2 , 18.6 ± 0.2 , 22.8 ± 0.2 , and 23.9 ± 0.2 degrees 2θ . In other such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 , 15.6 ± 0.2 , 18.6 ± 0.2 , 22.8 ± 0.2 , and 23.9 ± 0.2 degrees 2θ .

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[0297] In some embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 , 15.6 ± 0.2 , 18.6 ± 0.2 , 22.8 ± 0.2 , 23.3 ± 0.2 , and 23.9 ± 0.2 degrees 2θ . In some such embodiments, the pattern A
15 monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 , 15.6 ± 0.2 , 18.6 ± 0.2 , 22.8 ± 0.2 , 23.3 ± 0.2 , and 23.9 ± 0.2 degrees 2θ . In other such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of
20 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 , 15.6 ± 0.2 , 18.6 ± 0.2 , 22.8 ± 0.2 , 23.3 ± 0.2 , and 23.9 ± 0.2 degrees 2θ .

[0298] In some embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the
25 group consisting of 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 , 15.6 ± 0.2 , 16.0 ± 0.2 , 18.6 ± 0.2 , 22.8 ± 0.2 , 23.3 ± 0.2 , 23.9 ± 0.2 , and 28.3 ± 0.2 degrees 2θ . In some such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 , 15.6 ± 0.2 , 16.0 ± 0.2 , 18.6 ± 0.2 , 22.8 ± 0.2 , 23.3 ± 0.2 , 23.9 ± 0.2 ,
30 and 28.3 ± 0.2 degrees 2θ . In other such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 , 15.6 ± 0.2 , 16.0 ± 0.2 , 18.6 ± 0.2 , 22.8 ± 0.2 , 23.3 ± 0.2 , 23.9 ± 0.2 , and 28.3 ± 0.2 degrees 2θ . In

other such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising eight or more peaks selected from the group consisting of 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 , 15.6 ± 0.2 , 16.0 ± 0.2 , 18.6 ± 0.2 , 22.8 ± 0.2 , 23.3 ± 0.2 , 23.9 ± 0.2 , and 28.3 ± 0.2 degrees 2θ .

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[0299] In some embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern substantially as shown in Figure 10. The 2θ values for the peaks in Figure 10 (and their intensities) are as follows: 4.64 (62), 10.41 (38), 12.04 (38), 15.62 (44), 15.99 (44), 18.63 (49), 22.77 (60), 23.29 (40),
10 23.93 (100), and 28.31 (56).

[0300] This invention also relates, in part, to a process for preparing the pattern A monosodium salt. The pattern A monosodium salt was prepared by adding 1M aqueous NaOH (0.548ml) to compound **IB-L0-2.3** (225.72mg), seeding the
15 resulting suspension with crystalline N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydro-pyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, disodium salt (prepared as discussed below), and equilibrating the resulting suspension at ambient conditions. The pattern A monosodium salt was formed on
20 the following day through a solution-mediated process. The stoichiometry of the salt was presumed to be 1:1 based on the crystallization procedure. This invention also relates, in part, to a pattern B crystalline monosodium salt.

[0301] In some embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the
25 group consisting of 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , and 23.7 ± 0.2 degrees 2θ . In some such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , and 23.7 ± 0.2 degrees 2θ . In other such
30 embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , and 23.7 ± 0.2 degrees 2θ .

[0302] In some embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , 23.7 ± 0.2 , 28.8 ± 0.2 , 29.1 ± 0.2 , and 31.8 ± 0.2 degrees 2θ . In some such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , 23.7 ± 0.2 , 28.8 ± 0.2 , 29.1 ± 0.2 , and 31.8 ± 0.2 degrees 2θ . In other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , 23.7 ± 0.2 , 28.8 ± 0.2 , 29.1 ± 0.2 , and 31.8 ± 0.2 degrees 2θ . In other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising eight or more peaks selected from the group consisting of 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , 23.7 ± 0.2 , 28.8 ± 0.2 , 29.1 ± 0.2 , and 31.8 ± 0.2 degrees 2θ .

[0303] In some embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , 23.7 ± 0.2 , 28.8 ± 0.2 , 29.1 ± 0.2 , and 31.8 ± 0.2 degrees 2θ . In some such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising two or more peaks selected from the group consisting of 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , 23.7 ± 0.2 , 29.1 ± 0.2 , and 31.8 ± 0.2 degrees 2θ . In other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising two or more peaks selected from the group consisting of 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , 23.7 ± 0.2 , 28.8 ± 0.2 , and 31.8 ± 0.2 degrees 2θ . In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 ,

16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, and 31.8±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 19.2±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 16.3±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ.

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[0304] In some embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, and 16.3±0.2 degrees 2θ. In some such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 16.3±0.2, and 22.1±0.2 degrees 2θ. In other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 16.3±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such em-

bodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 19.2 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , and 23.7 ± 0.2 degrees 2θ . In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , and 23.7 ± 0.2 degrees 2θ . In further such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , 23.7 ± 0.2 , and 31.8 ± 0.2 degrees 2θ . In yet further such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , 23.7 ± 0.2 , 28.8 ± 0.2 , and 31.8 ± 0.2 degrees 2θ . In yet further such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , 23.7 ± 0.2 , 29.1 ± 0.2 , and 31.8 ± 0.2 degrees 2θ . In yet further such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4 ± 0.2 , 10.8 ± 0.2 , 14.4 ± 0.2 , 16.3 ± 0.2 , 17.0 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 21.6 ± 0.2 , 22.1 ± 0.2 , 23.7 ± 0.2 , 28.8 ± 0.2 , 29.1 ± 0.2 , and 31.8 ± 0.2 degrees 2θ .

[0305] In some embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern substantially as shown in Figure 12. The 2θ values for the peaks in Figure 12 (and their intensities) are as follows: 5.36 (100), 10.75 (42), 14.43 (20), 16.34 (60), 17.00 (25), 18.83 (18), 19.24 (18), 19.66 (12), 21.64 (29), 22.12 (41), 23.73 (32), 28.83 (9), 29.10 (9), and 31.78 (10).

[0306] This invention also relates, in part, to a process for preparing the pattern B monosodium salt. The pattern B monosodium salt can be prepared by suspending the pattern A monosodium salt (for example, - 30mg) in various organic solvents (e.g., ~ 125ul acetonitrile, ethanol, 1-propanol, or 2-propanol) at room temperature. The pattern B monosodium salt was also prepared by seeding a solution with pattern B monosodium salt. Compound **IB-L0-2.3** (12.5g) was dis-

solved in DMSO (37.5ml) at $\sim 68^{\circ}\text{C}$. 1.04g NaOH dissolved in 6.3ml of water, 6.3ml 2-propanol, and 12.5ml 35.2:1 v/v 2-propanol/water was added. The solution was seeded with 125mg of pattern B seeds slurried in 12.5ml of 35.2:1 v/v 2-propanol/water, and the crystallization slurry was incubated at $\sim 68^{\circ}\text{C}$ for
5 $\sim 1.5\text{h}$. 175m135.2:1 v/v 2-propanol/water at $\sim 68^{\circ}\text{C}$ was added over $\sim 7\text{h}$, and the crystallization slurry was cooled to $\sim 0^{\circ}\text{C}$ over no less than 7h. The crystals were isolated by filtration and analyzed by PXRD. The crystals were then dried at $\sim 50^{\circ}\text{C}$ under vacuum (approximately 3 inches of mercury). The dried crystals were analyzed by PXRD, which showed no change in comparison to the pre-
10 drying sample. The stoichiometry of the pattern B monosodium salt was confirmed by ion chromatography.

[0307] This invention also relates, in part, to a pattern C crystalline monosodium salt.

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[0308] In some embodiments, the pattern C monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.0 ± 0.2 , 12.0 ± 0.2 , 17.5 ± 0.2 , 18.8 ± 0.2 , and 22.7 ± 0.2 degrees 2θ . In some such embodiments, the pattern C monosodium salt has an X-
20 ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.0 ± 0.2 , 12.0 ± 0.2 , 17.5 ± 0.2 , 18.8 ± 0.2 , and 22.7 ± 0.2 degrees 2θ .

[0309] In some embodiments, the pattern C monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.0 ± 0.2 , 12.0 ± 0.2 , 17.5 ± 0.2 , 17.8 ± 0.2 , 18.8 ± 0.2 , and 22.7 ± 0.2 degrees 2θ . In some such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.0 ± 0.2 , 12.0 ± 0.2 , 17.5 ± 0.2 , 17.8 ± 0.2 , 18.8 ± 0.2 , and 22.7 ± 0.2 degrees 2θ . In other such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising five or
30 more peaks selected from the group consisting of 5.0 ± 0.2 , 12.0 ± 0.2 , 17.5 ± 0.2 , 17.8 ± 0.2 , 18.8 ± 0.2 , and 22.7 ± 0.2 degrees 2θ .

[0310] In some embodiments, the pattern C monosodium salt has an X-ray powder diffraction pattern substantially as shown in Figure 14. The 2θ values for the peaks in Figure 14 (and their intensities) are as follows: 4.97 (100), 12.03 (24), 17.55 (32), 17.80 (77), 18.79 (23), and 22.74 (33).

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[0311] This invention also relates, in part, to a process for preparing the pattern C monosodium salt. The pattern C monosodium salt was prepared as follows. Pattern B monosodium salt (100mg) was dissolved in 400ul DMSO and 2ml 12:1 v/v 2-propanol/H₂O at 70°C. Pattern B monosodium salt seed crystals
10 were added to the solution, and the solution was then cooled to ambient temperature over 20min. Filtration yielded crystals of the pattern C monosodium salt.

[0312] *G3. Crystalline Form of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, Disodium Salt.*
15

[0313] This invention also relates, in part, to a crystalline form of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-
20 2-yl)methanesulfonamide, disodium salt.

[0314] In some embodiments, the disodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 4.8 ± 0.2 , 9.6 ± 0.2 , 10.5 ± 0.2 , 13.0 ± 0.2 , 14.6 ± 0.2 , 15.4 ± 0.2 , 16.8 ± 0.2 , and 23.0 ± 0.2 degrees 2θ . In some such embodiments, the disodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the
25 group consisting of 4.8 ± 0.2 , 9.6 ± 0.2 , 10.5 ± 0.2 , 13.0 ± 0.2 , 14.6 ± 0.2 , 15.4 ± 0.2 , 16.8 ± 0.2 , and 23.0 ± 0.2 degrees 2θ . In other such embodiments, the disodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 4.8 ± 0.2 , 9.6 ± 0.2 , 10.5 ± 0.2 , 13.0 ± 0.2 ,
30 14.6 ± 0.2 , 15.4 ± 0.2 , 16.8 ± 0.2 , and 23.0 ± 0.2 degrees 2θ .

[0315] In some embodiments, the disodium salt has an X-ray powder diffraction

pattern comprising one or more peaks selected from the group consisting of 4.8±0.2, 9.6±0.2, 10.5±0.2, 13.0±0.2, 14.6±0.2, 15.4±0.2, 16.8±0.2, 22.7±0.2, 23.0±0.2, and 23.3±0.2 degrees 2θ. In some such embodiments, the disodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 4.8±0.2, 9.6±0.2, 10.5±0.2, 13.0±0.2, 14.6±0.2, 15.4±0.2, 16.8±0.2, 22.7±0.2, 23.0±0.2, and 23.3±0.2 degrees 2θ. In other such embodiments, the disodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 4.8±0.2, 9.6±0.2, 10.5±0.2, 13.0±0.2, 14.6±0.2, 15.4±0.2, 16.8±0.2, 22.7±0.2, 23.0±0.2, and 23.3±0.2 degrees 2θ.

[0316] In some embodiments, the disodium salt has an X-ray powder diffraction pattern substantially as shown in Figure 15. The 2θ values for the peaks in Figure 15 (and their intensities) are as follows: 4.80 (100), 9.59 (10), 10.51 (13), 12.98 (11), 14.56 (8), 15.38(12), 16.84 (6), 22.68 (10), 23.04 (6), and 23.33 (4).

[0317] This invention also relates, in part, to a process for preparing the disodium salt. The disodium salt was prepared by suspending compound **IB-L0-23** (52.83mg) in 1M aqueous NaOH (1.1ml) (the molar ratio compound:NaOH was 1:10). The solution was heated to 36°C, and the solid dissolved completely to yield a clear solution. The solution was naturally cooled to ambient temperature, and the salt crystallized in 24h. Alternatively, the disodium salt was prepared by suspending compound **IB-L0-2.3** (51 mg) in EtOH (1ml). NaOH in 1.2ml of 5:1 v/v EtOH/H₂O (2.1 molar equivalent) was added. The reaction mixture was concentrated and 2ml acetonitrile was added to induce crystallization. The stoichiometry of this solid was determined by ion chromatography.

G4. Crystalline Form of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, Monopotassium Salt.

[0318] This invention also relates, in part, to a crystalline form of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, monopotassium salt.

5 **[0319]** In some embodiments, the monopotassium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2 degrees 2θ. In some such
10 embodiments, the monopotassium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2 degrees 2θ. In other such embodiments, the
15 monopotassium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2 degrees 2θ.

[0320] In some embodiments, the monopotassium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 21.5±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2 degrees 2θ. In
20 some such embodiments, the monopotassium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 21.5±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2 degrees 2θ. In other
25 such embodiments, the monopotassium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 21.5±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2 degrees 2θ.

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[0321] In some embodiments, the monopotassium salt has an X-ray powder diffraction pattern substantially as shown in Figure 17. The 2θ values for the peaks in Figure 17 (and their intensities) are as follows: 4.97 (100), 9.94 (7), 11.33

(15), 13.28 (7), 16.91 (5), 18.13 (7), 19.14 (4), 20.00 (4), 21.13 (4), 21.45 (4), 23.54 (4), 24.84 (3), and 25.67 (6).

[0322] This invention also relates, in part, to a process for preparing the mono-
5 potassium salt. The monopotassium salt was prepared in aqueous medium. 0.366ml of 1M aqueous KOH was added to 150.56mg of compound **IB-L0-2.3** (molar ratio 1:1.2). The resulting suspension was equilibrated at ambient conditions. The monopotassium salt was formed on the following day through a solution-mediated process. Alternatively, the monopotassium salt was prepared by
10 suspending compound **IB-L0-2.3** (300mg) in 3ml acetonitrile. KOH in 1.3mL of H₂O (2.1 molar equivalent) was added. Additional 1ml H₂O was added to dissolve all solids. Afterwards, 12ml acetonitrile was added to induce crystallization. The stoichiometry of the salt was confirmed by ion chromatograph.

15 **G5. Crystalline Forms of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, Monocholine Salt.**

[0323] This invention also relates, in part, to crystalline forms of N-(6-(3-tert-
20 butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, monocholine salt, namely the pattern A and pattern B crystalline forms discussed below.

[0324] This invention relates, in part, to a pattern A crystalline monocholine salt.
25

[0325] In some embodiments, the pattern A monocholine salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 10.9±0.2, 12.1±0.2, 13.4±0.2, 15.5±0.2, 17.6±0.2, 17.8±0.2, 18.3±0.2, 19.5±0.2, and 21.9±0.2 degrees 2θ. In some such embodiments, the
30 pattern A monocholine salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 16.9±0.2, 12.1±6.2, 13.4±0.2, 15.5±0.2, 17.0±0.2, 17.8±0.2, 18.3±0.2, 19.5±0.2, and 21.9±0.2 degrees 2θ. In other such embodiments, the pattern A monocholine salt has an X-

ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 10.9 ± 0.2 , 12.1 ± 0.2 , 13.4 ± 0.2 , 15.5 ± 0.2 , 17.0 ± 0.2 , 17.8 ± 0.2 , 18.3 ± 0.2 , 19.5 ± 0.2 , and 21.9 ± 0.2 degrees 2θ .

5 **[0326]** In some embodiments, the pattern A monocholine salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 10.9 ± 0.2 , 12.1 ± 0.2 , 13.0 ± 0.2 , 13.4 ± 0.2 , 13.6 ± 0.2 , 15.5 ± 0.2 , 17.0 ± 0.2 , 17.8 ± 0.2 , 18.3 ± 0.2 , 19.5 ± 0.2 , 19.7 ± 0.2 , and 21.9 ± 0.2 degrees 2θ . In some such embodiments, the pattern A monocholine salt has an X-ray powder
10 diffraction pattern comprising three or more peaks selected from the group consisting of degrees 2θ . In other such embodiments, the pattern A monocholine salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of degrees 2θ .

15 **[0327]** In some embodiments, the pattern A monocholine salt has an X-ray powder diffraction pattern substantially as shown in Figure 19. The 2θ values for the peaks in Figure 19 (and their intensities) are as follows: 10.94 (42), 12.06 (20), 12.96 (26), 13.42 (64), 13.64 (27), 15.51 (18), 16.98 (78), 17.81 (26), 18.32 (100), 19.49 (48), 19.70 (33), and 21.91 (22).

20 **[0328]** This invention also relates, in part, to a process for preparing the pattern A monocholine salt. It was prepared in a solvent mixture of tetrahydrofuran (THF) and methanol. Compound **IB-L0-2.3** (56.79mg) was dissolved in THF at 60°C , 40.01mg of choline hydroxide solution (45wt% in methanol) was added
25 resulting in a molar ratio of 1:1.2. The crystals formed upon natural cooling to ambient temperature.

[0329] This invention also relates, in part, to a pattern B crystalline monocholine salt.

30 **[0330]** In some embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.0 ± 0.2 , 9.4 ± 0.2 , 11.0 ± 0.2 , 13.0 ± 0.2 , 13.7 ± 0.2 , 15.9 ± 0.2 ,

17.0±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, and 22.1±0.2 degrees 2θ. In some such embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.0±0.2, 9.4±0.2, 11.0±0.2, 13.0±0.2, 13.7±0.2, 15.9±0.2, 17.0±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, and 22.1±0.2 degrees 2θ. In other such embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.0±0.2, 9.4±0.2, 11.0±0.2, 13.0±0.2, 13.7±0.2, 15.9±0.2, 17.0±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, and 22.1±0.2 degrees 2θ.

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[0331] In some embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.0±0.2, 9.4±0.2, 11.0±0.2, 13.0±0.2, 13.3±0.2, 13.7±0.2, 15.9±0.2, 17.0±0.2, 17.4±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, 21.8±0.2, and 22.1±0.2 degrees 2θ. In some such embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.0±0.2, 9.4±0.2, 11.0±0.2, 13.0±0.2, 13.3±0.2, 13.7±0.2, 15.9±0.2, 17.0±0.2, 17.4±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, 21.8±0.2, and 22.1±0.2 degrees 2θ. In other such embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.0±0.2, 9.4±0.2, 11.0±0.2, 13.0±0.2, 13.3±0.2, 13.7±0.2, 15.9±0.2, 17.0±0.2, 17.4±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, 21.8±0.2, and 22.1±0.2 degrees 2θ.

[0332] In some embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern substantially as shown in Figure 21. The 2θ values for the peaks in Figure 21 (and their intensities) are as follows: 7.96 (41), 9.38 (34), 10.96 (24), 12.98 (76), 13.34 (33), 13.72 (37), 15.90 (100), 17.03 (60), 17.42 (37), 18.30 (31), 18.85 (93), 19.82 (90), 21.76 (38), and 22.06 (46).

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[0333] This invention also relates, in part, to a process for preparing the pattern B monocholine salt. It was prepared by suspending amorphous choline salt in ethyl acetate for seven days.

G6. Crystalline Form of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesumonamide, Dicholine Salt.

5 **[0334]** This invention also relates, in part, to a crystalline form of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, dicholine salt.

[0335] In some embodiments, the dicholine salt has an X-ray powder diffraction
10 pattern comprising one or more peaks selected from the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2, 19.8±0.2, and 21.9±0.2 degrees 2θ. In some such embodiments, the dicholine salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2,
15 19.8±0.2, and 21.9±0.2 degrees 2θ. In other such embodiments, the dicholine salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2, 19.8±0.2, and 21.9±0.2 degrees 2θ.

20 **[0336]** In some embodiments, the dicholine salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2, 19.8±0.2, 21.9±0.2, and 22.1±0.2 degrees 2θ. In some such embodiments, the dicholine salt has an X-ray powder diffraction pattern comprising three or more peaks selected from
25 the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2, 19.8±0.2, 21.9±0.2, and 22.1±0.2 degrees 2θ. In other such embodiments, the dicholine salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2, 19.8±0.2, 21.9±0.2, and 22.1±0.2 de-
30 grees 2θ.

[0337] In some embodiments, the dicholine salt has an X-ray powder diffraction pattern substantially as shown in Figure 23. The 2θ values for the peaks in Fi-

gure **23** (and their intensities) are as follows: 8.62 (28), 10.98 (29), 12.93 (50), 15.88 (100), 17.03 (42), 17.47 (29), 18.88 (66), 19.82 (57), 21.89 (42), 2.07 (41).

5 **[0338]** This invention also relates, in part, to a process for preparing the dicholine salt. It was prepared by suspending compound **IB-L0-2.3** (200mg) in 0.75ml MeOH. Choline hydroxide in MeOH (210ml, 45wt%, 2.10 molar equivalent) was added. The reaction mixture was concentrated, and 4ml acetonitrile and 6ml isopropyl acetate were added. The reaction mixture was then seeded with trace
10 amount of the compound **IB-L0-2.3** monopotassium salt seed crystals (discussed above). The reaction mixture started to crystallize shortly after. The stoichiometry of the salt was determined by solution ¹H NMR.

H. Compositions.

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[0339] This invention also is directed, in part, to compositions comprising one or more crystalline compounds and salts discussed in section G above. In some embodiments, the compositions comprise one or more substantially phase pure crystalline forms (compounds/salts/solvates/hydrates) discussed in section G
20 above. The compositions can be pharmaceutical compositions.

[0340] In some embodiments, the compositions further comprise one or more additional therapeutic agents. Such therapeutic agents can, but need not be, additional HCV inhibitors.

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[0341] The preferred composition depends on the method of administration, and typically comprises one or more conventional pharmaceutically acceptable carriers, adjuvants, and/or vehicles (together referred to as "excipients"). Formulation of drugs is generally discussed in, for example, Hoover, J., Remington's Pharmaceutical Sciences (Mack Publishing Co., 1975) and Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (Lippincott Williams &
30 Wilkins, 2005).

[0342] Solid dosage forms for oral administration include, for example, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds or salts are ordinarily combined with one or more excipients. If administered per os, the compounds or salts can be mixed with, for example, lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation, as can be provided in, for example, a dispersion of the compound or salt in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents, such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills additionally can be prepared with enteric coatings.

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[0343] Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions (including both oil-in-water and water-in-oil emulsions), solutions (including both aqueous and non-aqueous solutions), suspensions (including both aqueous and non-aqueous suspensions), syrups, and elixirs containing inert diluents commonly used in the art (*e.g.*, water). Such compositions also can comprise, for example, wetting, emulsifying, suspending, flavoring (*e.g.*, sweetening), and/or perfuming agents.

[0344] Parenteral administration includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (*e.g.*, sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Acceptable vehicles and solvents include, for example, water, 1,3-butanediol, Ringer's solution, isotonic sodium chloride solution, bland fixed oils (*e.g.*, synthetic mono- or diglycerides), fatty acids (*e.g.*, oleic acid), dimethyl acetamide, surfactants (*e.g.*, ionic and non-ionic detergents), and/or polyethylene glycols.

30

[0345] Formulations for parenteral administration may, for example, be prepared from sterile powders or granules having one or more of the excipients mentioned for use in the formulations for oral administration. A compound or salt of the invention can be dissolved in water, polyethylene glycol, propylene glycol, 5 ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. The pH may be adjusted, if necessary, with a suitable acid, base, or buffer.

[0346] Suppositories for rectal administration can be prepared by, for example, 10 mixing a compound or salt of the invention with a suitable nonirritating excipient that is solid at ordinary temperatures, but liquid at the rectal temperature, and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter, synthetic mono-, di-, or triglycerides, fatty acids, and/or polyethylene glycols.

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[0347] Topical administration includes the use of transdermal administration, such as transdermal patches or iontophoresis devices.

[0348] Other excipients and modes of administration known in the pharmaceuti- 20 cal art also may be used.

[0349] The preferred total daily dose of the compound or salt (administered in single or divided doses) is typically from about 0.001 to about 100mg/kg, more preferably from about 0.001 to about 30mg/kg, and even more preferably from 25 about 0.01 to about 10mg/kg (*i.e.*,mg of the compound or salt per kg body weight). Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. In many instances, the administration of the compound or salt will be repeated a plurality of times. Multiple doses per day typically may be used to increase the total daily dose, if desired. Factors affecting the preferred dosage regimen include the type, age, weight, sex, diet, and 30 condition of the patient; the severity of the pathological condition; the severity of the pathological condition; the route of administration; pharmacological considerations, such as the activity, efficacy, pharmacokinetic, and toxicology profiles of

the particular compound or salt used; whether a drug delivery system is utilized; and whether the compound or salt is administered as part of a drug combination. Thus, the dosage regimen actually employed can vary widely, and therefore, can derive from the preferred dosage regimen set forth above.

5

I. Methods of Use.

[0350] This invention also is directed, in part, to the crystalline forms of the inventions for use in inhibiting replication of an RNA virus. The use comprises exposing the virus to one or more compounds and/or salts of this invention. In some embodiments, replication of the RNA virus is inhibited *in vitro*. In other embodiments, replication of the RNA virus is inhibited *in vivo*. In some embodiments, the RNA virus whose replication is being inhibited is a single-stranded, positive sense RNA virus. In some such embodiments, the RNA virus whose replication is being inhibited is a virus from the *Flaviviridae* family. In some such
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embodiments, the RNA virus whose replication is being inhibited is HCV.

[0351] This invention also is directed, in part, to the crystalline forms of the inventions for use in inhibiting HCV RNA polymerase. The use comprises exposing the polymerase with one or more compounds and/or salts of this invention. In some embodiments, HCV RNA polymerase activity is inhibited *in vitro*. In other embodiments, HCV RNA polymerase activity is inhibited *in vivo*.
20

[0352] The term "inhibiting" means reducing the level of RNA virus replication/-HCV polymerase activity either *in vitro* or *in vivo*. For example, if a compound/salt of the invention reduces the level of RNA virus replication by at least about 10% compared to the level of RNA virus replication before the virus was exposed to the compound/salt, then the compound/salt inhibits RNA virus replication. In some embodiments, the compound/salt can inhibit RNA virus replication by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%.
25
30

[0353] This invention also is directed, in part, to the crystalline forms of the inventions for use in treating a disease that can be treated by inhibiting HCV RNA polymerase. Thus, this invention also is directed, in part, to the crystalline forms of the invention for use in treating hepatitis C in an animal in need of such treatment. These uses comprise administering to the animal one or more compounds and/or salts of the invention, and, optionally, one or more additional therapeutic agents. In some embodiments, a therapeutically effective amount of the compound(s) and/or salt(s) is administered to the animal. "Treating" means ameliorating, suppressing, eradicating, preventing, reducing the risk of, and/or delaying the onset of the disease being treated. Applicants specifically intend that the term "treating" encompass administration of the compounds and/or salts of the invention to an HCV-negative patient that is a candidate for an organ transplant. The methods of treatment are particularly suitable for use with humans, but may be used with other animals, particularly mammals. A "therapeutically-effective amount" or "effective amount" is an amount that will achieve the goal of treating the targeted condition.

[0354] In some embodiments, the uses comprise combination therapy, wherein the compound(s) and/or salt(s) of the invention is/are co-administered with a second (or even a third, fourth, etc.) compound, such as, for example, another therapeutic agent used to treat hepatitis C (*e.g.*, interferon or interferon/ribavirin combination, or an HCV inhibitor such as, for example, an HCV polymerase inhibitor or an HCV protease inhibitor). The compound(s) and/or salt(s) of this invention can also be co-administered with therapeutic agents other than therapeutic agents used to treat hepatitis C (*e.g.*, anti-HIV agents). In these co-administration embodiments, the compound(s) and/or salt(s) of the invention and the second, etc. therapeutic agent(s) may be administered in a substantially simultaneous manner (*e.g.*, or within about 5 minutes of each other), in a sequential manner, or both. It is contemplated that such combination therapies may include administering one therapeutic agent multiple times between the administrations of the other. The time period between the administration of each agent may range from a few seconds (or less) to several hours or days, and will depend on, for example, the properties of each composition and active ingredient

(e.g., potency, solubility, bioavailability, half-life, and kinetic profile), as well as the condition of the patient. The compound(s) and/or salt(s) of this invention and the second, etc. therapeutic agent may also be administered in a single formulation.

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[0355] This invention also is directed, in part, to a use of one or more crystalline forms of the invention, and, optionally one or more additional therapeutic agents to prepare a medicament. In some embodiments, the medicament is for co-administration with one or more additional therapeutic agents.

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[0356] In some embodiments, the medicament is for inhibiting replication of an RNA virus.

[0357] In some embodiments, the medicament is for treating hepatitis C.

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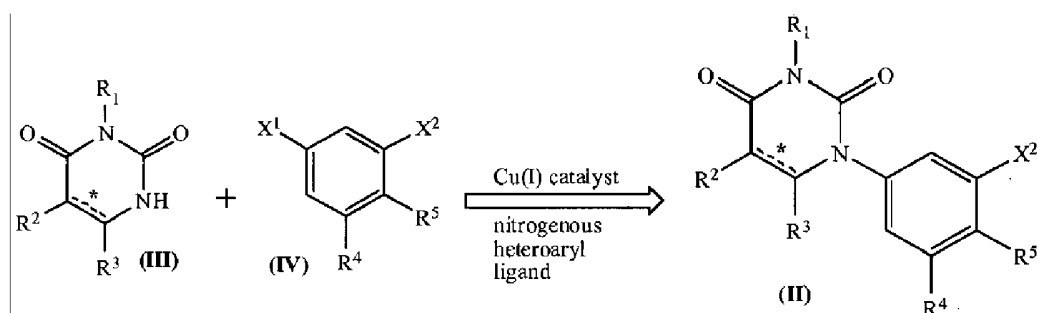
[0358] This invention also is directed, in part, to one or more crystalline forms of the invention, and, optionally one or more additional therapeutic agents, for use as a medicament. In some embodiments, the medicament is for inhibiting replication of an RNA virus. In other embodiments, the medicament is for treating hepatitis C.

20

J. Methods for Preparation.

[0359] This invention also is directed, in part, to a process for preparing compounds of formula II. The process comprises reacting a compound of formula III with a compound of formula IV in the presence of (i) copper (I) salt catalyst and (ii) nitrogenous heteroaryl ligand:

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[0360] In the above process, R^1 , R^2 , R^3 , R^4 , R^5 , X^1 , and X^2 are as discussed above.

[0361] Applicants have discovered that the process generally results in the substitution of the N1 hydrogen of uracil derivative compound **III** thus resulting in intermediate compound **II**. When X^2 in intermediate compound **II** is chloro, bromo, or iodo, then compound **II** is suitable for subsequent reaction (*e.g.*, Suzuki coupling with an appropriate boronic acid or boronate ester) to provide compound of formula **I**. In other words, when X^2 in intermediate compound **II** is chloro, bromo, or iodo, the above process is suitable for preparing compounds of formula **I** as well.

[0362] In some embodiments, compound **III** is uracil, and compound **IV** corresponds in structure to a compound selected from the group consisting of compound **IV-1**, **IV-Br**, and **IV-I** and **IV-Br** typically resulting in better yield than compound **IV-Cl**.

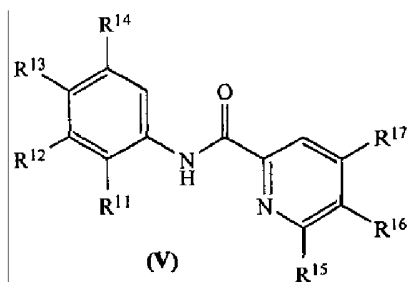
[0363] Suitable Cu(I) catalysts include, for example, CuI, CuBr, CuCl, Cu₂O, and CH₃C(O)OCu. In some embodiments, the catalyst is selected from the group consisting of CuI and CuBr. In some such embodiments, the catalyst is CuI. In other such embodiments, the catalyst is CuBr.

[0364] In some embodiments, the process is conducted in the presence of a base. In some such embodiments, the base is an inorganic base. Suitable inorganic bases include, for example, potassium, sodium, and cesium salts (*e.g.*, K₂CO₃, K₃PO₄, Cs₂CO₃, Na₂CO₃). In some embodiments, the base is selected from the group consisting of potassium salt and cesium salt. In some such embodiments, the salt is selected from the group consisting of K₃PO₄ and Cs₂CO₃. In some embodiments, the base comprises a potassium salt. In some such embodiments, the potassium salt is K₂CO₃. In other such embodiments, the potassium salt is K₃PO₄. In some embodiments, the base comprises a cesium salt. In some such embodiments, the potassium salt is Cs₂CO₃.

[0365] Typically, the process is conducted in the presence of a solvent. Suitable solvents include, for example, dimethylsulfoxide (DMSO), dimethylformamide (DMF), and acetonitrile (MeCN). In some embodiments, the solvent is DMSO.

5 [0366] Typically, the process is conducted at a temperature of from about 40 to about 130°C.

[0367] In some embodiments, the nitrogenous heteroaryl ligand comprises 8-hydroxyquinoline. In other embodiments, the ligand comprises 2-(2-pyridyl)-
10 benzimidazole. In yet other embodiments, the ligand comprises a picolinamide compound corresponding in structure to formula V:

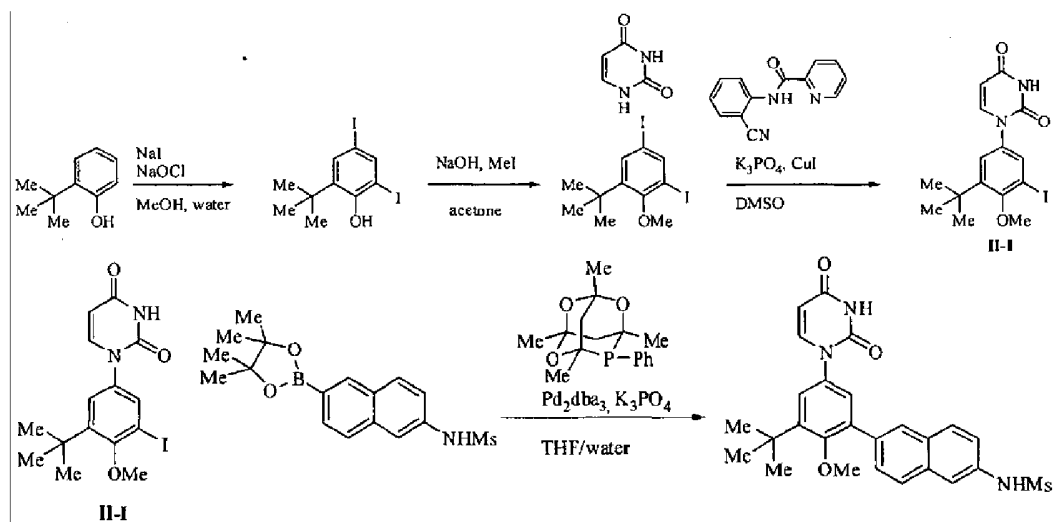


[0368] In formula V, R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , and R^{17} are independently selected from the group consisting of hydrogen, C_{1-4} -perfluoroalkyl, C_{1-4} -alkyloxy, C_{1-4} -haloalkyl, chloro, or cyano. In some embodiments, R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , and R^{17} are independently selected from the group consisting of hydrogen, methyl, methoxy, trifluoromethyl, chloro, and cyano. In some embodiments, the ligand of formula V comprises N-(4-cyanophenyl)picolinamide. In other embodi-
20 ments, the ligand of formula V comprises N-(2-cyanophenyl)picolinamide.

[0369] In some embodiments, the process comprises (a) preparing a compound of formula IV; and (b) reacting a compound of formula III with a compound of formula IV in the presense of (i) copper (I) salt catalyst and (ii) nitrogenous heteroaryl ligand, optionally in the presence of inorganic base.
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[0370] Compound of formula IV-I can be prepared by, for example, converting 2-tert-butylphenol into 2-tert-butyl-4,6-diiodophenol (by, for example, reacting it

with NaI and NaOCl), and then converting the 2-tert-butyl-4,6-diiodophenol into 1-tert-butyl-3,5-diiodo-2-methoxybenzene (by, for example, treating it with CH₃I in the presence of a base, such as, for example, NaOH).

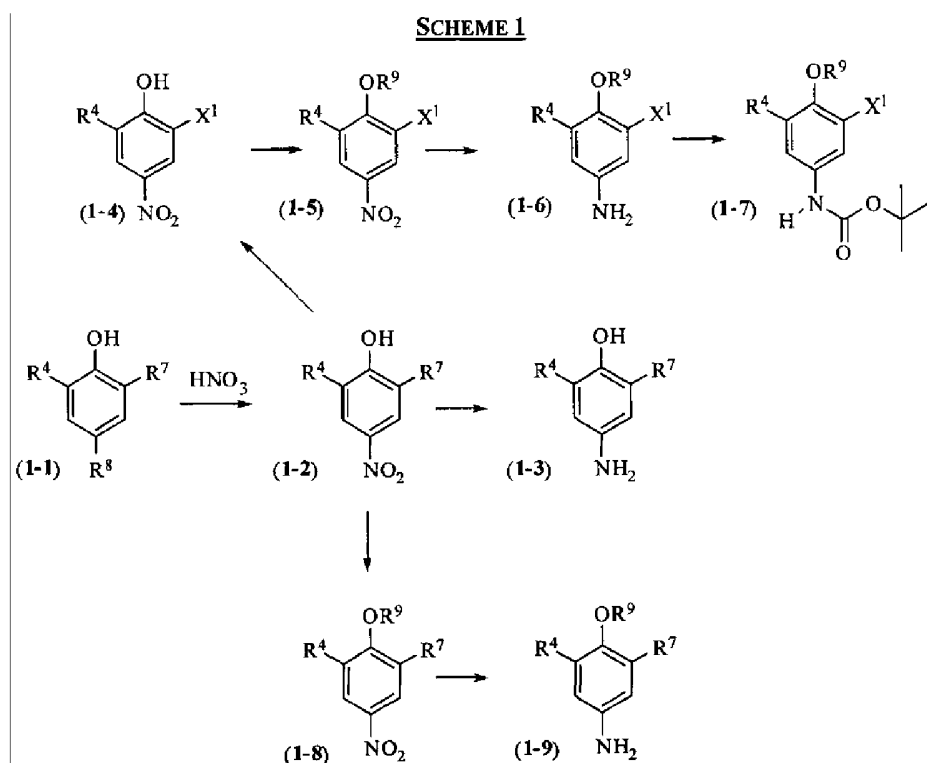


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[0371] Compound of formula IV-Br can be prepared by, for example, converting 2-tert-butylphenol into 2,4-dibromo-6-tert-butylphenol (by, for example, reacting it with 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione), and then converting the 2,4-dibromo-6-tert-butylphenol into 1,5-dibromo-3-tert-butyl-2-methoxybenzene (by, for example, treating it with CH₃I in the presence of KOtBu).

[0372] Additional information about the preparation of compounds of formulas I and II (and their salts) is provided in the general discussion and/or specific synthesis examples below. In the discussion below, R¹, R², R³, R⁴, R⁵, L, R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, X¹, and X² have the meaning discussed above unless otherwise stated.

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[0373] Compound (1-1), wherein R⁷ is, for example, hydrogen or -CO₂Me, and R⁸ is, for example, hydrogen or t-butyl, may be treated with nitric acid in solvents such as, for example, acetic acid or water in a temperature range of about 0 to about 35°C over about 1 to about 5h to provide compound (1-2). Compound (1-2) may then be reduced using conditions known to those skilled in the art to furnish the corresponding aniline (1-3). Typical conditions for this reduction include using hydrogen at a pressure of about 1 to about 5 atmospheres in the presence of a catalyst such as, for example, palladium or platinum on charcoal in a solvent such as, for example, tetrahydrofuran, ethyl acetate, ethanol, or hexane at or near ambient temperature over a period of about 1 to about 12h. Dependent on the functional groups present, an alternative reduction procedure may be more appropriate such as, for example, using iron powder in the presence of a mild acid such as, for example, ammonium chloride or dilute hydrochloric acid at reflux temperatures in a mixture of solvents containing, for example, methanol, water, and/or tetrahydrofuran over about 1 to about 12h. Another set of reduction conditions includes the use of sodium borohydride in a solvent mixture such as, for example, water and tetrahydrofuran. Yet another set of reduction conditions includes the use of tin(II) chloride in the presence of

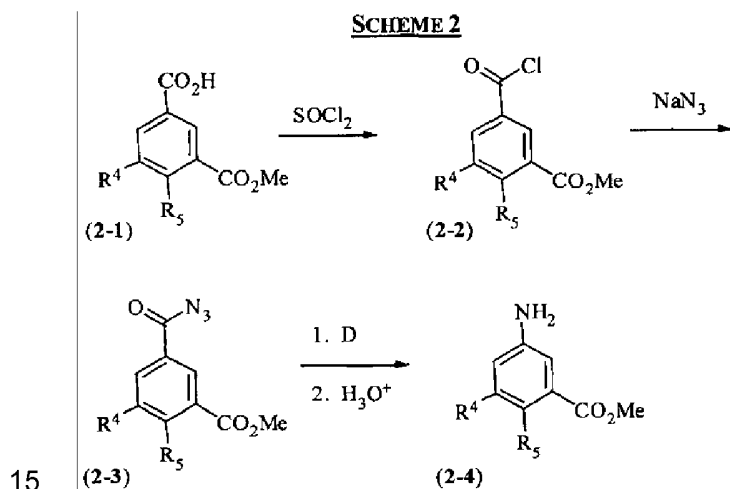
hydrochloric acid in such solvents as, for example, water and methanol or mixtures thereof.

[0374] Compound (1-2) may be modified prior to reduction. For example, treatment of compound (1-2), wherein R⁷ is hydrogen, with iodine monochloride in a mixture of methanol and water at or near ambient temperature over a period of about 8 to about 24h supplies compound (1-4), wherein X¹ is iodine. Alternatively, compound (1-2) can be treated with pyridinium hydrobromide perbromide in a solvent such as, for example, acetic acid at or near ambient temperature over a period of about 2 to about 16h to provide compound (1-4), wherein X¹ is bromine. Modifications may be introduced at the phenol moiety in compound (1-4). For example, the phenol may be alkylated with alkyl halides (e.g., methyl iodide), alkyl sulfates (e.g., methyl sulfate), alkenyl halides (e.g., allyl bromide), alkynyl halides (e.g., propargyl bromide) in the presence of a base such as, for example, potassium carbonate in acetone, sodium hydride in dimethylformamide, or potassium t-butoxide in tetrahydrofuran, at temperatures from about 0 to about 35°C over a period of about 1 to about 24h to provide compound (1-5), wherein R⁹ is, for example, alkyl, alkenyl, or alkynyl. Alternatively, alkylation may be achieved by using a reagent such as (trimethylsilyl) diazomethane in solvents such as, for example, methanol or t-butyl methyl ether, or mixtures thereof in a sealed tube at or near room temperature over about 8 to about 24h. Compound (1-5) may subsequently be reduced to compound (1-6) using the iron powder or tin(II) chloride conditions described above. An alternative reduction procedure employs hydrogenation at approximately 1 atmosphere pressure with a catalyst such as 5% platinum on sulfided carbon in a solvent such as methanol. Protection of the resultant aniline of compound (1-6) with, for example, a t-butyl carbamate can be achieved by treatment with di-tert-butyl dicarbonate in a solvent such as, for example, tetrahydrofuran or dioxane at a temperature of about 50 to about 65°C for about 1 to about 8h provides compound (1-7).

[0375] Modifications may also occur at the phenol moiety in compound (1-2). One skilled in the art may alkylate the phenol of compound (1-2) using, for

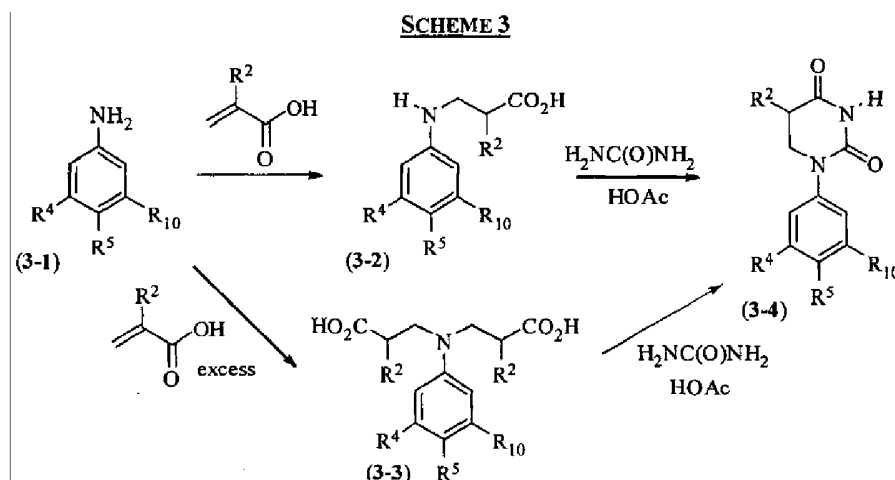
example, the conditions described above to obtain compound (1-8). Compound (1-8) is transformed into compound (1-9) using, for example, one or more of the appropriate reduction conditions described above.

- 5 **[0376]** Another modification of the phenol group in compound (1-2) is sulfonylation to furnish compound (1-8), wherein R⁹ is alkylsulfonyl, carbocyclisulfonyl, or haloalkylsulfonyl. Such a compound may be prepared by exposing compound (1-2) to sulfonyl chlorides such as, for example, methanesulfonyl chloride, cyclohexanesulfonyl chloride, benzenesulfonyl chloride, or 3-chloropropane
 10 sulfonyl chloride in the presence of a base such as, for example, triethylamine, diisopropylethylamine, or pyridine in a solvent such as, for example, dichloromethane at or near ambient temperature for a period of about 1 to about 24h. One skilled in the art can then transform compound (1-8) into compound (1-9) with an appropriate set of reduction conditions.

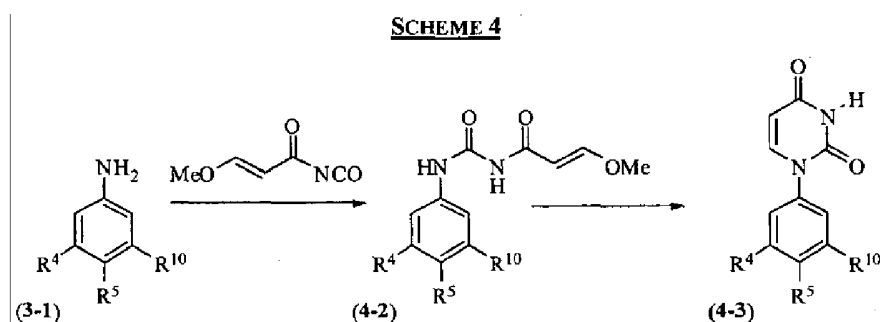


- [0377]** Aniline (2-4) can be prepared through use of the Curtius rearrangement. To this end, compound (2-1), wherein R⁴ is not amino, can be treated in refluxing thionyl chloride with a catalytic amount of dimethylformamide for about 1 to
 20 about 4h to obtain acid chloride (2-2). Treatment with thionyl chloride at the reflux temperature in solvents such as, for example, chloroform or toluene also furnishes compound (2-2). Compound (2-2) can be reacted with an aqueous solution of sodium azide in a solvent such as, for example, acetone over about 1 to about 8h to provide acyl azide (2-3). Compound (2-3) can then undergo a
 25 Curtius rearrangement in refluxing solvents such as dioxane or toluene. The in-

intermediate isocyanate is hydrolyzed with an aqueous acid such as dilute hydrochloric acid in a solvent such as dimethoxyethane to provide compound (2-4).

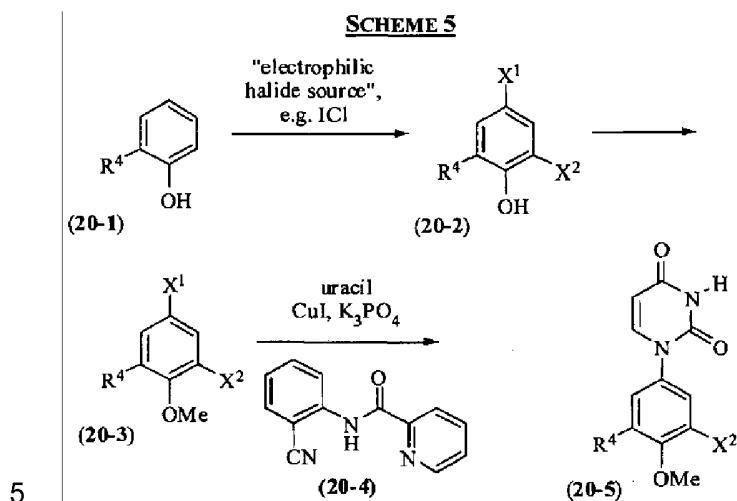


- 5 **[0378]** Compound (3-1), wherein R^{10} is, for example, hydrogen, bromine, iodine, or $-CO_2Me$, can be treated with an acrylic acid either neat at or near ambient temperature in a solvent such as, for example, toluene and heated to reflux over a period of about 15 to about 48h to supply compound (3-2). When excess of an acrylic acid is used, compound (3-3) is produced. Compound (3-2) or (3-3) can be treated with urea in a solvent such as, for example, acetic acid at about 100 to about 120°C over about 2 to about 48h to supply compound (3-4).



- 15 **[0379]** Compound (4-2) can be prepared from compound (3-1) dissolved in solvents such as, for example, dimethylformamide or dimethylacetamide by the addition of a benzene solution of (E)-3-methoxyacryloyl isocyanate (prepared as described by Santana, L.; et al. J. Heterocyclic Chem. 1999, 36, 293-295.) at a temperature of about -40 to about $-15^\circ C$ under an inert atmosphere and then warming to ambient temperature for from about 30 min to about 4h. Compound
- 20 (4-2) can be treated with an acid such as, for example, sulfuric acid in mixtures

of water and ethanol in a temperature range of from about 90 to about 110°C for about 1 to about 8h to supply compound (4-3). Alternatively, compound (4-2) can be cyclized to uracil (4-3) under the basic conditions described by Ueno, Y.; et al. J. Org. Chem. 70:7925-7935 (2005).

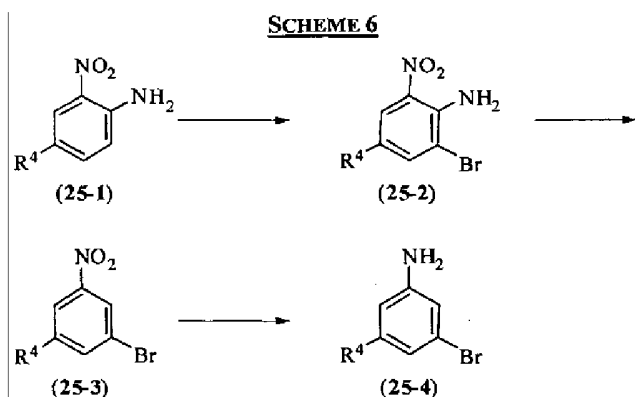


[0380] Phenol (20-1), wherein R⁴ is other than amino, is treated with a source of electrophilic halide, such as, for example, iodine monochloride to provide dihalogenated compound (20-2), wherein X¹ and X² are independently bromine or iodine. Compound (20-2) is transformed to compound (20-3) by reaction of an alkylating agent such as, for example, methyl sulfate with a base such as, for example, potassium carbonate in refluxing acetone. Alternatively, methyl iodide in the presence of a base such as, for example, potassium *t*-butoxide in a solvent such as, for example, tetrahydrofuran, or dimethylformamide also furnish compound (20-3). In yet another alternative, compound (20-2) can be methylated with (trimethylsilyl)diazomethane in a solvent such as, for example, *t*-butyl methyl ether. Compound (20-3) can be reacted with uracil, ligand (20-4), copper (1) iodide, and potassium phosphate in dimethyl sulfoxide at about 40°C to about 100°C to supply compound (20-5).

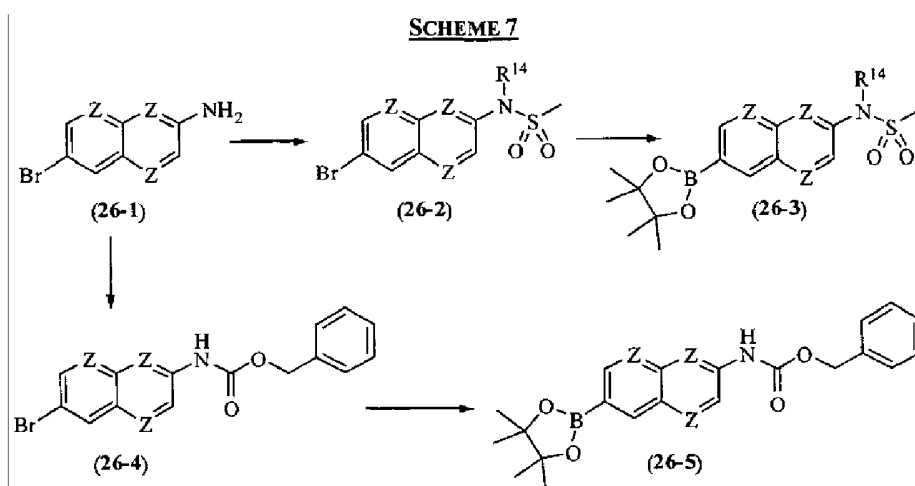
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[0381] For example, when in compound (20-3), R⁴ is *tert*-butyl, X¹ is iodo, and X² is iodo or bromo, compound (20-3) can be stirred with uracil and compound (20-4) in the presence of CuI and K₂PO₄ in DMSO for about 15 to about 24h at

about 60°C to supply compound (20-5). Alternatives to ligand (20-4) for making (20-5) are 8-hydroxyquinoline and 2-(2-pyridyl)-benzimidazole.



