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