- 5 **[0382]** Compound (25-1) can be brominated by treatment with, for example, pyridinium hydrobromide perbromide in a solvent such as, for example, acetic acid at or near ambient temperature over a period of about 1 to about 8h to give compound (25-2). The amino group of compound (25-2) can be removed by exposure to t-butyl nitrite in a solvent such as, for example, dimethylformamide at a temperature initially at ambient temperature and then increased to the range of about 50 to about 65 °C to give compound (25-3). Additional aliquots of t-butyl nitrite can be added at ambient temperature followed by heating until the transformation is complete. Compound (25-3) can be reduced to compound (25-4) by, for example treatment with iron and ammonium chloride.
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[0383] Compound (26-1), wherein each Z is independently N or CH can be converted to a boronic acid ester for use in Suzuki reactions. For example,

compound of formula **(26-1)** can be converted to compound **(26-2)**, wherein R¹⁴ is hydrogen or methanesulfonyl (when excess methanesulfonyl chloride is used) by treatment with methanesulfonyl chloride in pyridine at approximately ambient temperature in about 1 to about 8h.

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[0384] Compound **(26-2)** can be transformed to compound of **(26-3)** by treatment with pinacol-borane in the presence of a catalyst such as, for example, tris(dibenzylideneacetone)dipalladium (0), ligand such as, for example, tri-*t*-butylphosphine, and a base such as triethylamine in solvents such as, for example, tetrahydrofuran, dioxane, or toluene at temperatures ranging from ambient to about 130°C.

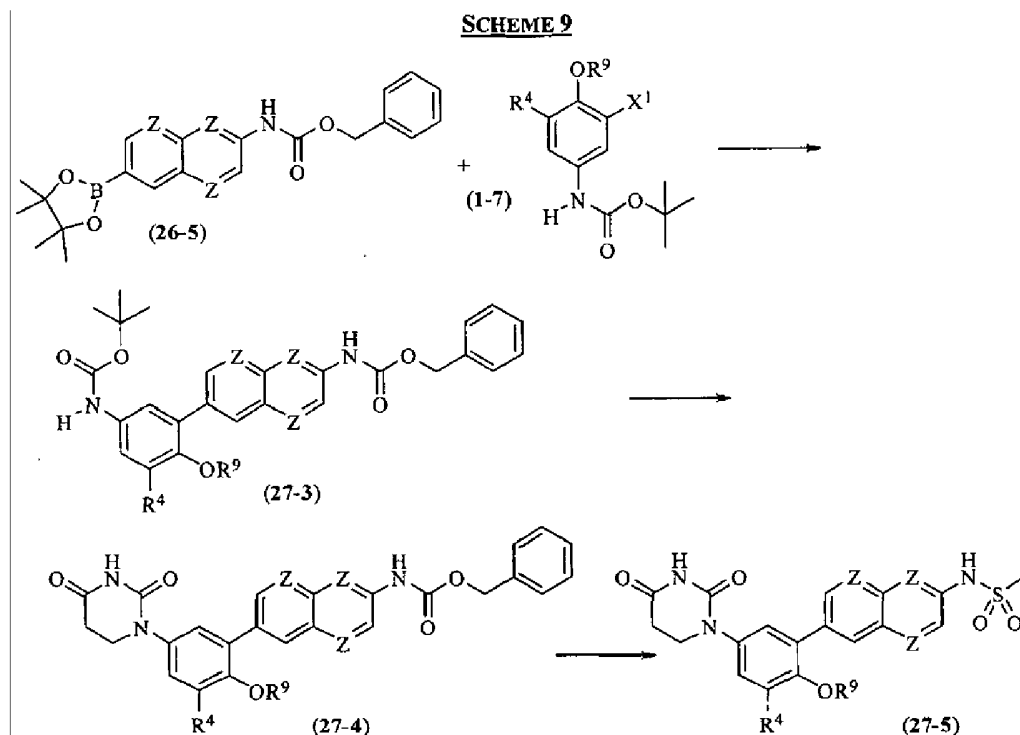
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[0385] Alternatively, compound **(26-2)** can be reacted with bis(pinacolato)diboron in the presence of a catalyst such as, for example, Combiphos® Pd6, dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct, or palladium acetate in the presence of a ligand such as, for example, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), and a base such as, for example, potassium acetate in solvents such as, for example, toluene, dioxane, tetrahydrofuran, dimethylformamide or dimethyl sulfoxide in temperatures from about 60 to about 130°C to give compound **(26-3)**.

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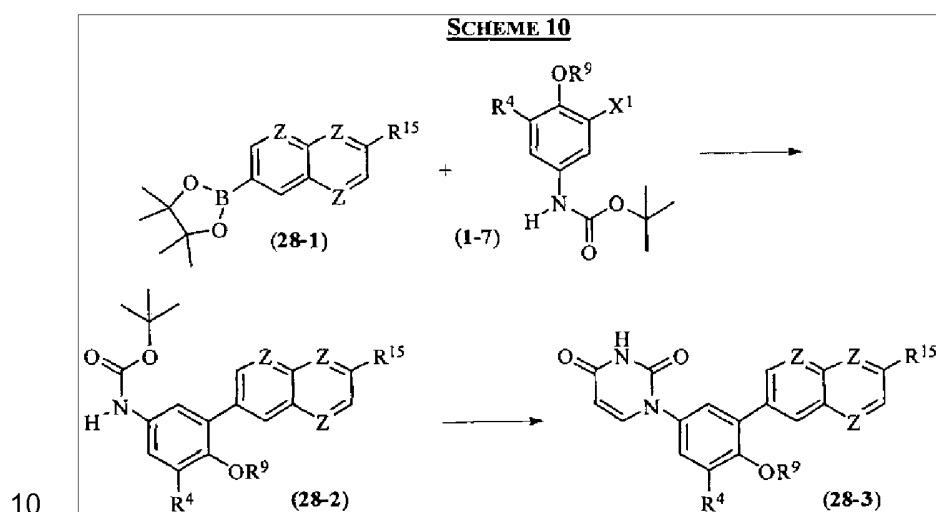
[0386] Compound **(26-3)** can be converted to protected compound **(26-4)** by treatment with benzyl chloroformate initially at about 0°C in the presence of saturated aqueous sodium bicarbonate in a mixture of acetone and water. This can be warmed to ambient temperature and maintained at that temperature for about 12 to about 24h. Subsequently, compound **(26-4)** can be converted to the boronic acid pinacol ester **(26-5)** using the reaction conditions described above.

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- [0387]** Compound (26-5), wherein each Z is independently N or CH, can be coupled with compound (1-7) under Suzuki reaction conditions to provide compound (27-3). Such conditions include, for example, use of a palladium catalyst such as, for example, tris(dibenzylideneacetone)palladium (0), palladium acetate, bis(triphenylphosphine)palladium (II) chloride, tetrakis(triphenylphosphine)-palladium, or dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct; base such as, for example, potassium carbonate, potassium phosphate, potassium *t*-butoxide, sodium carbonate, cesium carbonate, or cesium fluoride; and solvent such as, for example, toluene, ethanol, water, or tetrahydrofuran, or mixtures thereof heated in the temperature range from about 40 to about 130°C.
- [0388]** Compound (27-3) can be transformed to compound (27-4) in a three-step process. The initial step involves removal of the *t*-butoxycarbonyl protecting group with an acid such as, for example, trifluoroacetic acid in solvent such as, for example, dichloromethane or hydrochloric acid in dioxane at room temperature over about 1 to about 24h. Subsequently, the dihydropyrimidinedione can be introduced as described in Scheme 3.

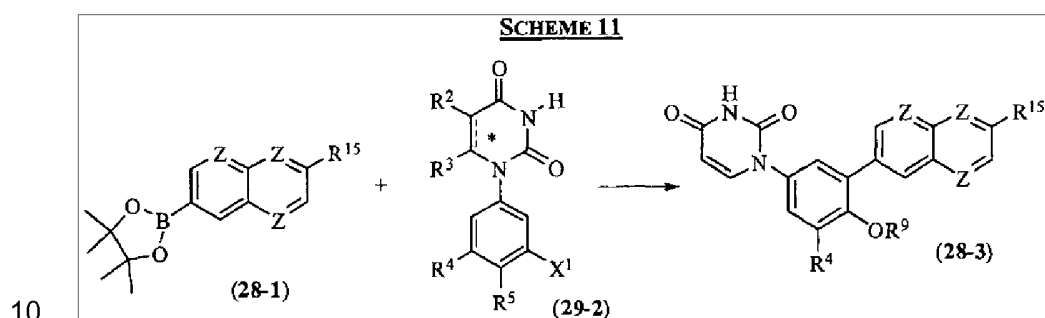
[0389] Compound (27-5) can be obtained from compound (27-4) in a two-step sequence. First, the protecting group is removed from the naphthyl amine under reductive conditions. Typically, hydrogenation (~1 atmosphere pressure) in the presence of a catalyst such as, for example, 10% palladium on charcoal in a solvent such as, for example, ethyl acetate at or near ambient temperature over a period of about 8 to about 24h. Second, the naphthyl amine can now be sulfonylated by treatment with methanesulfonyl chloride in the presence of a base such as triethylamine in a solvent (e.g., dichloromethane) at room temperature over about 20 min to about 4h.



[0390] Compound (28-1), wherein each Z is independently N or CH, and R¹⁵ is, for example, hydrogen, -NHSO₂Me, -N(SO₂Me)₂, or methoxy can be coupled with compound (1-7) under Suzuki reaction conditions to provide compound (28-2). Such conditions include, for example, use of palladium catalyst such as, for example, tris(dibenzylideneacetone) palladium (0), palladium acetate, bis(triphenylphosphine)palladium (II) chloride, tetrakis(triphenylphosphine)palladium, or dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct; a base such as potassium carbonate, potassium phosphate, potassium *t*-butoxide, sodium carbonate, cesium carbonate, or cesium fluoride; and solvent such as, for example, toluene, ethanol, water or tetrahydrofuran, or mixtures thereof heated in the temperature range from about 40 to about 130°C. The reaction is typically deoxygenated with an inert gas such as nitrogen prior

to heating. The heating may occur in conventional glassware, a sealed tube, or in a microwave reactor over about 1 to about 24h.

[0391] Compound **(28-2)** can be transformed to compound **(28-3)** in a three-step process. The initial step involves removal of the *t*-butoxycarbonyl protecting group with an acid such as, for example, trifluoroacetic acid in solvent such as, for example, dichloromethane or hydrochloric acid in dioxane at room temperature over about 1 to about 24h. Subsequently, the uracil can be introduced as described in Scheme 4.



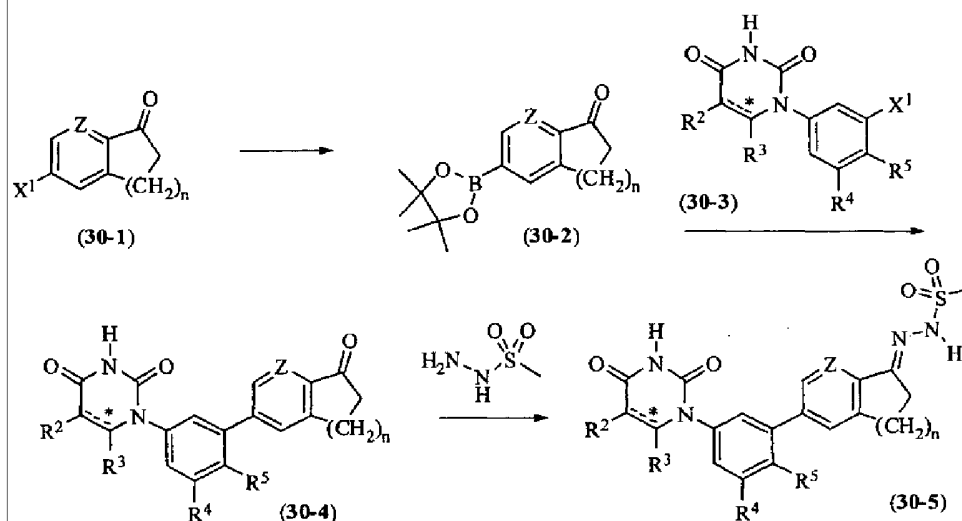
[0392] Compound **(28-1)**, wherein each Z is independently N or CH, and R¹⁵ is, for example, hydrogen, -NHSO₂Me, -N(SO₂Me)₂, or methoxy can be coupled with compound of formula **(29-2)**, wherein X¹ is, for example, bromine or iodine, under Suzuki reaction conditions to provide compound of formula **(28-3)**. Such conditions include, for example, use of palladium catalyst such as, for example, tris(dibenzylideneacetone)palladium (0), palladium acetate, bis(triphenylphosphine)palladium (II) chloride, tetrakis(triphenylphosphine) palladium, dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct, or bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane; base such as, for example, potassium carbonate, potassium phosphate, potassium *t*-butoxide, sodium carbonate, cesium carbonate, or cesium fluoride; and solvent such as, for example, toluene, ethanol, water, or tetrahydrofuran, or mixtures thereof heated in the temperature range from about 40 to about 130°C. The reaction is typically deoxygenated with an inert gas such as nitrogen prior to heating. The heating may occur in conventional glassware, a sealed tube, or in a microwave reactor over about 1 to about 24h.

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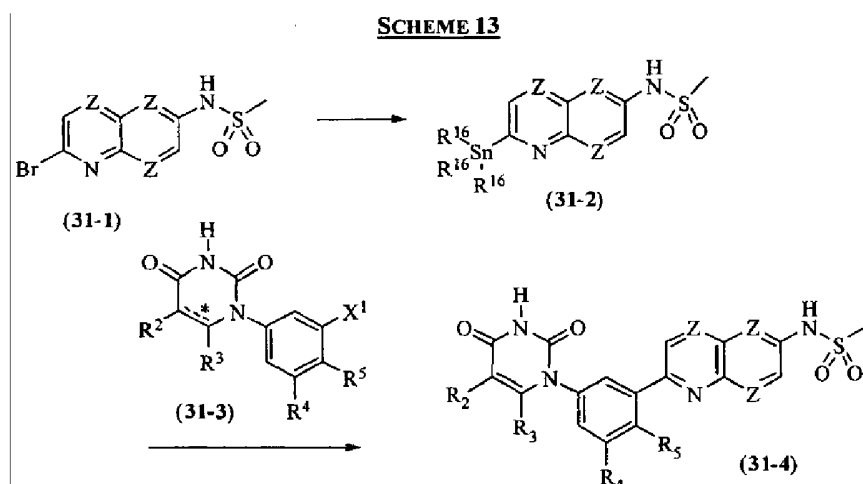
SCHEME 12



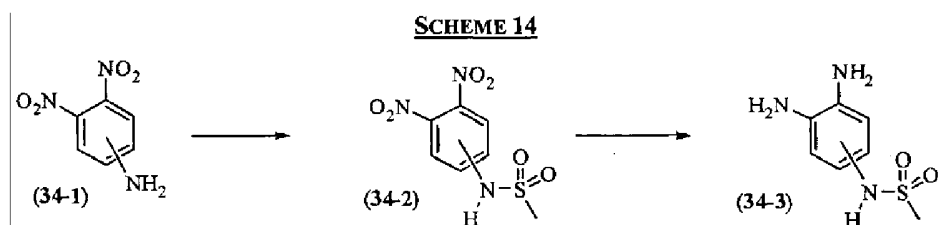
[0393] Compound (30-1), wherein X^1 is bromine or iodine, n is 1 or 2, and Z is CH or N, can be reacted with bis(pinacolato)diboron in the presence of a catalyst such as, for example, Combiphos® Pd6, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct, or palladium acetate in the presence of a ligand such as 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), and a base such as potassium acetate in solvents such as, for example, toluene, dioxane, tetrahydrofuran, dimethylformamide or dimethyl sulfoxide in temperatures from 60-130°C to give compound (30-2). The reaction is typically deoxygenated with an inert gas such as nitrogen prior to heating. The heating may occur in conventional glassware, a sealed tube, or in a microwave reactor over 1 to 24h. Compound (30-3) can be reacted with compound (30-2) to give compound (30-4) employing the conditions described in Scheme 11.

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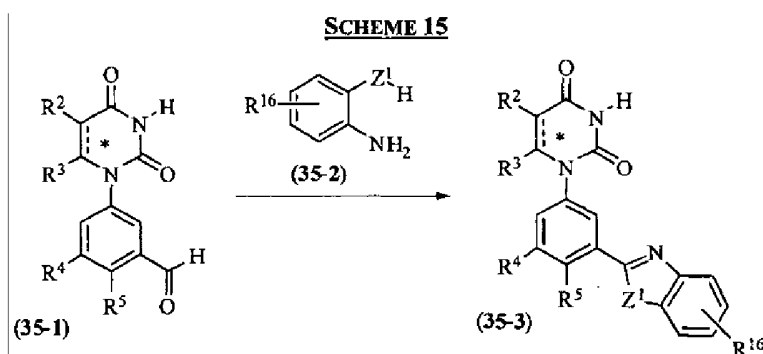
[0394] Treatment of compound (30-4) with methanesulfonylhydrazide in solvent such as, for example, tetrahydrofuran, methanol, or ethanol, or a mixture thereof at ambient temperature to about 100°C over a period of 8 to 48h provides compound (30-5).



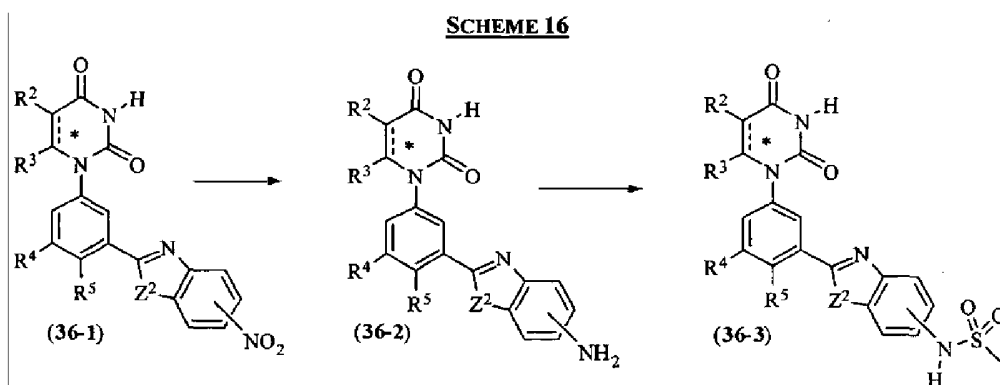
[0395] Compound (31-1) can be treated with hexamethylditin or hexabutylditin in the presence of a catalyst such as, for example, bis(triphenylphosphine)palladium (II) chloride in a solvent such as, for example, toluene or dioxane heated to about 50 to about 130°C to supply compound (31-2). Compound (31-2) can be treated with compound (31-3) in presence of catalyst such as, for example, tris(dibenzylidene acetone)palladium (0) and ligand such as tri(2-furyl)phosphine in solvent such as, for example, toluene, dioxane, or tetrahydrofuran heated to about 40 to about 130°C to give compound (31-4).



[0396] Dinitroaniline (34-1) can be sulfonated with methanesulfonyl chloride in the presence of a base like, for example, pyridine in a solvent such as, for example, dichloromethane at room temperature over a period of about 8 to about 36h to give compound (34-2). Compound (34-2) can be converted to compound (34-3) using iron powder in the presence of a mild acid such as, for example, ammonium chloride or dilute hydrochloric acid at reflux temperatures in a mixture of solvents, such as, for example, methanol, water, and tetrahydrofuran over about 1 to about 12h.

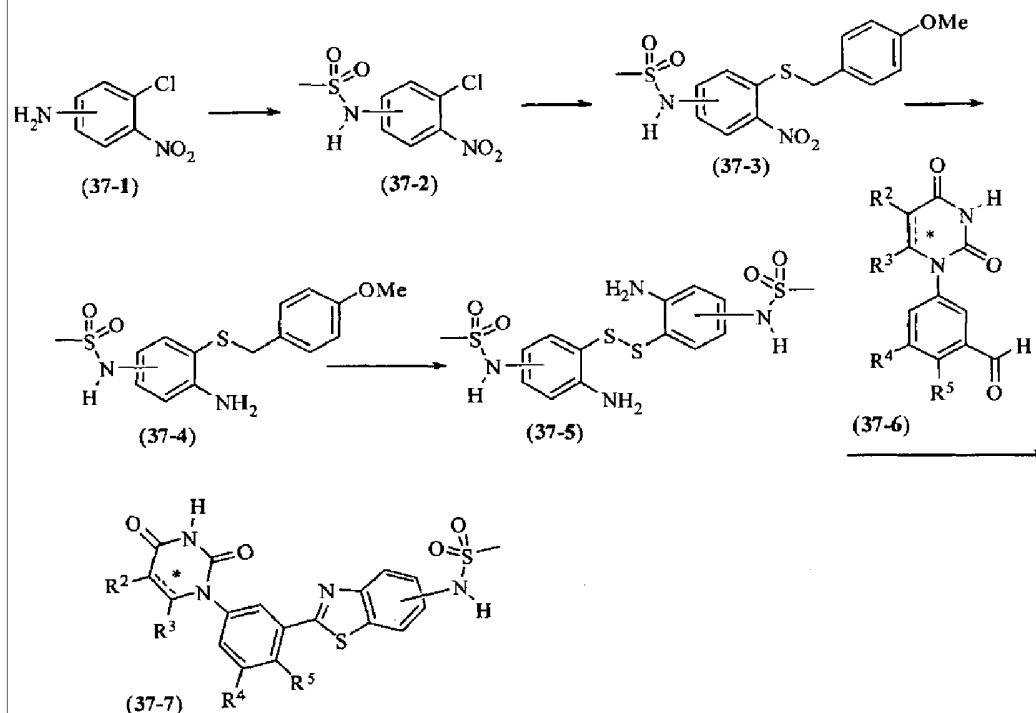


- [0397]** Compound (35-1) can be reacted with compound (35-2), wherein Z¹ is O, S, or NH and R¹⁶ is hydrogen, -NHSO₂Me, or NO₂, in the presence of charcoal exposed to air in solvent such as, for example, toluene heated from about 90 to about 110°C for about 24 to about 72h to give compound (35-3).

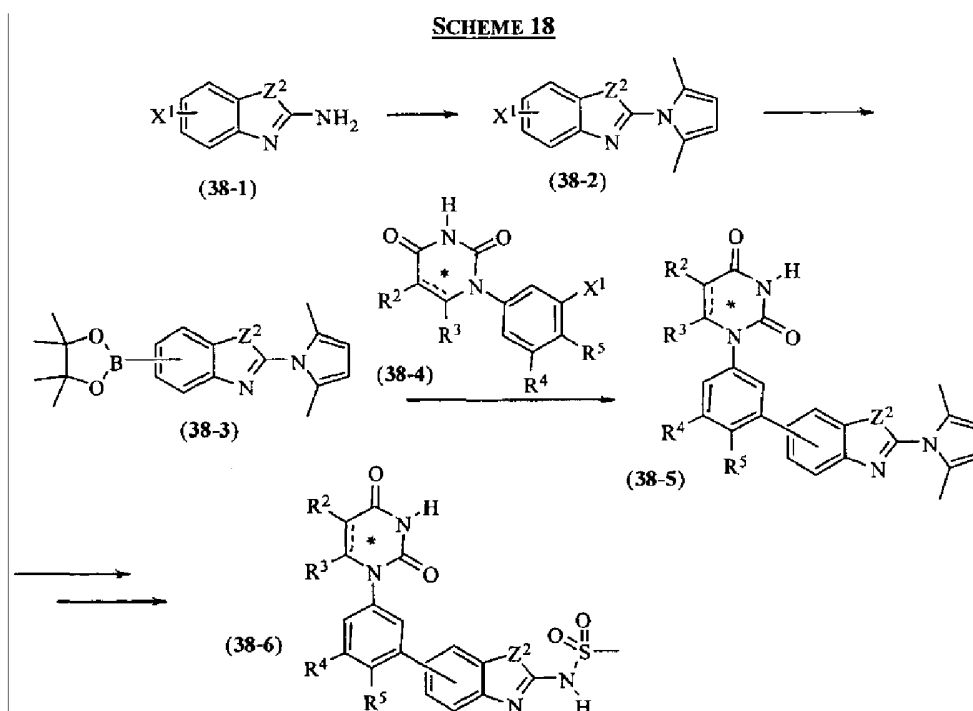


- [0398]** Compound (36-1), wherein Z² is O or S, can be reduced to compound (36-2) using iron powder in the presence of a mild acid such as, for example, ammonium chloride or dilute hydrochloric acid at temperatures of about 60 to about 90°C in solvents such as, for example, methanol, ethanol, water, and tetrahydrofuran, or mixtures thereof over about 30 min to about 12h. Compound (36-2) can be sulfonylated with methanesulfonyl chloride in the presence of a base like, for example, pyridine in a solvent such as, for example, dichloromethane at room temperature over a period of about 8 to about 36h.

SCHEME 17



[0399] Compound (37-1) can be sulfonated with methanesulfonyl chloride in the presence of a base like, for example, pyridine in a solvent such as, for example, dichloromethane at room temperature over a period of about 8 to about 36h to give compound (37-2). Compound (37-2) can be reacted with (4-methoxyphenyl)methanethiol in the presence of a base such as, for example, potassium carbonate in a solvent such as, for example, dimethylformamide heated to about 90 to about 110°C for about 8 to about 24h to give compound (37-3). Compound (37-3) can be reduced to compound (37-4) using iron powder in the presence of a mild acid such as, for example, ammonium chloride or dilute hydrochloric acid at temperatures of about 60 to about 90°C in solvent such as, for example, methanol, ethanol, water, and tetrahydrofuran, or mixtures thereof over about 30 min to about 12h. Compound (37-4) can be transformed to compound (37-5) in the presence of mercury(II) acetate, anisole, and trifluoroacetic acid at about 0 °C for about 30 to about 90 min and subsequently bubbling hydrogen sulfide through the mixture. Compound (37-5) can be treated with compound (37-6) in the presence of p-toluenesulfonic acid and triphenylphosphine in a solvent such as, for example, toluene heated to reflux for about 2 to about 16h to supply compound (37-7).



[0400] Compound (38-1), wherein X^1 is bromine or iodine and Z^2 is O or S, can be reacted with 2,5-hexanedione in the presence of a p-toluenesulfonic acid and pyridine heated in benzene to give compound of formula (38-2). Compound (38-2) can be reacted with bis(pinacolato)diboron in the presence of a catalyst such as, for example, Combiphos® Pd6, dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct, or palladium acetate in the presence of a ligand such as, for example, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), and a base such as, for example, potassium acetate in a solvent such as, for example, toluene, dioxane, tetrahydrofuran, dimethylformamide or dimethyl sulfoxide at a temperature from about 60 to about 130°C to give compound (38-3). Compound (38-3) can be reacted with compound (38-4) to give compound (38-5) under Suzuki reaction conditions. Such conditions include, for example, use of a palladium catalyst such as, for example, dihydrogen dichlorobis(di-t-butylphosphinito-KP)palladate(2-), tris(dibenzylideneacetone) palladium (0), palladium acetate, bis(triphenylphosphine)palladium (II) chloride, tetrakis (triphenylphosphine)palladium, or dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct; a base such as, for example, potassium acetate, potassium carbonate, potassium phosphate, po-

tassium *t*-butoxide, sodium carbonate, cesium carbonate, or cesium fluoride; and solvent such as, for example, toluene, ethanol, water or tetrahydrofuran, or mixtures thereof heated in the temperature range from about 40 to about 130°C.

- 5 **[0401]** Compound (**38-5**) can be treated with hydroxylamine hydrochloride in heated ethanol to remove the pyrrole-protecting group. Then treatment with methanesulfonyl chloride in the presence of a base such as, for example, pyridine in a solvent such as, for example, dichloromethane at or near ambient temperature supplies compound (**38-6**).

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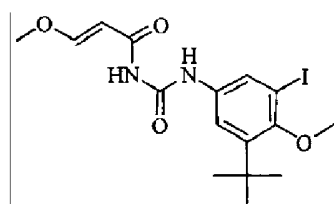
EXAMPLES

[0402] The following examples are merely illustrative, and not limiting to this disclosure in any way.

15

Example A. Preparation of (E)-N-(3-*tert*-butyl-5-iodo-4-methoxyphenyl)carbamoyl-3-methoxy acrylamide.

[0403]



20

Part A. Preparation of 2-*tert*-butyl-4-nitrophenol.

- [0404]** To a vigorously stirred solution of 2-*tert*-butylphenol (10g, 66.6mmol) in heptane (67ml) was added at a fast drip a solution of 70% nitric acid (4.25ml, 66.6mmol) diluted with water (4.25ml). The resulting dark red/brown mixture was stirred vigorously for 2h. The suspended solid was collected by filtration washed with hexane (300mL), water (200mL) and once again with hexane (200mL) to give a cocoa colored powder that was dried to constant mass (4.65g, 35.6%).

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Part B. Preparation of 2-tert-butyl-6-iodo-4-nitrophenol.

[0405] To the product from **Part A** (4.5g, 23.05mmol) dissolved in MeOH (120ml) and water (30mL) was added iodine monochloride (1.155ml, 23.05mmol) drop wise over a period of 10min. The mixture was stirred for 2h and diluted into 1L of water and allowed to stand overnight. The solid material was collected by filtration and washed 3x50mL with water and dried under vacuum overnight to give a tan solid (7.14g, 96%).

10 Part C. Preparation of 1-tert-butyl-3-iodo-2-methoxy-5-nitrobenzene.

[0406] To an ice bath cooled solution of the product from **Part B** (5.5g, 17.13mmol) in MTBE (15ml) in a 50mL pressure vessel was added 2.0M TMS diazomethane (12.85ml, 25.7mmol) followed by drop-wise addition of methanol (1.0mL) resulting in calm bubbling. The vessel was sealed and stirred at room temperature for 16h, cooled and the pressure was released. The solution was partitioned between EtOAc and water. The organic layer was washed with 1.0M HCl, saturated potassium carbonate solution, and saturated NaCl. The organic layer was dried over sodium sulfate, filtered and concentrated to give a red oil that was used without purification (5.4g, 84%).

Part D. Preparation of 3-tert-butyl-5-iodo-4-methoxyaniline.

[0407] A mixture of the product from **Part C** (5.80g, 17.31mmol), ammonium chloride (1.389g, 26.0mmol), and iron (4.83g, 87mmol) in THF/MeOH/water (200mL total, 2/2/1) was refluxed for 2h, cooled and filtered through Celite. The filtrate was evaporated and the residue was partitioned between water and EtOAc. The organic layer was washed with saturated brine, dried with sodium sulfate, filtered and evaporated to give a brown oil (5.28g, 100% yield).

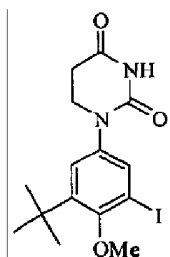
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Part E. Preparation of (E)-N-(3-tert-butyl-5-iodo-4-methoxyphenyl)carbamoyl-3-methoxy acrylamide.

[0408] To a solution of the product from **Part E** (3.05g, 10mmol) in DMF (50ml) at -20°C under N₂ was added at a fast drip a 0.4M solution in benzene of (E)-3-methoxyacryloyl isocyanate (50.0ml, 20.00mmol, prepared by the method of Santana et al., J. Heterocyclic Chem. 36:293 (1999)). The solution was stirred for 15min at -20°C, warmed to room temperature for 45min and diluted into EtOAc. The EtOAc layer was washed 4 x 300mL with water, 2 x 100mL with brine, dried (Na₂SO₄) and concentrated to a brown solid. The residue was triturated in Et₂O/hexane to give a fine powder that was collected by filtration and dried to give a tan powder (2.46g, 57%).

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Example B. Preparation of 1-(3-tert-butyl-5-iodo-4-methoxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione.

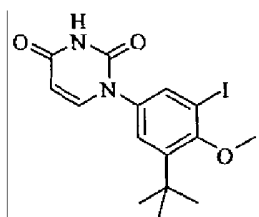
[0409]

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[0410] To a suspension of the product from **Example A** (2.46g, 5.69mmol) in ethanol (50ml) was added a solution of 5.5mL of H₂SO₄ in 50mL water and the mixture was heated at 110°C for 2.5h to give a clear solution. The solution was cooled and diluted with 50mL of water while stirring to give an off-white solid that was collected by filtration, washed with water and dried (2.06g, 90%).

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Example C. Preparation of 1-(3-tert-butyl-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

25 **[0411]**

Part A. Preparation of 2-tert-butyl-4,6-diiodophenol.

[0412] A solution of 2-tert-butylphenol (20.0g, 133mmol) in methanol (266mL) was treated with sodium hydroxide pellets (6.39g, 160mmol). The mixture was stirred until all the sodium hydroxide had dissolved and was then cooled in an ice-salt bath to -2°C. Sodium iodide (15.0g, 100mmol) was added and then 10 % sodium hypochlorite solution (45mL, 73.3mmol) was added drop wise at a rate such that the solution temperature rose no higher than 1.3°C. This sequence of events was repeated (3x) until a total of 60g (400mmol) of sodium iodide had been added and the sodium hypochlorite solution was added until the solution color changed from a light green-yellow color to the color of weak iced tea. This required all but 165mL of the 180mL total sodium hypochlorite solution measured out. With continued cooling at ca. 2°C, a solution of sodium thiosulfate pentahydrate (20g) in water (100mL) was added drop wise over 20min. After addition, the solution was acidified to pH 3 by drop wise addition of concentrated hydrochloric acid (ca. 35mL required of 40mL placed in the addition funnel). The precipitate was collected by filtration and washed with >1 liter of water. The salmon-colored solid was sucked as dry as possible, and dried in a vacuum oven at 50°C for 18h. These procedures afforded the product (49.61g, 93%) as a tan solid.

Part B. Preparation of 1-tert-butyl-3,5-diiodo-2-methoxybenzene.

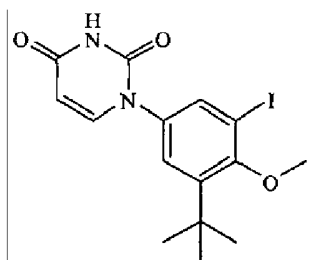
[0413] A solution of the product from **Part A** (20.0g, 49.7mmol) in acetone (140mL) was treated with methyl iodide (3.9mL, 8.83g, 62.2mmol) and 50 % (w/w) sodium hydroxide solution (3.02mL, 4.58g, 57.2mmol) followed by stirring at ambient temperature for 48h. The mixture was concentrated in vacuo to a volume of ca. 50-60mL, followed by dilution with heptane (80mL) and water (50mL). The layers were separated and the organic layer was extracted with saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded the product (20.59g, 99%) as a light yellow oil.

Part C. Preparation of 1-(3-tert-butyl-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0414] A suspension of the product from **Part B** (12.04g, 28.9mmol), uracil (3.89g, 34.7mmol), N-(2-cyanophenyl)picolinamide (1.29g, 5.79mmol) and tribasic potassium phosphate (12.9g, 60.8mmol) in DMSO (1.81mL) was degassed by nitrogen sparge for 1 h. The mixture was then treated with copper (I) iodide (551mg, 2.89mmol) and degassing was continued for another 10min. The mixture was then warmed at 60°C for 18h. The mixture was then poured into water (600mL) and acidified to pH 3 by addition of 4N hydrochloric acid solution. The mixture was diluted with ethyl acetate, and the organic layer was extracted with water (3x), saturated ammonium chloride solution (1x) and saturated sodium chloride solution. The solution was dried and treated with (3-mercaptopropyl) silica gel, followed by stirring for 2h. The mixture was filtered and concentrated in vacuo. The solid obtained was triturated with ether-ethyl acetate (>10:1) and collected by filtration and washed with ether. After drying in a vacuum oven at 50°C for 2h, these procedures afforded the product (2.75 g) as a white solid. The mother liquors were concentrated in vacuo to afford an amber solid. This material was chromatographed over a Flash 65 silica gel cartridge, eluting with 20-100 % ethyl acetate in hexanes. These procedures afforded a nearly white solid, which was triturated with ether-hexanes and collected by filtration. After drying in a vacuum oven for 3h, these procedures afforded another 4.31g of the product as a white solid. Total yield: 7.06g (61 %).

25 Example D. Preparation of 1-(3-tert-Butyl-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0415]



Part A. Preparation of 2-*tert*-butyl-4,6-diiodophenol.

5 [0416] 2-*tert*-Butylphenol (99.95g, 665.36mmol) was dissolved in 1250mL methanol and converted to the corresponding phenoxide with 31.96g (799.0mmol, 1.2equiv.) of sodium hydroxide by stirring the sodium hydroxide pellets at room temperature, and then cooling the reaction mixture in an ice/salt bath. Sodium iodide (299.34g, 1997.07mmol, 3.0equiv.) and 8.3% bleach (1265.83g, 1411.39mmol, 2.1equiv.) were added to the cold reaction solution in four equal
10 portions, the bleach being added while keeping the reaction mixture at <0°C. 500mL of 20% (w/w) sodium thiosulfate solution was added over an 18-minute period, with the temperature rising from -0.6°C to 2.5°C. The pH of the reaction mixture was adjusted to approximately 3 by adding 197.5mL of conc. HCl over a period of 97min with the reaction temperature going from 1.2°C to 4.1°C. The
15 resulting slurry was filtered, and the wet cake washed with ~ 2L of water. The wet cake was left on the Buchner funnel under vacuum overnight (approximately 15h) to yield 289.33g (potency adjusted yield = 254.61g) of the title product.

Part B. Preparation of 1-*tert*-butyl-3,5-diiodo-2-methoxybenzene.

20 [0417] The product from **Part A** (93% assay, 21.6g, 50mmol) was dissolved in 140mL of acetone. Methyl iodide (4.2mL, 67.5mmol, 1.35equiv.) was added, followed by 50% aqueous sodium hydroxide (5.0g, 62.5mmol, 1.25equiv.). The reaction was stirred overnight, then concentrated to approximately 50-60mL.
25 80mL of heptanes was added followed by 50mL of water, and the layers were shaken and separated, and the aqueous layer was back extracted with 20mL of heptanes. The organic layers were combined and washed twice with 50mL each of 10% aqueous NaCl to afford 91.1grams of a heptane solution, which assayed to 19.1g of the title compound.

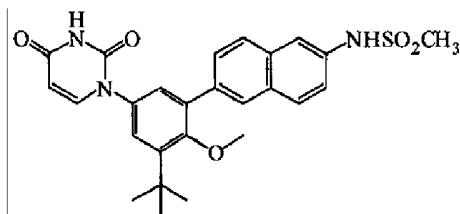
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Part C. Preparation of 1-(3-*tert*-Butyl-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0418] Uracil (33.3g, 297mmol, 1.2equiv.), K_3PO_4 (106g, 500mmol, 2.1equiv.), Cul (4.6g, 24.2mmol, 0.1equiv.), and *N*-(2-cyanophenyl)picolinamide (6.4g, 28.7mmol, 0.12equiv.) were charged to a flask and inerted with argon. The 1-*tert*-butyl-3,5-diiodo-2-methoxybenzene was solvent switched into MeCN, dissolved in 1L DMSO and sparged with argon and added to the solids. The reaction was heated to 60°C for 16h. After cooling, the reaction was diluted with 2L EtOAc and washed with 2.6L water (back extracted with 3 x 1L EtOAc). The combined organic layers were washed with 2 x 1L of 0.25M $(CuOAc)_2$ then 2 x 830mL 15% NH_4Cl then 800mL brine. The organic layer was then concentrated and chased with 1L heptane, then triturated with refluxing 85:15 (v/v) heptane:*i*PrOAc for 4h. After cooling, the product was collected by filtration and washed with an additional 330mL of 85:15 v/v heptanes:EtOAc to yield after drying 66.9g (70% yield) of the product as a white solid.

15 Example E. Preparation of *N*-(6-(3-*tert*-Butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0419]



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[0420] A solution of 100mL of water and 300mL of THF was sparged with nitrogen and then transferred via canula and nitrogen pressure to a flask containing 19.9965g (49.96mmol) of the product from **Example D**, 20.8234g (59.97mmol, 1.20equivalents) of *N*-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)methanesulfonamide, and 21.8711g (103.03mmol, 2.06equivalents) of potassium phosphate which had been purged with nitrogen. The resulting solution was again sparged with nitrogen.

[0421] THF (100mL) was sparged with nitrogen and then transferred via canula and nitrogen pressure to a flask containing 462.8mg (0.51mmol, 0.01 equiva-

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lents) of Pd₂dba₃ and 735.8mg (2.52mmol, 0.05 equivalents) of 1,3,5,7-tetra-methyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane, which had been purged with nitrogen. The resulting solution was again sparged with nitrogen.

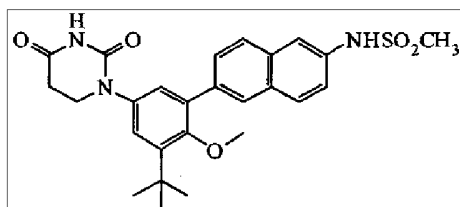
5 **[0422]** The initial THF/water solution was transferred via canula and nitrogen pressure to the flask containing the catalyst and ligand in THF. The reaction was warmed to 50°C and stirred overnight under positive nitrogen pressure. A sample of the reaction was taken the following morning. HPLC of the sample showed 0.28 PA% iodouracil starting material, 76.8 PA% product, and 5.2 PA%
10 boronate.

[0423] The reaction was cooled to room temperature and washed, in three portions, with a solution of 5.84g of L-cysteine and 81.4g of sodium chloride in 550mL of water which had been sparged with nitrogen. The THF solution was
15 filtered through a celite pad. The pad was rinsed with 100mL of THF, which was combined with the original THF solution. The THF solution was concentrated on the rotary evaporator to 136g. To the white slurry was added 405mL of ethyl acetate with good agitation. The slurry was filtered after stirring overnight. The wet cake was washed with 2X50mL of ethyl acetate. The solid, an ethyl acetate
20 solvate, was dried in the vacuum oven at 50°C. It weighed 25.49g.

[0424] The solid and 8.7g of 3-mercaptopropyl derivatized silica gel was stirred in 500mL of THF then filtered through a celite pad. The filtrate was concentrated on the rotary evaporator to give 13.08g of white solid. The solid that had been
25 filtered off on the celite pad was extracted with 500mL of THF at 60°C. The THF solution was concentrated to 66g and treated with 206mL of ethyl acetate. The solid which precipitated was filtered and dried, yielding 9.13g of product. This solid was combined with the original solid and slurried in 100mL of 200 proof 3A ethanol. It was filtered and dried in the vacuum oven at 50°C to give 20.74g of
30 product.

Example 1. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IA-L0-2.9).

5 [0425]



Part A. Preparation of 6-bromo-2-naphthoic acid.

[0426] A solution of methyl 6-bromo-2-naphthoate (7.70g, 29.0mmol) in 2:1
10 THF:water (150mL) was treated with lithium hydroxide hydrate (2.44g, 58.1mmol) followed by stirring at room temperature for 48h. Concentrated under vacuum, diluted with water and cooled to 0°C. Acidified to pH3 with 4N HCl. Solids were collected by filtration, dissolved in toluene-EtOAc (ca. 2L) and washed with brine. Dried over Na₂SO₄, filtered and concentrated under vacuum.
15 Brown solid was triturated with ether, collected by filtration, and dried under vacuum to give the title compound as a nearly white solid (5.07g, 70%).

Part B. Preparation of 6-bromonaphthalen-2-amine.

20 [0427] A solution of the product **Part A** (5.07g, 20.19mmol) and triethylamine (4.22mL, 3.07g, 30.3mmol) in dry DMF (155mL) was treated with the diphenylphosphoroyl azide (6.55mL, 8.34g, 30.3mmol) followed by stirring at room temperature for 3h. The solution was then treated with water (20mL) followed by warming at 100°C for 1h. The solution was cooled and the flask fitted with a
25 short-path distillation head and the DMF removed by distillation under high vacuum. The solid residue was dissolved in EtOAc and washed with saturated sodium bicarbonate solution. Filtered through celite and the filtrate was washed with water (3x) and then with brine. Dried over Na₂SO₄, filtered and concentrated under vacuum to give the title compound as a beige solid (4.48g, 100 %).

30

Part C. Preparation of benzyl 6-bromonaphthalen-2-ylcarbamate.

[0428] A mixture of the product from **Part B** (1.79g, 8.06mmol) and saturated sodium bicarbonate solution (18mL) in acetone (40mL) at 0 °C was treated drop wise with benzyl chloroformate. The mixture was stirred at 0°C for 1h, and then allowed to gradually warm to room temperature over 18h. The mixture was diluted with EtOAc and water and the layers separated. The organic layer was extracted with water and washed with brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with EtOAc/hexanes gave the title compound as a pink solid (1.5g, 52%).

Part D. Preparation of benzyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl carbamate.

[0429] A resealable Schlenk tube containing a solution of the product from **Part C** (1.42g, 3.99mmol), bis(pinacolato)diboron (1.11g, 4.39mmol), and potassium acetate (1.17g, 11.96mmol) in DMF (28mL) was degassed by three freeze-thaw cycles. The solution was treated with 1,1'-bis(diphenyl phosphino)ferrocene palladium (II) chloride dichloromethane complex (98mg, 0.12mmol), followed by degassing by two additional freeze-thaw cycles. The Schlenk tube was then sealed and the mixture warmed at 80°C for 18h. Cooled and diluted with ethyl acetate and water. The mixture was treated with Darco G-60 and then filtered through celite. The filtrate was extracted with water (4x) and saturated sodium chloride solution. Dried over Na₂SO₄, filtered and concentrated under vacuum afforded a light brown oil. Purification by silica gel column chromatography eluting with EtOAc/hexane gave the title compound as a colorless oil (910mg, 57%).

Part E. Preparation of 2-tert-butyl-4-nitrophenol.

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[0430] To a vigorously stirred solution of 2-tert-butylphenol (10g, 66.6mmol) in heptane (67ml) was added at a fast drip a solution of 70% nitric acid (4.25ml, 66.6mmol) diluted with water (4.25ml). The resulting dark red/brown mixture

was stirred vigorously for 2h. The suspended solid was collected by filtration washed with hexane (300mL), water (200mL) and once again with hexane (200mL) to give a cocoa colored powder that was dried to constant mass (4.65g, 35.6%).

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Part F. Preparation of 2-bromo-6-tert-butyl-4-nitrophenol.

[0431] A solution of the product from **Part E** (1.0g, 5.12mmol) in glacial acetic acid (10.25mL) was treated portion wise with pyridine hydrobromide perbromide (1.80g, 5.63mmol) followed by stirring at room temperature for 2h. Additional pyridinium hydrobromide perbromide (3.6g) was added in two portions and after another 3h of stirring, the reaction was complete. The mixture was poured into ice water, and the mixture treated with a small amount of sodium sulfite. The resulting solid was filtered and dried under vacuum to give the title compound as a brown solid (1.40g, 100 %).

15

Part G. Preparation of 1-bromo-3-tert-butyl-2-methoxy-5-nitrobenzene.

[0432] A solution of the product from **Part F** (1.40g, 5.11mmol) in 10:1 t-butylmethylether-methanol (25.55mL) was treated with 2.0M trimethylsilyldiazomethane in ether (5.5mL, 10.21mmol), followed by stirring at room temperature for 18h. The mixture was concentrated under vacuum to afford a yellow oil, which was purified by silica gel column chromatography eluting with EtOAc/hexanes to give the title compound as a yellow oil (1.36g, 92 %).

20

Part H. Preparation of tert-butyl 3-bromo-5-tert-butyl-4-methoxyphenylcarbamate.

[0433] A solution of the product from **Part G** (960mg, 3.33mmol) in methanol (17mL) was treated with 5 % platinum on sulfided carbon (100mg), followed by hydrogenation under balloon pressure for 3h, and then filtered through celite and concentrated under vacuum to afford the 3-bromo-5-tert-butyl-4-methoxyaniline as a yellow oil (860mg, 3.33mmol, 100%). A solution of this material in

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THF (17mL) was treated with di-tert-butyl dicarbonate (800mg, 3.66mmol) followed by warming at reflux for 2h. Concentration under vacuum afforded a beige solid, which was purified by silica gel column chromatography eluting with EtOAc/hexanes. Solid was triturated with hexanes, collected by filtration, and
5 dried under vacuum to give the title compound as a nearly white solid (890mg, 75 %).

Part I. Preparation of benzyl 6-(3-tert-butyl-5-(tert-butylcarbonyl)-2-methoxyphenyl) naphthalen-2-yl carbamate.

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[0434] Toluene (928ul) and EtOH (928ul) were combined with the product from **Part H** (133mg, 0.37mmol), the product from **Part D** (299mg, 0.74mmol) and 1M sodium carbonate (371ul, 0.37mmol) and de-gassed for 20min with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (8.6mg, 7.4umol) was added and
15 de-gassing continued 5-10min. Heated at 85-90°C for 18h, cooled and concentrated under vacuum. Purification by silica gel column chromatography eluting with EtOAc/hexanes gave the title compound (102mg, 49%).

Part J. Preparation of benzyl 6-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-ylcarbamate.

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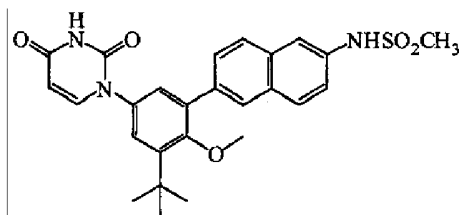
[0435] A solution of the product from **Part I** (100mg, 0.18mmol) in CH₂Cl₂ (1.0ml) was treated with trifluoroacetic acid (0.5ml, 6.5mmol) at room temperature for 1h. Concentrated under vacuum. Dissolved in ethyl acetate, washed
25 with 10% NaHCO₃, brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Dissolved in toluene (1.0ml) and added Et₃N (25ul, 0.18mmol) and acrylic acid (13ul, 0.19mmol) and the mixture was refluxed for 16h. Concentrated under vacuum. Dissolved in acetic acid (1.0ml, 17.5mmol) and added urea (11.9mg, 0.20mmol) and refluxed for 72h. Cooled and poured into ice water, extracted three times with CHCl₃, combined extracts, dried over Na₂SO₄, filtered
30 and concentrated under vacuum. Purification by silica gel column chromatography eluting with EtOAc/hexanes gave title compound (57.5mg, 58%).

Part K. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0436] Combined the product from **Part J** (56mg, 0.10mmol) and EtOAc (1.0ml) and added 10% palladium on carbon (10mg). Stirred under a balloon of H₂ gas for 16h. Filtered through Celite and concentrated under vacuum. Dissolved in CH₂Cl₂ (1.0ml), added Et₃N (16ul, 0.115mmol) and methanesulfonyl chloride (8.7ul, 0.112mmol) and stirred at room temperature for 30min. Concentrated under vacuum and purification by silica gel column chromatography eluting with EtOAc/hexanes gave the title compound (10mg, 20%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.34 - 1.48 (m, 9 H) 2.71 (t, *J*=6.62 Hz, 2 H) 3.08 (s, 3 H) 3.21 (s, 3 H) 3.82 (t, *J*=6.62 Hz, 2 H) 7.26 (s, 2 H) 7.41 (dd, *J*=8.82, 1.84 Hz, 1 H) 7.59 - 7.76 (m, 2 H) 7.89 - 8.04 (m, 3 H) 10.03 (s, 1 H) 10.34 (s, 1 H); MS (ESI+) *m/z* 496 (M+H)⁺; (ESI-) *m/z* 494 (M-H)⁻.

15

Example 2A. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.3).

20 **[0437]**

Part A. Preparation of N-(6-bromonaphthalen-2-yl)methanesulfonamide.

[0438] A solution of the product from **Example 1, Part B** (4.48g, 20.17mmol) in pyridine (100mL) was treated drop wise with methanesulfonyl chloride (1.97mL, 2.89 g, 25.2mmol) followed by stirring at room temperature for 1h. Diluted with toluene and concentrated under vacuum twice. The residue was extracted with EtOAc and washed with water, 1M citric acid and brine. Treated with Darco G-60, dried over Na₂SO₄, filtered through celite and concentrated under vacuum.

25

Solid was triturated with etherhexane, collected by filtration and dried under vacuum to give the title compound as a faint pink solid (3.32g, 55 %).

Part B. Preparation of N-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-naphthalen-2-yl) methanesulfonamide.

[0439] A mixture of the product from **Part A** (1.00g, 3.33mmol), bis(pincolato)di-boron (1.27g, 5.00mmol), potassium acetate (0.98 g, 9.99mmol) and Combi-phos Pd6 (84mg, 0.17mmol) in toluene (22mL) was heated at reflux for 3h.
10 Cooled and diluted with ethyl acetate and water. The mixture was treated with Darco G-60 and filtered through celite. The filtrate was washed with water and brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Oil was dissolved in ether and precipitated by addition of hexanes. The product was collected by filtration and washed with hexanes. Evaporation of the filtrate and purification by silica gel column chromatography eluting with EtOAc/hexanes. The
15 title compound from crystallization and chromatography was obtained as a white solid (927mg, 80%).

Part C. Preparation of tert-butyl 3-tert-butyl-4-methoxy-5-(6-(methylsulfonamido) naphthalen-2-yl)phenylcarbamate.

[0440] Combined the product from **Example 1, Part H** (87mg, 0.243mmol), the product from **Part B** (169mg, 0.486mmol), toluene (1.0ml), ethanol (1.0ml) and sodium carbonate (0.243ml, 0.243mmol) in a sealed tube and de-gassed with
25 N₂ gas for 20min. Tetrakis(triphenylphosphine)palladium(0) (5.61mg, 4.86μmol) was added and de-gassing was continued another 5-10 min. Heated at 90-95°C for 16h. Cooled and concentrated under vacuum. Purification by silica gel column chromatography eluting with EtOAc/hexanes gave the title compound (92.2mg, 76 %).

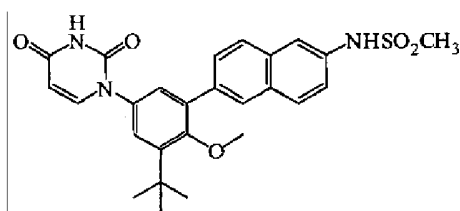
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Part D. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0441] A solution of the product from **Part C** (90mg, 0.180mmol) in CH₂Cl₂ (2.0ml) was treated with trifluoroacetic acid (1.0ml, 12.98mmol) at room temperature for 1h. Concentrated under vacuum, dissolved residue in EtOAc, washed with 10% NaHCO₃, and brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Dissolved in DMF (1.4ml) and cooled to -25°C and added (E)-3-methoxyacryloyl isocyanate (0.633ml, 0.361mmol) drop wise while maintaining the temperature below -10°C. Warmed to room temperature and stirred for 2h. Poured into ether, washed with water, and brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Added a mixture of H₂SO₄ (0.1ml, 1.876mmol), water (1.0ml) and EtOH (1.02ml) and stirred at 100°C 16h. Cooled and concentrated under vacuum. Poured into water, extracted with EtOAc, combined extracts and washed with brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with MeOH/CHCl₃ gave the title compound (53mg, 59%). ¹H NMR (300 MHz DMSO-*d*₆) δ 1.42 (s, 9 H) 3.08 (s, 3 H) 3.25 (s, 3 H) 5.65 (d, *J*=7.72 Hz, 1 H) 7.34 (dd, *J*=15.81, 2.57 Hz, 2 H) 7.42 (dd, *J*=8.82, 1.84 Hz, 1 H) 7.65 - 7.76 (m, 2 H) 7.80 (d, *J*=8.09 Hz, 1 H) 7.96 (t, *J*= 8.27 Hz, 2 H) 8.02 (s, 1 H) 10.04 (s, 1 H) 11.41 (s, 1 H); MS (ESI+) *m/z* 494 (M+H)⁺; (ESI-) *m/z* 492 (M-H)⁻.

Example 2B. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.3).

[0442]



25

Part A. Preparation of 2-tert-butyl-6-iodo-4-nitrophenol.

[0443] To the product from **Example 1, Part E** (4.5g, 23.05mmol) dissolved in MeOH (120min) and water (30mL) was added iodine monochloride (1.155ml, 23.05mmol) drop wise over a period of 10min. The mixture was stirred for 2h

30

and diluted into 1L of water and allowed to stand overnight. The solid material was collected by filtration and washed 3 x 50mL with water and dried under vacuum overnight to give a tan solid (7.14g, 96%).

5 **Part B. Preparation of 1-tert-butyl-3-iodo-2-methoxy-5-nitrobenzene.**

[0444] To an ice bath cooled solution of the product from **Part A** (5.5g, 17.13 mmol) in MTBE (15ml) in a 50mL pressure vessel was added 2.0M trimethylsilyl diazomethane (12.85ml, 25.7mmol) followed by drop-wise addition of methanol
10 (1.0mL) resulting in calm bubbling. The vessel was sealed and stirred at room temperature for 16h, cooled and the pressure was released. The solution was partitioned between EtOAc and water. The organic layer was washed with 1.0M HCl, saturated potassium carbonate solution, and saturated NaCl. The organic layer was dried over sodium sulfate, filtered and concentrated to give a red oil
15 that was used without purification (5.4g, 84%).

Part C. Preparation of 3-tert-butyl-5-iodo-4-methoxyaniline.

[0445] A mixture of the product from **Part B** (5.80g, 17.31mmol), ammonium
20 chloride (1.389g, 26.0mmol), and iron (4.83g, 87mmol) in THF/MeOH/water (200mL total, 2/2/1) was refluxed for 2h, cooled and filtered through Celite. The filtrate was evaporated and the residue was partitioned between water and EtOAc. The organic layer was washed with saturated brine, dried with sodium sulfate, filtered and evaporated to give a brown oil (5.28g, 100% yield).

25

Part D. Preparation of (E)-N-(3-tert-butyl-5-iodo-4-methoxyphenylcarbamoyl)-3-methoxy acrylamide.

[0446] To a solution of the product from **Part C** (3.05g, 10mmol) in DMF (50ml)
30 at -20 °C under N₂ was added at a fast drip a 0.4M solution in benzene of (E)-3-methoxyacryloyl isocyanate (50.0ml, 20.00mmol, prepared by the method of Santana et al., J. Heterocyclic. Chem. 36:293 (1999). The solution was stirred for 15min at -20 °C, warmed to room temperature for 45min and diluted with

EtOAc. The organic was washed with water and brine. Dried over Na₂SO₄, filtered and concentrated to a brown solid. The residue was triturated in Et₂O/hexane to give a fine powder that was collected by filtration and dried under vacuum to give the title compound as a tan powder (2.46g, 57%).

5

Part E. Preparation of 1-(3-tert-butyl-5-iodo-4-methoxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione.

[0447] To a suspension of the product from **Part D** (2.46g, 5.69mmol) in ethanol (50ml) was added a solution of 5.5mL of H₂SO₄ in 50mL water and the mixture was heated at 110°C for 2.5h to give a clear solution. Cooled and diluted with 50mL of water while stirring to give an off-white solid that was collected by filtration, washed with water and dried under vacuum to give the title compound (2.06g, 90%).

15

Part F. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

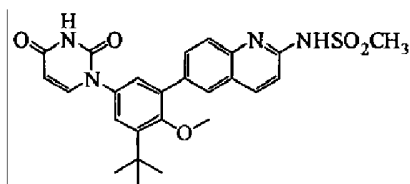
[0448] In a microwave tube, the product from **Part E** (104mg, 0.26mmol), the product from **Example 2A, Part B** (108mg, 0.31mmol), and 1.0M sodium carbonate solution (312μL, 0.31mmol) in 1:1 ethanol-toluene (1.7mL) was degassed by nitrogen sparge for 15min. 1,1'-Bis(diphenylphosphino) ferrocene palladium (II) chloride dichloromethane complex (9mg, 0.011mmol) was added, and degassing was continued for another 5min. The tube was sealed and heated in the microwave at 100°C for 1h. Diluted with dichloromethane and washed with 1M citric acid solution and brine. The organic layer was then stirred with (3-mercaptopropyl) silica gel for 1h. Filtered through celite and concentrated under vacuum. Triturated with ether, methanol, and then again with ether to give the title compound as a nearly white solid (32mg, 25 %). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.41 (d, J=1.84 Hz, 1 H) 10.04 (s, 1 H) 8.03 (s, 1 H) 7.96 (t, J=8.09 Hz, 2 H) 7.80 (d, J=8.09 Hz, 1 H) 7.63 - 7.79 (m, 2 H) 7.35 - 7.45 (m, 1 H) 7.37 (d, J=2.57 Hz, 1 H) 7.32 (d, J=2.57 Hz, 1 H) 5.65 (dd, J=8.09, 2.21 Hz,

30

1 H) 3.25 (s, 3 H) 3.09 (s, 3 H) 1.43 (s, 9 H). MS (+ESI) m/z (rel abundance): 494 (100, M+H), 511 (90, M+NH₄), 987 (20, 2M+H), 1009 (8, 2M+Na).

Example 3. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-2-yl)methanesulfonamide (compound IB-L0-2.5).

[0449]



10 **Part A. Preparation of (E)-N-(4-bromophenyl)-3-methoxyacrylamide.**

[0450] Combined 4-bromoaniline (285mg, 1.659mmol), CH₂Cl₂ (2.0ml) and pyridine (0.25ml, 3.09mmol) and slowly added (E)-3-methoxyacryloyl chloride (200 mg, 1.659mmol) and stirred at room temperature for 2h. The resulting yellow solid was filtered off and washed with water. The solid was dried under vacuum to give the title compound (406mg, 96 %).

Part B. Preparation of 6-Bromoquinolin-2(1H)-one.

20 [0451] The product from **Part A** (395mg, 1.542mmol) was added in portions to H₂SO₄ (4.5ml). Stirred for 3h at room temperature, poured onto crushed ice. Solid filtered, washed with water and dried under vacuum to give the title compound (203mg, 59 %).

25 **Part C. Preparation of 6-bromo-2-chloroquinoline.**

[0452] To phosphorus oxychloride (2.5ml, 26.8mmol) was added, in portions, the product from **Part B** (200mg, 0.893mmol). Refluxed for 1h, cooled to room temperature and poured onto crushed ice. Extracted with CHCl₃, extracts com-

bined, dried over mgSO_4 , filtered and concentrated under vacuum to give the title compound (173mg, 80%).

Part D. Preparation of 6-bromo-2-aminoquinoline.

5

[0453] The product from **Part C** (173mg, 0.713mmol), acetamide (843mg, 14.27 mmol) and potassium carbonate (493mg, 3.57mmol) were combined and heated at 200 °C for 2h. Cooled to room temperature, whereupon it solidified. Dissolved in a mixture of CHCl_3 and water. Aqueous layer was extracted twice
10 more with CHCl_3 , extracts were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with $\text{MeOH}/\text{CHCl}_3$ gave title compound (92mg, 58 %).

15 Part E. Preparation of N-(6-bromoquinolin-2-yl)-N-(methanesulfonyl)methanesulfonamide.

[0454] Combined the product from **Part D** (90mg, 0.403mmol) and CH_2Cl_2 (2.0ml) and added triethylamine (0.062ml, 0.444mmol) and methanesulfonyl chloride (0.035ml, 0.444mmol). Stirred at room temperature 16h. Added triethylamine (0.062ml, 0.444mmol) and methanesulfonyl chloride (0.035ml, 0.444mmol) and stirred at room temperature for 1h. Diluted with EtOAc, washed with 10% citric acid, 10% NaHCO_3 and brine. Dried over Na_2SO_4 , filtered and concentrated under vacuum. Dissolved in EtOAc and poured into excess hexane.
25 Solid collected by filtration to give the title compound (94mg, 61%).

Part F. Preparation of N-(methanesulfonyl)-N-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2-yl)methanesulfonamide.

30 [0455] Combined the product from **Part E** (94mg, 0.248mmol), bis(pinacolato)diboron (94mg, 0.372mmol), potassium acetate (73.0mg, 0.744mmol), CombiPhos[®] PD6 (6.22mg, 0.012mmol) and toluene (1.5ml) and refluxed 18h. Cooled to room temperature, diluted with EtOAc and water, filtered through Celite, se-

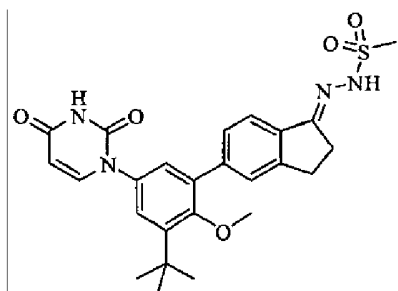
parated the phases, washed the organic phase with brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with EtOAc/hexanes gave title compound (67mg, 63%).

5 **Part G. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-2-yl)methanesulfonamide.**

[0456] Combined in a microwave tube the product from **Example 2B, Part E** (27mg, 0.067mmol), the product from **Part F** (37.4mg, 0.088mmol), ethanol (1.0ml), toluene (1.0ml) and 1M sodium carbonate (0.067ml, 0.067mmol) and
 10 the solution was degassed using N₂ gas for 20min. Tetrakis- (triphenylphosphine)palladium(0) (1.559mg, 1.349μmol) was added and the solution was degassed an additional 5min. The tube was sealed and heated in the microwave at 100°C for 45min. Cooled solution diluted with 1:1 EtOAc:water and filtered
 15 through Celite. Aqueous layer was extracted twice more with EtOAc, combined organic extracts and washed with brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with MeOH/CHCl₃ gave title compound (13.7mg, 41 %). ¹H NMR (300 MHz, CDCl₃) δ 1.45 (s, 9 H) 3.18 (s, 3 H) 3.30 (s, 3 H) 5.83 (dd, *J*=7.91, 2.02 Hz, 1 H)
 20 6.99 (d, *J* = 8.82 Hz, 1 H) 7.21 (d, *J*=2.57 Hz, 1 H) 7.36 (d, *J*=7.72 Hz, 1 H) 7.52 (d, *J*=8.46 Hz, 1 H) 7.82 - 7.91 (m, 2 H) 7.98 (d, *J*=9.19 Hz, 1 H) 8.29 (s, 1 H); MS (ESI+) *m/z* 495 (M+H)⁺; (ESI-) *m/z* 493 (M-H)⁻.

25 **Example 4. Preparation of (E)-N'-(5-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide (compound IB-L0-2.4).**

[0457]



Part A. Preparation of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-one.

[0458] A mixture of 5-bromo-2,3-dihydro-1H-inden-1-one (2.50g, 11.85mmol),
5 bis(pinacolato) diboron (3.61g, 14.21mmol), potassium acetate (3.49g, 35.5
mmol) and Combiphos Pd6 (178mg, 0.36mmol) in toluene (60mL) was heated
at reflux for 8h. Cooled, diluted with EtOAc and extracted with water (2 x) and
washed with brine. Dried over Na₂SO₄ and stirred for 1h with (3-mercaptopropyl)
silica gel. Filtered and concentrated under vacuum to afford a yellow so-
10 lid. Purification by silica gel column chromatography eluting with
EtOAc/hexanes gave a yellow solid. Triturated with cold hexanes, filtered and
dried under vacuum to give the title compound as a fine nearly white solid
(1.99g, 65%). A second crop of crystals (140mg) was obtained from the mother
liquors, bringing the yield to 70%.

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Part B. Preparation of 1-(3-tert-butyl-4-methoxy-5-(1-oxo-2,3-dihydro-1H-inden-5-yl)phenyl) pyrimidine-2,4(1H,3H)-dione.

[0459] In a microwave tube, a suspension of the product from **Example 2B**,
20 **Part E** (130mg, 0.33mmol), the product from **Part A** (101mg, 0.39mmol), and
1.0M sodium carbonate solution (390μL, 0.39mmol) in 1:1 ethanol-toluene
(1.20mL) was degassed by nitrogen sparge for 15min. The mixture was treated
with 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride dichloromethane
complex (13mg, 0.016mmol) and degassing was continued for another 5min
25 and heated at 100°C in the microwave for 1h. Cooled, diluted with EtOAc and
extracted with 1M citric acid solution and brine. The organic layer was then
stirred with (3-mercaptopropyl) silica gel for 1h. Filtered and concentrated under
vacuum. Purification by silica gel column chromatography eluting with EtOAc/
hexanes gave the title compound as a white solid (80mg, 61 %).

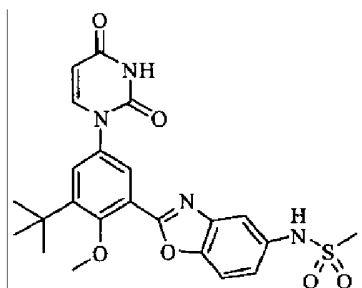
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Part C. Preparation of (E)-N'-(5-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide.

[0460] A suspension of the product from **Part B** (77mg, 0.19mmol) and methanesulfonylhydrazide (22mg, 0.20mmol) in 3:1 THF:MeOH (1.9mL) was warmed at 60°C for 24h. The mixture was concentrated under vacuum and the residue was purified by silica gel column chromatography eluting with EtOAc/hexanes to give the title compound as a white solid (62mg, 66 %). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.40 (d, J=1.84 Hz, 1 H) 9.94 (s, 1 H) 7.76 (dd, J=13.97, 8.09 Hz, 2 H) 7.52 - 7.59 (m, 1 H) 7.51 (d, J=8.46 Hz, 1 H) 7.11 - 7.40 (m, 2 H) 3.28 (s, 3 H) 2.96 - 3.19 (m, 5 H), 2.85 (m, 2 H), 1.40 (s, 9 H). MS (+ESI) m/z (rel abundance): 497 (100, M+H), 1015 (5, 2M+Na).

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Example 5. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]oxazol-5-yl)methanesulfonamide (compound IB-L0-2.6).

15 **[0461]**

Part A. Preparation of methyl 3-tert-butyl-2-hydroxy-5-nitrobenzoate.

[0462] Methyl 3,5-di-tert-butyl-2-hydroxybenzoate (28.66g, 108.4mmol) was dissolved with stirring in 430mL glacial acetic acid and the resulting mixture was treated drop wise with fuming nitric acid (90%, 179.26mL). When the addition was complete, the resulting mixture was stirred for 2.5h. The reaction mixture was poured into a 2.0L of crushed ice and allowed to stand 30min. Afterwards, 1.0L of water was added and the ice water mixture was allowed to melt. The mixture was then filtered, washed with water and dried to provide the title compound (24.57g, 89%).

25

Part B. Preparation of methyl 3-tert-butyl-2-methoxy-5-nitrobenzoate.

[0463] Methyl 3-tert-butyl-2-hydroxy-5-nitrobenzoate (11.41g, 45.0mmol), potassium carbonate(9.34g, 67.6mmol), acetone (200mL), and dimethyl sulfate (6.46g, 67.6mmol) were added together. The resultant mixture was then heated to reflux for 16h. The mixture was then filtered and the solid was washed with ethyl acetate. The resulting organic liquid was then concentrated under vacuum to an oil and redissolved in ethyl acetate (600mL). The organic solution was then washed with water, dried, filtered and concentrated under vacuum to an oil that was then subjected to purification via column chromatography (gradient of 5% to 40% EtOAc/Hexanes) to yield the title compound as an oil (10.42, 87%).

Part C. Preparation of methyl 5-amino-3-tert-butyl-2-methoxybenzoate.

[0464] Methyl 3-tert-butyl-2-methoxy-5-nitrobenzoate (10.42g, 39.0mmol), iron powder (325mesh, 10.89g, 195mmol), ammonium chloride (3.13g, 58.5mmol), water (30mL), and methanol (150mL) were added together. The resultant mixture was then refluxed for 1h. The mixture was then cooled to room temperature, filtered through celite, and the celite washed with methanol. The filtrate was then concentrated under vacuum and dissolved in ethyl acetate (600mL). The resultant solution was then washed with water and brine. The organic extract was then dried, filtered and concentrated under vacuum to yield the title compound as an oil (9.25g, 100%).

Part D. Preparation of (E)-methyl 3-tert-butyl-2-methoxy-5-(3-(3-methoxyacryloyl)ureido) benzoate.

[0465] The product obtained as described in **Part C** (2.0g, 8.43mmol) was dissolved in 30mL of N,N-dimethylacetamide and cooled to -25°C. A 0.5Molar solution of E-3-methoxyacryloyl isocyanate in benzene (21.9mL, 10.96mmol) was added drop wise and the resulting solution was stirred at ambient temperature for 4h, and then poured into water. The product was extracted into dichloro-

methane, washed with brine, dried over sodium sulfate, filtered and evaporated under vacuum to give 100% yield.

5 **Part E. Preparation of methyl 3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxybenzoate.**

[0466] The product from **Part D** (3.1g, 8.51mmol) was dissolved in ethanol (60mL). Sulfuric acid (6mL) was added to water (60mL) then this solution was added in one portion to the ethanol. The heterogeneous mixture was heated at
10 100°C for 3h. The ethanol was removed under vacuum, and then the aqueous solution was extracted with dichloromethane and evaporated to dryness. This residue was purified by flash chromatography, eluting with 1% methanol/dichloromethane to yield 1.23g (44%).

15 **Part F. Preparation of 3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxybenzoic acid.**

[0467] The product from **Part E** (1.23g, 3.7mmol) was taken up in ethanol (5 mL) and 1Molar sodium hydroxide solution (10mL) and stirred at ambient temperature for 18h. The solution was diluted with 1M HCl and the resulting solid
20 was filtered and dried to give 0.945 g (80%).

Part G. Preparation of 3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy benzaldehyde.

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[0468] The product from **Part F** (0.945g, 2.97mmol) was taken up in thionyl chloride (4.5mL) and the mixture was heated at 80°C for 40min. After evaporation to dryness, the acid chloride was dissolved in dry THF (8mL) and cooled to -78°C. A 1Molar solution of lithium tri-tert-butoxyaluminum hydride in THF
30 (3.0mL, 3.0mmol) was added drop wise. After 45min the cold reaction was quenched with 1M HCl (5mL), extracted into ethyl acetate, and purified by flash column, eluting with dichloromethane followed by 1% methanol/dichloromethane to give 0.635 g (71%).

Part H. Preparation of 1-(3-tert-butyl-4-methoxy-5-(5-nitrobenzo[d]oxazol-2-yl)phenyl) pyrimidine-2,4(1H,3H)-dione.

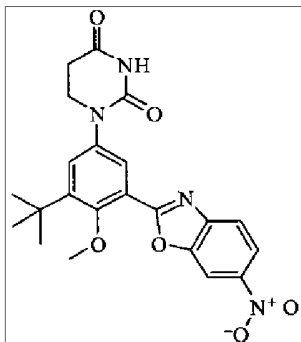
[0469] The product from **Part G** (400mg, 1.323mmol), 2-amino-4-nitrophenol (204mg, 1.323mmol), Charcoal (Darco KB, 191mg, 15.88mmol) and toluene (50mL) were added to a flask and the mixture was heated to 120°C, and stirred open to the air for 48h. Filtered through Celite and concentrated under vacuum. Purification by silica gel column chromatography eluting with CH₂Cl₂/MeOH gave the title compound (300mg, 52%).

10

Part I. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]oxazol-5-yl)methanesulfonamide.

[0470] To the product from **Part H** (300mg, 0.687mmol), iron (192mg, 3.44 mmol), and ammonium chloride (55mg, 1.031mmol) was added to a mixture of THF (15mL), EtOH (15mL) and water (4.5mL). The resultant solution was heated to 90°C for 45min, and cooled. Filtered through Celit, washed with ethanol, and concentrated under vacuum. The solid was dissolved in ethyl acetate, and washed with water. Dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with CH₂Cl₂/MeOH provided the aniline. The solid (75mg, 0.185mmol) was dissolved in CH₂Cl₂ (5mL), and pyridine (0.045mL, 0.554mmol) and methanesulfonyl chloride (0.025mL, 0.323mmol) were added and stirred at room temperature for 16h. CH₂Cl₂ was added followed by washing with a 1N HCl. Dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with CH₂Cl₂/MeOH provided the title compound as a solid (9.8mg, 3%, two steps). ¹H NMR (300MHz, DMSO-d₆): δ 11.46 (s, 1H), 9.85 (s, 1H), 7.91 (d, J=2.2Hz, 1H), 7.81 (dd, J=9.9, 8.8Hz, 2H), 7.68 (d, J=2.2Hz, 1H), 7.56 (d, J=2.6Hz, 1H), 7.33 (dd, J=8.8, 1.8Hz, 1H), 5.68 (d, J=7.7Hz, 1H), 3.64 (s, 3H), 3.00 (s, 3H), 1.42 (s, 9H). MS: m/z 485 (M+H)⁺.

25
30**Example 6. Preparation of 1-(3-tert-butyl-4-methoxy-5-(6-nitrobenzo[d]oxazol-2-yl)phenyl) dihydropyrimidine-2,4(1H,3H)-dione (compound IA-L0-2.6).**

[0471]**Part A. Preparation of 3-(3-tert-butyl-4-methoxy-5-(methoxycarbonyl)phenylamino) propanoic acid.**

5

[0472] The product from **Example 5, Part C** (16.44g, 69.3mmol) was dissolved in toluene (200mL). This mixture was heated to reflux and acrylic acid added over time (1mL of acrylic acid added every 3h, 5.23mL total, 76.2mmol). The mixture was then refluxed for 24h. The mixture was then cooled and concentrated under vacuum to dryness to yield an oil as the crude title compound that was used directly in the next reaction.

15

Part B. Preparation of methyl 3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxybenzoate.

[0473] The product from **Part A** (21.43g, 69.3mmol), urea (10.4g, 173mmol) and acetic acid (glacial, 200mL) were added together. The mixture was then heated to 120°C for 18.5h followed by concentration under vacuum to dryness to an oil. To this oil was added methanol (13mL), and ethyl acetate (350mL). The resultant mixture was allowed to stand for 24-48h whereby a precipitate formed. The resulting solid was filtered off and washed with a small amount of methanol (10mL) and then air dried to yield the title compound as a solid (15.26g, 66%).

Part C. Preparation of 3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxy benzoic acid.

[0474] The product from **Part B** (4.52g, 13.52mmol), methanol (70mL), and tetrahydrofuran (70mL) were added together. The mixture was then stirred vigorously until a homogenous solution resulted. Once homogenous, a solution of aqueous sodium hydroxide (1.0M, 68mL) was added. The mixture was then stirred for 12h, the mixture was then concentrated under vacuum to remove the organic solvent, followed by the addition of aqueous hydrochloric acid (1.0M, 80mL) that resulted in solid formation. The mixture was then concentrated under vacuum. To this material was added hydrochloric acid (12M, 100mL) and the resultant material heated to 100°C for 1.5h. The reaction was then cooled and water added. The resulting solid was filtered, washed with water, and dried to yield the title compound as a solid (3.55g, 82%).

Part D. Preparation of 3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxy benzaldehyde.

[0475] The product obtained in **Part C** (4.07g, 12.71mmol) and thionyl chloride (40.82mL, 559mmol) were combined and the mixture was refluxed for 2h, followed by concentration under vacuum to provide a light yellow colored solid product. The solid was dissolved in tetrahydrofuran (125mL), the solution cooled to -78°C and LiAl(O*t*Bu)₃ (1M, 14mL) was added slowly over 10min while maintaining the temperature at -78°C. The mixture was stirred at 78°C for 2h. The reaction was quenched with hydrochloric acid (aq., 1M, 25mL) at -78°C. The mixture was warmed to room temperature and ethyl acetate was added. The layers were separated and the aqueous layer was washed with ethyl acetate. The organic extracts were combined and washed with half saturated sodium bicarbonate solution. The organic layer was dried, filtered and concentrated under vacuum to yield a solid as the title compound (3.73g, 96%).

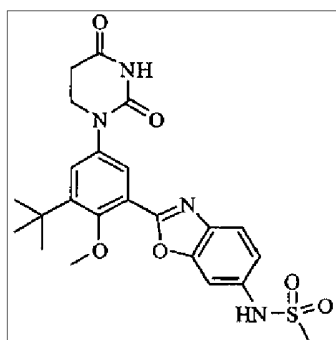
Part E. Preparation of 1-(3-tert-butyl-4-methoxy-5-(6-nitrobenzo[d]oxazol-2-yl)phenyl)dihydro pyrimidine-2,4(1H,3H)-dione.

[0476] A mixture of the product from **Part D** (75mg, 0.246mmol), 2-amino-5-nitrophenol (38mg, 0.0246mmol) and Darco KB charcoal (excess) was refluxed

in toluene (10mL) for 24h under exposure to atmospheric oxygen. Cooled, filtered and purified by reverse phase HPLC chromatography eluting with a 40-100% gradient of acetonitrile in water (0.1% TFA) to provide the title compound as a solid (96mg, 64%). ¹H NMR (300 MHz, DMSO-d₆): δ 1.42 (s, 9 H) 2.74 (t, J=6.80 Hz, 2 H) 3.66 (s, 3 H) 3.82 - 3.88 (m, 2 H) 7.56 (d, J=2.57 Hz, 1 H) 7.91 (d, J=2.57 Hz, 1 H) 8.09 (d, J=8.82 Hz, 1 H) 8.37 (dd, J=8.82, 2.21 Hz, 1 H) 8.84 (d, J=2.21 Hz, 1 H) 10.44 (s, 1 H). MS ESI+ (439) (M+H)+.

Example 7. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]oxazol-6-yl)methanesulfonamide (compound IA-L0-2.5).

[0477]



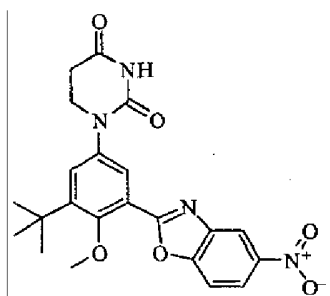
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[0478] The product from **Example 6** (96mg, 0.219mmol) was reacted with iron (0.614g, 1.10mmol), and ammonium chloride (0.176g, 0.329mmol) in the presence of a mixture of tetrahydrofuran (5mL), ethanol (5mL) and water (3mL). The slurry was heated to 90°C for 45min, cooled to ambient temperature. Filtered through a pad of celite (10g), washed with ethanol (20mL), and the filtrate was concentrated under vacuum to a solid. The resulting solid was dissolved in ethyl acetate and washed with water. Dried over Na₂SO₄, filtered and concentrated under vacuum to a yellow solid, providing the corresponding aniline. The solid was dissolved in dichloromethane (10mL), pyridine (0.670mL, 0.657mmol) and methanesulfonyl chloride (0.221mL, 0.329mmol) were added and the solution stirred at room temperature 16h. CH₂Cl₂ was added followed by washing with a 1N aq. HCl solution. Dried over Na₂SO₄, filtered and concentrated under

vacuum. Purification by silica gel column chromatography eluting with 98:2 CH₂Cl₂:MeOH gave the title compound as a solid (25mg, 21%, two steps). ¹H NMR (300 MHz, DMSO-d₆): δ 1.41 (s, 9 H) 2.73 (t, J=6.62 Hz, 2 H) 3.06 (s, 3 H) 3.61 (s, 3 H) 3.83 (t, J=6.62 Hz, 2 H) 7.28 (dd, J=8.46, 1.84 Hz, 1 H) 7.48 (d, J=2.57 Hz, 1 H) 7.65 (d, J=1.84 Hz, 1 H) 7.80 (d, J=1.47 Hz, 1 H) 7.82 (d, J=4.04 Hz, 1 H) 10.03 (s, 1 H) 10.41 (s, 1 H). MS ESI+ (487) (M+H)+.

Example 8. Preparation of 1-(3-tert-butyl-4-methoxy-5-(5-nitrobenzo[d]oxazol-2-yl)phenyl) dihydropyrimidine-2,4(1H,3H)-dione (compound IA-L0-2.7).

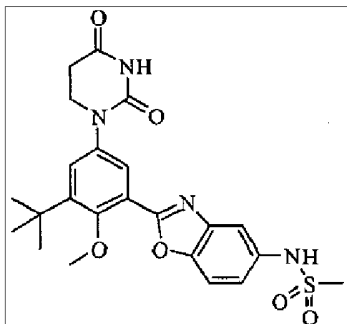
10

[0479]

[0480] The product from **Example 6, Part D** (150mg, 0.493mmol) was reacted with 2-amino-4-nitrophenol (76mg, 0.493mmol) according to the procedures from **Example 6, Part E** to provide the title compound as a solid (70mg, 32%). ¹H NMR (300 MHz, DMSO-d₆): δ 1.42 (s, 9 H) 2.74 (t, J=6.80 Hz, 2 H) 3.65 (s, 3 H) 3.85 (t, J=6.62 Hz, 2 H) 7.55 (d, J=2.57 Hz, 1 H) 7.89 (d, J=2.94 Hz, 1 H) 8.12 (d, J=8.82 Hz, 1 H) 8.40 (dd, J=9.01, 2.39 Hz, 1 H) 8.76 (d, J=2.21 Hz, 1 H) 10.43 (s, 1 H). MS ESI+ (439) (M+H)+.

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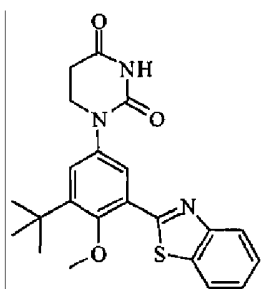
Example 9. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]oxazol-5-yl)methanesulfonamide (compound IA-L0-2.8).

[0481]

[0482] The product from **Example 8** (65mg, 0.148mmol) was reacted according to the procedures from **Example 7** to provide the title compound as a solid (42mg, 44%). ¹H NMR (300 MHz, DMSO-d₆): δ 1.41 (s, 9 H) 2.73 (t, J=6.43 Hz, 2 H) 3.01 (s, 3 H) 3.60 (s, 3 H) 3.83 (t, J=6.43 Hz, 2 H) 7.31 (dd, J=8.64, 2.02 Hz, 1 H) 7.49 (d, J=2.94 Hz, 1 H) 7.56 (d, J=2.21 Hz, 1 H) 7.67 (d, J=2.21 Hz, 1 H) 7.81 (s, 1 H) 9.82 (s, 1 H) 10.41 (s, 1 H). MS ESI+ (487) (M+H)+.

10

Example 10. Preparation of 1-(3-(benzo[d]thiazol-2-yl)-5-tert-butyl-4-methoxyphenyl)dihydro pyrimidine-2,4(1H,3H)-dione (compound IA-L0-2.3).

[0483]

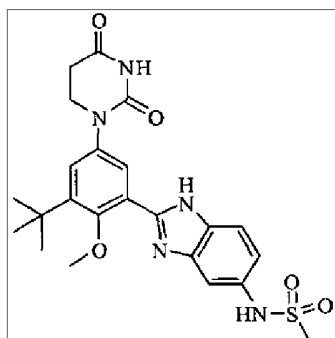
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[0484] The product from **Example 6, Part D** (75mg, 0.246mmol) was reacted with 2-aminobenzene thiol (0.026mL, 0.246mmol) according to the procedures from **Example 6, Part E** to provide the title compound as a solid (25mg, 25%). ¹H NMR (300 MHz, DMSO-d₆): δ 1.44 (s, 9 H) 2.73 (t, J=6.43 Hz, 2 H) 3.62 (s, 3 H) 3.84 (t, J=6.62 Hz, 2 H) 7.46 (d, J=2.57 Hz, 1 H) 7.48 - 7.60 (m, 2 H) 7.86 (d, J=2.57 Hz, 1 H) 8.13 (dd, J=17.28, 7.72 Hz, 2 H) 10.40 (s, 1 H). MS ESI+ (410) (M+H)+.

20

Example 11. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)methanesulfonamide (compound IA-L0-2.1).

5 [0485]



Part A. Preparation of N-(3,4-dinitrophenyl)methanesulfonamide.

10 [0486] A mixture of 3,4-dinitroaniline (5.27g, 28.8mmol), methanesulfonyl chloride (3.36mL, 43.1mmol) and pyridine (5.82mL, 71.9mmol) in CH₂Cl₂ (100mL) was stirred for 24h. Mixture was concentrated under vacuum to provide a crude semi-solid title compound that was used without further purification.

Part B. Preparation of N-(3,4-diaminophenyl)methanesulfonamide.

15

[0487] The product from **Part A** (7.51g, 28.8mmol) was reacted with iron (16g, 288mmol) and NH₄Cl (3.84g, 71.9mmol) in refluxing CH₃OH (100mL) and water (20mL) for 2 h. Filtered through celite and concentrated under vacuum. Purification by silica gel column chromatography eluting with MeOH/CH₂Cl₂ provided
20 the title compound as a dark semi-solid (0.5g, 8%).

Part C. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxy phenyl)-1H-benzo[d]imidazol-5-yl)methanesulfonamide.

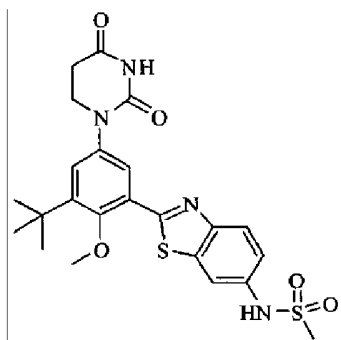
25 [0488] A mixture of the product from **Example 6, Part D** (200mg, 0.657mmol) was reacted with the product from **Part B** (132mg, 0.657mmol) according to the procedures from **Example 6, Part E** to provide the title compound as a solid

(112mg, 34%). ^1H NMR (300 MHz, DMSO- d_6): δ 1.43 (s, 9 H) 2.72 (t, $J=6.62$ Hz, 2 H) 2.93 (s, 3 H) 3.44 (s, 3 H) 3.82 (t, $J=6.43$ Hz, 2 H) 7.07 - 7.14 (m, 1 H) 7.38 (d, $J=2.57$ Hz, 1 H) 7.48 - 7.64 (m, 2 H) 7.72 (d, $J=2.57$ Hz, 1 H) 9.57 (s, 1 H) 10.38 (s, 1 H) 12.55 (s, 1 H)-MS ESI+ (486) (M+H)+.

5

Example 12. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]thiazol-6-yl)methanesulfonamide (compound IA-L0-2.2).

10 [0489]



Part A. Preparation of N-(3-chloro-4-nitrophenyl)methanesulfonamide.

[0490] A mixture of 3-chloro-4-nitroaniline (4.85g, 28.1mmol), methanesulfonyl chloride (3.29mL, 42.2mmol) and pyridine (6.82mL, 84mmol) in THF (100mL) was stirred for 24h. Poured in 1M HCl (500mL). The resulting precipitate was filtered and air-dried to provide the title compound as a solid (7.03g, 100%).

Part B. Preparation of N-(3-(4-methoxybenzylthio)-4-nitrophenyl)methanesulfonamide.

[0491] A mixture of the product from **Part A** (7.0g, 27.9mmol), (4-methoxyphenyl)methanethiol (3.89mL, 27.9mmol) and K_2CO_3 (11.58g, 84mmol) in DMF was heated at 100°C for 12h. Cooled and poured into 1M HCl (800mL). The resulting precipitate was filtered and air-dried to provide the title compound as a yellow solid (6.98g, 68%).

Part C. Preparation of N-(4-amino-3-(4-methoxybenzylthio)phenyl)methanesulfonamide.

5 [0492] The product from **Part B** (6.98g, 19.0mmol) was reacted according to the procedures from **Example 11, Part B** to provide the title compound as a yellow semi-solid (4.44 g, 69%).

Part D. Preparation of N,N'-(3,3'-disulfanediybis(4-amino-3,1-phenylene))-dimethane-sulfonamide.

10

[0493] The product from **Part C** (708mg, 2.09mmol) was reacted with mercuric (II) acetate (667mg, 2.09mmol), anisole (0.457mL, 4.18mmol) and TFA (10mL) at 0°C for 45min. Concentrated under vacuum and dissolved in MeOH. Hydrogen sulfide gas was bubbled into solution for 1h followed by filtration and concentration under vacuum. Purification by silica gel chromatography eluting with EtOAc/hexane gave the title compound as a yellowish solid (340mg, 75%).

15

Part E. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1-(2H)-yl)-2-methoxyphenyl)benzo[d]thiazol-6-yl)methanesulfonamide.

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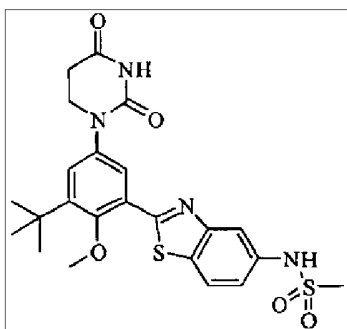
[0494] The product from **Part D** (100mg, 0.23mmol) was reacted with the product from **Example 6, Part D** (140mg, 0.46mmol), triphenylphosphine (60.4mg, 0.23mmol) and 4-methylbenzene- sulfonic acid

25 [0495] (0.0054mL, 0.046mmol) in refluxing toluene for 3h. Concentrated under vacuum and purified by reverse phase HPLC chromatography eluting a 40-100% gradient of acetonitrile in water (0.1% TFA) to give the title compound as a solid (99mg, 43%). ¹H NMR (300 MHz, DMSO-d₆): δ 1.43 (s, 9 H) 2.73 (t, J=6.62 Hz, 2 H) 3.07 (s, 3 H) 3.63 (s, 3 H) 3.83 (t, J=6.62 Hz, 2 H) 7.39 (dd, J=8.82, 2.21 Hz, 1 H) 7.45 (d, J=2.57 Hz, 1 H) 7.83 (d, J=2.57 Hz, 1 H) 7.95 (d, J=2.21 Hz, 1 H) 8.05 (d, J=8.82 Hz, 1 H) 10.03 (s, 1 H) 10.39 (s, 1 H). MS ESI+ (503) (M+H)⁺.

30

Example 13. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]thiazol-5-yl)methanesulfonamide (compound IA-L0-2.4).

5 [0496]



Part A. Preparation of N-(4-chloro-3-nitrophenyl)methanesulfonamide.

[0497] A mixture of 4-chloro-3-nitroaniline (5.0g, 29mmol), methanesulfonyl
 10 chloride (2.37mL, 30.4mmol) and pyridine (5.9mL, 72.4mmol) in THF (100mL)
 was stirred for 24h. Poured in 1M HCl (500mL). The resulting precipitate was fil-
 tered and air-dried to provide the title compound as a solid (6.7g, 92%).

Part B. Preparation of N-(4-(4-methoxybenzylthio)-3-nitrophenyl)methane-
 15 **sulfonamide.**

[0498] A mixture of the product from **Part A** (3.0g, 12mmol), (4-methoxyphe-
 nyl)methanethiol (1.67mL, 12mmol) and K₂CO₃ (4.96g, 36mmol) in DMF was
 heated at 100°C for 12h. Cooled and poured into 1M HCl (800mL). The resul-
 20 ting precipitate was filtered and air-dried to provide the title compound as a yel-
 low solid (1.95g, 44.2%).

Part C. Preparation of N-(3-amino-4-(4-methoxybenzylthio)phenyl)metha-
nesulfonamide.

25

[0499] The product from **Part B** (1.43g, 3.88mmol) was reacted according to the procedures from **Example 11, Part B** to provide the title compound as a white solid (1.31g, 100%).

5 **Part D. Preparation of N,N'-(4,4'-disulfanediybis(3-amino-4,1-phenylene))-dimethane-sulfonamide.**

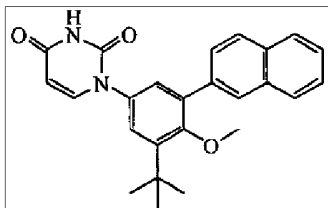
[0500] The product from **Part C** (75mg, 0.222mmol) was reacted with mercuric (II) acetate (70.6mg, 0.222mmol), anisole (0.048mL, 0.443mmol) and TFA (10mL) at 0°C for 45min. Concentrated under vacuum and dissolved in MeOH.
10 Hydrogen sulfide gas was bubbled into solution for 1h followed by filtration and concentration under vacuum. Purification by silica gel column chromatography eluting with EtOAc/Hexane gave the title compound as a yellowish solid (34mg, 71 %).

15

Part E. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxy phenyl)benzo[d]thiazol-5-yl)methanesulfonamide.

[0501] The product from **Part D** (50mg, 0.115mmol) was reacted with the product from **Example 6, Part D** (70mg, 0.230mmol), triphenylphosphine (30.2mg, 0.115mmol) and 4-methylbenzenesulfonic acid (0.00267mL, 0.023mmol) in refluxing toluene for 3h. Concentrated under vacuum and purified by reverse phase HPLC chromatography eluting with a 40-100% gradient of acetonitrile in water (0.1% TFA) to give the title compound as a solid (40mg, 33%). ¹H NMR
20 (300 MHz, DMSO-d₆): δ 1.43 (s, 9 H) 2.73 (t, J=6.80 Hz, 2 H) 3.05 (s, 3 H) 3.63 (s, 3 H) 3.84 (t, J=6.62 Hz, 2 H) 7.35 (dd, J=8.64, 2.02 Hz, 1 H) 7.46 (d, J=2.94 Hz, 1 H) 7.86 (d, J=2.94 Hz, 1 H) 7.92 (d, J=1.84 Hz, 1 H) 8.10 (d, J=8.46 Hz, 1 H) 9.98 (s, 1 H) 10.40 (s, 1 H). MS ESI+ (503) (M+H)+.

30 **Example 14. Preparation of 1-(3-tert-butyl-4-methoxy-5-(naphthalen-2-yl)-phenyl) pyrimidine-2,4(1H,3H)-dione (compound IB-L0-2.1).**

[0502]**Part A. Preparation of tert-butyl 3-tert-butyl-4-methoxy-5-(naphthalen-2-yl)phenyl carbamate.**

5

[0503] In a resealable Schlenk tube, a solution of the product from **Example 1, Part H** (200mg, 0.56mmol), naphthalene-2-boronic acid (144mg, 0.84mmol), and 1.0M sodium carbonate solution (558 μ L, 0.56mmol) in toluene (2.8mL) was degassed by nitrogen sparge for 10min. The mixture was treated with 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride dichloromethane complex (14mg, 0.017mmol) and degassing was continued for another 5min. The Schlenk tube was sealed and warmed at 95°C for 18h. Cooled and diluted with ethyl acetate and water. Treated with Darco G-60 and filtered through celite. Filtrate was extracted with water (2 x) and with brine. Dried over Na₂SO₄, filtered and concentrated. Purification by silica gel column chromatography eluting with 10-75 % EtOAc in hexanes gave the title compound as an oil (210mg, 93 %).

15

Part B. Preparation of 3-tert-butyl-4-methoxy-5-(naphthalen-2-yl)aniline.

[0504] The product from **Part A** (210mg, 0.52mmol) was dissolved in 4N HCl in dioxane (4.0mL) and stirred at room temperature for 1h. Concentration under vacuum afforded a solid, which was suspended in ethyl acetate and stirred with saturated sodium bicarbonate solution. The organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum to give the title compound, as a brown oil (111mg, 70 %).

25

Part C. Preparation of (E)-N-(3-tert-butyl-4-methoxy-5-(naphthalen-2-yl)phenyl)carbonyl-3-methoxyacrylamide.

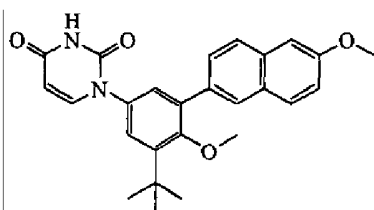
[0505] A solution of the product from **Part B** (111mg, 0.36mmol) in dry DMF (2.9mL) at -20°C was treated with (E)-3-methoxyacryloyl isocyanate solution (0.66mL, of 0.55M in benzene, 0.36mmol) followed by gradual warming to room temperature. After stirring for 30min, the mixture was cooled again to -20°C and more (E)-3-methoxyacryloyl isocyanate solution (1.0mL, 0.55mmol) was added. After warming again to room temperature for 30min, the reaction was complete. Diluted with EtOAc and extracted with water and brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with 10-100 % EtOAc in hexane gave the title compound as a light yellow oil (144mg, 92%).

Part D. Preparation of 1-(3-tert-butyl-4-methoxy-5-(naphthalen-2-yl)phenyl)pyrimidine-2,4(1H,3H)-dione.

[0506] A suspension of the product from **Part C** (144mg, 0.33mmol) in 2:2:1 ethanol-water-THF (15mL) was treated with 1N sulfuric acid solution (3.0mL) followed by warming at 100°C for 24h. Cooled and diluted with EtOAc and extracted with water and brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with 10-100% EtOAc in hexane gave the title compound as a white solid (62mg, 47 %). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.42 (s, 1 H), 8.08 (s, 1 H), 7.90 - 8.04 (m, 3 H), 7.81 (d, J=7.72 Hz, 1 H), 7.72 (d, J=8.46 Hz, 1 H), 7.56 (dd, J=6.25, 3.31 Hz, 2 H), 7.39 (d, J=2.57 Hz, 1 H), 7.33 (d, J=2.57 Hz, 1 H), 5.65 (d, J=7.72 Hz, 1 H), 3.24 (s, 3 H), 1.43 (s, 9 H). MS +ESI m/z (rel abundance): 401 (100, M+H), 418 (30, M+NH₄).

Example 15. Preparation of 1-(3-tert-butyl-4-methoxy-5-(6-methoxynaphthalen-2-yl)phenyl) pyrimidine-2,4(1H,3H)-dione (compound IB-L0-2.2).

[0507]



Part A. Preparation of tert-butyl 3-tert-butyl-4-methoxy-5-(6-methoxynaphthalen-2-yl)phenyl carbamate.

5 [0508] The product from **Example 1, Part H** (158mg, 0.44mmol) was reacted with 6-methoxy-naphthalen-2-ylboronic acid (107mg, 0.52mmol) according to the procedures from **Example 14, Part A** to provide the title compound as a white solid (92mg, 47 %).

10 **Part B. Preparation of 3-tert-butyl-4-methoxy-5-(6-methoxynaphthalen-2-yl)aniline.**

[0509] The product from **Part A** (92mg, 0.21mmol) was reacted according to the procedures from **Example 14, Part B** to provide the title compound as a pink solid (71 mg, 99%).

15

Part C. Preparation of (E)-N-(3-tert-butyl-4-methoxy-5-(6-methoxynaphthalen-2-yl)phenyl carbamoyl)-3-methoxyacrylamide.

20 [0510] The product from **Part B** (71mg, 0.21mmol) was reacted according to the procedures from **Example 14, Part C** to provide the title compound as a buff-colored solid (58mg, 59 %).

25

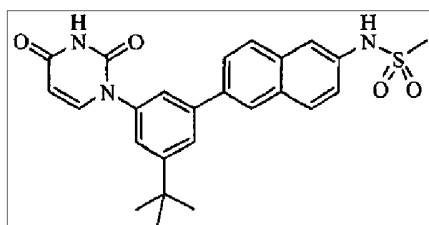
Part D. Preparation of 1-(3-tert-butyl-4-methoxy-5-(6-methoxynaphthalen-2-yl)phenyl) pyrimidine-2,4(1H,3H)-dione.

30 [0511] A solution of the product from **Part C** (58mg, 0.13mmol) in 2:1:1 ethanol-THF-water (4.0mL) was treated with 1.0M sulfuric acid solution (3.0mL) followed by warming at 95°C for 24h. Cooled and diluted with EtOAc. Extracted with water and brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with 10-100 % EtOAc in hexanes gave the product as a faint pink solid (28mg, 52%). ¹H NMR (300 MHz, DMSO-d₆): δ 11.41 (s, 1 H), 8.00 (s, 1 H), 7.91 (dd, J=8.64, 4.60 Hz, 2 H), 7.80 (d, J=7.72 Hz, 1 H), 7.67 (d, J=8.82 Hz, 1 H), 7.34 - 7.47 (m, 2 H), 7.21 - 7.32

(m, 1 H), 7.20 (dd, $J=9.01, 2.39$ Hz, 1 H), 5.65 (d, $J=7.72$ Hz, 1 H), 3.90 (s, 3 H), 3.24 (s, 3 H), 1.42 (s, 9 H). MS +ESI m/z (rel abundance): 431 (100, M+H), 448 (45, M+NH₄).

- 5 **Example 16. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl) phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.8).**

[0512]



10

Part A. Preparation of 2-bromo-4-tert-butyl-6-nitroaniline.

[0513] A suspension of 4-tert-butyl-2-nitroaniline (1.033g, 5.32mmol) in glacial acetic acid (7.8mL) was warmed with a heat gun until all solids had dissolved.

- 15 The solution was then cooled and treated portion wise with pyridinium hydrobromide perbromide (1.96g, 6.12mmol). After addition, the solution was stirred at room temperature for 1h. The mixture was added to water (50mL) and treated with a small amount of sodium sulfite. After stirring for 30min, the precipitate was collected by filtration. The solid obtained was washed with water and dissolved in EtOAc. Washed with water and brine. Dried over Na₂SO₄, filtered and concentrated under vacuum to provide the title compound as a yellow-orange solid (1.36g,94%).
- 20

Part B. Preparation of 1-bromo-3-tert-butyl-5-nitrobenzene.

25

[0514] A solution of tert-butyl nitrite (300μL of 90%, 261mg, 2.27mmol) in dry DMF (4mL) was warmed at 50°C and was treated with a solution of the product from **Part A** (414mg, 1.52mmol) in DMF (3.5mL). After a few minutes stirring, the solution began to bubble vigorously. After warming at 50°C for 1h, additional

(300 μ L) tert-butyl nitrite was added followed by warming at 50°C for 1h. After 18h at room temperature, tert-butyl nitrite (1.25mL) was added and the mixture warmed at 50°C for 2h. Cooled and diluted with EtOAc. Washed with water and brine. Dried over Na₂SO₄, filtered and concentrated under vacuum. Purification
5 by silica gel column chromatography eluting with 5-40 % ethyl acetate in hexanes gave the title compound as a light yellow oil (159mg, 41 %).

Part C. Preparation of 3-bromo-5-tert-butylaniline.

10 **[0515]** A solution of the product from **Part B** (770mg, 2.98mmol) in 3:3:1 methanol-water-THF (14.9mL) was treated with ammonium chloride (239mg, 4.47 mmol) and iron powder (833mg, 14.92mmol) followed by warming at reflux for 8h. Diluted with EtOAc and water and filtered through celite. The filtrate was extracted with water and brine. Dried over Na₂SO₄, filtered and concentrated un-
15 der vacuum to give the title compound as a yellow oil.

Part D. Preparation of (E)-N-(3-bromo-5-tert-butylphenylcarbonyl)-3-methoxy acrylamide.

20 **[0516]** A solution of the product from **Part C** (681mg, 2.99mmol) in dry DMF (23mL) at -30°C was treated drop wise with a 0.4M solution of (E)-3-methoxyacryloyl isocyanate in benzene (14.9mL, 5.96mmol). The solution was stirred at -30°C for 30min followed by warming gradually to room temperature, and then stirred for 18h. Diluted with EtOAc and washed with water and brine. Dried over
25 Na₂SO₄, filtered and concentrated under vacuum to afford a yellow solid, which was triturated with ether-hexanes and collected by filtration. Dried under vacuum to give the title compound as a light brown powder. (951mg, 90 %).

**Part E. Preparation of 1-(3-bromo-5-tert-butylphenyl)pyrimidine-2,4(1H,-
30 3H)-dione.**

[0517] A suspension of the product from **Part D** (951mg, 2.68mmol) in ethanol (25mL) was treated with a solution of concentrated sulfuric acid (2.60mL, 4.78g,

18.22mmol) in water (13.4mL) followed by warming at 100°C for 1h. Cooled and concentrated to remove ethanol. Cooled to 0°C and the precipitate was collected by filtration and washed with water. Dried under vacuum to give the title compound as an orange solid (619mg, 72 %).

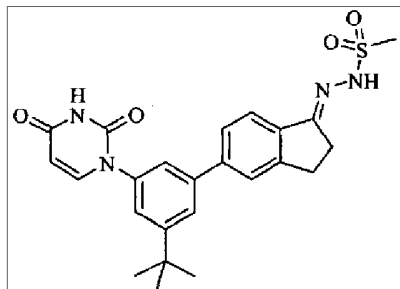
5

Part F. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)naphthalen-2-yl)methanesulfonamide.

[0518] In a microwave tube, a suspension of the product from **Part E** (104mg, 0.32mmol), the product from **Example 2A, Part B** (134mg, 0.39mmol), and 1.0M sodium carbonate solution (386µL, 0.39mmol) in 1:1 ethanol-toluene (2.1mL) was degassed by nitrogen sparge for 10min. The solution was treated with 1,1'-bis(di-tert-butylphosphino)ferrocene-palladium (II) dichloride (20mg, 0.031mmol) and degassing was continued for another 5min. The mixture was heated at 100°C in the microwave for 30min. Diluted with EtOAc and washed with water and brine. Dried over Na₂SO₄ and treated with (3-mercapto propyl) silica gel for 30min. Filtered and concentrated under vacuum to afford an amber solid, which was triturated with ether-hexanes. Collected the solid by filtration and dried under vacuum to provide the title compound (81 mg, 54 %). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.46 (s, 1 H) 10.05 (s, 1H), 8.25 (s, 1 H) 7.98 (dd, J=11.58, 9.01 Hz, 1 H) 7.86 - 7.93 (m, 1 H) 7.78 - 7.85 (m, 2 H) 7.72 (s, 1 H) 7.67 (s, 1 H) 7.31 - 7.51 (m, 2 H) 5.70 (dd, J=7.72, 2.21 Hz, 1 H) 3.08 (s, 3 H) 1.39 (s, 9 H).

Example 17. Preparation of (E)-N'-(5-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide (compound IB-L0-2.7).

[0519]



Part A. Preparation of 1-(3-tert-butyl-5-(1-oxo-2,3-dihydro-1H-inden-5-yl)phenyl)pyrimidine-2,4(1H,3H)-dione.

5

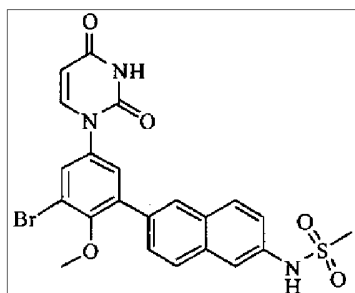
[0520] In a microwave tube, a suspension of the product from **Example 16, Part E**, the product from **Example 4, Part A** (144mg, 0.56mmol), 1.0M sodium carbonate solution (557 μ L, 0.56mmol) in 1:1 ethanol-toluene (3.0mL) was degassed by nitrogen sparge for 15min. 1,1'-Bis(di-t-butylphosphino) ferrocene palladium (II) chloride complex (15mg, 0.023 mmol) was added and degassing was continued for an additional 5 min. The tube was sealed and the mixture was heated at 100°C in the microwave for 30 min. Diluted with EtOAc and water. Washed with 1M citric acid solution, water, and brine. The organic was stirred with (3-mercaptopropyl) silica gel for 1h. Dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with 10-100 % EtOAc in hexanes gave the title compound as an off white solid (86mg, 50%).

Part B. Preparation of (E)-N'-(5-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide.

[0521] The product from **Part A** (80mg, 0.21mmol) was reacted according to the procedures from **Example 4, Part C** to provide the title compound as a white solid (73mg, 73 %). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.44 (s, 1 H) 9.92 (s, 1 H) 7.64 - 7.98 (m, 5 H) 7.57 (s, 1 H) 7.45 (s, 1 H) 5.68 (d, J=7.72 Hz, 1 H) 3.00 - 3.20 (m, 5 H) 2.85 (d, J=12.50 Hz, 2 H) 1.36 (s, 9 H). MS +ESI m/z (rel abundance): 467 (100, M+H).

Example 18. Preparation of N-(6-(3-bromo-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.69).

5 [0522]



Part A. Preparation of 2-bromo-4,6-diiodophenol.

10 [0523] A 1L round-bottom flask was charged with 2-bromophenol (Aldrich, 8.65 g, 50mmol) and methanol (100ml) to give a colorless solution. Sodium hydroxide (2.40g, 60.0mmol) was added and stirred until the hydroxide pellets had dissolved. The solution was cooled in an ice water bath and sodium iodide (5.6g, 37.4mmol) was added followed by drop-wise addition of sodium hypochlorite
15 (17mL, 27.5mmol) to give a transparent brown/red solution and gradual precipitation of a thick, white solid. The addition of sodium iodide and bleach was repeated 3 times to give an orange mixture that was stirred for 2h, treated with a solution of sodium thiosulfate in water (20g in 100mL), stirred for 15min and treated drop-wise with concentrated HCl to a constant pH of 1. The mixture was
20 stirred for 15min and filtered to collect a white solid that was washed repeatedly with water and dried to constant mass (14.7g, 69%).

Part B. Preparation of 1-bromo-3,5-diiodo-2-methoxybenzene.

25 [0524] A 500mL round-bottom flask was charged with the product from **Part A** (14.7g, 34.6mmol), iodomethane (2.70ml, 43.3mmol), and sodium hydroxide (2.101ml, 39.8mmol) in acetone (96ml) to give a tan solution. The mixture was stirred for 24h and concentrated. The residue was dissolved in ethyl acetate,

washed with water and saturated sodium chloride, dried over sodium sulfate, filtered and concentrated to give a white solid. The solid was recrystallized from hot hexane to give a white solid that was collected by filtration (12.3g, 81 %).

5 **Part C. Preparation of 1-(3-bromo-5-iodo-4-methoxyphenyl)pyrimidine-2,4-(1H,3H)-dione.**

[0525] A 250mL round-bottom flask was charged with the product from **Part B** (8.09g, 18.44mmol), pyrimidine-2,4(1H,3H)-dione (2.273g, 20.28mmol), N-(2-
10 cyanophenyl)picolinamide (0.823g, 3.69mmol), copper (I) iodide (0.351g, 1.844 mmol) and potassium phosphate (8.22g, 38.7mmol) in DMSO (70ml). The mixture was sealed, sparged with nitrogen for 15min and heated at 60°C for 16h. The mixture was partitioned with ethyl acetate and water. The organic layer was washed with 1M HCl, water, brine, dried with sodium sulfate, and filtered. The
15 filtrate was treated with 3-mercaptopropyl functionalized silica gel (Aldrich catalog # 538086), filtered through celite and evaporated to give an off-white solid (3.92g, 50%).

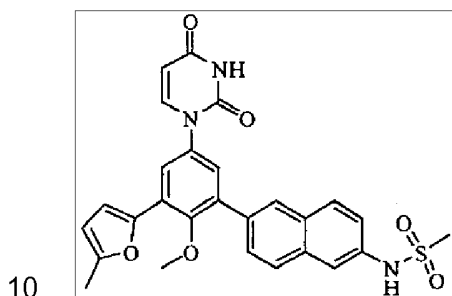
20 **Part D. Preparation of N-(6-(3-bromo-5-(2,4-dioxo-3,4-dihydropyrimidin-1-(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.**

[0526] To a 5mL microwave tube was added the product from **Part C** (212mg, 0.50mmol), the product from **Example 2A, Part B** (174mg, 0.50mmol), potassium phosphate (223mg, 1.05mmol), PA-Ph (CAS 97739-46-3, 4.38mg, 0.015
25 mmol) and tris(dibenzylideneacetone)dipalladium(0) (4.58mg, 5.00µmol) in tetrahydrofuran (3.0ml) and water (1.0ml). The tube was sealed and the mixture was sparged with nitrogen for 5min and then stirred for 24h. The reaction mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and
30 filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel (Aldrich catalog # 538086), filtered through celite and evaporated. The residue was triturated with methanol/ CH₂Cl₂ to give the title compound as a white solid (256mg, 51%). ¹H NMR(300 MHz, DMSO-D₆) δ ppm 3.08 (s, 3 H) 3.43 (s, 3 H)

5.68 (d, J=8.09 Hz, 1 H) 7.43 (dd, J=8.82, 2.21 Hz, 1 H) 7.60 (d, J=2.57 Hz, 1 H) 7.72 (m, 2 H) 7.82 (d, J=3.31 Hz, 1 H) 7.84 (d, J=1.84 Hz, 1 H) 7.96 (m, 2 H) 8.09 (s, 1 H) 10.07 (s, 1 H) 11.49 (s, 1 H). MS (ESI-) m/z 513.9, 515.9 (M-H)⁺.

- 5 **Example 19. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(5-methylfuran-2-yl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.58).**

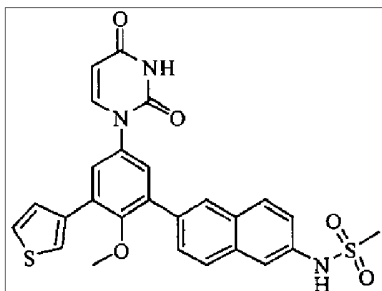
[0527]



- [0528] To a 5mL microwave tube was added the product of **Example 18** (52mg, 0.101 mmol), 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane (0.025ml, 0.121mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (3.28mg, 5.04 μ mol) and potassium phosphate (42.8mg, 0.201mmol) in THF (3.0ml) and water (1.0ml). The tube was sealed and the mixture was sparged with nitrogen for 5min and then heated at 50°C for 3h. The cooled mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and concentrated. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was purified by reverse phase chromatography to give the desired product as a white solid (23mg, 44%, m.p.174-178°C.) ¹H NMR (300 MHz, DMSO-D₆) δ ppm 2.38 (s, 3 H) 3.09 (s, 3 H) 3.33 (s, 3 H) 5.69 (dd, J=7.72, 2.21 Hz, 1 H) 6.30 (d, J=3.31 Hz, 1 H) 7.00 (d, J=3.31 Hz, 1 H) 7.43 (m, 2 H) 7.74 (d, J=2.57 Hz, 2 H) 7.78 (dd, J=8.46, 1.84 Hz, 1 H) 7.85 (d, J=8.09 Hz, 1 H) 7.97 (t, J=8.82 Hz, 2 H) 8.12 (s, 1 H) 10.05 (s, 1 H) 11.46 (d, J=2.21 Hz, 1 H). MS (ESI+) m/z 518 (M+H)⁺.
- 15
- 20
- 25

Example 20. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(thiophen-3-yl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.53).

5 [0529]



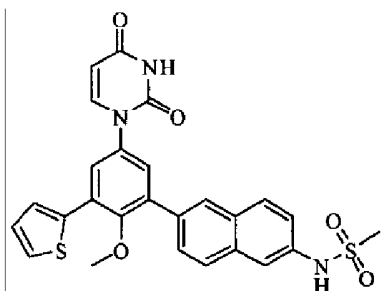
[0530] The title compound was prepared according to the procedure of **Example 19** substituting thiophen-3-ylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane to give a white solid (12mg, 23%). ¹H NMR (300 MHz, DMSO-D6) δ ppm 3.07 (s, 3 H) 3.22 (s, 3 H) 5.69 (d, J=7.72 Hz, 1 H) 7.41 (dd, J=8.64, 2.02 Hz, 1 H) 7.50 (d, J=2.94 Hz, 1 H) 7.59 (dd, J=5.13, 1.08 Hz, 1 H) 7.69 (m, 3 H) 7.76 (dd, J=8.64, 1.65 Hz, 1 H) 7.89 (d, J=7.72 Hz, 1 H) 7.95 (m, 3 H) 8.09 (s, 1 H) 10.05 (s, 1 H) 11.47 (s, 1 H). MS (ESI+) *m/z* 520 (M+H)⁺.

15

Example 21. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(thiophen-2-yl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.61).

20

[0531]

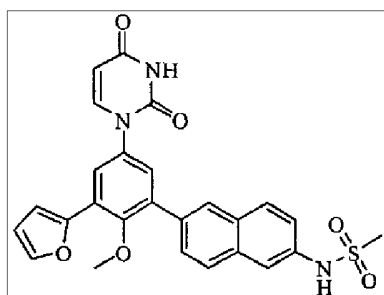


[0532] The title compound was prepared according to the procedure of **Exam-**

ple 19 substituting thiophen-2-ylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane to give a white solid (8mg, 15%). ¹H NMR (300 MHz, DMSO-D6) δ ppm 3.08 (s, 3 H) 3.30 (s, 3 H) 5.70 (d, J=8.09 Hz, 1 H) 7.19 (dd, J=5.33, 3.86 Hz, 1 H) 7.42 (dd, J=8.82, 2.21 Hz, 1 H) 7.49 (d, J=2.57 Hz, 1 H) 7.69 (dd, J=5.15, 1.20 Hz, 1 H) 7.80 (m, 3 H) 7.88 (d, J=7.72 Hz, 1 H) 7.92 (d, J=2.57 Hz, 1 H) 7.98 (m, 2 H) 8.12 (s, 1 H) 10.06 (s, 1 H) 11.48 (s, 1 H). MS (ESI+) *m/z* 520 (M+H)⁺.

Example 22. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(furan-2-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.59).

[0533]

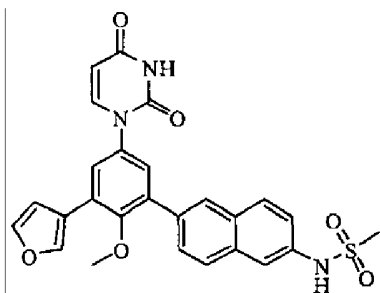


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[0534] The title compound was prepared according to the procedure of **Example 19** substituting furan-2-ylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane to give a white solid (16mg, 32%). ¹H NMR (300 MHz, DMSO-D6) δ ppm 3.09 (s, 3 H) 3.35 (s, 3 H) 5.69 (d, J=7.72 Hz, 1 H) 6.69 (dd, J=3.31, 1.84 Hz, 1 H) 7.11 (d, J=3.31 Hz, 1 H) 7.43 (dd, J=8.82, 2.21 Hz, 1 H) 7.49 (d, J=2.94 Hz, 1 H) 7.80 (m, 5 H) 7.96 (m, 2 H) 8.13 (s, 1 H) 10.06 (s, 1 H) 11.47 (s, 1 H). MS (ESI-) *m/z* 502.1 (M-H)⁺.

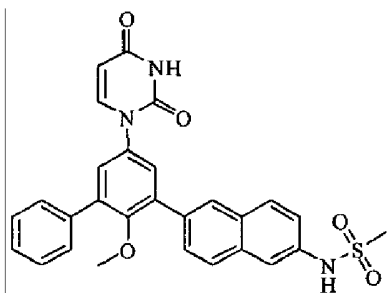
[0535] Example 23. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(furan-3-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.64).

25



[0536] The title compound was prepared according to the procedure of **Example 19** substituting furan-3-ylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane to give a white solid (6mg, 12%). ¹H NMR (300 MHz, DMSO-D6) δ ppm 3.09 (s, 3 H) 3.30 (s, 3 H) 5.69 (dd, J=7.71, 1.83 Hz, 1 H) 7.10 (dd, J=1.74, 0.78 Hz, 1 H) 7.42 (dd, J=8.82, 2.21 Hz, 1 H) 7.46 (d, J=2.57 Hz, 1 H) 7.73 (d, J=2.21 Hz, 1 H) 7.76 (d, J=2.57 Hz, 1 H) 7.78 (d, J=1.84 Hz, 1 H) 7.81 (t, J=1.84 Hz, 1 H) 7.86 (d, J=7.72 Hz, 1 H) 7.96 (t, J=8.82 Hz, 2 H) 8.10 (s, 1 H) 8.28 (s, 1 H) 10.05 (s, 1 H) 11.48 (s, 1 H). MS (ESI-) *m/z* 502.1 (M-H)⁺.

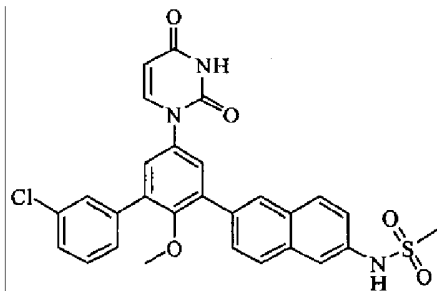
[0537] Example 24. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-biphenyl-3-yl)naphthalen-2-yl)methanesulfonamide (compound **IB-L0-2.71**).



[0538] The title compound was prepared according to the procedure of **Example 19** substituting phenylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane. The crude product was purified by silica gel chromatography eluting with 3% methanol/ CH₂Cl₂ to give a white solid (10mg, 8%). ¹H NMR (300 MHz, DMSO-D6) δ ppm 3.08 (s, 3 H) 3.12 (s, 3 H) 5.69 (dd, J=7.81, 1.47 Hz, 1 H) 7.36 (m, 5 H) 7.56 (d, J=2.57 Hz, 1 H) 7.64 (m, 2 H) 7.74 (d,

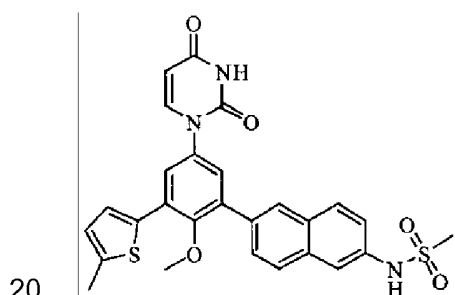
J=2.21 Hz, 1 H) 7.78 (dd, J=8.46, 1.84 Hz, 1 H) 7.94 (m, 3 H) 8.11 (s, 1 H) 10.04 (s, 1 H) 11.47 (s, 1 H). MS (ESI-) m/z 512 (M-H)⁺.

[0539] Example 25. Preparation of N-(6-(3'-chloro-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxybiphenyl-3-yl)naphthalen-2-yl)methanesulfonamide (compound **IB-L0-2.74**).



[0540] The title compound was prepared according to the procedure of **Example 19** substituting 3-chlorophenylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane to give a white solid (38mg, 68%). ¹H NMR (300 MHz, DMSO-D6) δ ppm 3.09 (s, 3 H) 3.13 (s, 3 H) 5.70 (dd, J=8.09, 2.21 Hz, 1 H) 7.43 (dd, J=8.82, 2.21 Hz, 1 H) 7.52 (m, 3 H) 7.62 (m, 2 H) 7.72 (m, 2 H) 7.79 (dd, J=8.46, 1.47 Hz, 1 H) 7.95 (m, 3 H) 8.12 (s, 1 H) 10.05 (s, 1 H) 11.47 (d, J=2.21 Hz, 1 H). MS (ESI-) m/z 546 (M-H)⁺.

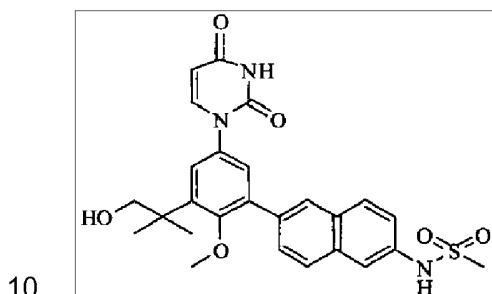
[0541] Example 26. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(5-methylthiophen-2-yl)phenyl)naphthalen-2-yl)methanesulfonamide (compound **IB-L0-2.73**).



[0542] The title compound was prepared according to the procedure of **Example 19** substituting 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane to

give a white solid (22mg, 41%). ^1H NMR (300 MHz, DMSO- D_6) δ ppm 2.49 (s, 3 H) 3.09 (s, 3 H) 3.29 (s, 3 H) 5.69 (dd, $J=8.09, 2.21$ Hz, 1 H) 6.87 (d, $J=2.57$ Hz, 1 H) 7.43 (m, 2 H) 7.54 (d, $J=3.68$ Hz, 1 H) 7.76 (m, 2 H) 7.85 (s, 1 H) 7.87 (d, $J=5.15$ Hz, 1 H) 7.98 (t, $J=9.01$ Hz, 2 H) 8.11 (s, 1 H) 10.06 (s, 1 H) 11.47 (d, $J=2.21$ Hz, 1 H). MS (ESI+) m/z 534 (M+H) $^+$.

[0543] Example 27. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenyl)naphthalen-2-yl)-methanesulfonamide (compound **IB-L0-2.54**).



[0544] Part A. Preparation of 2-(2-hydroxy-3,5-diiodophenyl)acetic acid.

To a 250mL round bottom flask was added 2-(2-hydroxyphenyl)acetic acid (Aldrich, 3.04g, 20mmol) in acetonitrile (50ml) to give a colorless solution. N-iodosuccinimide (9.00g, 40.0mmol) was added portionwise over 15min to give a red/brown transparent solution that was stirred for 16h. The mixture was concentrated and the resulting solid was triturated in 75mL of water and filtered to collect an orange solid that was dried under vacuum. The crude solid was recrystallized from toluene to give a light orange powder (6.0g, 74%).

Part B. Preparation of methyl 2-(3,5-diiodo-2-methoxyphenyl)acetate.

[0545] To a 250mL round-bottom flask was added the product from **Part A** (6g, 14.85mmol), potassium carbonate (6.16g, 44.6mmol), and dimethyl sulfate (4.12g, 32.7mmol) in acetone (49.5ml) to give a brown suspension. Heated at reflux for 16h, cooled, concentrated and the residue was partitioned between EtOAc and water. The EtOAc layer was washed with brine, dried (Na_2SO_4) and

concentrated to a brown oil that was chromatographed on a 40g silica cartridge eluting with 3:1 hexane/EtOAc to give a yellow oil (6.0g, 94%).

Part C. Preparation of methyl 2-(3,5-diiodo-2-methoxyphenyl)-2-methylpropanoate.

[0546] To a 100mL round-bottom flask under nitrogen was added the product from **Part B** (1.728g, 4mmol) in anhydrous THF (20ml) and HMPA (2ml) to give a colorless solution. Methyl iodide (1.251ml, 20.00mmol) was added and the solution was cooled to -40°C. Potassium t-butoxide(12.00ml, 12.00mmol) was added dropwise and the mixture was stirred at -40 to -20°C for 30min and quenched with 1M HCl to a pH of 1. The mixture was extracted 3 X 40ml with EtOAc. The extracts were combined, washed with brine, dried (Na₂SO₄) and concentrated. The crude product was flash chromatographed on a 40g ISCO silica cartridge eluting with 9:1 hexane/EtOAc to give the bis-methylated product as a yellow oil (1.63g, 89%).

Part D. Preparation of 2-(3,5-diiodo-2-methoxyphenyl)-2-methylpropanoic acid.

[0547] A suspension of the product from **Part C** (2.63g, 5.72mmol) in MeOH (40ml) and THF (40ml) was treated with 4.0M sodium hydroxide (28ml, 112 mmol) and heated at 80°C for 48 h. The organic solvent was evaporated and the remaining aqueous solution was acidified with 1M HCl producing a solid that was collected by filtration, washed with water and dried to give the desired carboxylic acid (2.46g, 96%).

Part E. Preparation of 2-(3,5-diiodo-2-methoxyphenyl)-2-methylpropan-1-ol.

[0548] A solution of the product from **Part D** (1.00g, 2.242mmol) in THF (40ml) was treated dropwise with borane THF complex 1.0M (20ml, 20mmol) and then heated at 50°C for 24 h. The mixture was treated with methanol (20mL), re-

fluxed for 30 min and concentrated. The resulting residue was washed with water, brine, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel eluting with hexane/EtOAc (4:1) to give the desired product (810mg, 84%).

5

Part F. Preparation of tert-butyl(2-(3,5-diiodo-2-methoxyphenyl)-2-methylpropoxy)-dimethylsilane.

[0549] A solution of the product from **Part E** (432mg, 1.000mmol) in DMF (5ml) was treated with tert-butyldimethylchlorosilane (301mg, 2.000mmol), and imidazole (204mg, 3.00mmol) and stirred for 2h. The mixture was partitioned between 1M HCl and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel eluting with hexane/EtOAc (9:1) to give the desired product (522mg, 96%).

15

Part G. Preparation of 1-(3-(1-(tert-butyldimethylsilyloxy)-2-methylpropan-2-yl)-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0550] To a 50mL round-bottom flask was added the product from **Part F** (520 mg, 0.952mmol), pyrimidine-2,4(1H,3H)-dione (117mg, 1.047mmol), N-(2-cyanophenyl)picolinamide (42.5mg, 0.190mmol), copper(I) iodide (18.13mg, 0.095 mmol) and potassium phosphate (424mg, 1.999mmol) in DMSO (5ml). The vessel was sealed, sparged with nitrogen and then heated at 60°C for 24h. The mixture was partitioned between 1M HCl and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was chromatographed on silica gel eluting with hexane/EtOAc (3:2) to give the product as a solid (285mg, 65%).

30

Part H. Preparation of N-(6-(3-(1-(tert-butyldimethylsilyloxy)-2-methylpropan-2-yl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

5 **[0551]** To a 5mL microwave tube was added the product from **Part G** (50mg, 0.094mmol), the product from **Example 2A, Part B** (32.7mg, 0.094mmol), potassium phosphate (42.0mg, 0.198mmol), PA-Ph (CAS 97739-46-3) (0.827mg, 2.83μmol) and tris(dibenzylideneacetone)palladium(0) (0.863mg, 0.943μmol) in THF (3.0ml) and water (1.0ml). The vessel was sealed and the mixture was
10 sparged with nitrogen for 5min and then heated at 50°C for 2h. The mixture was partitioned between 1M HCl and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was chromatographed on silica gel eluting with
15 hexane/EtOAc (3:7) to give a solid (32mg, 54%).

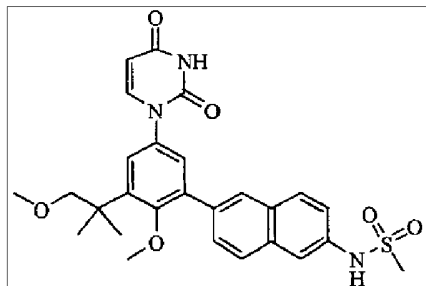
Part I. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

20 **[0552]** The product from **Part H** (31mg, 0.050mmol) in THF (2.0ml) was treated with 1M TBAF (0.3ml, 0.3mmol) in THF and stirred overnight. The mixture was partitioned with water and ethyl acetate. The organic layer was washed with brine three times, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel eluting with 2% to 8% methanol in
25 CH₂Cl₂ to give a solid (21mg, 83%). Melting point: 256-257°C. ¹H NMR (300 MHz, DMSO-D₆) δ ppm 1.35 (s, 6 H) 3.08 (s, 3 H) 3.23 (s, 3 H) 3.67 (d, J=4.78 Hz, 2 H) 4.72 (t, J=4.78 Hz, 1 H) 5.65 (d, J=8.09 Hz, 1 H) 7.36 (m, 3 H) 7.74 (m, 3 H) 7.98 (m, 3 H) 10.04 (s, 1 H) 11.41 (s, 1 H). MS (ESI+) *m/z* 527 (M+ NH₄)⁺.

30

Example 28. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(1-methoxy-2-methylpropan-2-yl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-LO-2.66).

[0553]



Part A. Preparation of 1,5-diiodo-2-methoxy-3-(1-methoxy-2-methylpropan-2-yl)benzene.

5

[0554] To a 25mL round-bottom flask was added the product from **Example 27, Part E.** (259mg, 0.6mmol) and sodium hydride (28.8mg, 1.200mmol) in THF (5 ml). The mixture was stirred for 30min and iodomethane (0.045 l, 0.720mmol) was added. The mixture was stirred for 16h and partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated to give an oil (235mg, 88%).

Part B. Preparation of 1-(3-iodo-4-methoxy-5-(1-methoxy-2-methylpropan-2-yl)phenyl)pyrimidine-2,4(1H,3H)-dione.

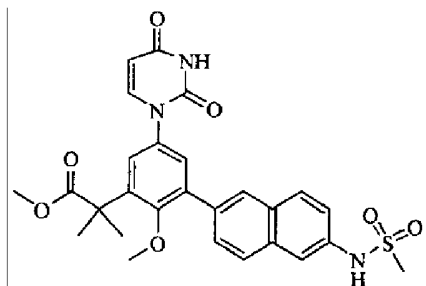
[0555] In a 25mL round-bottom flask was added the product from **Part A** (230mg, 0.516mmol), pyrimidine-2,4(1H,3H)-dione (63.6mg, 0.567mmol), N-(2-cyanophenyl)picolinamide (23.02mg, 0.103mmol), copper(I) iodide (9.82mg, 0.052mmol) and potassium phosphate (230mg, 1.083mmol) in DMSO (5ml). The vessel was sealed, sparged with nitrogen and heated at 60°C for 16h. The mixture was cooled and partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel eluting with 2% to 5% methanol in CH₂Cl₂ to give a solid (140mg, 63%).

Part C. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(1-methoxy-2-methylpropan-2-yl)phenyl)naphthalen-2-yl)methanesulfonamide.

5 **[0556]** In a 5ml microwave tube was added the product from **Part B** (43mg, 0.100mmol), the product from **Example 2A, Part B** (34.7mg, 0.100mmol), potassium phosphate (44.6mg, 0.210mmol), PA-Ph (CAS 97739-46-3) (0.876mg, 3.00 μ mol) and tris(dibenzylideneacetone)palladium(0) (0.915mg, 0.999 μ mol) in THF (3.0ml) and water (1.0ml). The vessel was sealed, sparged with nitrogen
 10 for 5min and heated at 50°C for 2h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was triturated with methanol/ CH₂Cl₂ (1:1) to give a solid (28mg, 54%). ¹H NMR
 15 (300 MHz, DMSO-D₆) δ ppm 1.39 (s, 6 H) 3.08 (s, 3 H) 3.23 (s, 3 H) 3.25 (s, 3 H) 3.61 (s, 2 H) 5.65 (d, J=7.72 Hz, 1 H) 7.27 (d, J=2.57 Hz, 1 H) 7.37 (d, J=2.57 Hz, 1 H) 7.42 (dd, J=8.64, 2.02 Hz, 1 H) 7.69 (dd, J=8.46, 1.84 Hz, 1 H) 7.73 (d, J=2.21 Hz, 1 H) 7.78 (d, J=7.72 Hz, 1 H) 7.95 (t, J=8.27 Hz, 2 H) 8.02 (s, 1 H) 10.04 (s, 1 H) 11.41 (s, 1 H). MS (ESI+) *m/z* 541 (M+ NH₄)⁺.

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Example 29. Preparation of methyl 2-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)phenyl)-2-methylpropanoate (compound IB-L0-2.70).

25 **[0557]**

Part A. Preparation of methyl 2-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-iodo-2-methoxyphenyl)-2-methylpropanoate.

[0558] To a 100mL round-bottom flask under N₂ was added the product from **Example 27, Part C** (410mg, 0.891mmol), 1H-pyrimidine-2,4-dione (120mg, 1.069mmol), and potassium phosphate tribasic (397mg, 1.872mmol) in DMSO (5ml) to give a colorless suspension. N-(2-cyanophenyl) picolinamide (39.8mg, 0.178mmol) was added and the mix was sparged with N₂ for 5min. Copper(I) iodide (16.97mg, 0.089mmol) was added and the mix was sparged once again for 10min, placed under N₂ and heated at 60°C for 18h. The mixture was cooled and partitioned between EtOAc and water adjusting the pH to 1 with HCl. The aqueous layer was extracted 2X with EtOAc. The organics were combined, washed with water, saturated NaHCO₃, and saturated NaCl. The organic layer was dried (Na₂SO₄), treated with 3-mercaptopropyl functionalized silica, filtered and concentrated. The crude product was purified by chromatography on an ISCO 40 g silica cartridge eluting with 3% MeOH in CH₂Cl₂ to give a white foam (269mg, 68%).

15

Part B. Preparation of methyl 2-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)phenyl)-2-methylpropanoate.

[0559] To a 20mL microwave tube was added the product from **Part A** (0.444g, 1.0mmol), the product from **Example 2A, Part B** (0.365g, 1.050mmol), and potassium phosphate tribasic (0.446g, 2.100mmol) in 3:1 tetrahydrofuran-water (12ml) and degassed by nitrogen sparge for 20min. The solution was then treated with PA-Ph (CAS 97739-46-3) (8.77mg, 0.030mmol) and tris(dibenzylideneacetone)palladium(0) (9.16mg, 10.00μmol) followed by degassing for another 5min. The microwave tube was then sealed and warmed at 50°C for 18h, cooled and partitioned between EtOAc and water adjusting the pH to 1 with 1M HCl. The EtOAc layer was washed with water, saturated NaHCO₃, and saturated NaCl. The organic layer was dried over sodium sulfate, stirred for 1h with 3-mercaptopropyl functionalized silica, filtered and concentrated. The crude product was purified by chromatography on an ISCO 12g silica cartridge eluting with 1-3% MeOH in CH₂Cl₂ to give light tan crystals (480mg, 98%). ¹H NMR (300 MHz, DMSO-D6) δ ppm 1.52 (s, 6 H) 3.08 (s, 3 H) 3.14 (s, 3 H) 3.64 (s, 3

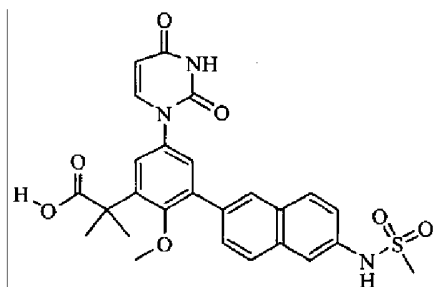
30

H) 5.67 (dd, J=8.09, 1.84 Hz, 1 H) 7.37 - 7.48 (m, 3 H) 7.65 (dd, J=8.46, 1.84 Hz, 1 H) 7.73 (d, J=2.21 Hz, 1 H) 7.83 (d, J=8.09 Hz, 1 H) 7.96 (dd, J=8.64, 5.70 Hz, 2 H) 8.01 (s, 1 H) 10.05 (s, 1 H) 11.45 (s, 1 H). MS (ESI-) m/z 536 (M-H)⁺.

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Example 30. Preparation of 2-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)phenyl)-2-methylpropanoic acid (compound IB-L0-2.77).

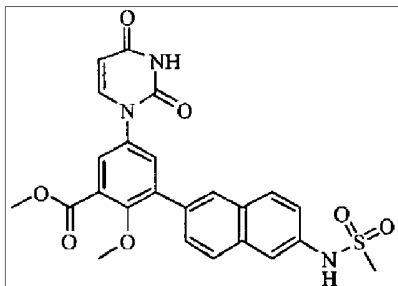
10 [0560]



[0561] A mixture of the product from **Example 29** (108mg, 0.2mmol) and sodium hydroxide (1mL, 4.00mmol) in methanol, THF, water (3:3:1, 10mL) was heated at 80°C for 18h, cooled and carefully acidified to pH 1 with concentrated HCl resulting in the formation of a white precipitate. The solid was collected by filtration, washed with water and dried. The crude material was triturated in 1mL of 1:1 EtOAc/MeOH, sonicated for 5min and the solid was collected by filtration as a bright white solid (58mg, 54% yield), mp >300°C. ¹H NMR (300 MHz, DMSO-D6) δ ppm 1.50 (s, 6 H) 3.08 (s, 3 H) 3.18 (s, 3 H) 5.66 (d, J=7.72 Hz, 1 H) 7.34 - 7.45 (m, 3 H) 7.67 (dd, J=8.64, 1.65 Hz, 1 H) 7.73 (d, J=1.84 Hz, 1 H) 7.82 (d, J=7.72 Hz, 1 H) 7.96 (dd, J=9.01, 4.60 Hz, 2 H) 8.02 (s, 1 H) 10.04 (s, 1 H) 11.43 (s, 1 H) 12.15 (s, 1 H). MS (ESI-) m/z 522 (M-H)⁺.

Example 31. Preparation of methyl 5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)benzoate (compound IB-L0-2.72).

[0562]



Part A. Preparation of methyl 3,5-diiodo-2-methoxybenzoate.

- 5 **[0563]** A mixture of 2-hydroxy-3,5-diiodobenzoic acid (3.9g, 10.0mmol) potassium carbonate (4.15g, 30.0mmol) and dimethyl sulfate (2.77g, 22.0mmol) in acetone (33ml) was heated at reflux for 16h, cooled and concentrated. The residue was dissolved in EtOAc and washed with water, brine, dried (Na₂SO₄), filtered and concentrated to give an off-white solid (4.2g, quantitative yield).

10

Part B. Preparation of methyl 5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-iodo-2-methoxybenzoate.

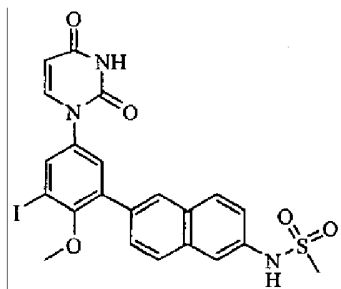
- [0564]** To a 100mL round-bottom flask under N₂ was added the product from
- 15 **Part A** (2.09g, 5.0mmol), 1H-pyrimidine-2,4-dione (0.67g, 6.0mmol), and potassium phosphate tribasic (2.2g, 10.5mmol) in DMSO (20ml) to give a colorless suspension. N-(2-cyanophenyl)picolinamide (220mg, 1.0mmol) was added and the mix was sparged with N₂ for 5min. Copper(I) iodide (95mg, 0.5mmol) was added and the mix was sparged once again for 10min, placed under N₂ and
- 20 heated at 60°C for 18h. The mixture was cooled and partitioned between EtOAc and water adjusting the pH to 1 with HCl. The aqueous layer was extracted 2X with EtOAc. The organics were combined, washed with water, saturated NaHCO₃, and saturated NaCl. The organic layer was dried (Na₂SO₄), treated with 3-mercaptopropyl functionalized silica, filtered and concentrated. The crude
- 25 product was purified by chromatography on an ISCO 40g silica cartridge eluting with 3% MeOH in CH₂Cl₂ to give a white foam (1.0g, 50 %).

Part C. Preparation of methyl 5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)benzoate.

[0565] A mixture of the product from **Part B** (101 mg, 0.25mmol), the product from **Example 2A, Part B** (91mg, 0.263mmol), and potassium phosphate tribasic (111mg, 0.525mmol) in 3:1 tetrahydro-furan-water (12mL) was degassed by nitrogen sparge for 20min. The solution was then treated with PA-Ph (CAS 97739-46-3) (2.192mg, 7.50 μ mol) and tris(dibenzylideneacetone)palladium(0) (2.289mg, 2.500 μ mol) followed by degassing for another 5min. The microwave tube was then sealed, warmed at 50°C for 18h, cooled and partitioned between EtOAc and water adjusting the pH to 1 with 1M HCl. The EtOAc layer was washed with water, saturated NaHCO₃, and saturated NaCl. The organic layer was dried Na₂SO₄, stirred for 1h with 3-mercaptopropyl functionalized silica, filtered and concentrated. The crude product was purified by chromatography on an ISCO 12g silica cartridge eluting with 3% MeOH in CH₂Cl₂ to give an off-white foam (80mg, 63 %). ¹H NMR (300 MHz, DMSO-D₆) δ ppm 3.09 (s, 3 H) 3.45 (s, 3 H) 3.89 (s, 3 H) 5.69 (d, J=7.72 Hz, 1 H) 7.43 (dd, J=8.82, 2.21 Hz, 1 H) 7.68 - 7.79 (m, 4 H) 7.84 (d, J=7.72 Hz, 1 H) 7.89 - 8.01 (m, 2 H) 8.09 (s, 1 H) 10.06 (s, 1 H) 11.49 (s, 1 H). MS (ESI-) *m/z* 494 (M-H)⁺.

20

Example 32. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-iodo-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.57).

25 **[0566]**

Part A. Preparation of 1,3,5-triiodo-2-methoxybenzene.

[0567] In a 250mL pressure vessel was added 2,4,6-triiodophenol (5g, 10.60 mmol) in MTBE (60ml) to give a yellow solution. The solution was cooled in an ice bath and 2.0M trimethylsilyldiazomethane (7.95ml, 15.90mmol) was added at a fast drip followed by dropwise addition of methanol (6mL) resulting in calm bubbling. The vessel was sealed and stirred at room temperature for 4h. The reaction solution was partitioned between EtOAc and water and the organic layer was washed with 1M HCl, saturated NaHCO₃, and saturated NaCl. The EtOAc was dried (MgSO₄), filtered and concentrated to give a tan solid that was used without purification (4.8g, 94 %).

10

Part B. Preparation of 1-(3,5-diiodo-4-methoxyphenyl)pyrimidine-2,4(1H,-3H)-dione.

[0568] To a 100mL round-bottom flask under N₂ was added the product from **Part A** (3.5g, 7.2mmol), 1H-pyrimidine-2,4-dione (0.97g, 8.64mmol), and potassium phosphate tribasic (3.2g, 15.0mmol) in DMSO (50ml) to give a colorless suspension. N-(2-cyanophenyl)picolinamide (320mg, 1.44mmol) was added and the mix was sparged with N₂ for 5min. Copper(I) iodide (137mg, 0.72mmol) was added and the mix was sparged once again for 10min, placed under N₂ and heated at 60°C for 18h. The mixture was cooled and partitioned between EtOAc and water adjusting the pH to 1 with HCl. The aqueous layer was extracted 2X with EtOAc. The organics were combined, washed with water, saturated NaHCO₃, and saturated NaCl, dried (Na₂SO₄), treated with 3-mercaptopropyl functionalized silica, filtered and concentrated. The resulting solid was triturated in 2:1 hexane/EtOAc to give an off white powder (2.2g, 62 %).

Part C. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-iodo-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

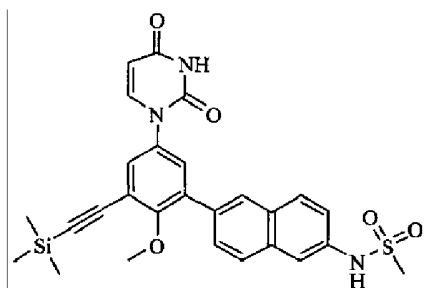
[0569] A mixture of the product from **Part B** 1-(3,5-diiodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione (118mg, 0.25mmol), the product from **Example 2A, Part B** (87mg, 0.25mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)-dichloride CH₂Cl₂ complex (10.21mg, 0.013mmol) and sodium carbonate (0.250

ml, 0.25mmol) in toluene (1.0ml) and ethanol (1.0ml) was sparged with nitrogen for 5min and microwaved at 100°C for 30min. The mixture was cooled and partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica eluting with ethyl acetate/hexane (2:3 to 4:1) to give the title compound (16mg, 11%). ¹H NMR (300 MHz, DMSO-D6) δ ppm 3.08 (s, 3 H) 3.35 (s, 3 H) 5.67 (d, J=8.09 Hz, 1 H) 7.42 (dd, J=8.82, 2.21 Hz, 1 H) 7.59 (d, J=2.57 Hz, 1 H) 7.73 (m, 2 H) 7.81 (d, J=8.09 Hz, 1 H) 7.95 (m, 3 H) 8.09 (s, 1 H) 10.06 (s, 1 H) 11.47 (s, 1 H). MS (ESI-) *m/z* 562 (M-H)⁺.

Example 33. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-((trimethylsilyl)ethynyl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.78).

15

[0570]



[0571] In a 5mL microwave tube were combined ethynyltrimethylsilane (0.044 ml, 0.32mmol), the product from **Example 32** (45.1mg, 0.08mmol), copper(I) iodide (0.762mg, 4.0μmol), bis(triphenyl-phosphine)palladium(II) chloride (2.81 mg, 4.0μmol) and triethylamine (0.056ml, 0.40mmol) in acetonitrile (2ml). The mixture was sparged with nitrogen for 5min, sealed and microwaved at 80°C for 20min. The reaction mixture was cooled and partitioned with ethyl acetate and water. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica eluting with 1-4% methanol in CH₂Cl₂ to give a solid, (18mg, 42%) m.p.175-178°C. ¹H NMR (300 MHz, DMSO-D6) δ ppm 0.25 (s, 9 H) 3.07 (s, 3 H) 3.65 (s, 3 H) 5.66 (dd,

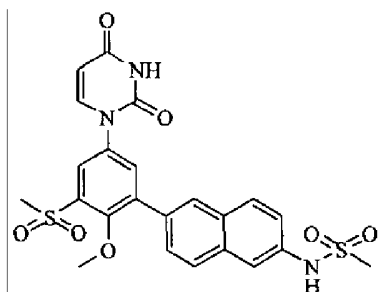
25

J=7.91, 2.02 Hz, 1 H) 7.41 (dd, J=8.82, 2.21 Hz, 1 H) 7.58 (m, 2 H) 7.69 (dd, J=8.46, 1.84 Hz, 1 H) 7.72 (d, J=2.21 Hz, 1 H) 7.81 (d, J=7.72 Hz, 1 H) 7.93 (m, 2 H) 8.05 (d, J=1.32 Hz, 1 H) 10.04 (s, 1 H) 11.45 (d, J=2.21 Hz, 1 H). MS (ESI+) m/z 534 (M+H)⁺.

5

Example 34. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(methylsulfonyl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.68).

10 [0572]



Part A. Preparation of 4-nitrobenzene-2-diazo-1-oxide.

[0573] To a 250mL round-bottom flask was added 2-amino-4-nitrophenol (6.165 g, 40.0mmol) in 48% tetrafluoroboric acid (15ml). Sodium nitrite (2.76g, 40.0mmol) in water (6ml) was added dropwise at 0°C and the mixture was stirred at room temperature for 30min. The solid was collected by filtration, washed with tetrafluoroboric acid and water. The solid was suspended in acetone (50ml), filtered and dried to give a solid (3.31g, 50%).

20

Part B. Preparation of 2-(methylthio)-4-nitrophenol.

[0574] To a 1L beaker was added the product from **Part A** (2.70g, 16.35mmol) in ice water (250g) to give a brown suspension. Copper (0.520g, 8.18mmol) was added, followed by addition of sodium thiomethoxide (2.292g, 32.7mmol) in water (50ml) slowly. The mixture was stirred at room temperature for 24h. The mixture was filtered and the filtrate was acidified with 1M HCl producing a solid that was collected by filtration and dried (2.53g, 84%).

Part C. Preparation of 2-(methylsulfonyl)-4-nitrophenol.

[0575] To a 250mL round-bottom flask was added the product from **Part B** (1.111 g, 6.00mmol) in MeOH (20ml) to give a brown suspension. Oxone (7.746 g, 12.60mmol) in water (20ml) was added slowly at 0°C. The mixture was warmed to room temperature, stirred for 1h and partitioned with ethyl acetate and 1M HCl. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel eluting with 1% to 5% methanol in CH₂Cl₂ to give a solid (0.472g, 36%).

10

Part D. Preparation of 2-iodo-6-(methylsulfonyl)-4-nitrophenol.

[0576] To a 50mL round-bottom flask was added the product from **Part C** (470mg, 2.164mmol) in MeOH (10ml) and water (2.5ml). Iodine monochloride (0.130ml, 2.60mmol) in CH₂Cl₂ (2.0mL) was added dropwise and the mixture was stirred at room temperature, poured into water (200mL) and stirred for 10min. The resulting solid was collected by filtration and dried (636mg, 86%).

Part E. Preparation of 1-iodo-2-methoxy-3-(methylsulfonyl)-5-nitrobenzene.

[0577] To a 50mL pressure vessel was added the product from **Part D** (630mg, 1.836mmol) in MTBE (6ml) to give a yellow solution. The mixture was cooled in an ice bath and 2M trimethylsilyl-diazomethane (1.377ml, 2.75mmol) was added at a fast drip followed by dropwise addition of MeOH (0.4ml) resulting in calm bubbling. The vessel was sealed and stirred at room temperature for 1h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated to give an off-white solid (655mg, 100%).

30

Part F. Preparation of 3-iodo-4-methoxy-5-(methylsulfonyl)aniline.

[0578] To a 250mL round-bottom flask was added the product from **Part E** (0.650g, 1.820mmol), ammonium chloride (0.146g, 2.73mmol), and iron (0.508 g, 9.10mmol) in THF/MeOH/water (50ml, 2/2/1). The mixture was refluxed for 2h, cooled and filtered. The filtrate was evaporated and the residue was partitioned with ethyl acetate and water. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated to give a solid (590mg, 99%).

Part G. Preparation of (E)-N-(3-iodo-4-methoxy-5-(methylsulfonyl)phenyl-carbamoyl)-3-methoxyacrylamide.

10

[0579] To a 100mL round-bottom flask was added the product from **Part F** (500mg, 1.528mmol) in DMF (15.0ml). The solution was cooled under nitrogen to -20°C and (E)-3-methoxyacryloyl isocyanate (15.28ml, 6.11mmol; prepared as described by Santana, L.; et al. J. Heterocyclic Chem. 1999, 36, 293-295) was added dropwise. The mixture was stirred at this temperature for 15min, then warmed to room temperature and stirred for 45min. The mixture was diluted with ethyl acetate and washed by water (3 x 50ml), brine (3 x 50ml), dried with sodium sulfate, filtered and evaporated. The residue was triturated with ethyl acetate/hexane to give a solid (425mg, 61%).

20

Part H. Preparation of 1-(3-iodo-4-methoxy-5-(methylsulfonyl)phenyl)pyrimidine-2,4(1H,3H)-dione.

[0580] To a 100mL round-bottom flask was added the product from **Part G** (420 mg, 0.925mmol) in ethanol (10ml) to give a suspension. Concentrated sulfuric acid (1mL, 18.76mmol) in water (10ml) was added and the mixture was heated at 110°C for 2h. The reaction mix was cooled, diluted with water (50ml) and stirred for 10min. The solid material was collected by filtration, washed with water and dried to give a white solid (325mg, 83%).

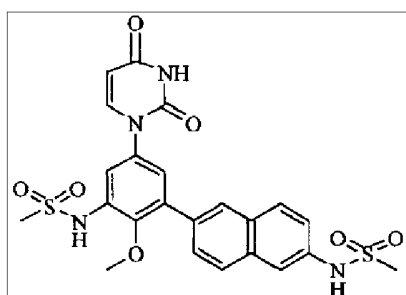
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Part I. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(methylsulfonyl)phenyl)naphthalen-2-yl)methanesulfonamide.

[0581] To a 5mL microwave tube was added the product from **Part H** (63.3mg, 0.15mmol), the product from **Example 2A, Part B** (52.1mg, 0.150mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride complex (6.12mg, 7.50 μ mol) and 1M sodium carbonate (0.150ml, 0.150mmol) in the solvents of toluene (1.0ml) and ethanol (1.0ml). The vessel was sealed and the mixture was sparged with nitrogen for 5min and microwaved at 100°C for 30min. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with 1% to 8% methanol in CH₂Cl₂ to give crude product. A final trituration in 1:1 methanol/ethyl acetate afforded pure solid (26mg, 34%). ¹H NMR (300 MHz, DMSO-D₆) δ ppm 3.10 (s, 3 H) 3.44 (s, 3 H) 3.45 (s, 3 H) 5.71 (d, J=8.09 Hz, 1 H) 7.44 (dd, J=8.82, 2.21 Hz, 1 H) 7.75 (d, J=1.84 Hz, 1 H) 7.80 (dd, J=8.46, 1.84 Hz, 1 H) 7.86 (d, J=8.09 Hz, 1 H) 7.91 (d, J=2.57 Hz, 1 H) 7.96 (d, J=2.57 Hz, 1 H) 8.00 (m, 2 H) 8.16 (d, J=1.47 Hz, 1 H) 10.10 (s, 1 H) 11.51 (s, 1 H). MS (ESI+) *m/z* 533 (M+NH₄)⁺.

Example 35. Preparation of N-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)phenyl)methanesulfonamide (compound IB-L0-2.75).

[0582]



Part A. Preparation of 2,4-diiodo-6-nitrophenol.

25

[0583] To a solution of 2-nitrophenol (2.78g, 20mmol) in MeOH (120ml) and water (30mL) was added dropwise a solution of iodine monochloride (2.105ml, 42.0mmol) in 10mL CH₂Cl₂. The mixture was stirred for 2h, poured into 600mL

water, stirred and sonicated for 30min. The mixture was filtered to collect a yellow solid that was washed 3x with water (50mL each wash) and dried to constant mass (7.3g, 93%). m

5 **Part B. Preparation of 1,5-diiodo-2-methoxy-3-nitrobenzene.**

[0584] A 50mL pressure vessel was charged with the product from **Part A** and MTBE (10ml) to give a yellow solution. The solution was cooled in an ice bath and 2M trimethylsilyldiazomethane (2.251ml, 4.50mmol) was added at a fast drop followed by dropwise addition of MeOH (0.6ml) resulting in calm bubbling. The vessel was sealed and stirred allowing warm to room temperature over 4h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated to give a yellow solid (1.22g, 100%).

15

Part C. Preparation of 3,5-diiodo-2-methoxyaniline.

[0585] In a 250 round-bottom flask was added the product from **Part B** (0.98g, 2.420mmol), ammonium chloride (0.194g, 3.63mmol), and iron (0.676g, 12.10 mmol) in THF/methanol/water (20ml/20ml/10ml). The mixture was refluxed for 16ho, cooled and filtered. The filtrate was evaporated and the residue was partitioned with water and ethyl acetate. The organic layer was dried with sodium sulfate, filtered and evaporated to give an oil (780mg, 86%).

25 **Part D. Preparation of 1-(3-amino-5-iodo-4-methoxyphenyl)pyrimidine-2,4-(1H,3H)-dione.**

[0586] In a 25mL round-bottom flask was added the product from **Part C** (650 mg, 1.734mmol), pyrimidine-2,4(1H,3H)-dione (214mg, 1.907mmol), N-(2-cyanophenyl)picolinamide (77mg, 0.347mmol), copper(I) iodide (33.0mg, 0.173 mmol) and potassium phosphate (773mg, 3.64mmol) in DMSO (5ml). The vessel was sealed and the mixture was sparged with nitrogen for 15min and heated at 60°C for 16h. The mixture was partitioned with ethyl acetate and 1M HCl. The

30

organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was chromatographed on silica eluting with 5:95 methanol/D CH₂Cl₂CM to give a solid (125mg, 20%).

5

Part E. Preparation of N-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-iodo-2-methoxyphenyl)methanesulfonamide.

[0587] A solution of the product from **Part D** (110mg, 0.306mmol) in pyridine (2ml) was treated with methanesulfonyl chloride (0.048ml, 0.612mmol) and stirred for 24h. The solvent was evaporated and the residue was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with 2% to 5% methanol in CH₂Cl₂ to give a solid (20mg, 15%).

15

Part F. Preparation of N-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)phenyl)methanesulfonamide.

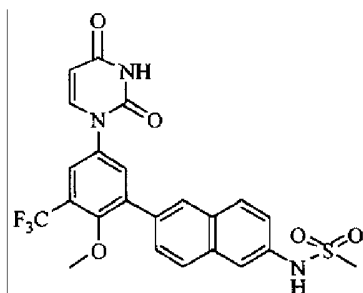
[0588] To a 5mL microwave tube was added the product from **Part E** (18mg, 0.041mmol), **Example 2A, Part B** (14.30mg, 0.041mmol), potassium phosphate (18.35mg, 0.086mmol), PA-Ph (CAS 97739-46-3) (0.361mg, 1.235μmol) and tris(dibenzylideneacetone)dipalladium(0) (0.377mg, 0.412μmol) in THF (3.0ml) and water (1.0ml). The vessel was sealed and the mixture was sparged with nitrogen for 5min and heated at 50°C for 2h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with 2% to 5% methanol in CH₂Cl₂ to give a solid. A final trituration in 1:1 methanol/ CH₂Cl₂ gave the desired product (7mg, 32%). ¹H NMR (300 MHz, DMSO-D₆) δ ppm 3.09 (s, 3 H) 3.17 (s, 3 H) 3.37 (s, 3 H) 5.69 (dd, J=7.91, 2.02 Hz, 1 H) 7.34 (d, J=2.57 Hz, 1 H) 7.43 (dd, J=8.82, 2.21 Hz, 1 H) 7.47 (d, J=2.57 Hz, 1 H) 7.73 (m, 2 H) 7.81 (d, J=8.09 Hz,

30

1 H) 7.94 (d, J=6.25 Hz, 1 H) 7.97 (d, J=6.62 Hz, 1 H) 8.07 (s, 1 H) 9.45 (s, 1 H) 10.05 (s, 1 H) 11.45 (d, J=1.84 Hz, 1 H). MS (ESI-) *m/z* 529 (M-H).

Example 36. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(trifluoromethyl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.56).

[0589]



10 **Part A. Preparation of 4-iodo-2-(trifluoromethyl)phenol.**

[0590] To a solution of 2-(trifluoromethyl) phenol (3.24g, 20mmol) in MeOH (40 ml) was added sodium hydroxide (0.960g, 24.0mmol) and stirred until the hydroxide was dissolved. The mixture was cooled to 0°C and sodium iodide was added (3.0g, 20mmol) followed by dropwise addition of 10% aqueous sodium hypochlorite (9.0ml, 14.6mmol). The addition of sodium iodide followed by sodium hypochlorite was repeated twice more. The mixture was stirred at ambient temperature for 2h and treated dropwise with concentrated HCl to pH 1. The mixture was extracted 3 X with EtOAc. The extracts were combined, washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with EtOAc/hexane (1:9) to give the mono-iodo product (5.0 g, 87%).

Part B. Preparation of 2-bromo-4-iodo-6-(trifluoromethyl)phenol.

25

[0591] In a 250mL round-bottom flask was added the product from **Part A** (5.00 g, 17.36mmol) and 1,3-dibromo-5,5-dimethylhydantoin (2.73g, 9.55mmol) in CHCl₃ (80ml) to give an orange solution. The mixture was stirred for 2h, washed

with water, brine, dried with sodium sulfate, filtered and evaporated. The crude product was purified on silica gel eluting with ethyl acetate/hexane (5:95) to give a solid (3.5g, 54%).

5 **Part C. Preparation of 1-bromo-5-iodo-2-methoxy-3-(trifluoromethyl)benzene.**

[0592] A mixture of the product from **Part B** (3.2g, 8.72mmol), iodomethane (1.36ml, 21.8mmol), and 50% sodium hydroxide (0.507ml, 9.59mmol) in acetone (20ml) was stirred for 24h. The solvent was evaporated and the residue was partitioned with ethyl acetate and water. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The crude material was purified on silica gel eluting with ethyl acetate/hexane (5:95) to give a solid (2.67g, 80%).

15

Part D. Preparation of 1-(3-bromo-4-methoxy-5-(trifluoromethyl)phenyl)pyrimidine-2,4 (1H,3H)-dione.

[0593] In a 20mL microwave tube was added the product from **Part C** (762mg, 2.0mmol), pyrimidine-2,4(1H,3H)-dione (247mg, 2.2mmol), N-(2-cyanophenyl)picolinamide (89mg, 0.4mmol), copper(I) iodide (38.1mg, 0.2mmol) and potassium phosphate (892mg, 4.2mmol) in DMSO (10ml). The vessel was sealed and the mixture was sparged with nitrogen for 15min and heated at 60°C for 16h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was purified on silica gel eluting with ethyl acetate/hexane (2:3) to give the desired product (63mg, 9%).

30 **Part E. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(trifluoromethyl)phenyl)naphthalen-2-yl)methanesulfonamide.**

[0594] In a 5mL microwave tube was added the product from **Part D** (60mg,

0.164mmol), the product from **Example 2A, Part B** (62.8mg, 0.181mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (5.36mg, 8.22 μ mol) and potassium phosphate (69.8mg, 0.329mmol) in THF/water (3ml/1ml). The vessel was sealed and the mixture was sparged with nitrogen for 5min and

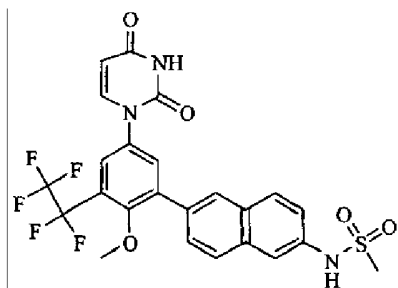
5 heated at 60°C for 2h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was purified by reverse phase chromatography to give the title compound as a solid

10 (26mg, 31%). ¹H NMR (300 MHz, DMSO-D6) δ ppm 3.10 (s, 3 H) 3.37 (s, 3 H) 5.71 (dd, J=7.72, 2.21 Hz, 1 H) 7.44 (dd, J=8.82, 2.21 Hz, 1 H) 7.75 (s, 1 H) 7.78 (d, J=1.84 Hz, 1 H) 7.88 (m, 3 H) 7.98 (d, J=3.31 Hz, 1 H) 8.01 (d, J=3.68 Hz, 1 H) 8.15 (s, 1 H) 10.09 (s, 1 H) 11.51 (d, J=2.21 Hz, 1 H). MS (ESI-) *m/z* 504.1 (M-H)⁺.

15

Example 37. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(perfluoroethyl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.60).

20 [0595]



Part A. Preparation of 1-methoxy-4-nitro-2-(perfluoroethyl)benzene.

[0596] To a 250mL round-bottom flask was added 2-bromo-1-methoxy-4-nitro-

25 benzene (3.5g, 15.08mmol), copper(I) iodide (5.75g, 30.2mmol), and sodium 2,2,3,3,3-pentafluoropropanoate (5.25g, 28.2mmol) in DMF (75ml) and toluene (25ml) to give a tan suspension. The mixture was heated at 150°C and toluene was removed by a Dean-Stark trap. The mixture was heated at 155°C for 6h

under nitrogen, cooled and poured into 100mL of water and 100mL of ether, filtered through a 1-inch plug of Celite and the plug was rinsed with ether. The filtrate layers were separated. The organic layer was washed with brine, dried (Na_2SO_4) filtered and concentrated. The dark oil was flash chromatographed on an Isco 40g silica cartridge eluting with 4:1 hexane/EtOAc to give a yellow oil that was a (3:1) mix of desired material and starting material (1.5g, 37%).

Part B. Preparation of 4-nitro-2-(perfluoroethyl)phenol.

10 **[0597]** In a 100mL round-bottom flask was added the product from **Part A** (1.4 g, 5.16mmol) and pyridine hydrochloride (4g, 34.6mmol) neat. The mixture was heated at 210°C for 20min, cooled, and partitioned between EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was flash chromatographed on an Isco 12g silica cartridge
15 eluting with 3:2 hexane/EtOAc to give a yellow oil (1.3g, 98%).

Part C. Preparation of 2-iodo-4-nitro-6-(perfluoroethyl)phenol.

[0598] In a 100mL round-bottom flask was added the product from **Part B** (1.3
20 g, 5.06mmol) and N-iodosuccinimide (1.251g, 5.56mmol) in acetonitrile (16.85 ml) to give a yellow solution. The solution was stirred for 16h, diluted with 100mL EtOAc and washed 2 x 50ml with 10% sodium thiosulfate, brine, dried (Na_2SO_4) and concentrated to an orange semisolid. The semisolid was flash chromatographed on an Isco 40g silica cartridge eluting with 3:1 hexane EtOAc
25 to give a deep yellow/orange oil (1.3g, 67%).

Part D. Preparation of 1-iodo-2-methoxy-5-nitro-3-(perfluoroethyl)benzene.

[0599] In a 100mL round-bottom flask was added the product from **Part C** (1.04
30 g, 2.72mmol) potassium carbonate (0.563g, 4.07mmol) and dimethyl sulfate (0.411g, 3.26mmol) in acetone (20ml) to give a brown suspension. The mixture was heated at gentle reflux for 16h, cooled, diluted into EtOAc, washed with water and brine. The organic layer was dried Na_2SO_4 , filtered and concentrated to

a yellow oil that was purified by flash chromatography on an Isco 40g silica cartridge eluting with 9:1 hexane/EtOAc (600mg, 56%).

Part E. Preparation of 3-iodo-4-methoxy-5-(perfluoroethyl)aniline.

5

[0600] In a 250mL round-bottom flask was added the product from **Part D** (0.6 g, 1.511mmol), iron (0.422g, 7.56mmol), and ammonium chloride (0.121g, 2.267mmol) in a solvent mix of EtOH (9ml), THF (9ml) and water (3ml) to give a brown suspension that was heated at 95-100°C for 2h. The reaction mix was filtered through a plug of Celite and the Celite was rinsed repeatedly with EtOH. The filtrate was concentrated and the residue was dissolved in EtOAc, washed with water, brine, dried (Na₂SO₄), filtered and concentrated to give an oil (560 mg, 99%).

15 **Part F. Preparation of 1,5-diiodo-2-methoxy-3-(perfluoroethyl)benzene.**

[0601] In a 25mL round-bottom flask under nitrogen was added the product from **Part E** (0.565g, 1.539mmol), tert-butyl nitrite (0.293ml, 2.463mmol), copper(I) iodide (0.293g, 1.539mmol), sodium iodide (0.231g, 1.539mmol) and iodine (0.195g, 0.770mmol) in DME (15.39ml) to give a brown suspension. The mixture was heated at 60°C for 3h, cooled and filtered through Celite washing the Celite pad well with EtOAc. The EtOAc filtrate was treated with 10% sodium thiosulfate, brine, dried (Na₂SO₄), filtered and concentrated to a dark oil. The crude material was purified by flash chromatography on an Isco 40g silica cartridge eluting with 95:5 hexane/EtOAc to give a yellow oil (360mg, 49%).

Part G. Preparation of 1-(3-iodo-4-methoxy-5-(perfluoroethyl)phenyl)pyrimidine-2,4(1H,3H)-dione.

30 [0602] In a 20mL microwave tube was added the product from **Part F** (0.36g, 0.753mmol), 1H-pyrimidine-2,4-dione (0.101g, 0.904mmol), potassium phosphate tribasic (0.336g, 1.582mmol) N-(2-cyanophenyl)picolinamide (0.034g, 0.151mmol) and copper(I) iodide (0.014g, 0.075mmol) in DMSO (7ml). The ves-

sel was sealed and the mixture was sparged with N₂ for 30min, heated at 60°C for 24h, cooled and diluted into EtOAc. The EtOAc layer was washed with 1M HCl, saturated NaHCO₃, and saturated NaCl, dried (Na₂SO₄), filtered and concentrated. The residue was flash chromatographed on an Isco 40g silica cartridge eluting with hexane --> 1:1 hexane/EtOAc to give a yellow foam (100mg, 29%).

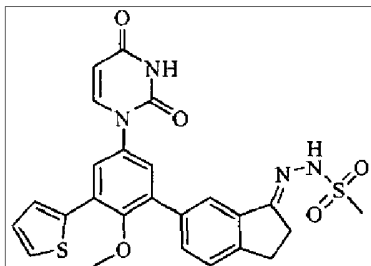
Part H. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(perfluoroethyl)phenyl)naphthalen-2-yl)methanesulfonamide.

10

[0603] In a 5mL microwave tube were combined the product from **Part G** (0.10 g, 0.216mmol), **Example 2A, Part B** (0.075g, 0.216mmol), and potassium phosphate tribasic (0.096g, 0.454mmol) in 3:1 tetrahydrofuran-water (5mL) and degassed by nitrogen sparge for 10min. The mixture was then treated with PA-
15 Ph (CAS 97739-46-3) (1.898mg, 6.49µmol) and tris(dibenzylideneacetone)dipalladium(0) (1.982mg, 2.164µmol) followed by degassing for another 5min. The flask was then sealed and stirred at 50°C for 16h and partitioned between EtOAc and water. The EtOAc layer was washed with 0.1M HCl, saturated NaHCO₃, and saturated NaCl. The organic was dried Na₂SO₄, stirred for 0.5h with
20 3-mercapto-propyl functionalized silica to remove metals, filtered and concentrated. The crude product was purified by chromatography on an Isco 12g silica cartridge eluting with CH₂Cl₂ --> 3% MeOH in CH₂Cl₂ to give a light yellow foam (84mg, 99%) m.p. 162-165°C. ¹H NMR (300 MHz, DMSO-D₆) δ ppm 3.10 (s, 3 H) 3.33 (s, 3 H) 5.70 (d, J=7.72 Hz, 1 H) 7.44 (dd, J=8.82, 2.21 Hz, 1 H) 7.70 -
25 7.76 (m, 2 H) 7.80 (d, J=2.57 Hz, 1 H) 7.86 (d, J=8.09 Hz, 1 H) 7.91 (d, J=2.57 Hz, 1 H) 8.00 (dd, J=8.82, 2.94 Hz, 2 H) 8.12 (s, 1 H) 10.10 (s, 1 H) 11.50 (s, 1 H). MS (ESI-) *m/z* 554 (M-H)⁺.

Example 38. Preparation of (E)-N'-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1-(2H)-yl)-2-methoxy-3-(thiophen-2-yl)phenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide (compound IB-L0-2.51).

30

[0604]

Part A. Preparation of 1-(3-bromo-4-methoxy-5-(1-oxo-2,3-dihydro-1H-inden-5-yl)phenyl)pyrimidine-2,4(1H,3H)-dione.

5

[0605] In a 100mL round-bottom flask was added the product from **Example 18, Part C** (846mg, 2.00mmol), **Example 4, Part A** (516mg, 2.000mmol), potassium phosphate (892mg, 4.20mmol), PA-Ph (CAS 97739-46-3) (17.54mg, 0.060mmol) and tris(dibenzylideneacetone)-dipalladium(0) (18.31mg, 0.020 mmol) in THF (12.0ml) and water (4.0ml). The vessel was sealed and the mixture was sparged with nitrogen for 5min and stirred at ambient temperature for 72h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered through celite and evaporated. The residue was purified with silica gel eluting with 1 to 4% methanol in CH₂Cl₂ to give a solid (690mg, 81%).

15

Part B. Preparation of (E)-N'-(5-(3-bromo-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide.

20

[0606] In a 50mL round-bottom flask was added the product from **Part A** (685 mg, 1.603mmol) and methanesulfonohydrazide (194mg, 1.764mmol) in MeOH (20ml). The mixture was warmed to 40°C and stirred for 24h. The mixture was cooled, filtered and washed with methanol to give a solid (569mg, 68%).

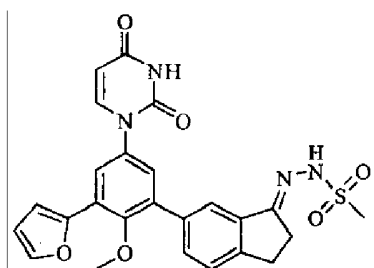
25

Part C. Preparation of (E)-N'-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(thiophen-2-yl)phenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide.

[0607] In a 5mL microwave tube was added the product from **Part B** (52mg, 0.100mmol), thiophen-2-ylboronic acid (12.81mg, 0.100mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (3.26mg, 5.01 μ mol) and potassium phosphate (42.5mg, 0.200mmol) in THF (3.0ml) and water (1.0ml). The mixture was sparged by nitrogen for 5min and heated at 50°C for 3h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered through celite and evaporated. The residue was purified by reverse phase chromatography AA method to give a white solid (27mg, 52%). ¹H NMR (300 MHz, DMSO-D6) δ ppm 2.86 (m, 2 H) 3.09 (s, 3 H) 3.14 (m, 2 H) 3.32 (s, 3 H) 5.69 (d, J=7.72 Hz, 1 H) 7.18 (dd, J=5.15, 3.68 Hz, 1 H) 7.41 (d, J=2.57 Hz, 1 H) 7.63 (m, 3 H) 7.75 (m, 2 H) 7.86 (d, J=8.09 Hz, 1 H) 7.91 (d, J=2.94 Hz, 1 H) 9.96 (s, 1 H) 11.48 (s, 1 H). MS (ESI+) *m/z* 523 (M+H)⁺.

15

Example 39. Preparation of (E)-N'-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1-(2H)-yl)-3-(furan-2-yl)-2-methoxyphenyl)-2,3-dihydro-1H-inden-1-ylidene)-methanesulfonohydrazide (compound IB-L0-2.55).

20 **[0608]**

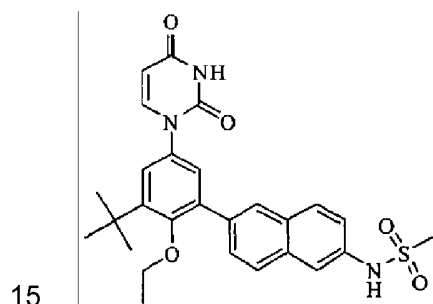
[0609] In a 5ml microwave tube was added the product from **Example 38, Part B** (52mg, 0.100mmol), furan-2-ylboronic acid (11.20mg, 0.100mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (3.26mg, 5.01 μ mol) and potassium phosphate (42.5mg, 0.200mmol) in THF (3.0ml) and water (1.0ml). The mixture was sparged by nitrogen for 5min and heated at 50°C for 3h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and

25

filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered through celite and evaporated. The residue was purified by reverse phase chromatography AA method to give a solid (24mg, 47%). ¹H NMR (300 MHz, DMSO-D6) δ ppm 2.86 (m, 2 H) 3.09 (s, 3 H) 3.14 (m, 2 H) 3.36 (s, 3 H) 5.68 (d, J=8.09 Hz, 1 H) 6.69 (dd, J=3.31, 1.84 Hz, 1 H) 7.09 (d, J=3.31 Hz, 1 H) 7.41 (d, J=2.57 Hz, 1 H) 7.62 (m, 2 H) 7.75 (d, J=8.09 Hz, 1 H) 7.80 (d, J=2.57 Hz, 1 H) 7.86 (m, 2 H) 9.97 (s, 1 H) 11.46 (s, 1 H). MS (ESI+) *m/z* 507 (M+H)⁺.

- 10 **Example 40. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-ethoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.23).**

[0610]



Part A. Preparation of 2-tert-butyl-4-iodophenol.

- [0611] To a 250mL round-bottom flask was added 2-tert-butylphenol (3.76g, 25 mmol) in MeOH (50.0ml) to give a colorless solution. Sodium hydroxide (1.200 g, 30.0mmol) was added and the mix was stirred until the hydroxide was completely dissolved. The solution was cooled to 0°C and treated with sodium iodide (1.75g, 11.6mmol) followed by dropwise addition of 10% sodium hypochlorite solution (7.2ml, 11.6mmol). The addition of sodium iodide followed by sodium hypochlorite was repeated twice and the mixture was stirred at 0°C for 30min.
- 25 The mixture was treated with 10% w/w solution of sodium thiosulfate, stirred for 30min and treated with concentrated HCl dropwise to a constant pH of 1. The mixture was extracted 3X with EtOAc. The extracts were combined, washed with brine, dried (MgSO₄), filtered and concentrated. The crude oil was flash

chromatographed on an ISCO 80g silica cartridge eluting with hexane --> 4:1 hexane/EtOAc to give a yellow oil (5.2g, 75%).

Part B. Preparation of 2-bromo-6-tert-butyl-4-iodophenol.

5

[0612] To a 250mL round-bottom flask was added the product from **Part A** (4.8g, 17.38mmol) and 1,3-dibromo-5,5-dimethylhydantoin (2.61g, 9.13mmol) in chloroform (87ml) to give an orange solution. The reaction mixture was stirred for 2h resulting in a black solution that was washed with water, brine, dried (Na₂SO₄) and concentrated. The black oil was flash chromatographed on a
10 120g Isco silica cartridge eluting with hexane to give a pinkish solid (4.84g, 78%).

Part C. Preparation of 1-bromo-3-tert-butyl-2-ethoxy-5-iodobenzene.

15

[0613] To a 50mL round-bottom flask was added the product from **Part B** (888 mg, 2.5mmol), ethyl iodide (409mg, 2.63mmol), and potassium carbonate (415 mg, 3.00mmol) in acetone (12ml) to give a green suspension. The mixture was heated at reflux for 16h, cooled and concentrated. The residue was partitioned
20 between water and EtOAc. The organic layer was washed twice with brine, dried over Na₂SO₄, filtered and concentrated to a red oil. The oil was flash chromatographed on an Isco 40g silica cartridge eluting with hexane to give a clear oil (820mg, 86%).

25 **Part D. Preparation of 1-(3-bromo-5-tert-butyl-4-ethoxyphenyl)pyrimidine-2,4(1H,3H)-dione.**

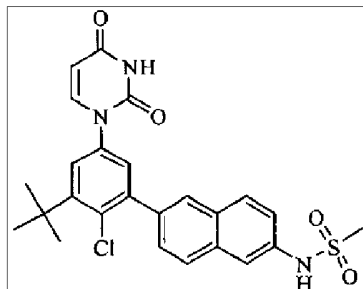
[0614] In a 20mL microwave tube under nitrogen flush was added the product from **Part C** (0.4g, 1.044mmol), 1H-Pyrimidine-2,4-dione (0.140g, 1.253mmol),
30 and potassium phosphate tribasic (0.465g, 2.193mmol) in DMSO (5ml) to give a colorless suspension. N-(2-cyanophenyl)picolinamide (0.047g, 0.209mmol) was added and the mix was sparged with nitrogen for 10min. Copper(I) iodide (0.020 g, 0.104mmol) was added and the mix was sparged once again for 10min,

placed under nitrogen and heated at 60°C for 18h. The mixture was cooled and partitioned between EtOAc and water adjusting the pH to 1 with HCl. The aqueous layer was extracted 2X with EtOAc. The organics were combined, washed with water, saturated NaHCO₃, and saturated NaCl. The organic layer
5 was dried (Na₂SO₄), stirred with 3-mercaptopropyl functionalized silica for 1h, filtered and concentrated. The crude product was purified by chromatography on an ISCO 12g silica cartridge eluting with 2% MeOH in CH₂Cl₂ to give a white powder (266mg, 69%).

10 **Part E. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-ethoxyphenyl)naphthalen-2-yl)methanesulfonamide.**

[0615] In a 5mL microwave tube was added the product from **Part D** (55.1mg, 0.15mmol), the product from **Example 2A, Part B** (52.1mg, 0.150mmol), potas-
15 sium phosphate tribasic (63.7mg, 0.300mmol) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (4.89mg, 7.50μmol) in THF (3ml) water (1ml). The mixture was sparged for 10min with nitrogen, heated sealed at 50°C for 4h, cooled and diluted into EtOAc. The EtOAc layer was washed with 1M HCl, saturated NaHCO₃, saturated NaCl, dried (Na₂SO₄) and treated simultaneously with
20 mercaptopropyl silica gel, filtered and concentrated. The residue was flash chromatographed on a 12g Isco silica cartridge eluting with 2% MeOH in CH₂Cl₂ to give a solid, (16mg, 21%) m.p. 196-202°C. ¹H NMR (300 MHz, DMSO-D₆) δ ppm 1.00 (t, J=6.99 Hz, 3 H) 1.44 (s, 9 H) 3.09 (s, 3 H) 3.43 (q, J=7.11 Hz, 2 H) 5.64 (dd, J=7.91, 1.29 Hz, 1 H) 7.32 (d, J=2.94 Hz, 1 H) 7.36 (d, J=2.94 Hz, 1
25 H) 7.41 (dd, J=8.82, 2.21 Hz, 1 H) 7.72 (s, 1 H) 7.74 (d, J=1.47 Hz, 1 H) 7.80 (d, J=7.72 Hz, 1 H) 7.90 - 8.00 (m, 2 H) 8.05 (s, 1 H) 10.04 (s, 1 H) 11.41 (s, 1 H). MS (ESI-) *m/z* 506 (M-H)⁺.

Example 41. Preparation of N-(6-(3-tert-butyl-2-chloro-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)naphthalen-2-yl)methanesulfonamide
30 **(compound IB-L0-2.14).**

[0616]**Part A. Preparation of 2-bromo-6-tert-butyl-4-iodoaniline.**

5

[0617] In a 50mL round-bottom flask was added 2-bromo-6-tert-butylaniline [prepared by the method of Onitsuka, et.al. Organometallics, 25(5), 2006, pp 1270-1278] (1.18g, 5.17mmol) and sodium bicarbonate (0.782g, 9.31mmol) in water (5ml). The mixture was cooled in an ice bath and iodine (1.444g, 5.69mmol) was added in several portions. The mixture was warmed to ambient temperature and stirred for 16h. The mixture was treated with aqueous sodium thiosulfate, extracted by ethyl acetate, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with 5% ethyl acetate in hexane to give an oil (1.2g, 65%).

15

Part B. Preparation of 1-bromo-3-tert-butyl-2-chloro-5-iodobenzene.

[0618] To a mixture of tert-butyl nitrite (0.198ml, 1.5mmol) and copper(II) chloride (161mg, 1.2mmol) in acetonitrile (5mL) was added the product from **Part A** (354mg, 1.0mmol) as a solution in acetonitrile (5mL). The mixture was heated at 60°C for 30min, cooled, partitioned with ethyl acetate and 1M HCl. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with 5% ethyl acetate in hexane to give the product (300mg, 81%).

25

Part C. Preparation of 1-(3-bromo-5-tert-butyl-4-chlorophenyl)pyrimidine-2,4(1H,3H)-dione.

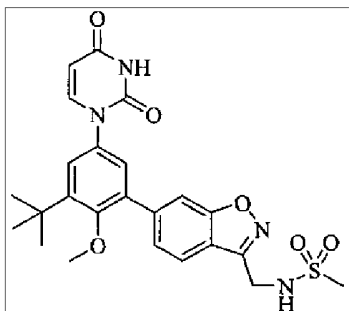
[0619] In a 20mL microwave tube was added the product from **Part B** (300mg, 0.803mmol), pyrimidine-2,4(1H,3H)-dione (99mg, 0.884mmol), N-(2-cyanophenyl)picolinamide (35.9mg, 0.161mmol), copper(I) iodide (15.30mg, 0.080 mmol) and potassium phosphate (358mg, 1.687mmol) in DMSO (5ml). The mixture was sealed, purged with nitrogen and heated at 60°C for 4h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was purified on silica gel eluting with 10% to 40% ethyl acetate in hexane to give a solid (175mg, 61 %).

Part D. Preparation of N-(6-(3-tert-butyl-2-chloro-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)naphthalen-2-yl)methanesulfonamide.

[0620] In a 5mL microwave tube was added the product from **Part C** (35.8mg, 0.10mmol), the product from **Example 2A, Part B** (38.2mg, 0.110mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (3.26mg, 5.00µmol) and potassium phosphate (42.5mg, 0.200mmol) in THF/Water (3ml:1ml). The mixture was purged with nitrogen for 5min and heated at 60°C for 2h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was purified on silica gel eluting with 1:1ethyl acetate/hexane to give a solid that was triturated with 1% methanol in CH₂Cl₂ to give a white solid (29mg, 55%), melting point: > 280°C. ¹H NMR (300 MHz, DMSO-D₆) δ ppm 1.53 (s, 9 H) 3.08 (s, 3 H) 5.69 (d, J=7.72 Hz, 1 H) 7.42 (m, 2 H) 7.52 (dd, J=8.46, 1.84 Hz, 1 H) 7.56 (d, J=2.57 Hz, 1 H) 7.74 (d, J=1.84 Hz, 1 H) 7.84 (d, J=7.72 Hz, 1 H) 7.88 (s, 1 H) 7.91 (d, J=8.82 Hz, 1 H) 7.95 (d, J=9.19 Hz, 1 H) 10.04 (s, 1 H) 11.46 (s, 1 H). MS (ESI-) *m/z* 496 (M-H)⁺.

Example 42. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[d]isoxazol-3-yl)methyl)methanesulfonamide (compound IB-L0-2.45).

5 [0621]



Part A. Preparation of *N*-((6-bromobenzo[d]isoxazol-3-yl)methyl)-*N*-(4-methoxybenzyl)-methanesulfonamide.

10

[0622] To a refluxing solution of 6-bromo-3-methylbenzo[d]isoxazole (1.0g, 4.72 mmol) in CCl₄ (25ml) was added 1-bromopyrrolidine-2,5-dione (0.923g, 5.19 mmol) and benzoic peroxyanhydride (0.114g, 0.472mmol). The mixture was refluxed for 6h, and then cooled to room temperature, filtered thru celite, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using CH₂Cl₂ as the eluent to give the dibromide as a solid (0.84g, 43%). To a solution of the dibromide (0.20g, 0.687mmol) and *N*-(4-methoxybenzyl)methanesulfonamide (0.148g, 0.687mmol) in EtOH (3ml) was added 1N aq. NaOH (0.722ml, 0.722mmol), and the resulting mixture was stirred at 80°C for 15 90min. The mixture was partitioned between 0.1N aq. HCL (10mL) and EtOAc (2 x 10mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 2:3 EtOAc:hexanes as eluent to give the title compound as an oil (65mg, 22%).

25

Part B. Preparation of *N*-(4-methoxybenzyl)-*N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]isoxazol-3-yl)methyl)methanesulfonamide.

[0623] A solution of the product from **Part A** (56mg, 0.132mmol), bis(pinacolato)diboron (37mg, 0.145mmol), and potassium acetate (39mg, 0.395mmol) in 1,4-dioxane (1.3mL) was degassed by bubbling with N₂ gas for 15min. 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (3mg, 0.004mmol) was added, and the resulting mixture was stirred at 80°C for 16h, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 1:2 EtOAc:hexanes as the eluent to give the title compound as a colorless oil (49mg, 79%).

10 **Part C. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*-yl)-2-methoxyphenyl)benzo[*d*]isoxazol-3-yl)methyl)-*N*-(4-methoxybenzyl)methanesulfonamide.**

[0624] A mixture of the product from **Example C** (31.8mg, 0.079mmol), the product from **Part B** (45mg, 0.095mmol) in EtOH (0.5mL), toluene (0.5mL) 1M aq. Na₂CO₃ (0.095mL, 0.095mmol) was degassed by bubbling with N₂ gas for 10min. 1,1'- Bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (2mg, 2.4μmol) was added, and degassing with N₂ was continued for 5min. The reaction mixture was sealed and heated at 100°C in a microwave reactor for 1h. The mixture was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using 1:9 MeOH:CHCl₃ as the eluent. The title compound was obtained as a light brown solid (41mg, 83%).

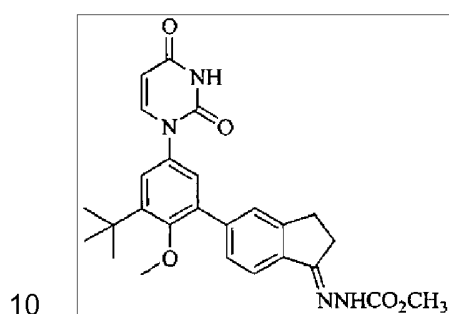
25 **Part D. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*-yl)-2-methoxyphenyl)benzo[*d*]isoxazol-3-yl)methyl)methanesulfonamide.**

[0625] A solution of the product from **Part C** (39mg, 0.063mmol) in TFA (0.5mL) was stirred at 40°C for 6h. TFA was removed in vacuo and the crude product was purified by column chromatography on silica gel using 4% MeOH in CHCl₃ as the eluent to give the title compound (13mg, 41%). ¹H NMR (300 MHz, CDCl₃) δ 8.39 (s, 1 H) 7.74 - 7.82 (m, 2 H) 7.57 (dd, *J*=8.27, 1.65 Hz, 1 H) 7.36

(d, $J=7.72$ Hz, 1 H) 7.25 (d, $J=2.57$ Hz, 1 H) 7.19 (d, $J=2.94$ Hz, 1 H) 5.82 (dd, $J=7.72, 2.21$ Hz, 1 H) 5.25 - 5.33 (m, 1 H) 4.70 (d, $J=6.25$ Hz, 2 H) 3.29 (s, 3 H) 3.12 (s, 3 H) 1.45 (s, 9 H).

- 5 **Example 43. Preparation of methyl 2-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ylidene)-hydrazinecarboxylate (compound IB-L0-2.24).**

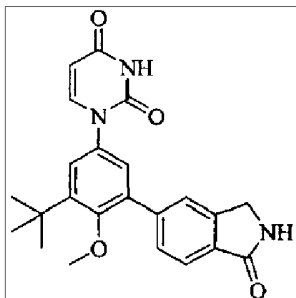
[0626]



- [0627] To a solution of the product from **Example 4, Part B** (0.05g, 0.124mmol) in MeOH (1ml) was added methyl carbazate (17mg, 0.185mmol). The mixture was stirred at 60°C for 16h, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 5% MeOH in CH₂Cl₂ as the eluent to give the title compound (44mg, 74%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.40 (s, 1 H) 10.05 (s, 1 H) 7.78 (d, $J=8.09$ Hz, 1 H) 7.69 (d, $J=7.72$ Hz, 1 H) 7.45 - 7.57 (m, 2 H) 7.24 - 7.33 (m, 2 H) 5.64 (d, $J=8.09$ Hz, 1 H) 3.71 (s, 3 H) 3.28 (s, 3 H) 3.06 - 3.16 (m, 2 H) 2.78 - 2.88 (m, 2 H) 1.40 (s, 9 H).
- 15
- 20

Example 44. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(1-oxoisoindolin-5-yl)phenyl)-pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-230).

[0628]

**Part A. Preparation of 5-bromo-2-(2,4-dimethoxybenzyl)isoindolin-1-one.**

5

[0629] To a solution of methyl 4-bromo-2-(bromomethyl)benzoate (1.0g, 3.25 mmol) and (2,4-dimethoxyphenyl)methanamine (0.65g, 3.90mmol) in THF (16 mL) was added triethylamine (0.91mL, 6.5mmol), and the resulting mixture was stirred at room temperature for 16h. The resulting solid was filtered off, and the
10 filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 1:4 EtOAc:hexanes as the eluent to give the title compound as a colorless solid (0.52g, 44%).

Part B. Preparation of 2-(2,4-dimethoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one.

15

[0630] The product from **Part A** (100mg, 0.276mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound as an oil (107mg, 95%).

20

part C. Preparation of 1-(3-tert-butyl-5-(2-(2,4-dimethoxybenzyl)-1-oxoisoindolin-5-yl)-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0631] The product from **Part C** (44mg, 0.111mmol) was subjected to the conditions described for **Example 42, Part C** to give the title compound (50mg, 81%).

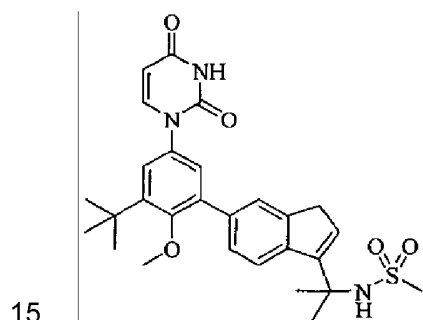
25

Part D. Preparation of 1-(3-tert-butyl-4-methoxy-5-(1-oxoisoindolin-5-yl)-phenyl) pyrimidine-2,4(1H,3H)-dione.

[0632] A solution of the product from **Part C** (48mg, 0.086mmol) in CH₂Cl₂ (0.3 ml) and TFA (0.6ml, 7.79mmol) was stirred at room temperature for 16h, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 5% MeOH in CHCl₃ as the eluent to give the title compound as a colorless solid (22mg, 63%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.41 (d, *J*=1.84 Hz, 1 H) 8.61 (s, 1 H) 7.72 - 7.83 (m, 3 H) 7.62 - 7.69 (m, 1 H) 7.29 - 7.36 (m, 2 H) 5.65 (dd, *J*=8.09, 2.21 Hz, 1 H) 4.44 (s, 2 H) 3.25 (s, 3 H) 1.41 (s, 9 H).

10 **Example 45. Preparation of *N*-(2-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)propan-2-yl)methanesulfonamide (compound IB-L0-2.41).**

[0633]



Part A. Preparation of 6-bromo-1*H*-indene-3-carbonitrile.

[0634] To a solution of 5-bromo-2,3-dihydro-1*H*-inden-1-one (1g, 4.74mmol) in anhydrous THF (15ml) at -10°C was added 2M lithium diisopropylamide in THF (0.242ml, 0.483mmol) dropwise. The resulting mixture was stirred at -10°C for 15min before diethylcyanophosphonate (0.791ml, 5.21mmol) was added dropwise. Following the addition, the mixture was allowed to warm to room temperature, and was stirred at room temperature for 3h. The mixture was cooled to
25 -78°C and borontrifluoride diethyl etherate (1.196ml, 9.52mmol) was added dropwise. Following the addition, the mixture was stirred at -78°C for 1h and was then allowed to warm to room temperature and was stirred at room temperature for 16h. The mixture was concentrated in vacuo, and the residue was

partitioned between EtOAc (50mL) and H₂O (2 x 50mL). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using 9:1 EtOAc:hexanes as the eluent. The title compound was obtained as an tan solid (0.72g, 69%).

5

Part B. Preparation of *N*-(2-(6-bromo-1*H*-inden-3-yl)propan-2-yl)methanesulfonamide.

[0635] Anhydrous cerium(III) chloride (0.224g, 0.909mmol) was flame dried under vacuum and placed under dry N₂. Anhydrous THF (1.5ml) was added, and the resulting mixture was stirred under N₂ at 45°C for 48h. The mixture was cooled to room temperature, and the product from **Part A** (0.1 g, 0.454mmol) was added. The resulting mixture was cooled to -78°C, and a 1.5M solution of methyl-lithium lithium bromide complex (0.757ml, 1.136mmol) in Et₂O was added dropwise over 15min. Following the addition, the mixture was allowed to warm to -20°C and was stirred for 24h. Concentrated aq. NH₄OH (0.3mL) was added dropwise, and the mixture was allowed to warm to room temperature, was stirred for 30min, and was then filtered and washed with THF (2 x 5mL). The filtrate was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using 5% MeOH in CH₂Cl₂ as the eluent to give a solid (23mg, 20%). To a solution of this solid (23mg, 0.091mmol) in CH₂Cl₂ (1mL) was added methanesulfonyl chloride (0.011mL, 0.137mmol). The mixture was cooled to 0°C and diisopropylethylamine (0.024ml, 0.137mmol) was added dropwise. The resulting mixture was stirred at room temperature for 90min, and was then partitioned between 0.1 N aq. HCl (2mL) and CH₂Cl₂ (3 x 2mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel to give the title compound (17mg, 56%).

30 **Part C. Preparation of *N*-(2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-inden-3-yl)propan-2-yl)methanesulfonamide.**

[0636] The product from **Part C** (50mg, 0.151mmol) was subjected to the condi-

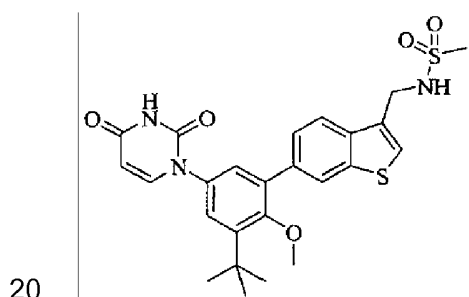
tions described for **Example 42, Part B** to give the title compound as a colorless solid (37mg, 65%).

Part D. Preparation of N-(2-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)propan-2-yl)methanesulfonamide.

[0637] The product from **Part C** (35mg, 0.093mmol) was subjected to the conditions described for **Example 42, Part C** to give the title compound as a colorless solid (41mg, 84%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.40 (s, 1 H) 7.94 (d, *J*=8.09 Hz, 1 H) 7.78 (d, *J*=8.09 Hz, 1 H) 7.65 (d, *J*=1.50 Hz, 1 H) 7.56 (s, 1 H) 7.48 (dd, *J*=8.09, 1.47 Hz, 1 H) 7.27 (s, 2 H) 6.48 (s, 1 H) 5.63 (d, *J*=8.09 Hz, 1 H) 3.43 (s, 2 H) 3.25 (s, 3 H) 2.63 (s, 3 H) 1.68 (s, 6 H) 1.41 (s, 9 H).

Example 46. Preparation of N-((6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-3-yl)methyl)methanesulfonamide (compound IB-L0-2.11).

[0638]



Part A. Preparation of ethyl 6-bromobenzo[*b*]thiophene-2-carboxylate.

[0639] A solution of ethyl thioglycolate (0.65g, 5.42mmol), 4-bromo-2-fluorobenzaldehyde (1.0g, 4.93mmol) and triethylamine (1.25mL, 12.3mmol) in DMSO (5mL) was heated at 75°C for 2h. The mixture was partitioned between H₂O (50mL) and CH₂Cl₂ (2 x 50mL), and the combined organic layers were dried over Na₂SO₄. The drying agent was filtered off, and the solvent was removed in vacuo to give the title compound as an oil (1.29g, 92%).

Part B. Preparation of 6-bromobenzo[*b*]thiophene-2-carboxylic acid.

[0640] To a solution of the product from **Part A** (1.21g, 4.24mmol) in THF (10mL) was added a solution of LiOH (0.305g, 12.73mmol) in H₂O (4mL) and the resulting mixture was stirred at 40°C for 2h. The mixture was partitioned between H₂O (50mL) and CH₂Cl₂ (50mL). The aqueous layer was adjusted to pH = 2 using 1N HCl, and extracted with CH₂Cl₂ (2 x 50mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound as an oil (1.04g, 95%).

10

Part C. Preparation of 6-bromobenzo[*b*]thiophene.

[0641] The product from **Part B** (0.70g, 2.73mmol) and DBU (1.35mL, 8.94 mmol) were combined in DMA (6mL) in a sealed tube and heated at 200°C in a microwave reactor for 70min. The resulting dark solution was diluted with 1 M HCl (20mL) and extracted with CH₂Cl₂ (2 x 20mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using CH₂Cl₂ as the eluent to give the title compound as an oil (0.484g 83%).

20

Part D. Preparation of 6-bromo-3-(chloromethyl)benzo[*b*]thiophene.

[0642] To a solution of the product from **Part C** (0.484g, 2.27mmol) in benzene (0.20mL) was added 37% aq. formaldehyde solution (1mL) and concentrated HCl (1mL). The resulting mixture was heated at 70°C for 1h. while HCl gas was bubbled through the mixture. The mixture was partitioned between H₂O (20mL) and CH₂Cl₂ (2 x 20mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using CH₂Cl₂ to give the title compound as a waxy solid (0.49g, 82%).

30

Part E. Preparation of *N*-((6-bromobenzo[*b*]thiophen-3-yl)methyl)-*N*-(2,4-dimethoxybenzyl) methanesulfonamide.

[0643] To a solution of the product from **Part D** (275mg, 1.05mmol) and *N*-(2,4-dimethoxybenzyl)-methanesulfonamide (284mg, 1.15mmol) in DMA (6mL) was added K₂CO₃ (160mg, 1.15mmol), and the mixture was stirred at room temperature for 3h. The mixture was partitioned between H₂O (20mL) and Et₂O (2 x 20mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 2% EtOAc in CH₂Cl₂ as the eluent to give the title compound as a waxy solid (316mg, 64%).

10 **Part F. Preparation of *N*-(2,4-dimethoxybenzyl)-*N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-3-yl)methyl)methanesulfonamide.**

[0644] The product from **Part E** (300mg, 0.64mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound as a waxy solid (248mg, 75%).

Part G. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-3-yl)methyl)-*N*-(2,4-dimethoxybenzyl)methanesulfonamide.

[0645] The product from **Part F** (214mg, 0.414mmol) was subjected to the conditions described for **Example 42, Part C** to give the title compound as a light yellow solid (238mg, 87%).

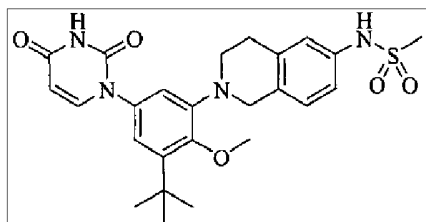
25 **Part H. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-3-yl)methyl)methanesulfonamide.**

30 **[0646]** To a solution of the product from **Part G** (230mg, 0.34mmol) in CH₂Cl₂ (4mL) was added trifluoroacetic acid (0.5mL), and the mixture was stirred at room temperature for 30min. The solution was diluted with CH₂Cl₂ (10mL) and extracted with saturated aq. NaHCO₃ (2 x 10mL). The organic layer was dried

over Na₂SO₄, filtered and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel eluting with 3% MeOH in CH₂Cl₂ to give the title compound as an off-white solid (149mg, 84%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.41 (s, 1 H) 8.16 (d, *J*=1.10 Hz, 1 H) 8.02 (d, *J*=8.46 Hz, 1 H) 7.79 (d, *J*=7.72 Hz, 1 H) 7.71 (s, 1 H) 7.60 - 7.66 (m, 2 H) 7.29 - 7.38 (m, 2 H) 5.65 (d, *J*=7.72 Hz, 1 H) 4.44 (d, *J*=5.88 Hz, 2 H) 3.24 (s, 3 H) 2.95 (s, 3 H) 1.42 (s, 9 H).

Example 47. Preparation of *N*-(2-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)methanesulfonamide (compound IB-L0-2.19).

[0647]



15

Part A. Preparation of 1-(3-amino-5-*tert*-butyl-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione.

[0648] To a solution of the product from **Example 5, Part F** (170mg, 0.534 mmol) and triethylamine (223uL, 1.6mmol) in THF (5mL) was added diphenylphosphoryl azide (173uL, 0.80mmol). The resulting mixture was stirred at room temperature for 1h, and was then stirred at 45°C for 1h. Water (280uL) was added, and the resulting mixture was stirred at 50°C for 1h, and then stirred at room temperature for 16h. The solution was diluted with H₂O (10mL), and the resulting solid was filtered off. The solid was suspended in 1M aq. HCl and filtered to give the amine product as the HCl salt. This salt was suspended in aq. NaHCO₃ (20mL) and extracted with EtOAc (2 x 20mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound as a colorless solid (55mg, 36%).

Part B. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(6-nitro-3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)pyrimidine-2,4(1*H*,3*H*)-dione.

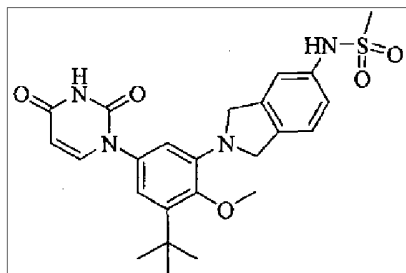
[0649] A solution of the product from **Part A** (100mg, 0.28mmol) and 2-(2-(methylsulfonyloxy)-ethyl)-4-nitrobenzyl methanesulfonate (196mg, 0.68mmol) were in anhydrous DMA (4mL) was stirred at 80°C for 18h. The cooled mixture was partitioned between H₂O (20mL) and EtOAc (2 x 20mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was suspended in CH₂Cl₂ and filtered to remove unreacted aniline starting material. The filtrate was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel eluting with 1% MeOH in CH₂Cl₂ to give the title compound as a light yellow solid (39.3mg, 31%).

Part C. Preparation of *N*-(2-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)methanesulfonamide.

[0650] To a solution of the product from **Part B** (35mg, 0.078mmol) in THF (0.5 mL), MeOH (0.5mL) and H₂O (0.25mL) was added Fe powder (17.4mg, 0.41mmol) and NH₄Cl (6.2mg, 0.12mmol), and the resulting mixture was stirred at 70°C for 1h. The hot mixture was filtered through celite and rinsed with THF and MeOH. The filtrate was concentrated and dried in vacuo to give a solid. To a solution of the solid (32mg, 0.076mmol) and pyridine (26uL, 0.32mmol) in CH₂Cl₂ (1.5mL) was added methanesulfonyl chloride (7.7uL, 0.099mmol). The mixture was stirred at room temperature for 1h then concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 5% MeOH in CH₂Cl₂ to give the title compound as a light yellow solid (7mg, 19%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.71 (d, J=8.09 Hz, 1 H) 7.14 - 7.21 (m, 1 H) 7.05 - 7.12 (m, 3 H) 6.98 (d, J=2.57 Hz, 1 H) 5.65 (d, J=7.72 Hz, 1 H) 4.18 (s, 2 H) 3.86 (s, 3 H) 3.03 (t, J=4.23 Hz, 2 H) 2.99 (s, 3 H) 1.38 (s, 9 H).

Example 48. Preparation of *N*-(2-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)isoindolin-5-yl)methanesulfonamide (compound IB-L0-2.79).

5 [0651]



Part A. Preparation of (4-nitro-1,2-phenylene)bis(methylene)dimethanesulfonate.

10

[0652] To a solution of 4-nitrophthalic acid (500mg, 2.37mmol) in THF (24mL) at room temperature was added a 1M solution of BH₃•THF complex (9.95mL, 9.95mmol) dropwise. This solution was stirred at 65°C for 1h, and then allowed to cool to room temperature. To the mixture was added MeOH (1mL), and the mixture was stirred for 30min and concentrated in vacuo. The residue was partitioned between 1M aq. HCl (20mL) and EtOAc (2 x 20mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 3% MeOH in CH₂Cl₂ to give an oil (253mg, 58%). To a solution of the oil (250 mg, 2.37mmol) and triethylamine (438uL, 3.14mmol) in anhydrous CH₂Cl₂ (30mL) at 0°C was added methanesulfonyl chloride (234uL, 3.0mmol) dropwise. The solution was stirred at room temperature for 18h, and was partitioned between 1M aq. HCl (20mL) and CH₂Cl₂ (2 x 20mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with CH₂Cl₂ to give the title compound (150mg, 32%).

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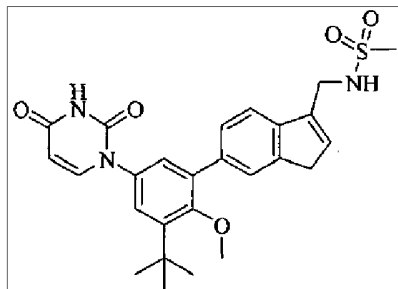
Part B. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(5-nitroisindolin-2-yl)-phenyl) pyrimidine-2,4(1*H*,3*H*)-dione.

[0653] To a solution of the product of **Part A** (110mg, 0.324mmol) and the product of **Example 47, Part A** (113mg, 0.389mmol) in anhydrous 1,4-dioxane (4mL) was added sodium bicarbonate (60mg, 0.71mmol) and diisopropylethylamine (142uL, 0.81mmol) and the resulting mixture was stirred at 95°C for 16h. The mixture was partitioned between 0.5M aq. HCl (10mL) and CH₂Cl₂ (2 x 10mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 1% MeOH in CH₂Cl₂ to give the title compound as a light yellow solid (110mg, 78%).

Part C. Preparation of *N*-(2-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*-yl)-2-methoxyphenyl)isindolin-5-yl)methanesulfonamide.

[0654] The product from **Part B** (100mg, 0.25mmol) was subjected to the conditions described for **Example 47, Part C** to give the title compound as an off-white solid (53mg, 45%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.37 (s, 1 H) 9.70 (s, 1 H) 7.71 (d, J=7.72 Hz, 1 H) 7.34 (d, J=8.09 Hz, 1 H) 7.23 (d, J=1.84 Hz, 1 H) 7.13 (dd, J=8.09, 1.84 Hz, 1 H) 6.98 (d, J=2.57 Hz, 1 H) 6.81 (d, J=2.21 Hz, 1 H) 5.62 (d, J=7.72 Hz, 1 H) 4.52 (s, 2 H) 4.50 (s, 2 H) 3.63 (s, 3 H) 2.98 (s, 3 H) 1.38 (s, 9 H).

Example 49. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide (compound IB-L0-2.13).

[0655]

Part A. Preparation of 5-bromo-1-(trimethylsilyloxy)-2,3-dihydro-1H-indene-1-carbonitrile.

[0656] To a solution of 5-bromo-2,3-dihydro-1H-inden-1-one (1 0.0g, 47.4mmol) and *N*-methyl-morpholine *N*-oxide (1.67g, 14.21mmol) in CH₂Cl₂ (50ml) was added trimethylsilylcyanide (7.05g, 71.1mmol), and the resultant solution was stirred at room temperature for 72h, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as the eluent to give the title compound as a colorless liquid (12.65g, 86%).

Part B. Preparation of 1-(aminomethyl)-5-bromo-2,3-dihydro-1H-inden-1-ol.

[0657] To a solution of the product from **Part A** (18.44g, 59.4mmol) in anhydrous Et₂O (250mL) under N₂ gas at 0°C was added a 1M solution of LiAlH₄ in Et₂O (62.4mL, 62.4mmol) dropwise over 1h. Following the addition, the mixture was allowed to warm to rt and was stirred at room temperature for 2h. The mixture was cooled in an ice bath while H₂O (4.3mL) was added dropwise, followed by the addition of 15% aq. NH₄OH (4.3mL), and then H₂O (13mL). The mixture was stirred at room temperature for 15min, and then filtered through celite and rinsed with EtOAc. The filtrate was concentrated in vacuo, and the residue was suspended in Et₂O (40mL) to give a precipitate that was filtered and dried to give the title compound as a colorless solid (10.0g, 70%).

Part C. Preparation of (6-bromo-1H-inden-3-yl)methanamine hydrochloride salt.

5 **[0658]** To a solution of the product from **Part B** (10.0g, 41.3mmol) in MeOH (100mL) was added 6N aq. HCl (125mL) and the mixture was stirred at 70°C for 3h and then allowed to cool to room temperature. MeOH was removed in vacuo to give a precipitate that was collected by filtration, washed with H₂O, and dried in vacuo to provide the title compound as a colorless solid (9.89g, 92%).

10 **Part D. Preparation of *N*-((6-bromo-1*H*-inden-3-yl)methyl)methanesulfonamide.**

[0659] To a suspension of the product from **Part C** (6.46g, 24.8mmol) in anhydrous CH₂Cl₂ (260mL) was added methanesulfonyl chloride (3.86mL, 49.6
15 mmol) and diisopropylethylamine (13.0mL, 74.4mmol), and the resulting mixture was stirred at room temperature for 10h. The solution was washed with 1N aq. HCl (2 x 300mL), and the organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was suspended in Et₂O (100mL) to give a precipitate that was collected by filtration and dried to give the title compound as
20 a colorless solid (6.25g, 83%).

Part E. Preparation of *N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-inden-3-yl)methyl)methanesulfonamide.

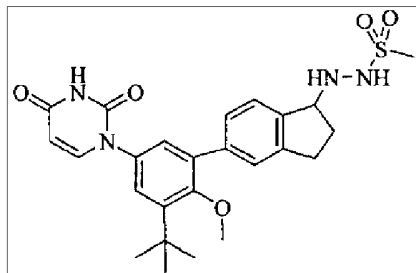
25 **[0660]** A solution of the product from **Part D** (2.0g, 6.62mmol), bis(pinacolato)-diboron (1.85g, 7.28mmol), potassium acetate (1.95g, 19.86mmol) and 1,1'-bis-(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.27g, 0.331mmol) in anhydrous 1,4-dioxane (80mL) under N₂ was stirred at 95°C for 8h. The cooled mixture was filtered through celite, washed with EtOAc
30 (2 x 20mL) and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 1:2 EtOAc:hexanes as the eluent to give the title compound as a colorless oil (2.02g, 87%).

Part F. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide.

[0661] A mixture of the product from **Part E** (3.14g, 8.99mmol), the product
5 from **Example C** (3.78g, 9.44mmol), tripotassium phosphate (3.82, 17.98mmol),
1,3,5,7-tetramethyl-2,4,8-trioxa-6-phospha-6-phenyl-adamantane (Cytec
[97739-46-3]) (105mg, 0.36mmol), and tris(dibenzylideneacetone)-dipalladium(0)
(165mg, 0.18mmol) was placed under N₂ gas. To the mixture was added, via
10 canula, a mixture of THF (45mL) and H₂O (155mL) that had been degassed by
bubbling Ar gas for 10min. The resulting mixture was further degassed by bubb-
ling with Ar for an additional 15min. The mixture was stirred at 50°C for 1.5h
while Ar was continuously bubbled through the solution. Additional tris(dibenzyl
ideneacetone)dipalladium(0) (55mg, 0.6mmol) in THF (2mL) was added, and the
mixture was stirred at 50°C for 1h. The mixture was allowed to cool to rt, and
15 was partitioned between CH₂Cl₂ (300ml) and 1N aq. HCl (150mL). To the oran-
ge organic layer was added 3-mercaptopropyl-functionalized silica gel (10g, Al-
drich) and mgSO₄, and the mixture was stirred at room temperature for 16h, filte-
red and concentrated in vacuo. The crude product was purified by column
chromatography on silica gel using 3:1 EtOAc:hexanes as the eluent to give the
20 title compound as a colorless solid (2.7g, 61%). ¹H NMR (300 MHz, DMSO-d₆)
δ 11.40 (s,1H), 7.78 (d, J=7.4Hz,1H), 7.66 (s,1H), 7.60 (d,J=7.7Hz,1H), 7.50
(m,2H), 7.25 (m,2H), 6.56 (m,1H), 5.64 (dd, J=2.2,7.7Hz,1H), 4.18 (d,
J=5.1Hz,2H), 3.46 (s,2H), 3.25 (s,3H), 2.96 (s,3H), 1.41 (s,9H).

25 **Example 50. Preparation of *N*-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyri-
midin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methanesul-
fonohydrazide (compound IB-L0-2.31).**

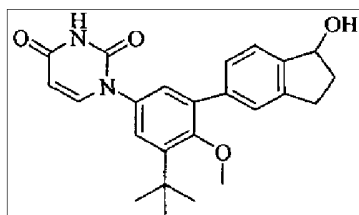
[0662]



[0663] To a solution of the product from **Example 4, Part C** (100mg, 0.20 mmol) was in THF (2mL) and MeOH (2mL) was added 2 drops of 10% HCl in MeOH, followed by sodium cyanoborohydride (19mg, 0.302mmol). The mixture was adjusted to pH 4 with the addition of 10% HCl in MeOH, and was then stirred at room temperature for 1h. The resulting mixture was partitioned between saturated aq. sodium bicarbonate (5mL) and CH₂Cl₂ (20mL), and the organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel using 3% MeOH in CH₂Cl₂ as the eluent to provide the title compound as a colorless solid (58mg, 58%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.39(s,1H), 8.18(d,J=3.7Hz,1H), 7.77(d,J=7.7Hz,1H), 7.51 (d,J=8.1Hz, 1H), 7.38(m,2H), 7.27(d,J=2.6Hz,1H), 7.21(d,J=2.9Hz,1H), 5.63(d,J=7.7Hz,1H), 5.25(m,1H), 4.39(m,1H), 3.27(s,3H), 2.98(m,1H), 2.83(s,3H), 2.78(m,1H), 2.22(m,1H), 2.07(m,1H), 1.40(s,9H).

Example 51. Preparation of 1-(3-*tert*-butyl-5-(1-hydroxy-2,3-dihydro-1H-inden-5-yl)-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.36).

[0664]



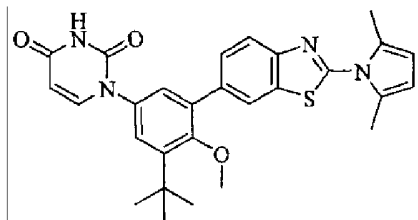
[0665] To a solution of the product from **Example 4, Part B** (150mg, 0.371

mmol) in MeOH (3mL) and CH₂Cl₂ (3mL) was added sodium borohydride (28mg, 0.742mmol), and the mixture was stirred at room temperature for 1h. The mixture was partitioned between 1N aq. HCl (10mL) and CH₂Cl₂ (20mL), and the organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 5% MeOH in CH₂Cl₂ as the eluent to provide the title compound as a colorless solid (90mg, 60%). ¹H NMR (300MHz, DMSO-d₆): δ 11.39(s,1H), 7.44(d, J= 4.0Hz, 1H), 7.40 (m, 2H), 7.21 (d, J= 2.6 Hz, 1H), 7.26 (d, J= 2.6 Hz, 1H), 5.63 (d, J= 8.1 Hz, 1H), 5.29 (d, J= 5.9 Hz,1H), 5.09 (m, 1H), 3.26 (s, 3H), 2.97 (m, 1H), 2.79 (m, 1H), 2.38 (m, 1H), 1.83 (m, 1H), 1.40 (s, 9H).

Example 52. Preparation of 1-(3-*tert*-butyl-5-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzo[*d*]thiazol-6-yl)-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.47).

15

[0666]



Part A. Preparation of 6-bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzo[*d*]thiazole.

20

[0667] A solution 6-bromobenzo[*d*]thiazol-2-amine (5.75g, 25.1mmol), hexane-2,5-dione (2.95mL, 25.1mmol), and PPTS (0.95g, 3.76mmol) in benzene (100 ml) was refluxed for 16h while water was removed with a Dean-Stark trap. The cooled mixture was poured into EtOAc (100mL) and extracted with saturated aq. NaHCO₃ (2 x 100mL) and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 9:1 EtOAc:hexanes as the eluent to give the title compound as an orange oil (6.46g, 84%).

Part B. Preparation of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole.

[0668] A mixture of the product from **Part A** (3.24g, 10.54mmol), bis(pinacolato)diboron (4.01g, 15.81mmol), bis(di-tert-butyl(hydroxy)phosphino)palladium(II) dichloride (0.264g, 0.527mmol), and potassium acetate (3.10g, 31.6mmol) in anhydrous toluene (25mL) was degassed by bubbling with N₂ gas for 15min, and then heated at reflux under N₂ for 72h. The cooled mixture was filtered through celite and washed with EtOAc, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 9:1 EtOAc:hexanes as the eluent to give the title compound (2.77g, 74%).

Part C. Preparation of 1-(3-tert-butyl-5-(2-(2,5-dimethyl-1H-pyrrol-1-yl)benzo[d]thiazol-6-yl)-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

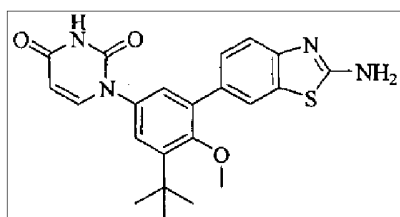
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[0669] The product from **Part B** (405mg, 1.4mmol) was subjected to the conditions described for **Example 42, Part C** to give the title compound (430mg, 68%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.43 (d, *J*=2.21 Hz, 1 H) 8.32 (d, *J*=1.47 Hz, 1 H) 8.12 (d, *J*=8.46 Hz, 1 H) 7.80 (d, *J*=7.72 Hz, 1 H) 7.76 (dd, *J*=8.46, 1.84 Hz, 1 H) 7.35 (q, *J*=2.57 Hz, 2 H) 5.97 (s, 2 H) 5.66 (dd, *J*=7.72, 2.21 Hz, 1 H) 3.30 (s, 3 H) 2.30 (s, 6 H) 1.43 (s, 9 H).

25

Example 53. Preparation of 1-(3-(2-aminobenzo[d]thiazol-6-yl)-5-tert-butyl-4-methoxy-phenyl)pyrimidine-2,4(1H,3H)-dione (compound IB-L0-2.27).

[0670]



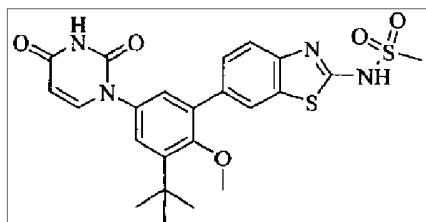
[0671] To a solution of the product from **Example 52** (4.0g, 8.0mmol) in trifluoroacetic acid (50mL) was added a few drops of H₂O, and the resulting mix-

30

ture was stirred at 80°C for 2.5h, and then concentrated in vacuo. A solution of the residue in MeOH was neutralized using conc. NH₄OH, concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using 9:1 CH₂Cl₂:MeOH as the eluent to give the title compound (3.3g, 98%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.40 (s, 1 H) 7.81 (s, 1 H) 7.77 (d, J=8.09 Hz, 1 H) 7.57 (s, 1 H) 7.40 (s, 1 H) 7.33 - 7.38 (m, 1 H) 7.25 (s, 1 H) 5.60 - 5.69 (m, 1 H) 3.26 (s, 3 H) 1.40 (s, 9 H).

Example 54. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]thiazol-2-yl)methanesulfonamide (compound IB-L0-2.28).

[0672]

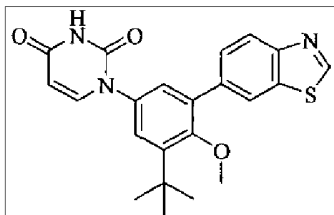


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[0673] To a solution of the product from **Example 53** (0.35g, 0.83mmol) in anhydrous CH₂Cl₂ (50mL) was added methanesulfonyl chloride (194μL, 2.49 mmol) and pyridine (1.34mL, 16.6mmol). The resulting mixture was stirred at room temperature for 16h and concentrated in vacuo. The crude product was purified by C-18 reverse-phase HPLC using an acetonitrile:H₂O (0.1% TFA) gradient to give the title compound (19mg, 4%). ¹H NMR (300 MHz, DMSO-d₆) δ 13.09 (s, 1 H) 11.41 (d, J=1.84 Hz, 1 H) 7.96 (d, J=1.47 Hz, 1 H) 7.77 (d, J=8.09 Hz, 1 H) 7.57 (dd, 1 H) 7.42 (d, J=8.09 Hz, 1 H) 7.25 - 7.32 (m, 2 H) 5.64 (dd, J=8.09, 2.21 Hz, 1 H) 3.25 (s, 3 H) 3.02 (s, 3 H) 1.40 (s, 9 H).

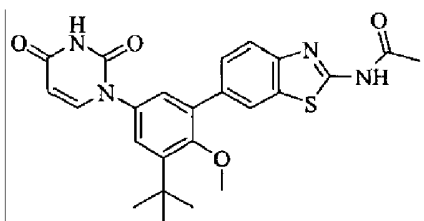
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Example 55. Preparation of 1-(3-(benzo[d]thiazol-6-yl)-5-tert-butyl-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione (compound IB-L0-2.33).

[0674]

[0675] To a solution of the product from **Example 53** (30mg, 0.071mmol) in anhydrous 1,4-dioxane (3mL) under N₂ was added isoamyl nitrite (19μL, 0.142 mmol). The resulting mixture was stirred at reflux for 1h, and concentrated in vacuo. The crude product was purified by C-18 reverse-phase HPLC using an acetonitrile:H₂O (0.1 % TFA) gradient to give the title compound (14mg, 48%).
¹H NMR (300 MHz, DMSO-d₆) δ 11.42 (d, *J*=1.84 Hz, 1 H) 9.44 (s, 1 H) 8.34 (d, *J*=1.47 Hz, 1 H) 8.19 (d, *J*=8.46 Hz, 1 H) 7.79 (d, *J*=7.72 Hz, 1 H) 7.73 (dd, *J*=8.46, 1.84 Hz, 1 H) 7.32 - 7.37 (m, 2 H) 5.65 (dd, *J*=7.91, 2.39 Hz, 1 H) 3.24 (s, 3 H) 1.42 (s, 9 H).

Example 56. Preparation of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*d*]thiazol-2-yl)acetamide (compound IB-L0-2.49).

[0676]

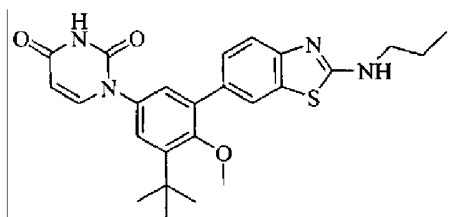
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[0677] A mixture of the product from **Example 53** (30mg, 0.071mmol) and acetic anhydride (3mL) was stirred at 100°C for 2h, and then allowed to cool to room temperature. The resulting solid was collected by filtration, washed with H₂O, and dried to give the title compound as an off-white solid (29mg, 88%).
¹H NMR (300 MHz, DMSO-d₆) δ 12.42 (s, 1 H) 11.41 (d, *J*=2.21 Hz, 1 H) 8.12 (d, *J*=1.47 Hz, 1 H) 7.82 (d, *J*=8.46 Hz, 1 H) 7.78 (d, *J*=8.09 Hz, 1 H) 7.61 (dd,

J=8.46, 1.84 Hz, 1 H) 7.31 (q, J=2.70 Hz, 2 H) 5.64 (dd, J=8.09, 2.21 Hz, 1 H)
3.24 (s, 3 H) 2.22 (s, 3 H) 1.41 (s, 9 H).

Example 57. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(2-(propylamino)benzo[*d*]thiazol-6-yl)phenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.46).

[0678]



10

Part A. Preparation of 1-(3-*tert*-butyl-5-(2-chlorobenzo[*d*]thiazol-6-yl)-4-methoxyphenyl) pyrimidine-2,4(1*H*,3*H*)-dione.

[0679] To a mixture of the product from **Example 53** (50mg, 0.118mmol) and
15 copper(II) chloride (24mg, 0.178mmol) in acetonitrile (3mL) at 0°C was added
tert-butyl nitrite (21µL, 0.178mmol). The mixture was stirred at 0°C for 1h, and
then warmed to 65°C and stirred for 2h. The mixture was concentrated in vacuo
and purified by column chromatography on silica gel using 5% MeOH in CH₂Cl₂
to give the title compound as an off-white solid (43mg, 82%).

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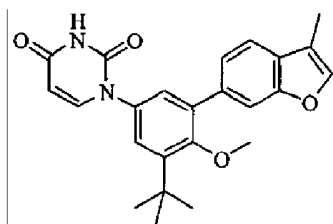
Part B. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(2-(propylamino)benzo[*d*]thiazol-6-yl) phenyl)pyrimidine-2,4(1*H*,3*H*)-dione.

[0680] A mixture of the product from **Part A** (50mg, 0.11mmol), 1-aminopro-
25 pane (9µL, 0.11mmol), and K₂CO₃ (15.6mg, 0.11mmol) in anhydrous DMF (5
mL) was stirred at 100°C for 24h. The mixture was concentrated in vacuo and
purified by column chromatography on silica gel using 2% MeOH in EtOAc as
the eluent to give the title compound as an off-white solid (21mg, 40 %). ¹H
NMR (300 MHz, DMSO-*d*₆) δ 11.39 (d, *J*=1.84 Hz, 1 H) 8.12 (t, *J*=5.52 Hz, 1 H)
30 7.82 (d, *J*=1.47 Hz, 1 H) 7.77 (d, *J*=7.72 Hz, 1 H) 7.44 (t, *J*=9.01 Hz, 1 H) 7.37 -

7.41 (m, 1 H) 7.25 (s, 2 H) 5.63 (dd, $J=7.91, 2.02$ Hz, 1 H) 3.33 - 3.38 (m, 2 H)
3.26 (s, 3 H) 1.56 - 1.69 (m, 2 H) 1.40 (s, 9 H) 0.94 (t, $J=7.35$ Hz, 3 H).

Example 58. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(3-methylbenzofuran-6-yl)phenyl)-pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.42).

[0681]



10 **Part A. Preparation of methyl 2-(2-acetyl-5-bromophenoxy)acetate.**

[0682] A solution of 1-(4-bromo-2-hydroxyphenyl)ethanone (1.35g, 6.28mmol) in anhydrous DMF (16mL) was treated in several portions with sodium hydride (377mg of 60% in oil, 226mg, 9.42mmol) followed by stirring at room temperature for 30min. The mixture was then treated with methyl bromoacetate (871 μ L, 1.45g, 9.48mmol) dropwise (solution became warm after addition was complete) followed by stirring at room temperature for 18h. The mixture was diluted with ethyl acetate and extracted with water (4x) and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded a nearly colorless solid, which was purified by column chromatography on silica gel, eluting with 20-100% ethyl acetate in hexanes. These procedures afforded the title compound as a colorless solid (1.47g, 82%).

Part B. Preparation of 2-(2-acetyl-5-bromophenoxy)acetic acid.

25

[0683] A solution of the product from **Part A** (1.47g, 5.12mmol) in tetrahydrofuran (26mL) was treated with 1.0N sodium hydroxide solution (6.7mL, 6.7mmol) followed by stirring at room temperature for 3h, at which point the reaction was complete. The mixture was concentrated in vacuo to remove tetrahydrofuran

and then was diluted with water and cooled to 0°C. The mixture was acidified to pH 3 by addition of 1N hydrochloric acid solution, and then the product extracted with ethyl acetate. The organic layer was extracted with saturated sodium chloride solution and dried (Na₂SO₄). Concentration in vacuo afforded the title compound as a colorless solid (1.36g, 97%).

Part C. Preparation of 6-bromo-3-methylbenzofuran.

[0684] A solution of the product from **Part B** (500mg, 1.83mmol) in acetic anhydride (9.2mL) was treated with sodium acetate (300mg, 3.66mmol) followed by warming at reflux for 18h. The mixture was cooled to room temperature and diluted with toluene and concentrated in vacuo to azeotropically remove acetic anhydride. This process was repeated 3x. The mixture was then diluted with ethyl acetate and stirred with saturated sodium bicarbonate solution for 1h. The layers were separated and the organic layer was extracted with saturated sodium chloride solution. Drying (Na₂SO₄) and concentration in vacuo afforded amber oil, which was purified by column chromatography on silica gel, eluting with 8-50 % ethyl acetate in hexanes. These procedures afforded the title compound as a colorless liquid (316mg, 82%).

20

Part D. Preparation of 4,4,5,5-tetramethyl-2-(3-methylbenzofuran-6-yl)-1,3,2-dioxaborolane.

[0685] In a microwave tube, a mixture of the product from **Part C** (303mg, 1.44 mmol), bis(pinacolato)diboron (401mg, 1.58mmol) and potassium acetate (423 mg, 4.31 mmol) in anhydrous dioxane (5mL) was degassed by nitrogen sparge for 15min. The mixture was treated with 1,1'-bis-(diphenylphosphino)ferrocene palladium (II) chloride dichloromethane complex (24mg, 0.029mmol) followed by degassing for another 5min. The microwave tube was sealed and the mixture was warmed at 90°C for 18h. The mixture was cooled and diluted with ethyl acetate and extracted with water and saturated sodium chloride solution. The organic layer was dried (Na₂SO₄) and stirred with (3-mercaptopropyl) silica gel for 1h. The mixture was filtered and concentrated in vacuo to afford a brown

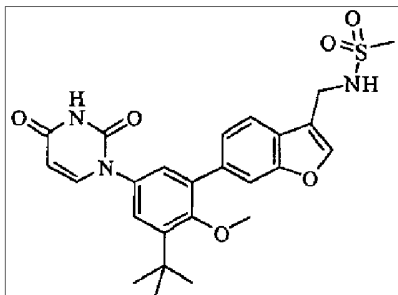
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semisolid, which was purified by column chromatography on silica gel, eluting with 8-40% ethyl acetate in hexanes. These procedures afforded the title compound as colorless oil, which slowly solidified upon standing (307mg, 83%).

5 **Part E. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(3-methylbenzofuran-6-yl)phenyl)-pyrimidine-2,4(1*H*,3*H*)-dione.**

[0686] In a microwave tube, a solution of the product from **Part D** (307mg, 1.19 mmol), the product from **Example C** (414mg, 1.03mmol), 1,3,5,7-tetramethyl-
10 2,4,8-trioxa-6-phospha-6-phenyl-adamantane (Cytex [97739-46-3]) (15mg, 0.052mmol), and tribasic potassium phosphate (439mg, 2.07mmol) in 3:1 tetrahydrofuran-water (8mL) was degassed by nitrogen sparge for 20min. The mixture was treated with tris(dibenzylideneacetone)dipalladium (0) (12mg, 0.012 mmol) followed by degassing for another 10min. During this period, the solution
15 turned from an initially deep maroon color to a greenish brown color. The microwave tube was sealed and the solution warmed at 50°C for 56h. The solution was cooled and diluted with ethyl acetate and acidified with 1M citric acid solution. The organic layer was extracted with saturated sodium chloride solution, dried (Na₂SO₄), and then stirred with (3-mercaptopropyl) silica gel for 1h. After
20 filtration and concentration in vacuo, the residue obtained was purified by column chromatography on silica gel, eluting with 4-20% acetone in dichloromethane, followed by a second column chromatography on silica gel, eluting with 20-100% ethyl acetate in hexanes. These procedures afforded the title compound as a colorless solid (355mg). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.40 (d, *J*=1.84 Hz, 1 H) 7.74 - 7.92 (m, 2H) 7.58-7.76 (m, 2 H) 7.46 (dd, *J*=8.09, 1.47 Hz, 1 H) 7.30 (q, *J*=2.82 Hz, 2 H) 5.64 (dd, *J*=8.09, 2.21 Hz, 1 H) 3.22 (s, 3 H) 2.25 (s, 3 H) 1.41 (s, 9 H).

Example 59. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzofuran-3-yl)methyl)methanesulfonamide (compound IB-L0-2.18).
30

[0687]**Part A. Preparation of 6-bromo-3-(bromomethyl)benzofuran.**

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[0688] A solution of the product from **Example 58, Part C** (1.0g, 4.74mmol) and dibenzoyl peroxide (287mg, 1.19mmol) in chlorobenzene (24mL) at reflux was treated in four portions with N-bromosuccinimide (843mg, 4.74mmol) over 30 min. The mixture was then stirred at reflux for 2h. The mixture was cooled, filtered and concentrated and purified by column chromatography on silica gel, eluting with 7-30% chloroform in hexanes. The procedures afforded the title compound as a light yellow oil (438mg, 32%).

15 **Part B. Preparation of *N*-((6-bromobenzofuran-3-yl)methyl)-*N*-(4-methoxybenzyl)methane-sulfonamide.**

[0689] A solution of the product from **Part A** (515mg, 1.78mmol), *N*-(4-methoxybenzyl)methane-sulfonamide (421mg, 1.95mmol), and potassium carbonate (260mg, 1.95mmol) in anhydrous DMF (8.9mL) was stirred at 70°C for 3h. The mixture was cooled and diluted with ethyl acetate and extracted with water (4x). The organic layer was then extracted with saturated sodium chloride solution and dried (Na₂SO₄). Concentration in vacuo afforded a beige solid. This material was purified by column chromatography on silica gel, eluting with 20-100% ethyl acetate in hexanes. These procedures afforded the title compound as a colorless solid (224mg, 35%).

25 **Part C. Preparation of *N*-(4-methoxybenzyl)-*N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-yl)methyl)methanesulfonamide.**

[0690] The product from **Part B** (186mg, 0.44mmol) was subjected to the conditions described for **Example 58, Part D** to afford the title compound as a colorless solid (177mg, 86%).

5 **Part D. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzofuran-3-yl)methyl)-*N*-(4-methoxybenzyl)methanesulfonamide.**

[0691] In a microwave tube, a suspension of the product from **Part C** (169mg, 10 0.36mmol), the product from **Example C** (143mg, 0.36mmol), and 1.0M sodium carbonate solution (0.5mL, 0.50mmol) in 1:1 ethanol-toluene (3mL) was degassed by nitrogen sparge for 20min. The solution was treated with 1,1-bis(diphenylphosphino)ferrocene-palladium(II) chloride dichloromethane complex (7mg, 9 μ mol) followed by degassing for another 5min. The microwave tube was sealed
15 and the mixture heated a 100°C in the microwave oven for 1h. The mixture was diluted with ethyl acetate and water, and acidified with 1M citric acid solution. The organic layer was extracted with saturated sodium chloride solution, dried (Na₂SO₄), and allowed to stand overnight over (3-mercaptopropyl) silica gel. Filtration and concentration in vacuo afforded an off white foam which was purified
20 by column chromatography on silica gel, eluting with 5-30% ethyl acetate in dichloromethane. The procedures afforded the title compound as a colorless solid (96mg, 43%).

25 **Part E. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzofuran-3-yl)methyl)methanesulfonamide.**

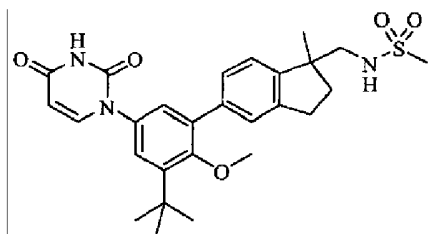
[0692] A solution of the product from **Part D** (88mg, 0.14mmo) in dichloromethane (1.4mL) was treated with trifluoroacetic acid (1.4mL) followed by stirring at room temperature for 18h, and then stirring at 40°C for 2h. The mixture was
30 concentrated in vacuo to afford a dark, purple-brown foam, which was subjected to column chromatography on silica gel, eluting with 5-50% ethyl acetate in methylene chloride to afford an impure material, which was purified by reverse phase chromatography on a C-18 column, eluting with 1% water-TFA/acetoni-

trile. The procedures afforded the title compound as a solid (3.9mg). ^1H NMR (300 MHz, $\text{DMSO-}d_6$): δ 11.31 - 11.48 (m, 1 H) 8.01 (s, 1 H) 7.68 - 7.94 (m, 2 H) 7.40 - 7.65 (m, 2 H) 7.10 - 7.38 (m, 2 H) 5.65 (dd, $J=7.91$, 2.02 Hz, 1 H) 4.33 (d, $J=5.88$ Hz, 2 H) 3.23 (s, 3 H) 2.95 (s, 3 H) 1.41 (s, 9 H).

5

Example 60. Preparation of *N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-methyl-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.25).

10 [0693]



Part A. Preparation of 5-bromo-1-(1,3-dithian-2-yl)-2,3-dihydro-1*H* inden-1-ol.

15

[0694] A solution of 1,3-dithiane (11.96g, 99mmol) in anhydrous tetrahydrofuran (100mL) at -30°C was treated dropwise over 10min with *n*-butyllithium (2.5M in hexanes, 38.4mL, 96mmol) followed by stirring at -15°C for 2h. The solution was then treated with a solution of 5-bromo-2,3-dihydro-1*H*-inden-1-one (15g, 71.1mmol) in anhydrous tetrahydrofuran (250mL) over 1h, maintaining the temperature between -9°C and 2°C . The mixture was then allowed to set in the refrigerator at $2-8^\circ\text{C}$ for 18h. The solution was concentrated in vacuo to afford a maroon oil, which was treated with 1 N hydrochloric acid solution and extracted with ether. The ether layer was extracted with saturated sodium chloride solution, dried (Na_2SO_4) and concentrated in vacuo to afford an amber oil (23.55g).

25

Part B. Preparation of 2-(5-bromo-2,3-dihydro-1*H*-inden-1-ylidene)-1,3-dithiane.

[0695] A solution of the product from **Part A** (23.55g, 71.1mmol) in benzene (350mL) was treated with p-toluenesulfonic acid monohydrate (3.0g) followed by stirring at reflux for 1h while removing water by means of a Dean-Stark trap. The mixture was extracted with saturated sodium bicarbonate solution and then
5 with saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded the product as an amber, oil (22.27g).

Part C. Preparation of 5-bromo-2,3-dihydro-1H indene-1-carboxylic acid.

10 **[0696]** A solution of the product from **Part B** (22.27g, 71.1mmol) in glacial acetic acid (375mL) was treated with concentrated hydrochloric acid solution (125mL) followed by stirring at reflux for 3h. The mixture was cooled and concentrated in vacuo by azeotroping off the acetic acid and water with toluene (3x). The brown
15 oil obtained was filtered through a plug of 70-230 mesh silica gel in a 2L sintered glass funnel (volume of silica gel ca. 1800mL) eluting with dichloromethane to remove non-polar impurities (1,3-propanedithiol, *inter alia*) and then with ethyl acetate to elute the title compound, which was obtained as a brown solid (9.85 g, 58%).

20 **Part D. Preparation of methyl 5-bromo-2,3-dihydro-1H indene-1-carboxylate.**

[0697] A suspension of the product from **Part C** (9.85g, 40.9mmol) in methanol (400mL) was treated with 4 N hydrogen chloride in 1,4-dioxane (125mL) and
25 the mixture was stirred at reflux for 8h. The mixture was concentrated in vacuo to afford brown oil, which was purified by column chromatography on silica gel, eluting with 0-30% methyl t-butyl ether in chloroform. These procedures afforded the title compound as an amber oil (7.99g, 77%).

30 **Part E. Preparation of methyl 5-bromo-1-methyl-2,3-dihydro-1H indene-1-carboxylate.**

[0698] A solution of the product from **Part D** (2.03g, 7.96mmol) in anhydrous

tetrahydrofuran (40mL) at -78°C under N₂ was treated dropwise with lithium bis(trimethylsilyl)amide (1.0M in tetrahydrofuran, 9.55mL, 9.55mmol) over 10 min. The solution was stirred at -78°C for 45min and then treated with methyl iodide (1.55mL, previously dried by passage through a plug of basic alumina).

5 The mixture was then gradually allowed to warm to rt and was stirred for 18h. The mixture was quenched by addition of saturated ammonium chloride solution (2mL). The mixture was concentrated in vacuo to remove tetrahydrofuran and the residue was diluted with ethyl acetate. The mixture was extracted with saturated ammonium chloride solution and with saturated sodium chloride solution.

10 Drying (Na₂SO₄) and concentration in vacuo afforded the title compound as an amber oil (2.06g, 96%).

Part F. Preparation of 5-bromo-1-methyl-2,3-dihydro-1*H*-indene-1-carboxylic acid.

15

[0699] A solution of the product from **Part E** (2.06g, 7.65mmol) and potassium trimethylsilanoate (5.5g of 90%, 4.91g, 38.3mmol) in tetrahydrofuran (40mL) was stirred at reflux for 3h. The mixture was cooled and concentrated in vacuo to remove tetrahydrofuran. The maroon residue was dissolved in water (ca.

20 175mL) and extracted with methyl t-butyl ether. The aqueous phase was cooled to 0°C and acidified to pH 3 by addition of concentrated hydrochloric acid solution. The mixture was extracted with ethyl acetate (2x) and then with saturated sodium chloride solution. The solution was dried (Na₂SO₄) and treated with Darco G-60, followed by filtration through celite. The filtrate was concentrated in

25 vacuo to afford the title compound as a light yellow solid (1.93g, 99%).

Part G. Preparation of 5-bromo-1-methyl-2,3-dihydro-1*H*-indene-1-carboxamide.

30 **[0700]** A solution of the product from **Part F** (1.56g, 6.12mmol) and DMF (473 μL, 447mg, 6.12mmol) in hexanes (100mL) was treated with oxalyl chloride (1.61mL, 2.32g, 18.4mmol) followed by stirring at room temperature for 1h. The mixture was treated with celite and then filtered through celite. The filtrate was

concentrated in vacuo and dissolved in acetone (75mL) and cooled to 0°C. The solution was treated with 28% aqueous ammonia solution (75mL) followed by stirring at 0°C for 30min and then warming to room temperature. The mixture was concentrated in vacuo and extracted with ethyl acetate. The organic layer
5 was extracted with saturated sodium chloride solution and dried (Na₂SO₄). Concentration in vacuo afforded the title compound as an oil (1.55g, 100%).

Part H. Preparation of (5-bromo-1-methyl-2,3-dihydro-1*H*-inden-1-yl)methanamine hydrochloride.

10

[0701] In a flask equipped with a vigreux column and a short path distillation head, a solution of the product from **Part G** (1.21g, 4.76mmol) in anhydrous tetrahydrofuran (8mL) was warmed to a gentle reflux and treated dropwise with borane-dimethylsulfide complex (904μL, 723mg, 9.52mmol). The resulting mixture was stirred at reflux for 2h. The solution was cooled to rt and carefully
15 treated with methanol until bubbling ceased, followed by careful treatment with 4N hydrogen chloride in 1,4-dioxane solution (4mL). The mixture was then concentrated in vacuo. The colorless solid obtained was triturated with ether and collected by filtration. After drying in a vacuum oven at 50°C for 2h, the title
20 compound was obtained as a colorless solid (893mg, 68%).

Part I. Preparation of *tert*-butyl (5-bromo-1-methyl-2,3-dihydro-1*H*-inden-1-yl)methylcarbamate.

[0702] A suspension of the product from **Part H** (893mg, 3.23mmo) in tetrahydrofuran (16mL) was treated with di-*tert*-butyl dicarbonate (846mg, 3.87mmol) and saturated sodium bicarbonate solution (7.2mL, ca. 6.46mmol) followed by stirring at room temperature for 18h. The mixture was diluted with ethyl acetate and extracted with water and saturated sodium chloride solution. The solution
30 was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography, eluting with 5-40% ethyl acetate in hexanes. These procedures afforded the title compound as a colorless solid (1.03g, 94%).

Part J. Preparation of *tert*-butyl (1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yl)methylcarbamate.

5 [0703] The product from **Part I** (1.03g, 3.03mmol) was subjected to the conditions described for **Example 58, Part D** to afford the title compound as a colorless solid (977mg, 83%).

Part K. Preparation of *tert*-butyl (5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-methyl-2,3-dihydro-1*H*-inden-1-yl)-
10 **methylcarbamate.**

[0704] The product from **Part J** (965mg, 2.49mmol) was subjected to the conditions described for **Example 59, Part D** to afford the title compound as a colorless solid (618mg, 47%).

15

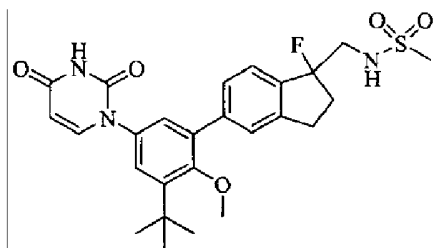
Part L. Preparation of *N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-methyl-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide.

20 [0705] The product from **Part K** (446mg, 0.84mmol) was dissolved in 4N hydrogen chloride in dioxane solution (125mL), followed by stirring at room temperature for 18h. The suspension of colorless solid obtained was then concentrated in vacuo. This material was suspended in dichloromethane (5mL) and cooled to 0°C, followed by sequential treatment with triethylamine (280µL, 203mg, 2.01
25 mmol) and methanesulfonyl chloride (81µL, 120mg, 1.05mmol). The mixture was stirred at 0°C for 1h and then warmed to room temperature and diluted with dichloromethane. The mixture was extracted with 1M citric acid solution and then dried (Na₂SO₄) and concentrated in vacuo. The residue was dissolved in 3:1 tetrahydrofuran-water (8mL) and treated with potassium carbonate (231 mg,
30 1.68mmol) followed by stirring at room temperature for 1h. The mixture was concentrated in vacuo and the residue diluted with water and then acidified to ca. pH 2 by addition of 1M citric acid. The product was extracted with ethyl acetate and the organic layer was extracted with saturated sodium chloride solu-

tion. Drying (Na_2SO_4) and concentration in vacuo afforded a colorless solid, which was purified by column chromatography on silica gel, eluting with 30-100% ethyl acetate in hexanes. The procedures afforded the title compound as a colorless solid (184mg, 43%). ^1H NMR (300 MHz, $\text{DMSO-}d_6$): δ 11.39 (s, 1 H) 7.77 (d, $J=7.72$ Hz, 1 H) 7.14 - 7.48 (m, 5 H) 7.06 (t, $J=6.62$ Hz, 1 H) 5.63 (d, $J=7.72$ Hz, 1 H) 3.18 - 3.33 (m, 3 H) 2.96 - 3.15 (m, 2 H) 2.85 - 3.00 (m, 2 H) 2.70 - 2.87 (m, 3 H) 2.10 - 2.34 (m, 1 H) 1.63 - 1.90 (m, 1 H) 1.40 (s, 9 H) 1.20 - 1.34 (m, 3 H).

- 10 **Example 61. Preparation of *N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.12).**

[0706]



15

Part A. Preparation of 5-(5-bromo-2,3-dihydro-1*H*-inden-1-ylidene)-2,2,3,3,7,7,8,8-octamethyl-4,6-dioxo-3,7-disilanonane.

- 20 **[0707]** To a solution of the product from **Example 60, Part C** (1.2g, 4.98mmol) in anhydrous THF (5mL) was added TBSCl (1.726g, 11.45mmol), and the resulting yellow solution was cooled to 0°C in an ice bath. A 1.0M solution of LiHMDS in THF (11.95mL, 11.95mmol) was added dropwise over 5min, and the resulting dark red solution was stirred at 0°C for 90min, and then at room
- 25 temperature for 6h. The solvent was removed in vacuo and the oily semi solid residue was treated with pentane (2 x 35mL) to precipitate LiCl. The slurry was filtered and the solvent was removed in vacuo to give the title compound as a brown oil (2.3g).

Part B. Preparation of 5-bromo-1-fluoro-2,3-dihydro-1*H*-indene-1-carboxylic acid.

[0708] To a mixture of 1-chloromethyl-4-fluoro-1,1-diazoniabicyclo[2.2.2.]octane bis(tetrafluoroborate)(Selectfluor, 2.26g, 6.37mmol in CH₃CN (20mL) was added the product from **Part A** (2.3g, 4.90mmol) in CH₃CN (6mL). The resulting yellow-orange solution was stirred at room temperature overnight. The reaction mixture was poured into 50mL 1N HCl (aqueous), extracted with EtOAc (2 x 35mL). The combined organic extracts are washed with 0.5N NaOH (3 x 30mL).
10 The combined aqueous extracts are washed with EtOAc (2 x 25mL), then adjusted mixture to pH 1 with 5N HCl (10mL). The resulting cloudy brown solution was extracted with EtOAc (2 x 50mL), the combined organic layers were washed with 10% NaCl and then treated with decolorizing carbon and stirred for 1h. The mixture was dried over anhydrous Na₂SO₄(s), filtered through Celite
15 and the solvent removed in vacuo to give the title compound as leaving a yellow oil (0.84g).

Part C. Preparation of 5-bromo-1-fluoro-2,3-dihydro-1*H*-indene-1-carbonyl chloride.

20 **[0709]** To a solution of the product from **Part B** (0.95g, 3.67mmol) in CH₂Cl₂ was added oxalyl chloride (0.96mL, 11.00mmol), followed by DMF (0.28mL). The resulting bubbling solution was stirred at room temperature for 2h, filtered through Celite, and the solvent was removed in vacuo to give the title compound as a brown oil (0.99g).
25

Part D. Preparation of 5-bromo-1-fluoro-2,3-dihydro-1*H*-indene-1-carboxamide.

30 **[0710]** To a solution of the product from **Part C** (0.99g, 3.57mmol) in acetone (20mL) and at 0°C was added aqueous NH₄OH (28%, 0.28mL, 3.57mmol), and the resulting dark brown mixture was stirred at 0°C for 1h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between water and

EtOAc (2 x 50mL). The combined organic extracts were washed with 1N H₃PO₄, 10% NaHCO₃ (aq), 10% NaCl, and dried over anhydrous Na₂SO₄(s), filtered and concentrated in vacuo. The brown solid was purified by column chromatography on silica gel using a solvent gradient of CH₂Cl₂/MeOH (99/1 to 96/4). The
5 title compound was obtained as a brown solid (0.205g, 22 %).

Part E. Preparation of *tert*-butyl (5-bromo-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)methylcarbamate.

10 **[0711]** To a solution of the product from **Part D** (0.234g, 0.907mmol) in anhydrous THF (5mL) at 80°C was added borane-DMS complex (0.172mL, 1.813 mmol) dropwise. The reaction flask was equipped with a short-path condenser, and the mixture was stirred at reflux for 2h, collecting THF and DMS. The mixture was then cooled to room temperature and MeOH (5mL) was added, followed by 4N HCl in 1,4-dioxane (5mL). The solvent was removed in vacuo to give
15 a colorless solid (0.25g, 98%). The solid was dissolved in THF (5mL), and to the solution was added triethylamine (0.137mL, 0.980mmol), followed by di-*tert*-butyl dicarbonate (0.214g, 0.980mmol). The cloudy mixture was stirred at room temperature for 30min, and 10% aq. NaHCO₃ (1mL) was added. The resulting
20 mixture was stirred at room temperature for 18h and then concentrated in vacuo to an oily residue. The residue was dissolved in EtOAc (50mL), washed with water, 1N H₃PO₄, 10% NaCl, and dried over anhydrous Na₂SO₄(s). The drying agent was filtered off, and the solvent was removed in vacuo to give the title compound as an oil (0.27g, 88%).

25

Part F. Preparation of *tert*-butyl (1-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-inden-1-yl)methylcarbamate.

[0712] The product from **Part E** (0.27g, 0.784mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound as a tan solid
30 (0.159g, 52 %).

Part G. Preparation of *tert*-butyl (5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)methylcarbamate.

- 5 **[0713]** To a solution of the product from **Part F** (0.159g, 0.405mmol), the product from **Example C** (0.162g, 0.405 mol), 1,3,5,7 tetramethyl-2,4,8-trioxa-6-phospha-6-phenyl adamantane (PA-Ph, CAS 97739-46-3) (3.55 g, 0.012mmol) in THF (3mL) was added K₃PO₄ (0.181g, 0.851mmol) and water (1mL), followed by tris(dibenzylideneacetone)dipalladium(0) catalyst (3.71mg, 0.00405mmol).
- 10 The resulting mixture was degassed by bubbling with N₂ for 20min, and then stirred at room temperature for 12h. The reaction mixture was diluted with EtOAc (50mL), washed with 1N H₃PO₄, 10% NaHCO₃, 10% NaCl, and dried over anhydrous Na₂SO₄(s). The mixture was filtered and solvent was removed in vacuo to give a brown oil, which was purified by column chromatography on
- 15 silica gel, eluting with 98/2 CH₂Cl₂/MeOH. The title compound was isolated as a colorless solid (0.118g, 54%).

Part H. Preparation of *N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide.

20

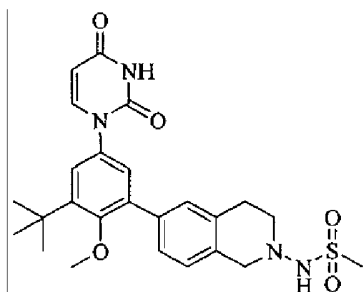
- [0714]** The product from **Part G** (0.118g, 0.219mmol) was dissolved in 4N HCl in 1,4-dioxane (2mL) and stirred at room temperature for 1h. The solvent was removed in vacuo and the residue was suspended in CH₂Cl₂ and evaporated (2
- 25 x 4mL) to give a colorless solid (0.10g, 96%). This solid was dissolved in CH₂Cl₂ (1mL) and the resulting slurry was stirred in an ice bath. Triethylamine (0.059mL, 0.422mmol) was added to the slurry resulting in a clear solution and to this was added methanesulfonyl chloride (0.02mL, 0.253mmol). The resulting mixture was stirred in the ice bath for 1h. The reaction mixture was diluted with
- 30 CH₂Cl₂ 50mL, washed with 1N H₃PO₄, 10% NaHCO₃, 10% NaCl, and dried over anhydrous Na₂SO₄(s). The drying agent was filtered off, and solvent was removed in vacuo leaving a crude product that was purified by column chromatography on silica gel, eluting with a gradient of 1:1 to 3:7 hexane:EtOAc. The title

compound was obtained as a colorless solid (64mg, 62 %). ^1H NMR (300 MHz, DMSO- d_6) δ 11.39 (s, 1 H) 7.77 (d, $J=7.72$ Hz, 1 H) 7.30 - 7.48 (m, 3 H) 7.12 - 7.32 (m, 3 H) 5.63 (d, $J=7.72$ Hz, 1 H) 3.27 (s, 3 H) 2.94 - 3.08 (m, 4 H) 2.91 (s, 3 H) 2.17 - 2.38 (m, 1 H) 1.76 - 1.97 (m, 1 H) 1.40(s, 9H).

5

Example 62. Preparation of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanesulfonamide (compound IB-L0-2.43).

10 [0715]



Part A. Preparation of *N*-(3-bromophenethyl)-2,2,2-trifluoroacetamide.

15 [0716] To a solution of 2-(3-bromophenyl)ethanamine (10g, 50.0mmol) in dichloromethane (200ml) at 0°C were added 2,6-lutidine (6.40ml, 55.0mmol) and then trifluoroacetic anhydride (7.77ml, 55.0mmol) dropwise, and the reaction was stirred at room temperature overnight. Water was added at 0°C and the reaction was washed with 1M HCl, H₂O, and sat NaHCO₃. The organic was
20 dried over MgSO_4 , filtered and concentrated to provide the title compound as a tan solid (14.7g, 99%).

Part B. Preparation of 1-(6-bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoro-ethanone.

25

[0717] To the product from **Part A** (14.70g, 49.6mmol) and paraformaldehyde (2.39g, 80mmol) was added a mixture of acetic acid (81ml) and sulfuric acid (53.7ml) at room temperature. The suspension was stirred for 60h during which

time it became a solution. The reaction was poured into cold water. The reaction was diluted with ethyl acetate and washed with water, sat NaHCO_3 , and brine. The organic layer was dried over MgSO_4 , filtered and concentrated to provide the title compound, contaminated with the 8-bromo isomer, as a colorless
5 oil (10.5 g, 67%).

Part C. Preparation of 6-bromo-1,2,3,4-tetrahydroisoquinoline.

[0718] To a solution of the product from **Part B** (9.5g, 30.8mmol) in methanol
10 (231ml) and water (77ml) at room temperature was added potassium carbonate (8.52g, 61.7mmol) and the reaction was stirred at room temperature for 30min. The reaction was diluted with water and 25% isopropanol in chloroform and the pH was adjusted to 9 with 1N HCl. The mixture was extracted twice with 25% isopropanol in chloroform. The combined organic layers were dried over
15 MgSO_4 , filtered and concentrated to give the title compound, contaminated with the 8-bromo isomer (6.55g, quantitative).

Part D. Preparation of 6-bromo-2-nitroso-1,2,3,4-tetrahydroisoquinoline.

[0719] To a solution of the product from **Part C** (6.55g, 30.9mmol) in acetic acid
20 (61.8ml) and 3N aq. hydrochloric acid (10.29ml, 30.9mmol) at 0°C was added 1.9M sodium nitrite (20.64ml, 39.2mmol) dropwise, and the reaction was stirred at room temperature overnight. The solvent was evaporated and the reaction was diluted with 25% isopropanol in chloroform and sat NaHCO_3 . The aqueous
25 layer was extracted twice with 25% isopropanol in chloroform. The combined organic layers were dried over MgSO_4 , filtered and concentrated to give the title compound, contaminated with the 8-bromo isomer (6.97 g, 94%).

Part E. Preparation of 6-bromo-3,4-dihydroisoquinolin-2(1H)-amine.

30

[0720] To a solution of the product from **Part D** (0.5g, 2.074mmol) in methanol (4.15ml) was added zinc (0.542g, 8.30mmol) and the reaction was cooled to 0°C, followed by dropwise addition of AcOH (4.15ml). The reaction was warmed

to rt and the reaction was stirred for 2.5h. The reaction was filtered and the solid was washed with methanol. The filtrate was evaporated and the residue was diluted with water and 25% isopropanol in chloroform and saturated NaHCO₃ was added. A white solid was removed by filtration, and the aqueous layer was extracted twice with 25% isopropanol in chloroform. The combined organic layers were dried overmgSO₄, filtered and concentrated to give the title compound, contaminated with the 8-bromo isomer (0.472g, quantitative).

10 **Part F. Preparation of *tert*-butyl 6-bromo-3,4-dihydroisoquinolin-2(1*H*)-yl-carbamate.**

[0721] A solution of the product from **Part E** (0.472g, 2.078mmol) in THF (20.78 ml) was cooled to 0°C followed by addition of di-*tert*-butyl dicarbonate (0.531ml, 2.286mmol), and the reaction was stirred at room temperature overnight. Solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel (isolated lower R_f product) using a gradient starting with dichloromethane and ending with 10% ethyl acetate in dichloromethane to give the title compound (49mg, 73%).

20 **Part G. Preparation of *tert*-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-2(1*H*)-ylcarbamate.**

[0722] A solution of the product from **Part F** (100mg, 0.306mmol), bis(pinacolato)diboron (85mg, 0.336mmol), and potassium acetate (57.3μl, 0.917mmol) in 1,4-dioxane (3.0mL) was degassed by bubbling with N₂ gas for 15min. 1,1'-Bis-(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (11.18mg, 0.015mmol) was added, and the resulting mixture was stirred at 95°C for 16h. The cooled solution was diluted with 25% isopropanol in chloroform and washed with water. The organic layer was dried overmgSO₄, filtered and concentrated in vacuo. The product was purified by column chromatography on silica gel eluting with a gradient starting with dichloromethane and ending with 25% ethyl acetate in dichloromethane to give the title compound (70mg, 61%).

part H. Preparation of *tert*-butyl 6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-ylcarbamate.

5 **[0723]** A mixture of the product from **Example C** (74.8mg, 0.187mmol), the product from **Part G** (70mg, 0.187mmol) in EtOH (1.0mL), toluene (1.05mL) 1M aq. Na₂CO₃ (281μl, 0.281mmol) was degassed by bubbling with N₂ gas for 10min. 1,1'- Bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (6.84mg, 9.35μmol) was added, and degassing with N₂ was
10 continued for 5min. The reaction mixture was sealed and heated at 78°C for 16h. The reaction was cooled and diluted with 25% isopropanol in chloroform and washed with water. The organic was dried overmgSO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel, eluting with a gradient starting with dichloromethane and ending with ethyl
15 acetate to give the title compound (53mg, 54%).

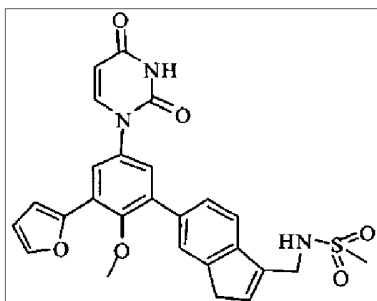
Part I. Preparation of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanesulfonamide.

20 **[0724]** To a solution of the product from **Part H** (25mg, 0.048mmol) in dichloromethane (0.5mL) at room temperature was added TFA (0.5mL) and the reaction was stirred for 30min, and then concentrated in vacuo. The residue was diluted with 25% isopropanol in chloroform and washed with sat NaHCO₃. The organic
25 layer was dried overmgSO₄, filtered and concentrated to give a solid (17.8mg, 88%). To a solution of the solid in pyridine (0.5mL) at 0°C was added methanesulfonyl chloride (12.6μl, 0.162mmol) and the reaction was stirred at room temperature for 90min. Methanol was added and the reaction was stirred for 10min. The residue was diluted with 25% isopropanol in chloroform and washed
30 with sat NaHCO₃. The organic layer was dried overmgSO₄, filtered and concentrated, and the product was purified by column chromatography on silica gel eluting with a gradient starting with dichloromethane and ending with ethyl acetate to give the title compound (11mg, 52%). ¹H NMR (300 MHz, DMSO-d₆) δ

11.39 (s, 1 H) 8.53 (s, 1 H) 7.76 (d, $J=7.72$ Hz, 1 H) 7.11 - 7.42 (m, 5 H) 5.63 (d, $J=7.72$ Hz, 1 H) 4.04 (s, 2 H) 3.28 (s, 3 H) 3.10 (d, $J=5.52$ Hz, 2 H) 2.98 (s, 3 H) 2.90 - 3.05 (m, 2 H) 1.40 (s, 9 H).

- 5 **Example 63. Preparation of *N*-((6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-(furan-2-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide (compound IB-L0-2.65).**

[0725]



Part A. Preparation of *N*-((6-(3-bromo-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide.

- 15 [0726] The product from **Example 18, Part C** (0.242gm, 0.573mmol) and the product from **Example 49, Part E** (0.200gm, 0.57mmol) was subjected to the conditions described for **Example 49, Part F** to give the title compound as an off-white solid (0.104gm, 35%).

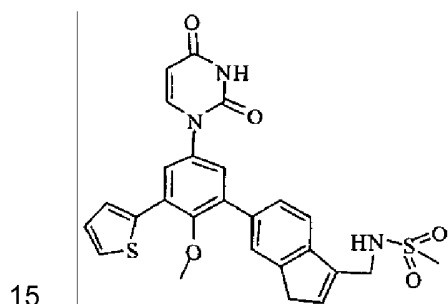
- 20 **Part B. Preparation of *N*-((6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-(furan-2-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide.**

- [0727] A solution of the product from **Part A** (25.2mg, 0.049mmol) in 3:1 v/v THF-water (1.3mL) was combined in a microwave tube at room temperature with furan-2-ylboronic acid (6.91mg, 0.062mmol) and potassium phosphate (16.84mg, 0.097mmol). To this was added 1,1'-bis(di-tert-butyl-phosphino)ferrocene palladium dichloride (1.65mg, 2.53umole). The tube was sealed and the resulting mixture was purged with nitrogen for 4min and then heated for 16.5h in
- 25

an oil bath at 50°C. The reaction mixture was partitioned between dilute HCl and ethyl acetate, and the organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was purified by chromatography on silica gel (ethyl acetate-hexanes) to give the title compound as an off white solid (11.4mg, 46%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.45 (s, 1 H) 7.80 - 7.89 (m, 2 H) 7.73 - 7.79 (m, 2 H) 7.56 - 7.63 (m, 2 H) 7.50 (t, *J*=6.07 Hz, 1 H) 7.3 (d, *J*=2.94 Hz, 1 H) 7.09 (d, *J*=3.31 Hz, 1 H) 6.68 (dd, *J*=3.68, 1.84 Hz, 1 H) 6.58 (s, 1 H) 5.68 (d, *J*=7.72 Hz, 1 H) 4.19 (d, *J*=5.15 Hz, 2 H) 3.48 (s, 2 H) 3.34 (s, 3 H) 2.96 (s, 3 H).

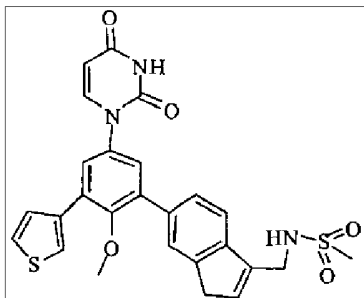
- 10 **Example 64. Preparation of *N*-((6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxy-3-(thiophen-2-yl)phenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide (compound IB-L0-2.63).**

[0728]



[0729] The product from **Example 63, Part A** (26.5mg, 0.051mmol) was reacted with thiophen-2-yl boronic acid (8.3mg, 0.065mmol) as described in **Example 63, Part B** to give the title compound as an off white solid (8.6mg, 32%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.47 (s, 1 H) 7.86 (d, *J*=7.72 Hz, 2 H) 7.55 - 7.78 (m, 5 H) 7.50 (t, *J*=6.25 Hz, 1 H) 7.38 (d, *J*=2.57 Hz, 1 H) 7.16 - 7.21 (m, 1 H) 6.58 (s, 1 H) 5.69 (d, *J*=7.72 Hz, 1 H) 4.19 (d, *J*=4.78 Hz, 2 H) 3.48 (s, 2 H) 3.30 (s, 3 H) 2.96 (s, 3 H).

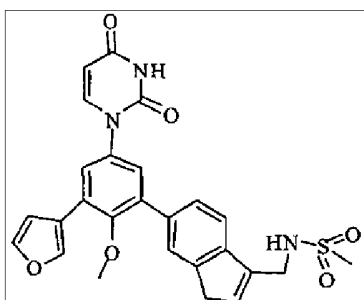
- 25 **Example 65. Preparation of *N*-((6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxy-3-(thiophen-3-yl)phenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide (compound IB-L0-2.62).**

[0730]

[0731] The product from **Example 63, Part A** (25.9mg, 0.050mmol) was reacted with thiophen-3-yl boronic acid (8.1mg, 0.063mmol) as described in **Example 63, Part B** to give the title compound as an off-solid (8.6mg, 33%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.45 (d, *J*=1.84 Hz, 1 H) 7.93 (d, *J*=2.94 Hz, 1 H) 7.87 (d, *J*=7.72 Hz, 1 H) 7.53 - 7.75 (m, 6 H) 7.49 (t, *J*=6.25 Hz, 1 H) 7.39 (d, *J*=2.57 Hz, 1 H) 6.57 (s, 1 H) 5.68 (dd, *J*=7.91, 2.02 Hz, 1 H) 4.19 (d, *J*=5.15 Hz, 2 H) 3.47 (s, 2 H) 3.21 (s, 3 H) 2.96 (s, 3 H).

Example 66. Preparation of *N*-((6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-(furan-3-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide (compound IB-L0-2.67).

15

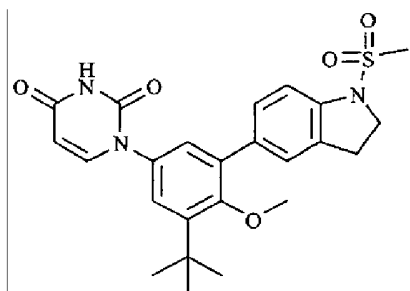
[0732]

[0733] The product from **Example 63, Part A** (25.9mg, 0.050mmol) was reacted with furan-3-yl boronic acid (7.2mg, 0.064mmol) as described in **Example 63, Part B** to give the title compound as an off-white solid (10.6mg, 45%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.46 (s, 1 H) 7.84 (d, *J*=8.09 Hz, 1 H) 7.80 (t, *J*=1.84 Hz, 1 H) 7.68 - 7.75 (m, 2 H) 7.54 - 7.64 (m, 2 H) 7.50 (t, *J*=6.07 Hz, 1

H) 7.35 (d, $J=2.57$ Hz, 1 H) 7.08 (d, $J=1.47$ Hz, 1 H) 6.57 (s, 1 H) 5.68 (d, $J=8.09$ Hz, 1 H) 3.47 (s, 2 H) 3.30 (s, 3 H) 2.96 (s, 3 H).

Example 67. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(1-(methylsulfonyl)indolin-5-yl) phenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.32).

[0734]



Part A. Preparation of 5-bromo-1-(methylsulfonyl)indoline.

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[0735] To DMF (5.0ml) was added sodium hydride (53mg, 1.3mmol) and the solution stirred at room temperature for 30min. 5-Bromoindoline (240mg, 1.2mmol) was added and the solution was stirred at room temperature for 30min. Methanesulfonyl chloride (94ul, 1.2mmol) was added and the solution stirred at room temperature overnight, then concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 2% CH₃OH/CHCl₃ to give the title compound (202mg, 60%).

15

Part B. Preparation of 1-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) indoline.

20

[0736] The product from **Part A** (192mg, 0.70mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound (114mg, 51%).

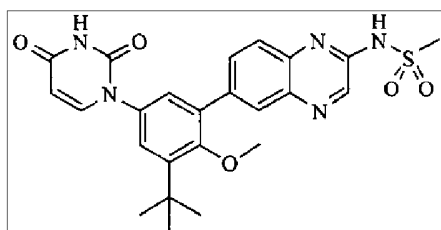
25

Part C. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(1-(methylsulfonyl)indolin-5-yl)phenyl) pyrimidine-2,4(1*H*,3*H*)-dione.

[0737] The product from **Example C** (58mg, 0.145mmol) and the product from **Part B** (56.2mg, 0.174mmol) were subjected to the conditions described for **Example 42, Part C** to give the title compound as a colorless solid (12mg, 18%). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.40 (d, *J*=1.84 Hz, 1 H) 7.76 (d, *J*=7.72 Hz, 1 H) 7.53-7.67 (m, 1 H) 7.45 (s, 1 H) 7.32-7.41 (m, 2 H) 7.23 (dd, *J*=13.60, 2.57 Hz, 2 H) 5.63 (dd, *J*=8.09, 2.21 Hz, 1 H) 3.99 (t, *J*=8.46 Hz, 2 H) 3.29 (s, 3 H) 3.18 (t, *J*=8.46 Hz, 2 H) 3.04 (s, 3 H).

Example 68. Preparation of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)quinoxalin-2-yl)methanesulfonamide (compound IB-L0-2.26).

[0738]



15 **Part A. Preparation of *N*-(4-bromo-2-nitrophenyl)-3-oxobutanamide.**

[0739] A solution of diketene (0.32ml, 4.15mmol) in toluene (2ml) was added to an 80°C solution of 4-bromo-2-nitroaniline (900mg, 4.15mmol) in toluene (7ml) and the solution was heated at reflux for 5h. Triethylamine (0.58ml, 4.15mmol) in toluene (2ml) was added and refluxing was continued for 30min. The cooled solution was concentrated in vacuo and the crude product purified by column chromatography on silica gel eluting with 2:1 hexane/EtOAc to give the title compound as a yellow solid (920mg, 74%).

25 **Part B. Preparation of 6-bromoquinoxalin-2(1H)-one.**

[0740] To a solution of sodium hydroxide (337mg, 8.4mmol) in H₂O (2.1ml) was added the product from **Part A** (423mg, 1.4mmol) and stirring was continued at 65°C for 1h. The cooled solution was diluted with H₂O (4ml) and sodium boro-

hydride (31.9mg, 0.84mmol) was added and stirring was continued at room temperature for 1.5h. Ice was added to the solution followed by dropwise addition of 6N HCl until acidic. The resulting solid was collected by filtration, washed with H₂O, and dried in a vacuum oven to give the title compound (273mg, 86%).

5

Part C. Preparation of 6-bromo-2-chloroquinoxaline.

[0741] To a flask containing phosphorus oxychloride (3.4ml, 36.5mmol) was added the product from **Part B** (255mg, 1.1 mmol) and the solution was heated at 60°C overnight. The solution was cooled to room temperature, poured over ice and the resulting solid collected by filtration to give the title compound (239mg, 87%).

15

Part D. Preparation of 6-bromo-N-(4-methoxybenzyl)quinoxalin-2-amine.

[0742] To a solution of the product from **Part C** (2.8g, 11.5mmol) in ethanol (58ml) was added (4-methoxyphenyl)methanamine (7.5ml, 57.5mmol) and the solution was stirred at room temperature for 1h. Solvent was concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with 20% EtOAc/hexane to give the title compound (1.97g, 50%).

25

Part E. Preparation of N-(4-methoxybenzyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) quinoxalin-2-amine.

[0743] The product from **Part D** (500mg, 1.45mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound (378mg, 66%).

30

Part F. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(2-(4-methoxybenzylamino)quinoxalin-6-yl)phenyl)pyrimidine-2,4(1*H*,3*H*)-dione.

[0744] The product from **Part E** (133mg, 0.34mmol) was subjected to the conditions described for **Example 42, Part C** to give the title compound (125mg, 82%).

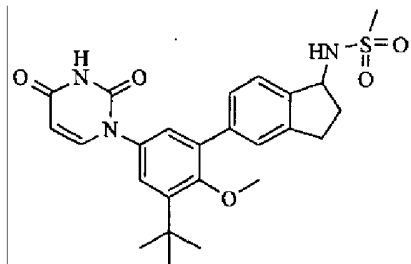
5 **Part G. Preparation of N-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)quinoxalin-2-yl)methanesulfonamide.**

[0745] To a solution of the product from **Part F** (87mg, 0.16mmol) in CH₂Cl₂ (1.6ml) and H₂O (0.07ml) was added DDQ (40.4mg, 0.18mmol) and stirred vigorously at room temperature for 1h. The solution was filtered through Celite and the dark solid collected on the Celite was dissolved in 5ml CH₃OH. The methanol solution was filtered, solvent removed in vacuo and the crude intermediate was dissolved in pyridine (0.6ml). Methanesulfonyl chloride (11ul, 0.14mmol) was added and the solution was heated at 60°C overnight. The cooled solution was concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with 2% CH₃OH/CHCl₃ to give the title compound (7.7mg, 12%). ¹H NMR (300 MHz, CDCl₃) δ 8.42 (s, 1 H) 8.29 (s, 1 H) 8.13 (s, 1 H) 7.88 (d, 1 H) 7.54 (s, 1 H) 7.19-7.43 (m, 4 H) 5.83 (dd, *J*=7.91, 2.39 Hz, 1H) 3.32 (s, 3 H) 3.27 (s, 3 H) 1.46 (s, 9 H).

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Example 69. Preparation of N-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methanesulfonamide (compound IB-L0-2.44).

25 [0746]



Part A. Preparation of 5-bromo-2,3-dihydro-1*H*-inden-1-ol.

[0747] A suspension of 5-bromo-2,3-dihydro-1H-inden-1-one (2.07g, 9.81mmol) in ethanol (49mL) was treated with the sodium borohydride (186mg, 4.90mmol) all at once. After a few minutes, the solution warmed slightly and all solids dissolved. After stirring at room temperature for 1h, the mixture was concentrated in vacuo to remove ethanol. The gum obtained was partitioned between ethyl acetate and water. The organic layer was extracted with saturated sodium bicarbonate solution (2 x) and saturated sodium chloride solution. Drying (Na₂SO₄) and concentration in vacuo afforded the title compound (3.05g, 98%) as a colorless oil, which crystallized upon pumping under high vacuum overnight.

Part B. Preparation of 1-azido-5-bromo-2,3-dihydro-1H-indene.

[0748] A solution of the product from **Part A** (1.01g, 4.73mmol) in toluene (8.1 mL) was treated with the diphenyl phosphoroyl azide (1.23mL, 1.56g, 5.67 mmol) followed by cooling to 0°C. The solution was treated dropwise with DBU (855µL, 863mg, 5.67mmol) followed by stirring at 0°C for 2h, and then warming to room temperature for 48h. The mixture was diluted with ethyl acetate and extracted with water and 1 M citric acid solution, and then with saturated sodium chloride solution. Drying (Na₂SO₄) and concentration in vacuo afforded a brown oil, which was purified by flash chromatography, eluting with 5-50 % ethyl acetate in hexanes. These procedures afforded the title compound (889mg, 79%) as a light yellow oil.

Part C. Preparation of 5-bromo-2,3-dihydro-1H-inden-1-amine.

[0749] To a -15°C solution of 1M lithium aluminum hydride in THF (0.84ml, 0.84 mmol) in THF (0.88ml) was added dropwise a solution of the product from **Part B** (200mg, 0.84mmol) and the solution was warmed to room temperature and stirred overnight. The solution was cooled to -10°C and 4:1 THF:H₂O (0.5ml) was added dropwise. The solution was stirred at room temperature for 4h, filtered through Celite and the filtrate concentrated in vacuo to give the title compound (151mg, 85%).

Part D. Preparation of *N*-(5-bromo-2,3-dihydro-1*H*-inden-1-yl)methanesulfonamide.

[0750] To a solution of the product from **Part C** (150mg, 0.71mmol) in pyridine (3.5ml) was added methanesulfonyl chloride (61 μ l, 0.78mmol) and the solution was stirred at room temperature overnight. The solution was concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with 20% EtOAc/hexane to give the title compound (111 mg, 54%).

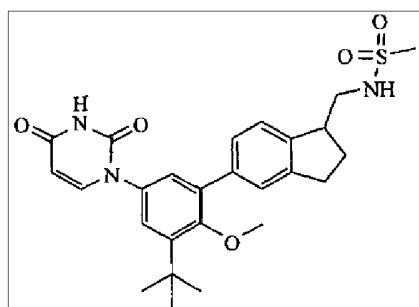
10 **Part E. Preparation of *N*-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methanesulfonamide.**

[0751] The product from **Part D** (109mg, 0.38mmol) was subjected to the conditions described for **Example 42, Part B** and **Part C** to give the title compound (39mg, 60%). ^1H NMR (300 MHz, DMSO- d_6) δ 11.39 (d, $J=1.84$ Hz, 1 H) 7.77 (d, $J=7.72$ Hz, 1 H) 7.58 (d, $J=8.82$ Hz, 1 H) 7.39-7.48 (m, 3 H) 7.27 (d, $J=2.57$ Hz, 1 H) 7.19-7.23 (m, 1 H) 5.63 (dd, $J=8.09, 2.21$ Hz, 1 H) 4.86 (q, $J=7.97$ Hz, 1 H) 3.27 (s, 3 H) 3.04 (s, 3 H) 2.90-3.01 (m, 1 H) 2.71-2.90 (m, 1 H) 2.52-2.62 (m, 1 H) 1.85-1.98 (m, 1 H) 1.40 (s, 9 H).

Example 70. Preparation of *N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.17).

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[0752]



Part A. Preparation of (*E*)-5-bromo-1-(methoxymethylene)-2,3-dihydro-1*H*-indene.

[0753] To a suspension of (methoxymethyl)triphenylphosphonium chloride (39.7 g, 116mmol) in THF (210ml) at -20°C was added dropwise 1M potassium t-butoxide (95ml, 95mmol) and the solution stirred at -20°C for 20min. To this solution was added dropwise a solution of 5-bromo-2,3-dihydro-1*H*-inden-1-one (10.0g, 47.4mmol) in THF (230ml) and stirring was continued at -20°C for 30min then warmed to room temperature and stirred for 2h. The solution was filtered through Celite and the filtrate was concentrated in vacuo to give crude product which was purified by chromatography on a silica gel cartridge eluting with CH₂Cl₂/hexane to give the title compound (10.56g, 93%).

Part B. Preparation of 5-bromo-2,3-dihydro-1*H*-indene-1-carbaldehyde.

[0754] To a solution of the product from **Part A** (1.44g, 6.0mmol) in CH₂Cl₂ (30ml) at -78°C was added dropwise 1M boron tribromide in CH₂Cl₂ (13.8ml, 13.8mmol) and stirring was continued at -78°C for 4h. The solution was poured into an ice-saturated sodium bicarbonate mixture and stirred vigorously. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2x), the organic extracts were combined, dried (Na₂SO₄), and concentrated in vacuo to give crude product which was purified by column chromatography on silica gel eluting with 10% EtOAc/hexane to give the title compound (604mg, 45%).

Part C. Preparation of 1-(5-bromo-2,3-dihydro-1*H*-inden-1-yl)-*N*-(4-methoxybenzyl)-methanamine.

[0755] To a solution of the product from **Part B** (300mg, 1.3mmol) in CH₃OH (18.5ml) was added 4-methoxybenzylamine (0.17ml, 1.3 mmol) and decabornane (49mg, 0.4mmol) and stirring was continued at room temperature for 1h, solvent was concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with 3% CH₃OH/CHCl₃ to give the title compound (264mg, 57%).

Part D. Preparation of *N*-((5-bromo-2,3-dihydro-1*H*-inden-1-yl)methyl)-*N*-(4-methoxybenzyl)methanesulfonamide.

[0756] To a solution of the product from **Part C** (88mg, 0.25mmol) in CH₂Cl₂ (1.0ml) was added triethylamine (39ul, 0.28mmol) and methanesulfonyl chloride (22ul, 0.28mmol) and stirring was continued at room temperature for 1h, solvent was concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with EtOAc/hexane to give the title compound (55mg, 51%).

10

Part E. Preparation of *N*-(4-methoxybenzyl)-*N*-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide.

[0757] The product from **Part D** (1.15g, 2.71mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound (840mg, 66%).

Part F. Preparation of *N*-((5-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide.

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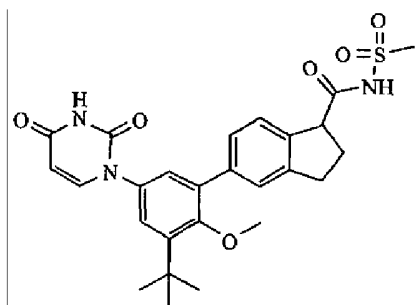
[0758] The product from **Part E** (840mg, 2.1mmol) was subjected to the conditions described for **Example 42, Part C** and the isolated material (1.28g, 2.07mmol) was dissolved in CH₂Cl₂ (10ml) and trifluoroacetic acid (10ml) was added slowly. After stirring at room temperature for 1h, solvent was concentrated in vacuo and the crude product was suspended in 10% NaHCO₃, extracted with CH₂Cl₂ (3x), the organic extracts combined, dried (Na₂SO₄), and solvent concentrated in vacuo to give crude product which was purified by column chromatography on silica gel eluting with 2% CH₃OH/CHCl₃ to give title compound (0.84g, 81 %). ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.39 (s, 1 H) 7.77 (d, *J*=8.09 Hz, 1 H) 7.29-7.59 (m, 3 H) 7.25 (d, *J*=2.94 Hz, 1H) 7.10-7.22 (m, 2 H) 5.63 (dd, *J*=7.72, 1.84 Hz, 1 H) 3.93 (s, 3 H) 3.26 (s, 2 H) 3.23-3.40 (m, 1 H)

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2.89 (s, 3 H) 2.71-3.09 (m, 2 H) 2.14-2.32 (m, 1 H) 1.75-1.95 (m, 1 H) 1.40 (s, 9 H).

Example 71. Preparation of 5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-*N*-(methylsulfonyl)-2,3-dihydro-1*H*-indene-1-carboxamide (compound IB-L0-2.34).

[0759]



10

Part A. Preparation of 5-bromo-2,3-dihydro-1*H*-indene-1-carboxylic acid.

[0760] To a solution of the product from **Example 70, Part B** (300mg, 1.3mmol) and 2-methyl-2-pentene (8ml) in tert-butanol (32ml) was added a solution of sodium chlorite (1.36g, 0.12mmol) in H₂O (122ml) containing sodium dihydrogen phosphate (1.07g, 8.9mmol) and the mixture was stirred vigorously for 20min at room temperature. Solvents were concentrated in vacuo and the residue was diluted with H₂O, extracted with EtOAc (3x), extracts combined, dried (Na₂SO₄), and concentrated in vacuo to give the title compound (180mg, 56%).

20

Part B. Preparation of 5-bromo-*N*-(methylsulfonyl)-2,3-dihydro-1*H*-indene-1-carboxamide.

[0761] To a solution of the product from **Part A** (100mg, 0.42mmol) in CH₂Cl₂ (1.7ml) was added carbonyldiimidazole (67.3mg, 0.42mmol) and the reaction was stirred for 2h at room temperature. Methanesulfonamide (39.5mg, 0.42mmol) and DBU (62.5mg, 0.42mmol) were added and stirring was continued at room temperature for 2h. Solution was diluted with CH₂Cl₂, washed 1N HCl,

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brine, dried (Na₂SO₄), concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with 20% EtOAc/hexane to give the title compound (121 mg, 92%).

5 **Part C. Preparation of *N*-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-indene-1-carboxamide.**

[0762] The product from **Part B** (159mg, 0.5mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound (144mg,
10 79%).

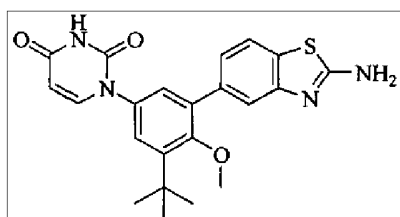
Part D. Preparation of 5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1-(2*H*)-yl)-2-methoxyphenyl)-*N*-(methylsulfonyl)-2,3-dihydro-1*H*-indene-1-carboxamide.

15 [0763] The product from **Part C** (134mg, 0.34mmol) was subjected to the conditions described for **Example 42, Part C** to give title compound (14mg, 8%). ¹H NMR (300 MHz, CDCl₃) δ 8.11 (m, 1 H) 7.08-7.57 (m, 7 H) 5.80 (dd, *J*=7.91, 2.39 Hz, 1 H) 4.07 (dd, *J*=9.01, 6.07 Hz, 1 H) 3.33 (s, 3 H) 3.08 (s, 3 H) 2.91-
20 3.22 (m, 1 H) 2.35-2.74 (m, 1 H) 1.44 (s, 9H) 1.17-1.34 (m, 1 H) 0.60-1.00 (m, 1 H).

Example 72. Preparation of 1-(3-(2-aminobenzo[d]thiazol-6-yl)-5-*tert*-butyl-4-methoxy-phenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.39).

25

[0764]



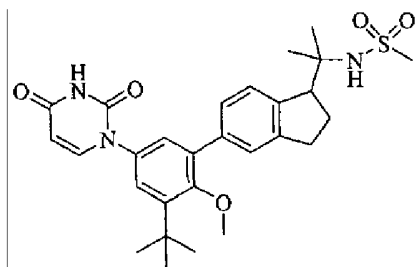
[0765] The title compound was prepared using the procedures described for the
30 preparation of **Example 53**, substituting 5-bromo[d]thiazol-2-amine for 6-bromo-

benzo[d]thiazol-2-amine. ^1H NMR (300 MHz, DMSO- d_6) δ 11.40 (d, $J=1.84$ Hz, 1 H) 8.40 (s, 2 H) 7.84 (d, $J=8.09$ Hz, 1 H) 7.78 (d, $J=7.72$ Hz, 1 H) 7.54 (d, $J=1.47$ Hz, 1 H) 7.27 - 7.32 (m, 3 H) 5.64 (dd, $J=8.09, 2.21$ Hz, 1 H) 3.27 (s, 3 H) 1.41 (s, 9 H).

5

Example 73. Preparation of *N*-(2-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)propan-2-yl)methanesulfonamide (compound IB-L0-2.29).

10 [0766]

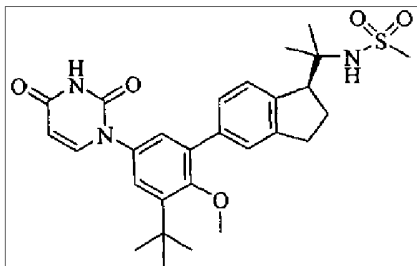


[0767] To a solution of the product from **Example 45, Part D** (20mg, 0.038 mmol) in 1:1 benzene: MeOH (0.6ml) was added platinum(IV) oxide (1mg). The resulting mixture was stirred under 1 atm H_2 at room temperature for 1h, and then filtered thru celite, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 3% MeOH in CHCl_3 as the eluent to give the title compound as a solid (14mg, 70%). ^1H NMR (300 MHz, DMSO- d_6) δ 11.39 (s, 1 H) 7.77 (d, $J=7.72$ Hz, 1 H) 7.58 (d, $J=8.09$ Hz, 1 H) 7.28 - 7.38 (m, 2 H) 7.21 - 7.26 (m, 2 H) 7.07 (s, 1 H) 5.63 (d, $J=7.72$ Hz, 1 H) 3.61 (dd, $J=8.64, 5.33$ Hz, 1 H) 3.25 (s, 3 H) 3.00 (s, 3 H) 2.75 - 2.98 (m, 2 H) 1.97 - 2.21 (m, 2 H) 1.40 (s, 9 H) 1.24 (d, $J=8.46$ Hz, 6 H).

Example 74. Preparation of (*S*)-*N*-(2-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)propan-2-yl)methanesulfonamide (compound IB-L0-2.22).

25

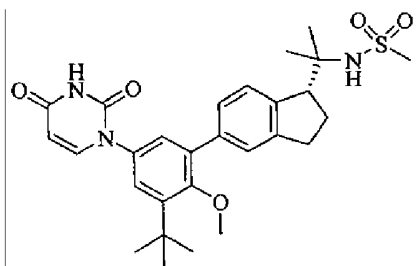
[0768]



[0769] The product from **Example 73** (10mg) was subjected to chiral chromatography (Chiralpak AD-H column; eluting with 1:3 2-PrOH:hexanes(0.1% TFA)). Isolation of the earlier eluting component gave the title compound (4.4mg). ¹H NMR identical to the product from **Example 103**.

Example 75. Preparation of (*R*)-*N*-(2-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydro-10 pyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)propan-2-yl)methanesulfonamide (compound IB-L0-2.37).

[0770]



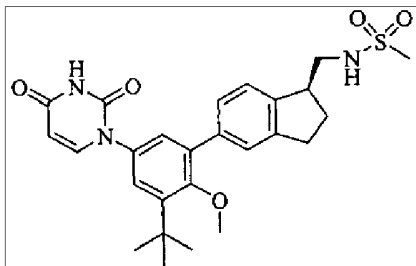
15

[0771] The product from **Example 73** (10mg) was subjected to chiral chromatography (Chiralpak AD-H column; eluting with 1:3 2-PrOH:hexanes(0.1% TFA)). Isolation of the later eluting component gave the title compound (4.2mg). ¹H NMR identical to the product from **Example 73**.

20

Example 76. Preparation of (*S*)-*N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydro-20 pyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methyl)-methanesulfonamide (compound IB-L0-2.9).

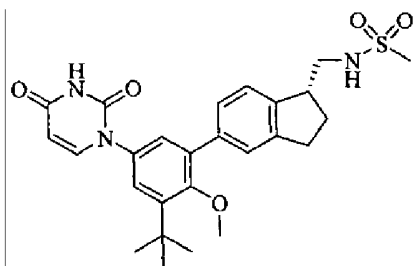
[0772]



[0773] The product from **Example 70, Part F** (20mg) was subjected to chiral chromatography (Chiralpak AD-H column; eluting with 1:4 2-PrOH:hexanes (0.1% TFA)). Isolation of the earlier eluting component gave the title compound (5.3mg). ¹H NMR identical to the product from **Example 70, Part F**.

Example 77. Preparation of (*R*)-*N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.15).

[0774]

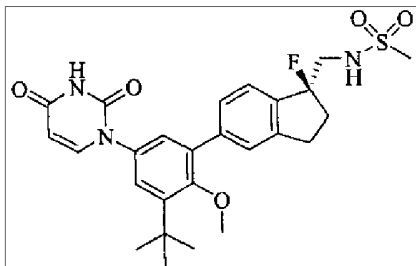


15

[0775] The product from **Example 70, Part F** (20mg) was subjected to chiral chromatography (Chiralpak AD-H column; eluting with 1:4 2-PrOH:hexanes (0.1% TFA)). Isolation of the later eluting component gave the title compound (5.7mg). ¹H NMR identical to product from **Example 70, Part F**.

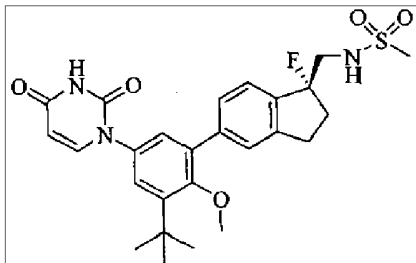
20

Example 78. Preparation of (*S*)-*N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.20).

[0776]

[0777] The product from **Example 61, Part H** was subjected to the conditions described in **Example 74** to give the title compound. ¹H NMR identical to the product from **Example 61, Part H**.

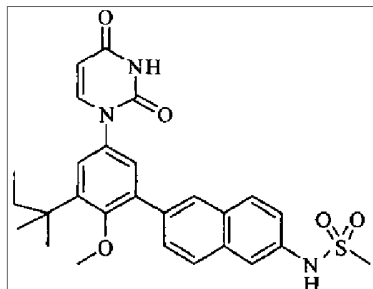
Example 79. Preparation of (*R*)-*N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)-methyl)methanesulfonamide (compound IB-L0-2.10).

[0778]

[0779] The product from **Example 61, Part H** was subjected to the conditions described in **Example 104** to give the title compound. ¹H NMR identical to the product from **Example 61, Part H**.

Example 80. Preparation of *N*-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxy-3-*tert*-pentylphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.52).

[0780]



Part A. Preparation of 1-(3-tert-butyl-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0781] 2-*tert*-Amylphenol (5.0g, 30mmol) was reacted according to the procedure from **Example C, Part A, Part B, and Part C** to provide the title product as a colorless solid.(6.7g, 56% overall yield for 3 steps).

10

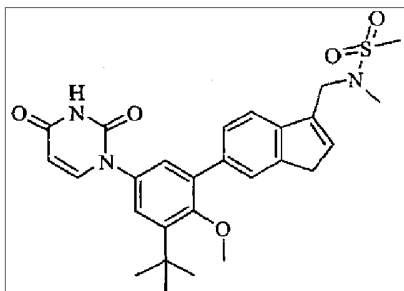
Part B. Preparation of *N*-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxy-3-*tert*-pentylphenyl)naphthalen-2-yl)methanesulfonamide.

[0782] The product from **Part A** (100mg, 0.241mmol), the product from **Example 2A, Part B** (92mg, 0.266mmol), sodium carbonate (38.4mg, 0.362mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (9.9mg, 0.012mmol) were dissolved in a toluene (4mL) and ethanol (4mL) solvent mixture which was sparged with nitrogen for 10min, then the mixture heated to 85°C for 18h. To the solution was then added CH₂Cl₂ (20mL) followed by 1N aqueous HCl (10mL), the organic layer separated 3-mercapto-propyl silica gel (100mg) and magnesium sulfate added. The solution was concentrated and purified by column chromatography on silica gel using 3% MeOH in CH₂Cl₂ as the eluent to provide the title compound as a colorless solid (71mg, 58%). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.41(s, 1H), 10.04 (s, 1H), 8.03 (s, 1H), 7.95 (t, *J*=8.7Hz, 2H), 7.79 (d, *J*=7.7Hz, 1H), 7.73(d, *J*=1.8Hz, 1H), 7.69(dd, *J*=8.8,1.6Hz, 1H), 7.42 (dd, *J*=8.8,2.2Hz, 1H), 7.37 (d, *J*=2.6Hz, 1H), 7.25 (d, *J*=2.6Hz, 1H), 5.65 (dd, *J*=8.1,1.6Hz, 1H), 3.22 (s, 3H), 3.08 (s, 3H), 1.84 (m, 2H), 1.38 (s, 6H), 0.73 (t, *J*=7.5Hz, 3H).

25

Example 81. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)-*N*-methylmethanesulfonamide (compound IB-L0-2.16).

5 [0783]



Part A. Preparation of *N*-methyl-*N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-inden-3-yl)methyl)methanesulfonamide.

10

[0784] To a solution of the product from **Example 49, Part E** (210mg, 0.60 mmol) in anhydrous THF (5ml) was added a 1.0M solution of lithium bis(trimethylsilyl)amide in toluene (0.60ml, 0.60mmol), and the resulting mixture was stirred at room temperature for 5min. Iodomethane (0.075ml, 1.20mmol) was added and the mixture was stirred at room temperature for 2h, and was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried with sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a gradient of ethyl acetate/ in hexane (10% to 25%) to give the title compound as a solid (125mg, 57%).

15

20

Part B. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)-*N*-methylmethanesulfonamide.

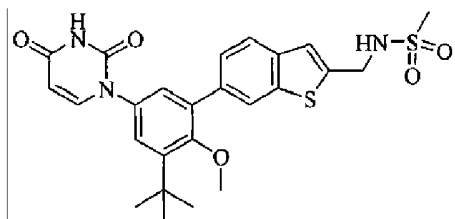
25

[0785] A mixture of the product from **Example C** (60.0mg, 0.15mmol), the product of **Part A** (54.5mg, 0.15mmol), potassium phosphate (66.9mg, 0.315 mmol), PA-Ph (CAS 97739-46-3, 1.32mg, 4.5 μ mol) and tris(dibenzylideneace-

tone)dipalladium(0) (1.37mg, 1.5 μ mol) in tetrahydrofuran (3.0ml) and water (1.0ml) was purged with N₂ for 30min. The mixture was stirred at 50°C for 2h, and then partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered through celite and concentrated in vacuo. The crude product was purified by column chromatography on C-18 reversed-phase silica gel using a solvent gradient of 10-100% acetonitrile in water(0.1% TFA) to give the title compound as a solid (19mg, 24%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.40 (d, J=1.84 Hz, 1 H) 7.78 (d, J=7.72 Hz, 1 H) 7.65 (m, 2 H) 7.49 (dd, J=7.72, 1.47 Hz, 1 H) 7.26 (m, 2.57 Hz, 2 H) 6.63 (s, 1 H) 5.64 (dd, J=7.72, 2.21 Hz, 1 H) 4.26 (s, 2 H) 3.51 (s, 2 H) 3.26 (s, 3 H) 3.01 (s, 3 H) 2.72 (s, 3 H) 1.41 (s, 9 H).

Example 82. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-2-yl)methyl)methanesulfonamide (compound IB-L0-2.40).

[0786]



20

Part A. Preparation of ethyl 6-bromobenzo[*b*]thiophene-2-carboxylate.

[0787] To a solution of 4-bromo-2-fluorobenzaldehyde (1.02g, 4.83mmol) in DMSO (4mL), was added ethyl 2-mercaptoacetate (0.58mL, 5.31mmol), followed by Et₃N (1.35mL, 9.65mmol), and the mixture was heated at 80°C for 3h. The resulting dark mixture was poured into water (50mL) and extracted with EtOAc (2 x 50mL). The combined organic extracts were washed with 10% NaCl, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound as a light yellow waxy solid (1.29g, 94%).

Part B. Preparation of (6-bromobenzo[*b*]thiophen-2-yl)methanol.

[0788] To a solution of the product from **Part A** (0.82g, 2.88mmol) in Et₂O (20mL) at 0°C was added a 1M solution of lithium aluminum hydride in Et₂O (3.16mL, 3.16mmol) dropwise, and the resulting slurry was stirred between 5-10°C for 1h. The slurry was treated with 0.3mL H₂O, 0.3mL 15 % aq NaOH, 0.7mL H₂O, stirred 30min, filtered and concentrated in vacuo to give the title compound as a colorless solid (0.58g, 83%).

10 Part C. Preparation of 6-bromo-2-(bromomethyl)benzo[*b*]thiophene.

[0789] A mixture of the product from Part B (85mg, 0.35mmol), *N*-bromosuccinimide (74mg, 0.413mmol) and triphenylphosphine (106mg, 0.403mmol) in CH₂Cl₂ (2mL) was stirred at room temperature for 2h. The reaction mixture was diluted with 50mL CH₂Cl₂, washed with water, 10% NaHCO₃ and 10% NaCl, dried over anhydrousMgSO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with 9:1 hexane:-EtOAc to yield the title compound as a white solid (96mg, 89%).

20 Part D. Preparation of *N*-(4-methoxybenzyl)methanesulfonamide.

[0790] To a solution of (4-methoxyphenyl)methanamine (1.317g, 9.60mmol) in CH₂Cl₂ (10mL) was added methanesulfonyl chloride (0.34mL, 4.36mmol) dropwise. The mixture was stirred at room temperature for 2h. The reaction mixture was diluted with 50mL CH₂Cl₂ washed with 1N H₃PO₄, 10% NaCl, dried over anhydrousmgSO₄, filtered and concentrated in vacuo to give the title compound as a white solid (0.84g, 89%).

30 Part E. Preparation of *N*-((6-bromobenzo[*b*]thiophen-2-yl)methyl)-*N*-(4-methoxybenzyl)-methanesulfonamide.

[0791] A solution of the product from **Part D** (0.223g, 1.037mmol) in EtOH (2mL) and 1.0M NaOH (1.1mL, 1.1mmol) was added to a slurry containing the

product from **Part C** (0.317g, 1.037mmol) in EtOH (4mL). The resulting slurry was heated at reflux for 1h, and then concentrated in vacuo to give a pasty solid. The residue was partitioned between 40mL water and 40mL EtOAc. The organic layer was washed with 1N H₃PO₄, 10% NaHCO₃, 10% NaCl, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo leaving a yellow oil. The crude product was purified by column chromatography on silica gel eluting with CH₂Cl₂ to give the title compound as a colorless solid (0.15g, 33%).

Part F. Preparation of *N*-(4-methoxybenzyl)-*N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-2-yl)methyl)methanesulfonamide.

[0792] The product from **Part E** (0.15g, 0.34mmol) was subjected to the conditions described for the preparation of **Example 42, Part B** to give the title compound as a colorless solid (0.121g, 73%).

Part G. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-2-yl)methyl)-*N*-(4-methoxybenzyl)methanesulfonamide.

[0793] The product from **Part F** (24mg, 0.049mmol) was subjected to the conditions described for the preparation of **Example 42, Part C** to give the title compound as a colorless solid (20mg, 65%).

Part H. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-2-yl)methyl)methanesulfonamide.

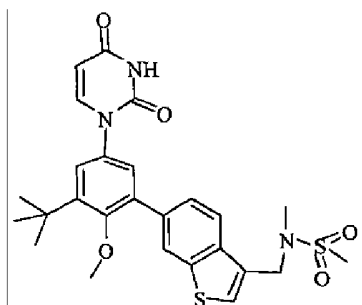
[0794] A solution of the product from **Part G** (14mg, 0.022mmol) in CH₂Cl₂ (0.3 mL) and TFA (0.3mL) was stirred at room temperature for 4h and then concentrated in vacuo. The residue was partitioned between 10mL CH₂Cl₂ and 2mL 10% aq. NaHCO₃ and the organic layer was concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 99:1 CH₂Cl₂:MeOH to give the title compound as a colorless solid (5mg, 44%). ¹H

NMR (300 MHz, DMSO- d_6) δ 11.40 (s, 1 H) 8.09 (s, 1 H) 7.82 - 7.97 (m, 3 H) 7.79 (d, $J=7.72$ Hz, 1 H) 7.47 - 7.63 (m, 1 H) 7.40 (s, 1 H) 7.26 - 7.34 (m, 1 H) 5.64 (d, $J=7.72$ Hz, 1 H) 4.48 (d, $J=5.88$ Hz, 2 H) 3.23 (s, 3 H) 2.95 (s, 3 H) 1.41 (s, 9 H).

5

Example 83. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-3-yl)methyl)-*N*-methylmethanesulfonamide (compound IB-L0-2.21).

10 [0795]



Part A. Preparation of *N*-((6-bromobenzo[*b*]thiophen-3-yl)methyl)-*N*-methylmethanesulfonamide.

15

[0796] A mixture of the product from **Example 46, Part D** (0.100g, 0.382mmol), *N*-methylmethane-sulfonamide (45.9mg, 0.421mmol) and potassium carbonate (0.127g, 0.918mmol) in *N,N*-dimethylacetamide (5mL). The mixture was stirred at 80°C for 11 h, cooled to room temperature and partitioned between diethyl-
 20 ether and water (3x), dried over MgSO_4 , filtered and concentrated in vacuo to give the title compound as a colorless waxy solid (0.128g, quant.).

Part B. Preparation of *N*-methyl-*N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-3-yl)methyl)methanesulfonamide.

25

[0797] The product from **Part A** (0.128g, 0.382mmol) was subjected to the conditions described for the preparation of **Example 42, Part B** to give the title compound as a colorless, crystalline solid (0.120g, 82%).

Part C. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-3-yl)methyl)-*N*-methylmethanesulfonamide.

5 [0798] The product from **Part B** (50.6mg, 0.133mmol) was subjected to the conditions described for the preparation of **Example 49, Part F** to give the title compound as a colorless solid (61.5mg, 88%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.41 (s, 1 H) 8.17 (d, *J*=1.47 Hz, 1 H) 8.09 (d, *J*=8.09 Hz, 1 H) 7.74-7.85 (m, 2 H) 7.63 (dd, *J*=8.46, 1.47 Hz, 1 H) 7.29 - 7.36 (m, 2 H) 5.65 (d, *J*=7.72 Hz, 1 H)
10 4.52 (s, 2 H) 3.24 (s, 3 H) 3.03 (s, 3 H) 2.70 (s, 3 H) 1.42 (s, 9 H).

The following compounds were prepared utilizing the above discussion:

[0799] *N*-(2-(3-*tert*-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1*H*-benzo[*d*]imidazol-5-yl)-*N*-(methylsulfonyl)methanesulfonamide
15 (compound **IA-L0-2.10**) ¹H NMR (300 MHz, DMSO-*D*₆) δ ppm 1.45 (s, 9 H) 2.73 (t, *J*=6.62 Hz, 2 H) 3.48 (s, 3 H) 3.56 (s, 6 H) 3.83 (t, *J*=6.80 Hz, 2 H) 4.05 (s, 1 H) 7.38 (dd, *J*=8.46, 1.84 Hz, 1 H) 7.46 (d, *J*=2.57 Hz, 1 H) 7.71 (d, *J*=8.46 Hz, 1 H) 7.76 (d, *J*=2.57 Hz, 1 H) 7.82 (d, *J*=1.84 Hz, 1 H) 10.41 (s, 1 H).

20

[0800] *N*-((6-(3-*tert*-butyl-2-chloro-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-phenyl)benzo [*b*]thiophen-3-yl)methyl)methanesulfonamide (compound **IB-L0-2.35**). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.52 (s, 9 H) 2.95 (s, 3 H) 4.44 (d, *J*=5.88 Hz, 2 H) 5.68 (d, *J*=8.09 Hz, 1 H) 7.40 (d, *J*=2.57 Hz, 1 H) 7.46 (dd, *J*=8.09, 1.47 Hz, 1 H) 7.56 (d, *J*=2.57 Hz, 1 H) 7.62 (t, *J*=6.07 Hz, 1 H) 7.72 (s, 1 H) 7.83 (d, *J*=8.09 Hz, 1 H) 8.01 (m, 2 H) 11.46 (s, 1 H).

[0801] 1-(3-*tert*-butyl-5-(2-chlorobenzo[*d*]thiazol-6-yl)-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound **IB-L0-238**). ¹H NMR (300 MHz, DMSO-*D*₆) δ
30 ppm 1.41 (s, 9 H) 3.24 (s, 3 H) 5.65 (dd, *J*=8.09, 2.21 Hz, 1 H) 7.34 (s, 2 H) 7.73 (dd, *J*=8.64, 1.65 Hz, 1 H) 7.79 (d, *J*=8.09 Hz, 1 H) 8.07 (d, *J*=8.46 Hz, 1 H) 8.30 (d, *J*=1.84 Hz, 1 H) 11.42 (d, *J*=1.84 Hz, 1 H).

[0802] N-(2-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-6-yl)methanesulfonamide (compound **IB-L0-2.48**).

[0803] 1-(3-tert-butyl-4-methoxy-5-(1-oxo-2,3-dihydro-1H-inden-5-yl)phenyl)pyrimidine-2,4(1H,3H)-dione (compound **IB-L0-2.50**).

[0804] N,N'-(6,6'-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-1,3-phenylene) bis(naphthalene-6,2-diyl))dimethanesulfonamide (compound **IB-L0-2.76**). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.08 (s, 6 H) 3.13 (s, 3 H) 5.72 (d, J=8.18 Hz, 1 H) 7.43 (dd, J=8.46, 1.84 Hz, 2 H) 7.59 (s, 2 H) 7.79 (m, 4 H) 7.96 (m, 5 H) 8.14 (s, 2 H) 10.05 (s, 2 H) 11.48 (s, 1 H).

HCV Polymerase Inhibition Assay

[0805] Either two-fold serial dilutions (fractional inhibition assay) or a narrower range of dilutions spanning the IC₅₀ of the inhibitor (tight binding assay) of the inhibitors were incubated with 20mM Tris-Cl pH 7.4, 2mM MnCl₂, 1mM dithiothreitol, 1mM ethylene diamine tetraacetic acid (EDTA), 60 to 125μM GTP and 20 to 50nM Δ21 NS5B (HCV Strain 1B (BK, Genbank accession number M58335, or H77, Genbank accession number AF011751)) for 15min at room temperature. The reaction was initiated by the addition of 20μM CTP, 20μM ATP, 1μM ³H-UTP (10mCi/umol), 5nM template RNA and 0.1 U/μl RNase inhibitor (RNasin, Promega), and allowed to proceed for 2 to 4h at room temperature. Reaction volume was 50μl. The reaction was terminated by the addition of 1 volume of 4mM spermine in 10mM Tris-Cl pH 8.0, 1mM EDTA. After incubation for at least 15 min at room temperature, the precipitated RNA was captured by filtering through a GF/B filter (Millipore) in a 96 well format. The filter plate was washed three times with 200μl each of 2mM spermine, 10mM Tris-Cl pH 8.0, 1mM EDTA, and 2 times with ethanol. After air-drying, 30μl of Microscint 20 scintillation cocktail (Packard) was added to each well, and the retained cpm were determined by scintillation counting. IC₅₀ values were calculated by a two-variable nonlinear regression equation using an uninhibited control and a fully inhibited control sample to determine the minimum and maximum for the curve.

Tight-binding assays were performed on those compounds exhibiting IC₅₀ values less than 0.005μM in the fractional inhibition assay in order to more precisely measure the IC₅₀ values. Retained cpm were plotted vs. inhibitor concentration and fit to equation 1 using non-linear regression (ref. 1) to obtain the IC₅₀ values:

$$\text{Retained cpm} = A[\text{sqrt}\{(IC_{50} + I_t - E_t)^2 + 4 * IC_{50} * E_t\} - (IC_{50} + I_t - E_t)] \quad (\text{eqn 1})$$

where $A = V_{\text{max}}[S]/2(K_m + [S])$; I_t = total inhibitor concentration and E_t = total active concentration of enzyme.

[0806] Ref. Morrison, J. F. and S. R. Stone. 1985. Approaches to the study and analysis of the inhibition of enzymes by slow- and tight-binding inhibitors. Comments Mol. Cell. Biophys. 2: 347-368.

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[0807] The sequence of the template RNA used was: 5'-GGGCGAAUUG GGCCCUCUAG AUGCAUGCUC GAGCGGCCGC CAGUGUGAUG GAUAUCUGCA GAAUUCGCCC UUGGUGGCUC CAUCUUAGCC CUAGUCACGG CUAGCUGUGA AAGGUCCGUG AGCCGCUUGA CUGCAGAGAG UGCUGA-UACU GGCCUCUCUG CAGAUCAAGUC-3'.

20

[0808] When tested by the above method, the compounds of this invention inhibit HCV polymerase 1A and/or 1B. The legend in the table below is as follows: A -- IC₅₀ ≤ 0.01μM; B -- 0.1μM ≥ IC₅₀ > 0.01μM; C -- 1μM ≥ IC₅₀ > 0.1μM; and D -- IC₅₀ > 1μM; ND - not determined.

25

Table IC₅₀

compound	1a	1b	compound	1a	1b
			IA-L0-2.1	C	C
IA-L0-2.2	B	B	IA-L0-2.3	C	C
IA-L0-2.4	B	B	IA-L0-2.5	C	C
IA-L0-2.6	C	C	IA-L0-2.7	C	C

compound	1a	1b	compound	1a	1b
IA-L0-2.8	B	B	IA-L0-2.9	A	A
IA-L0-2.10	D	D	IB-L0-2.1	C	C
IB-L0-2.2	C	C	IB-L0-2.3	A	A
IB-L0-2.4	A	A	IB-L0-2.5	B	B
IB-L0-2.6	B	B	IB-L0-2.7	B	B
IB-L0-2.8	B	B	IB-L0-2.9	A	A
IB-L0-2.10	A	B	IB-L0-2.11	A	A
IB-L0-2.12	A	B	IB-L0-2.13	A	B
IB-L0-2.14	A	A	IB-L0-2.15	A	B
IB-L0-2.16	A	B	IB-L0-2.17	A	B
IB-L0-2.18	A	B	IB-L0-2.19	A	B
IB-L0-2.20	A	B	IB-L0-2.21	B	B
IB-L0-2.22	B	B	IB-L0-2.23	B	A
IB-L0-2.24	B	B	IB-L0-2.25	B	B
IB-L0-2.26	B	B	IB-L0-2.27	B	B
IB-L0-2.28	B	B	IB-L0-2.29	B	B
IB-L0-2.30	B	B	IB-L0-2.31	B	B
IB-L0-2.32	B	B	IB-L0-2.33	B	B
IB-L0-2.34	B	B	IB-L0-2.35	B	B
IB-L0-2.36	B	C	IB-L0-2.37	C	C
IB-L0-2.38	C	B	IB-L0-2.39	C	C
IB-L0-2.40	C	C	IB-L0-2.41	C	C
IB-L0-2.42	C	C	IB-L0-2.43	C	C
IB-L0-2.44	C	C	IB-L0-2.45	C	C
IB-L0-2.46	C	C	IB-L0-2.47	D	D
IB-L0-2.48	D	D	IB-L0-2.49	D	D
IB-L0-2.50	B	B	IB-L0-2.51	A	B
IB-L0-2.52	A	B	IB-L0-2.53	A	B
IB-L0-2.54	A	B	IB-L0-2.55	A	B
IE-L0-2.56	A	B	IB-L0-2.57	A	B

compound	1a	1b	compound	1a	1b
IB-L0-2.58	A	B	IB-L0-2.59	A	B
IB-L0-2.60	A	B	IB-L0-2.61	A	B
IB-L0-2.62	B	B	IB-L0-2.63	B	B
IB-L0-2.64	B	B	IB-L0-2.65	B	A
IB-L0-2.66	B	B	IB-L0-2.67	B	B
IB-L0-2.68	B	B	IB-L0-2.69	B	B
IB-L0-2.70	B	C	IB-L0-2.71	C	C
IB-L0-2.72	C	C	IB-L0-2.73	C	C
IB-L0-2.74	C	C	IB-L0-2.75	C	D
IB-L0-2.76	C	D	IB-L0-2.77	D	D
IB-L0-2.78	D	D	IB-L0-2.79	B	B

HCV Polymerase Replicon Assay

[0809] Two stable subgenomic replicon cell lines were used for compound characterization in cell culture: one derived from genotype 1a-H77 and one derived from genotype 1b-Con1 (obtained from Apath, LLC, St. Louis, MO). All replicon constructs were bicistronic subgenomic replicons similar to those described by Bartenschlager and coworkers (Lohmann et al., Replication of Subgenomic Hepatitis C Virus RNAs in a Hepatoma Cell Line, SCIENCE 285:110-3(1999)). The genotype 1a replicon construct contains NS3-NS5B coding region derived from the H77 strain of HCV (1a-H77) (Blight et al., Efficient Replication of Hepatitis C Virus Genotype 1a RNAs in Cell Culture, J. VIROL. 77:3181-90 (2003)). The replicon also has a firefly luciferase reporter and a neomycin phosphotransferase (Neo) selectable marker. These two coding regions, separated by the FMDV 2a protease, comprise the first cistron of the bicistronic replicon construct, with the second cistron containing the NS3-NS5B coding region with addition of adaptive mutations E1202G, K1691R, K2040R and S2204I. The 1b-Con1 replicon construct is identical to the 1a-H77 replicon, except that the NS3-NS5B coding region was derived from the 1b-Con1 strain, and the adaptive mutations are E1202G, T1280I and S2204I. Replicon cell lines

were maintained in Dulbecco's modified Eagles medium (DMEM) containing 10% (v/v) fetal bovine serum (FBS), 100 IU/ml penicillin, 100mg/ml streptomycin (Invitrogen), and 200mg/ml G418 (Invitrogen).

5 **[0810]** The inhibitory effects of compounds on HCV replication were determined by measuring activity of the luciferase reporter gene. Briefly, replicon-containing cells were seeded into 96 well plates at a density of 5000 cells per well in 100ul DMEM containing 5% FBS. 16-24h later, the compounds were diluted in dime-
 10 thyl sulfoxide (DMSO) to generate a 200x stock in a series of eight half-log dilu-
 tions. The dilution series was then further diluted 100-fold in the medium con-
 taining 5% FBS. Medium with the inhibitor was added to the overnight cell cul-
 ture plates already containing 100ul of DMEM with 5% FBS. In assays measu-
 ring inhibitory activity in the presence of human plasma, the medium from the
 overnight cell culture plates was replaced with DMEM containing 40% human
 15 plasma and 5% FBS. The cells were incubated for three days in the tissue cul-
 ture incubators and were then lysed for RNA extraction. For the luciferase as-
 say, 30ul of Passive Lysis buffer (Promega) was added to each well, and then
 the plates were incubated for 15min with rocking to lyse the cells. Luciferin solu-
 tion (50 to 100ul, Promega) was added to each well, and luciferase activity was
 20 measured with a Victor II luminometer (Perkin-Elmer). The percent inhibition of
 HCV RNA replication was calculated for each compound concentration and the
 EC₅₀ value was calculated using nonlinear regression curve fitting to the 4-pa-
 rameter logistic equation and GraphPad Prism 4 software.

25 **[0811]** When tested by the above method, the compounds of this invention in-
 hibit HCV polymerase 1A and/or 1B. The legend in the table below is as follows:
 A -- EC₅₀ ≤ 0.01uM; B -- 0.1uM ≥ EC₅₀ > 0.01uM; C -- 1uM ≥ EC₅₀ > 0.1uM; and
 D -- EC₅₀ > 1uM; ND - not determined.

30 **Table EC₅₀**

compound	1a	1b	compound	1a	1b
			IA-L0-2.1	D	D

compound	1a	1b	compound	1a	1b
IA-L0-2.2	C	B	IA-L0-2.3	C	C
IA-L0-2.4	D	C	IA-L0-2.5	D	D
IA-L0-2.6	D	D	IA-L0-2.7	D	C
IA-L0-2.8	C	B	IA-L0-2.9	A	A
IA-L0-2.10	ND	ND	IB-L0-2.1	D	C
IB-L0-2.2	D	D	IB-L0-2.3	A	A
IB-L0-2.4	ND	A	IB-L0-2.5	B	A
IB-L0-2.6	C	B	IB-L0-2.7	C	B
IB-L0-2.8	ND	B	IB-L0-2.9	A	A
IB-L0-2.10	A	A	IB-L0-2.11	B	A
IB-L0-2.12	B	A	IB-L0-2.13	B	A
IB-L0-2.14	C	B	IB-L0-2.15	C	B
IB-L0-2.16	C	A	IB-L0-2.17	B	A
IB-L0-2.18	C	B	IB-L0-2.19	B	B
IB-L0-2.20	C	B	IB-L0-2.21	C	B
IB-L0-2.22	C	B	IB-L0-2.23	C	B
IB-L0-2.24	B	B	IB-L0-2.25	C	B
IB-L0-2.26	D	C	IB-L0-2.27	C	B
IB-L0-2.28	D	C	IB-L0-2.29	C	B
IB-L0-2.30	C	B	IB-L0-2.31	C	B
IB-L0-2.32	C	B	IB-L0-2.33	C	C
IB-L0-2.34	D	C	IB-L0-2.35	D	C
IB-L0-2.36	C	B	IB-L0-2.37	D	C
IB-L0-2.38	D	D	IB-L0-2.39	D	C
IB-L0-2.40	D	C	IB-L0-2.41	C	C
IB-L0-2.42	C	C	IB-L0-2.43	D	C
IB-L0-2.44	D	D	IB-L0-2.45	D	C
IB-L0-2.46	ND	ND	IB-L0-2.47	ND	ND
IB-L0-2.48	ND	ND	IB-L0-2.49	ND	ND
IB-L0-2.50	C	C	IB-L0-2.51	B	A

compound	1a	1b	compound	1a	1b
IB-L0-2.52	B	A	IB-L0-2.53	B	B
IB-L0-2.54	B	B	IB-L0-2.55	B	A
IB-L0-2.56	C	A	IB-L0-2.57	C	B
IB-L0-2.58	B	A	IB-L0-2.59	C	B
IB-L0-2.60	C	B	IB-L0-2.61	C	B
IB-L0-2.62	C	B	IB-L0-2.63	C	B
IB-L0-2.64	C	A	IB-L0-2.65	C	B
IB-L0-2.66	C	B	IB-L0-2.67	C	B
IB-L0-2.68	D	C	IB-L0-2.69	C	B
IB-L0-2.70	D	C	IB-L0-2.71	C	B
IB-L0-2.72	D	C	IB-L0-2.73	C	C
IB-L0-2.74	D	C	IB-L0-2.75	D	D
IB-L0-2.76	ND	ND	IB-L0-2.77	ND	ND
IB-L0-2.78	ND	ND	IB-L0-2.79	C	C

Patentkrav

1. Krystallinsk form af N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1-(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamid eller en krystallinsk form af et salt af N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamid.

2. Krystallinsk form ifølge krav 1, hvor den krystallinske form er valgt fra gruppen bestående af et solvat, et hydrat og en opløsningsfri krystallinsk form.

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3. Krystallinsk form ifølge krav 1, hvor den krystallinske form er valgt fra gruppen bestående af:

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidethanolsolvat,

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krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidacetonitrilsolvat,

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidethylacetatsolvat,

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krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid-2-propanolsolvat,

25

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmethanolsolvat,

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid-1-propanolsolvat,

30

krystallinsk opløsningsfri N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid,

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidhydrat,

5 krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt,

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidnatriumsalt,

10 krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmonokaliumsalt,

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmonocholinsalt,

15 krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidicholinsalt.

4. Krystallinsk form ifølge krav 1, hvor den krystallinske form er valgt fra gruppen bestående af:
20

krystalmønster A, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-phenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt,

25 krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-phenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt,
and

30 krystalmønster C, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-phenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt.

5. Krystallinsk form ifølge krav 1, hvor den krystallinske form er krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt.

- 5 6. Krystallinsk form ifølge krav 1, hvor den krystallinske form er valgt fra gruppen bestående af:

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidethanolsolvat med et
10 røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 8.3 ± 0.2 , 9.7 ± 0.2 , 10.6 ± 0.2 , 13.6 ± 0.2 , 17.2 ± 0.2 , 19.2 ± 0.2 , 22.7 ± 0.2 , 26.9 ± 0.2 og 29.4 ± 0.2 grader 2θ ,

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidacetonitrilsolvat med et
15 røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 5.3 ± 0.2 , 8.3 ± 0.2 , 9.7 ± 0.2 , 10.5 ± 0.2 , 13.8 ± 0.2 , 17.2 ± 0.2 , 19.1 ± 0.2 og 19.5 ± 0.2 grader 2θ ,

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidethylacetatsolvat med et
20 røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 7.9 ± 0.2 , 9.3 ± 0.2 , 9.7 ± 0.2 , 10.6 ± 0.2 , 18.7 ± 0.2 , 38.5 ± 0.2 og 44.7 ± 0.2 grader 2θ ,

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid-2-propanolsolvat med et
25 røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 16.3 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 19.4 ± 0.2 , 21.6 ± 0.2 og 22.5 ± 0.2 grader 2θ ,

krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmethanolsolvat med et
30 røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 8.4 ± 0.2 , 9.7 ± 0.2 , 10.1 ± 0.2 , 13.8 ± 0.2 , 17.4 ± 0.2 , 19.3 ± 0.2 og 19.6 ± 0.2 grader 2θ ,

- krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid-1-propanolsolvat med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 8.2 ± 0.2 , 9.3 ± 0.2 , 10.1 ± 0.2 , 15.7 ± 0.2 ,
5 16.2 ± 0.2 , 18.4 ± 0.2 , 19.3 ± 0.2 , 21.6 ± 0.2 og 22.8 ± 0.2 grader 2θ ,
- krystallinsk opløsningsfri N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 6.2 ± 0.2 , 7.9 ± 0.2 , 9.9 ± 0.2 , 16.2 ± 0.2 og
10 18.3 ± 0.2 grader 2θ ,
- krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidhydrat med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 6.4 ± 0.2 , 12.9 ± 0.2 , 17.9 ± 0.2 og 18.9 ± 0.2 grader 2θ ,
15 krystalmønster A, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-phenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 , 15.6 ± 0.2 , 18.6 ± 0.2 , 22.8 ± 0.2 og 23.9 ± 0.2 grader 2θ ,
- 20 krystalmønster B N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-phenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 5.4 ± 0.2 , 10.8 ± 0.2 , 16.3 ± 0.2 og 22.1 ± 0.2 grader 2θ ,
- 25 krystalmønster C N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-phenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 5.0 ± 0.2 , 12.0 ± 0.2 , 17.5 ± 0.2 , 18.8 ± 0.2 og 22.7 ± 0.2 grader 2θ ,
- 30 krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-naphthalen-2-yl)methansulfonamidnatriumsalt med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe

- valgt fra gruppen bestående af 4.8 ± 0.2 , 9.6 ± 0.2 , 10.5 ± 0.2 , 13.0 ± 0.2 , 14.6 ± 0.2 , 15.4 ± 0.2 , 16.8 ± 0.2 og 23.0 ± 0.2 grader 2θ ,
krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmonokaliums salt med et
5 røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 5.0 ± 0.2 , 9.9 ± 0.2 , 11.3 ± 0.2 , 13.3 ± 0.2 , 16.9 ± 0.2 , 18.1 ± 0.2 , 19.1 ± 0.2 , 20.0 ± 0.2 , 21.1 ± 0.2 , 23.5 ± 0.2 , 24.8 ± 0.2 og 25.7 ± 0.2 grader 2θ ,
krystalmønster A, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1
10 (2H)-yl)-2-methoxy-phenyl)naphthalen-2-yl)methansulfonamidmonocholin-salt med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 10.9 ± 0.2 , 12.1 ± 0.2 , 13.4 ± 0.2 , 15.5 ± 0.2 , 17.0 ± 0.2 , 17.8 ± 0.2 , 18.3 ± 0.2 , 19.5 ± 0.2 og 21.9 ± 0.2 grader 2θ ,
krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-
15 yl)-2-methoxy-phenyl)naphthalen-2-yl)methansulfonamidmonocholinsalt med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 8.0 ± 0.2 , 9.4 ± 0.2 , 11.0 ± 0.2 , 13.0 ± 0.2 , 13.7 ± 0.2 , 15.9 ± 0.2 , 17.0 ± 0.2 , 18.3 ± 0.2 , 18.9 ± 0.2 , 19.8 ± 0.2 og 22.1 ± 0.2 grader 2θ , og
20 krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamididicholinsalt med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 8.6 ± 0.2 , 11.0 ± 0.2 , 12.9 ± 0.2 , 17.0 ± 0.2 , 17.5 ± 0.2 , 18.9 ± 0.2 , 19.8 ± 0.2 og 21.9 ± 0.2 grader 2θ .
25
7. Krystallinsk form ifølge krav 1, hvor den krystallinske form er valgt fra gruppen bestående af:
- krystalmønster A, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-
30 yl)-2-methoxy-phenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 4.6 ± 0.2 , 10.4 ± 0.2 , 12.0 ± 0.2 ,

15.6±0.2, 16.0±0.2, 18.6±0.2, 22.8±0.2, 23.3±0.2, 23.9±0.2 og 28.3±0.2 grader 2θ,

5 krystalmønster B,N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-phenyl)naphthalen-2-yl)methanesulfonamidmononatriumsalt med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 28.8±0.2, 29.1±0.2 og 31.8±0.2 grader 2θ, og

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krystalmønster C, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1-(2H)-yl)-2-methoxy-phenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 5.0±0.2, 12.0±0.2, 15 17.5±0.2, 17.8±0.2, 18.8±0.2 og 22.7±0.2 grader 2θ.

8. Krystallinsk form ifølge krav 1, hvor den krystallinske form er:

20 krystalmønster B,N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt med et røntgenstrålingspulverdiffraktionsmønster omfattende en eller flere toppe valgt fra gruppen bestående af 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 28.8±0.2, 29.1±0.2 og 31.8±0.2 grader 2θ.

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9. Sammensætning omfattende (a) en eller flere krystallinske former af et vilkårligt af kravene 1 til 8, (b) en eller flere excipienser og eventuelt (c) et eller flere yderligere terapeutiske midler.

30 10. Sammensætning ifølge krav 8, hvor det yderligere terapeutiske middel er valgt fra gruppen bestående af HCV-inhibitorer og anti-HIV-midler.

11. Sammensætning ifølge krav 9, hvor det ene eller de flere yderligere terapeutiske midler er valgt fra gruppen bestående af HCV-proteaseinhibitorer og anti-HIV-midler.
- 5 12. Sammensætning ifølge krav 9, hvor det ene eller de flere yderligere terapeutiske midler er HCV-inhibitorer.
13. Sammensætning ifølge krav 9, omfattende krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-
10 2-yl)methansulfonamidmononatriumsalt og et eller flere yderligere terapeutiske midler valgt fra gruppen bestående af HCV-inhibitorer og anti-HIV-midler.
14. Sammensætning ifølge krav 9, omfattende krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-
15 2-yl)methansulfonamidmononatriumsalt og en eller flere HCV-inhibitorer.
15. Krystallinsk form ifølge et vilkårligt af kravene 1 til 8, eller en sammensætning af et vilkårligt af kravene 9 til 14 til anvendelse ved inhibering af replikation af en ribonucleinsyre (RNA) virus.
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16. Krystallinsk form eller sammensætning ifølge krav 15, hvor RNA-virussen er hepatitis-virus (HCV).
17. Krystallinsk form ifølge et vilkårligt af kravene 1 til 8 eller sammensætningen ifølge et vilkårligt af kravene 9 til 14 til anvendelse ved behandling af hepatitis C i et pattedyr med behov for en sådan behandling.
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18. Krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1-(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt
30 og eventuelt et eller flere yderligere terapeutiske midler til anvendelse ved behandling af hepatitis C i et pattedyr med behov for en sådan behandling.

19. Krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1-(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt, ribavirin og en HCV-inhibitor til anvendelse ved behandling af hepatitis C i et pattedyr med behov for en sådan behandling.
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20. Krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1-(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt og en HCV-inhibitor til anvendelse ved behandling af hepatitis C i et pattedyr med behov for en sådan behandling.
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21. Fremgangsmåde til fremstilling af et krystalmønster A, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt omfattende:
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- tilsætning af 1M vandig NaOH til N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid, podning af den resulterende opslæmning med krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid-dinatriumsalt, og ækvilibrering af den resulterende opslæmning ved omgivelsesbetingelser.
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22. Fremgangsmåde ifølge krav 21, hvor det krystallinske dinatriumsalt er fremstillet ved en fremgangsmåde omfattende:
- 25
- opslæmning af forbindelsen N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid i 1M vandig NaOH ved et molært forhold mellem forbindelse:NaOH på 1:10; opvarmning af opslæmningen til 36°C til dannelse af en opløsning, og afkøling af opløsningen til omgivelsestemperatur til dannelse af krystallinsk N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid-dinatriumsalt.
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23. Fremgangsmåde ifølge krav 21, hvor det krystallinske dinatriumsalt er fremstillet ved en fremgangsmåde omfattende:
- 5 opslæmning af forbindelsen N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid i ethanol,
tilsætning af 2,1 molær ækvivalent NaOH i 5:1 volumen/volumen ethanol/H₂O til opslæmningen,
opkoncentrering af reaktionsblandingen, og
10 tilsætning af acetonitril til at fremkalde krystallisation af N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid-dinatriumsalt.
24. Fremgangsmåde til fremstilling af krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt omfattende:
- 15 opslæmning af krystalmønster A, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt i et organisk opløsningsmiddel valgt fra gruppen bestående af acetonitril, ethanol, 1-propanol og 2-propanol ved stuetemperatur til dannelselse af krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt.
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- 25
25. Fremgangsmåde ifølge krav 24, hvor det krystallinske mønster A mononatriumsalt fremstilles ved en fremgangsmåde ifølge et vilkårligt af kravene 21 til 23.
- 30 26. Fremgangsmåde til fremstilling af krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamidmononatriumsalt omfattende;

podning af en opløsning af N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid med krystalmønster B, N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid-mononatriumsalt.

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27. Fremgangsmåde ifølge krav 26 omfattende:

opløsning af N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid i DMSO ved ca. 68°C,

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tilsætning af ca. 0,08 ækvivalent vægtmæssigt NaOH opløst i 1:1 volumen/volumen 2-propanol/vand og ca. identisk volumen 35,2:1 volumen/volumen 2-propanol/vand,

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podning af opløsningen med 0,01 ækvivalent krystalmønster B N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid-mononatriumsalt-kim opslæmmet i 35,2:1 volumen/volumen 2-propanol/vand,

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inkubering af den krystallinske opslæmning til ca. 68°C i ca. 1,5 time, tilsætning af 35,2:1 volumen/volumen 2-propanol/vand ved ca. 68°C i ca. 7 timer,

afkøling af krystallisationsopslæmningen til ca. 0°C i ikke mindre end 7 timer, og

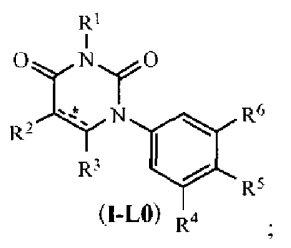
isolering af krystallerne ved filtrering.

25 28. Fremgangsmåde ifølge krav 27, som yderligere omfatter at tørre krystallerne ved ca. 50°C under et vakuum på ca. 3 tommer kviksølv.

29. Fremgangsmåde til fremstilling af en forbindelse svarende i struktur til formel I-L0:

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- hvor C^* er valgt fra gruppen bestående af enkelte carbon-carbonbindinger og dobbelte carbon-carbonbindinger,
- R^1 er valgt fra gruppen bestående af hydrogen og methyl,
- 5 R^2 er valgt fra gruppen bestående af hydrogen, halogen, hydroxy, methyl, cyclopropyl og cyclobutyl,
- R^3 er valgt fra gruppen bestående af hydrogen, halogen, oxo og methyl,
- R^4 is er valgt fra gruppen bestående af halogen, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl og heterocyclyl, hvor:
- 10
- (a) amino, aminocarbonyl og aminosulfonyl eventuelt er substitueret med:
- (1) en eller to substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl og alkylsulfonyl eller
- 15 (2) to substituenten, som sammen med aminonitrogenet danner en enkeltrings heterocyclyl, og
- (b) alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy og alkylsulfonyl, eventuelt er substitueret med en eller flere substituenten uafhængigt valgt fra gruppen bestående af halogen, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl og heterocyclyl, hvor:
- 20 amino eventuelt er substitueret med:
- (1) en eller to substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl og heterocyclylalkyl eller
- 25 (2) to substituenten, som sammen med aminonitrogenet danner en enkeltrings heterocyclyl, og
- (c) carbocyclyl og heterocyclyl eventuelt er substitueret med op til tre substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, halogen,

oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl og heterocyclyl, hvor:

amino eventuelt er substitueret med:

(1) en eller to substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl og heterocyclylalkyl, eller

(2) to substituenten, som sammen med aminonitrogenet danner en enkeltrings heterocyclyl,

R^5 er valgt fra gruppen bestående af hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, carbocyclylsulfonyloxy, halogenalkylsulfonyloxy og halogen,

R^6 er valgt fra gruppen bestående af sammensmeltet 2-rings carbocyclyl og sammensmeltet 2-rings heterocyclyl, hvor hver sådan substituent eventuelt er substitueret med en eller flere substituenten uafhængigt valgt fra gruppen bestående af R^E , R^F , R^G , R^H , R^I , R^J og R^K ,

hvert R^E er uafhængigt valgt fra gruppen bestående af halogen, nitro, hydroxy, oxo, carboxy, cyano, amino, imino, azido og aldehyd, hvor:

aminen eventuelt er substitueret med en eller to substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og alkynyl,

hvert R^F er uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og alkynyl, hvor:

hver sådan substituent eventuelt er substitueret med en eller flere substituenten uafhængigt valgt fra gruppen bestående af carboxy, hydroxy, halogen, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano og aminocarbonyl, hvor:

amino, imino, aminosulfonyl, aminocarbonyl, carbocyclyl og heterocyclyl eventuelt er substitueret med en eller to substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkylsulfonylamino, hydroxy og alkyloxy,

hvor:

aminodelen af alkylsulfonylamino eventuelt er substitueret med en substituent valgt fra gruppen bestående af alkyl, alkenyl og alkynyl,

hvert R^G er uafhængigt valgt fra gruppen bestående af carbocyclyl og heterocyclyl, hvor:

- 5 hver sådan substituent eventuelt er substitueret med en eller flere substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, carboxy, hydroxy, halogen, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano og aminocarbonyl, hvor:

amino, aminosulfonyl og aminocarbonyl eventuelt er substitueret med en eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl og alkynylsulfonyl,

- 15 hvert R^H er uafhængigt valgt fra gruppen bestående af alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, alkenylsulfonyloxy og alkynylsulfonyloxy, hvor:

hver substituent eventuelt er substitueret med en eller flere substituenter uafhængigt valgt fra gruppen bestående af carboxy, hydroxy, halogen, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano og aminocarbonyl, hvor:

amino, aminosulfonyl og aminocarbonyl eventuelt er substitueret med en eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl og alkynylsulfonyl,

- 25 hvert R^I er uafhængigt valgt fra gruppen bestående af alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, aminocarbonyl, alkyloxycarbonyl, carbocyclylcarbonyl og heterocyclylcarbonyl, hvor:

(a) alkylcarbonyl, alkenylcarbonyl og alkynylcarbonyl eventuelt er substitueret med en eller flere substituenter uafhængigt valgt fra gruppen bestående af carboxy, hydroxy, halogen, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano og aminocarbonyl, og

- (b) aminocarbonyl eventuelt er substitueret med en eller to substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkyloxyalkyl, carbocyclyl, heterocyclyl, alkylsulfonyl og alkylsulfonylamino, hvor:
- carbocyclyl og heterocyclyl eventuelt er substitueret med en eller to substituenten uafhængigt valgt fra gruppen bestående af halogen, alkyl og oxo,
- 5 hver R^J er uafhængigt valgt fra gruppen bestående af carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, alkyloxycarbonylamino, alkenyloxycarbonylamino, alkynyloxy-carbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino,
- 10 aminocarbonylamino, alkyloxycarbonylaminoimino, alkylsulfonylaminoimino, alkenylsulfonylaminoimino og alkynylsulfonylaminoimino, hvor:
- (a) aminodelen af sådanne substituenten eventuelt er substitueret med en substituent uafhængigt valgt fra gruppen bestående af carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkenyl, alkynyl, alkylcarbonyl,
- 15 alkenylcarbonyl, alkynylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl og alkylsulfonyl, hvor:
- (1) carbocyclyliden af carbocyclylalkyl og heterocyclyliden af heterocyclylalkyl eventuelt er substitueret med en eller flere substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halogen, nitro, cyano, azido, oxo og amino, og
- 20 (2) aminodelen af aminocarbonylalkyl eventuelt er substitueret med en eller to substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og alkynyl,
- (b) alkyl, alkenyl og alkynyl i sådanne substituenten er eventuelt substitueret med en eller flere substituenten uafhængigt valgt fra gruppen bestående af carboxy, halogen, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl og cyano, hvor:
- 25 amino eventuelt er substitueret med en eller to substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy og alkynyloxy, hvor:
- 30 alkyl eventuelt er substitueret med en eller flere hydroxy,
- (c) carbocyclyl- og heterocyclyl-delene af sådanne substituenten eventuelt er substitueret med en eller flere substituenten uafhængigt valgt fra gruppen be-

stående af alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halogen, nitro, cyano, azido og amino, hvor:

amino eventuelt er substitueret med en eller to substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og alkynyl, og

- 5 hvert R^k er uafhængigt valgt fra gruppen bestående af aminosulfonyl, alkylsulfonyl, alkenylsulfonyl og alkynylsulfonyl, hvor:

(a) alkylsulfonyl, alkenylsulfonyl og alkynylsulfonyl eventuelt er substitueret med en eller flere substituenten uafhængigt valgt fra gruppen bestående af carboxy,

hydroxy, halogen, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, al-

- 10 kenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano og aminocarbonyl, hvor:

amino, aminosulfonyl og aminocarbonyl eventuelt er substitueret med en eller to substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og al-

- 15 kynyl, og

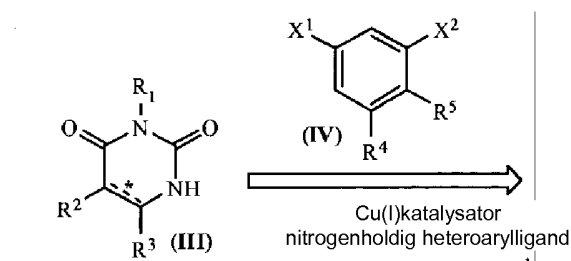
(b) aminosulfonyl eventuelt er substitueret med en eller to substituenten uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og alkynyl,

hvor fremgangsmåden omfatter at omsætte en forbindelse med formel III med en forbindelse med formel IV i nærvær af

- 20 (1) kobber(I)saltkatalysator, og

(2) en nitrogenholdig heteroaryliligand,

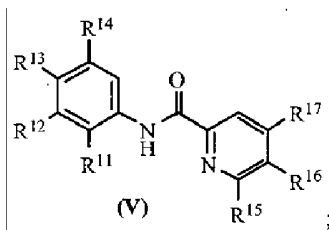
hvor X^1 er halogen, og X^2 er valgt fra gruppen bestående af chlor, brom og jod



25

30. Fremgangsmåde ifølge krav 29, hvor fremgangsmåde udføres i nærvær af en base.

31. Fremgangsmåde ifølge krav 30, hvor basen er valgt fra gruppen bestående af kaliumsalt, natriumsalt og cæsiumsalt.
32. Fremgangsmåde ifølge krav 29, hvor den nitrogenholdige heteroarylligand omfatter en picolinamidforbindelse svarende i struktur til formel V:



- og
- 10 **R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶** og **R¹⁷** er uafhængigt valgt fra gruppen bestående af hydrogen, C₁₋₄-perfluoralkyl, C₁₋₄-alkyloxy, C₁₋₄-halogenalkyl, chlor og cyano.
33. Fremgangsmåde ifølge krav 32, hvor den nitrogenholdige heteroarylligand er valgt fra gruppen bestående af 8-hydroxyquinolin, 2-(2-pyridyl)-benzimidazol,
- 15 N-(4-cyano-phenyl)picolinamid og N-(2-cyanophenyl)picolinamid.
34. Fremgangsmåde ifølge krav 29, hvor kobberkatalysatoren er valgt fra gruppen bestående af CuI, CuBr, CuCl, Cu₂O og CH₃C(O)OCu.

Figure 1

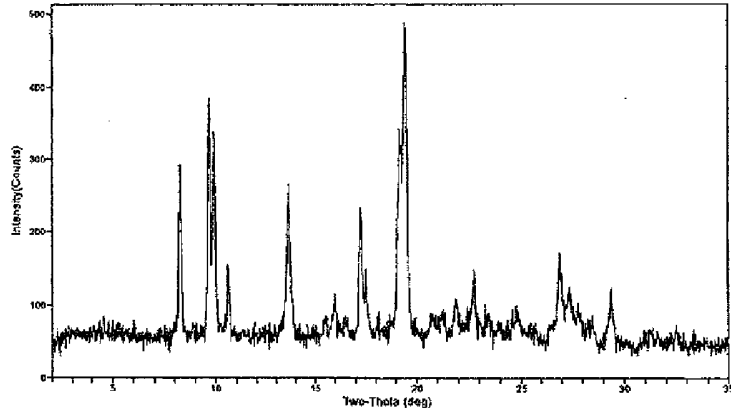


Figure 2

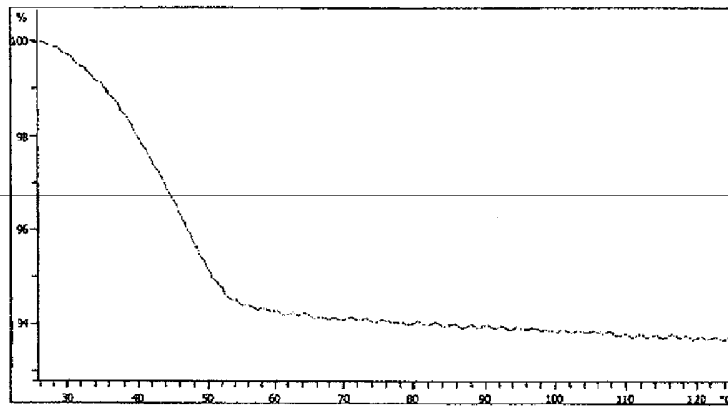


Figure 3

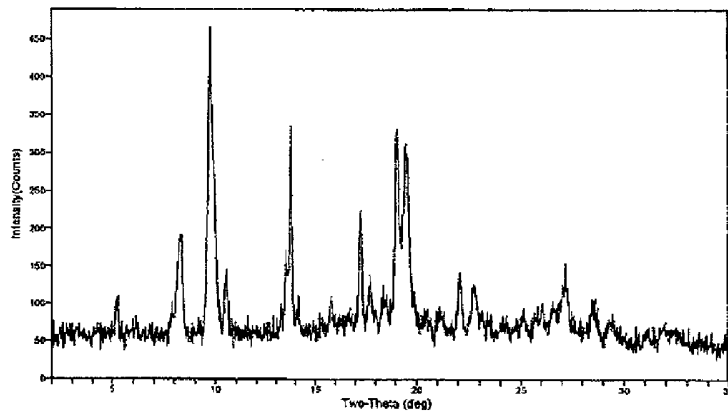


Figure 4

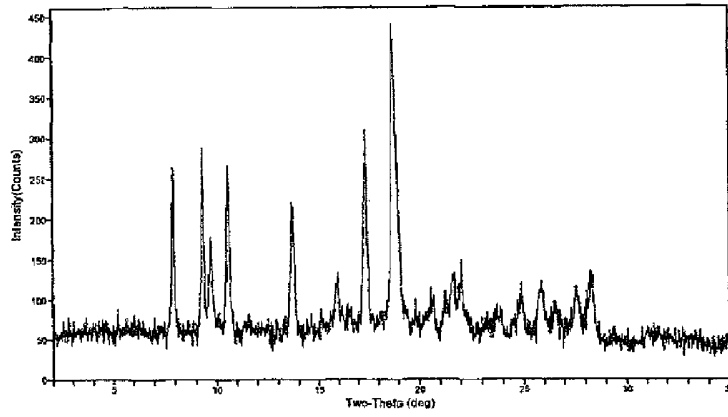


Figure 5

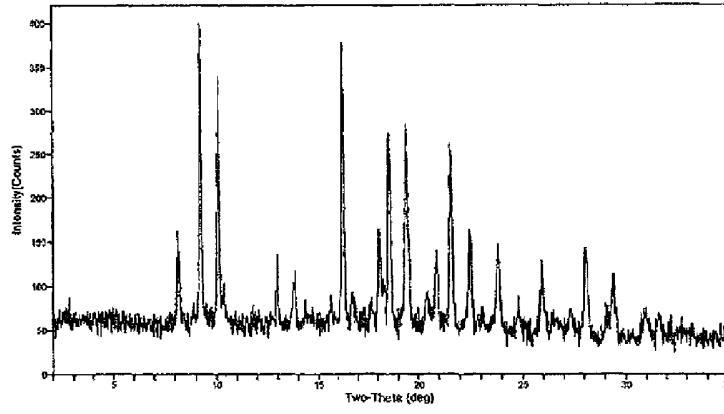


Figure 6

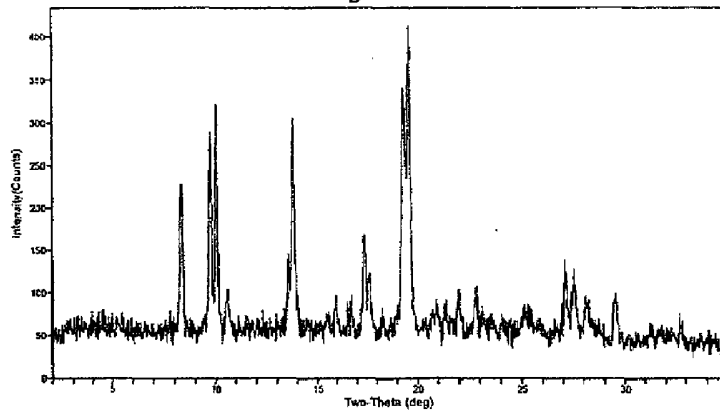


Figure 7

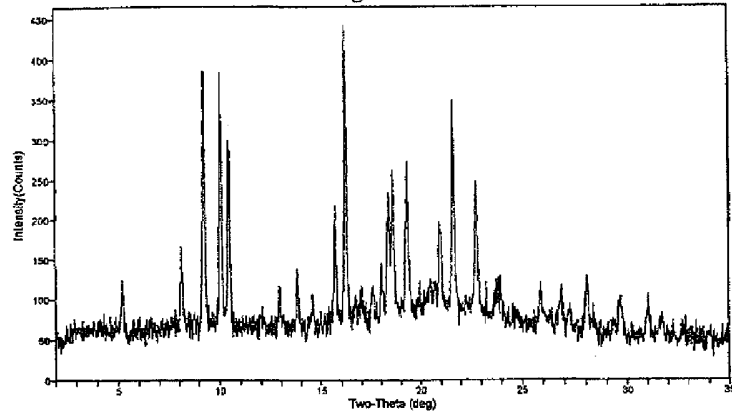


Figure 8

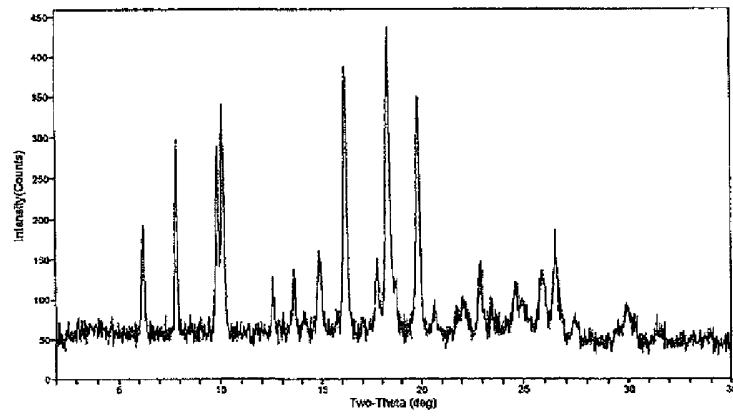


Figure 9

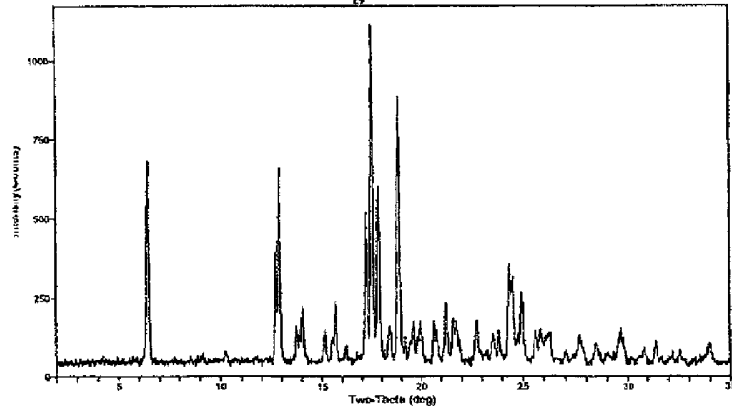


Figure 10

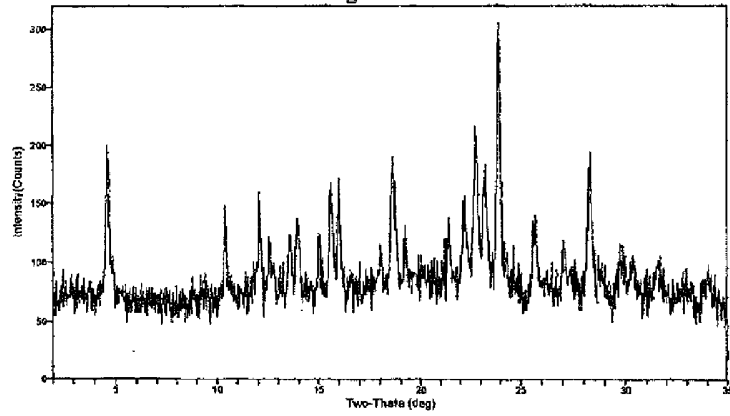


Figure 11

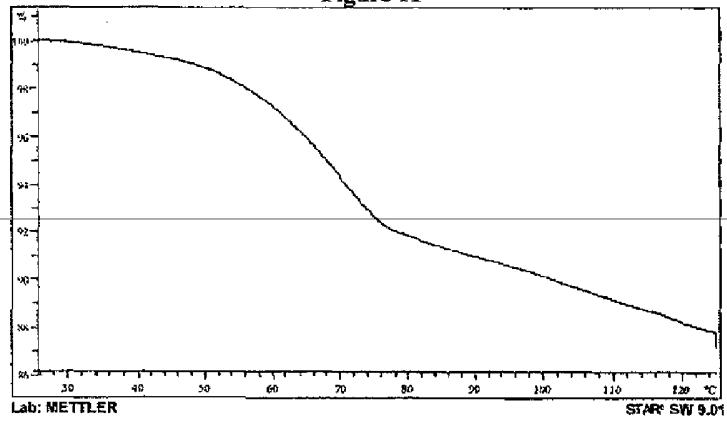


Figure 12

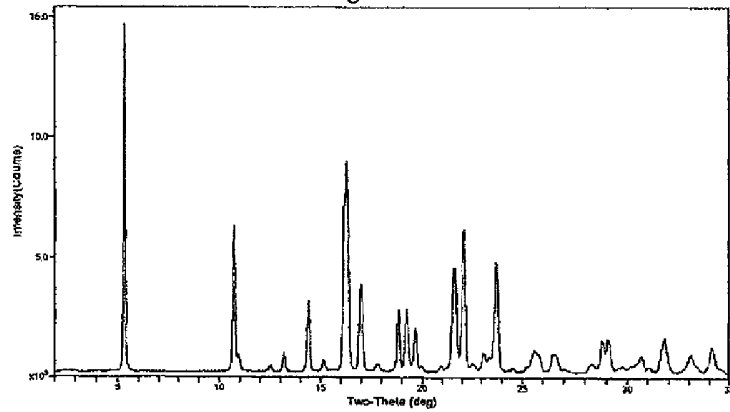


Figure 13

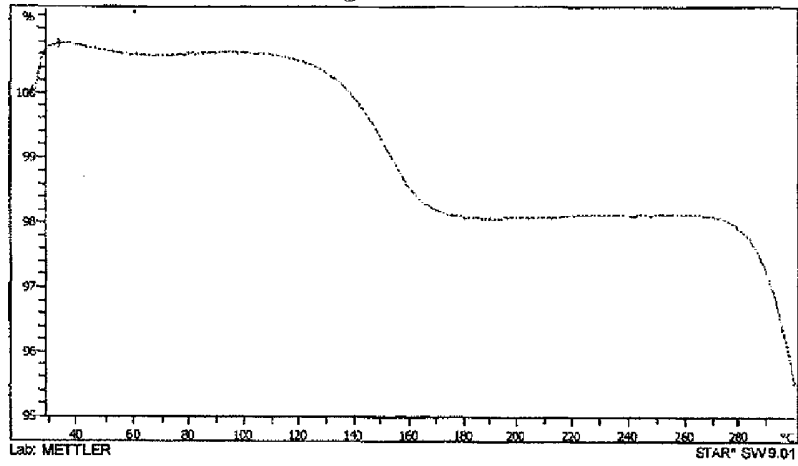


Figure 14

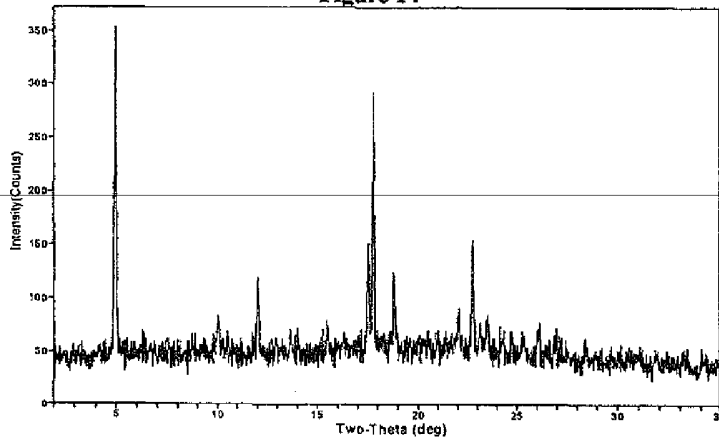


Figure 15

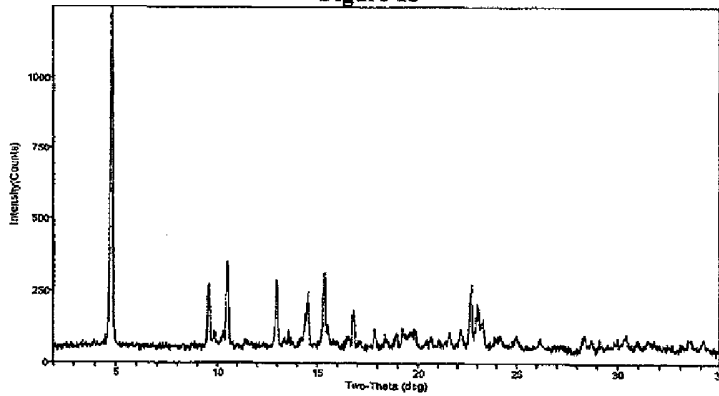


Figure 16

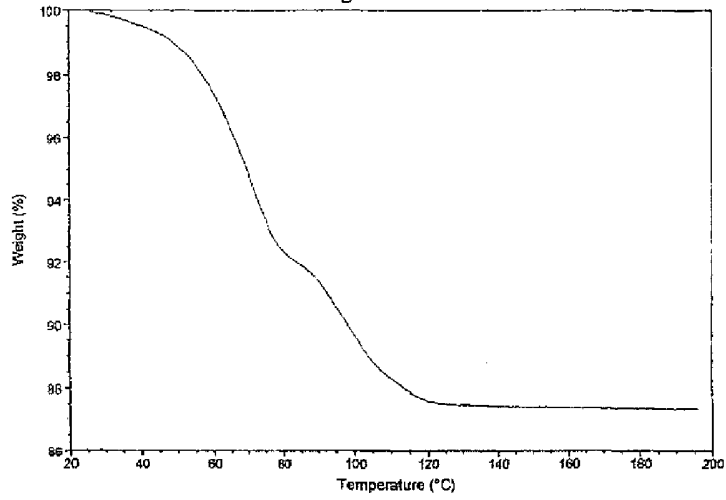


Figure 17

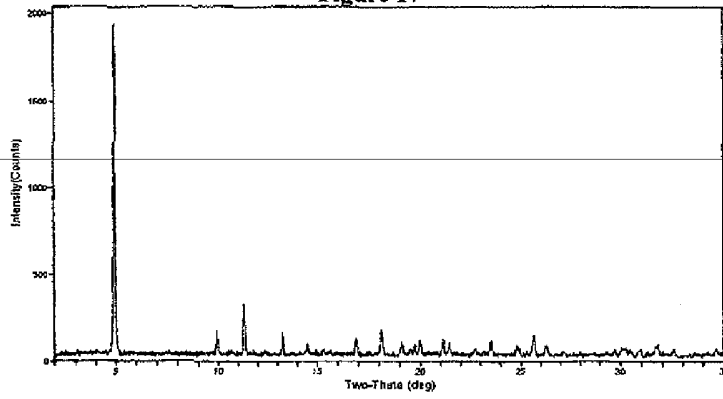


Figure 18

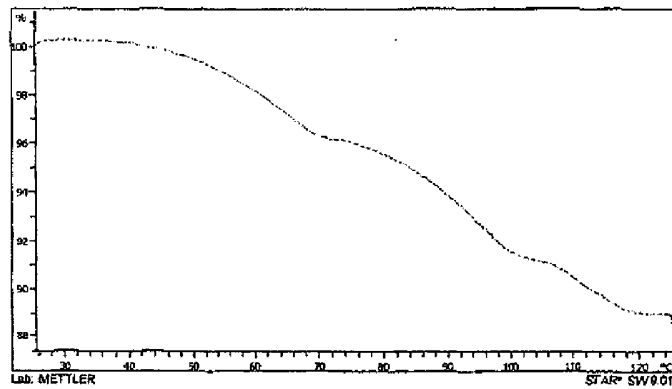


Figure 19

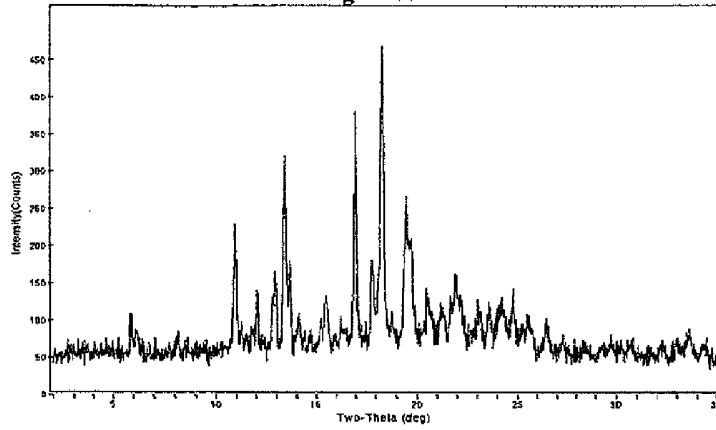


Figure 20

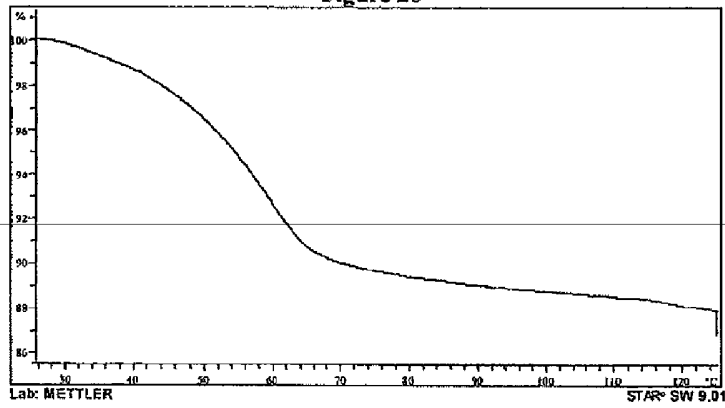


Figure 21

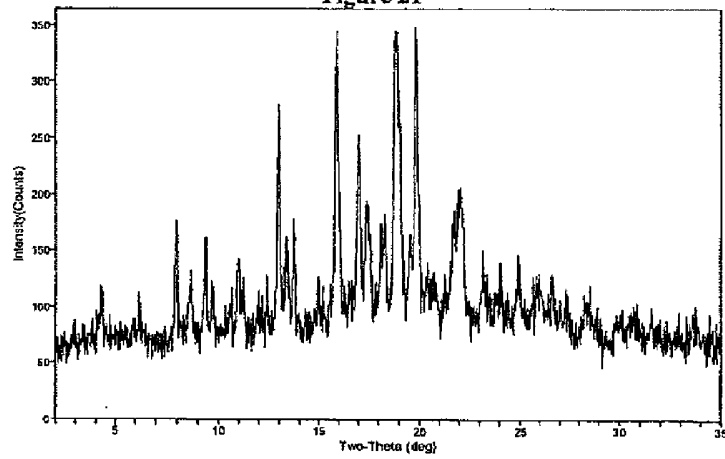


Figure 22

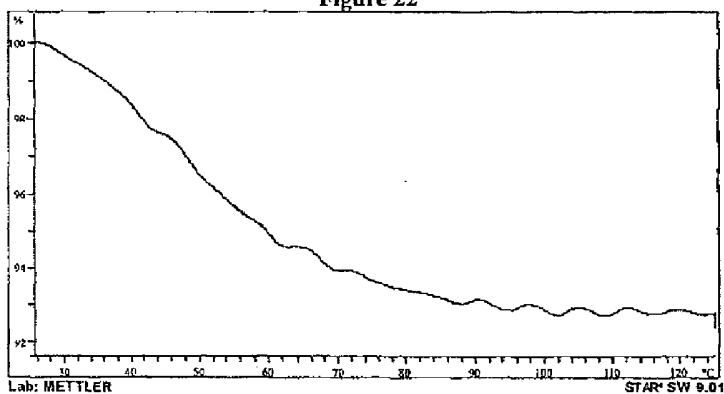


Figure 23

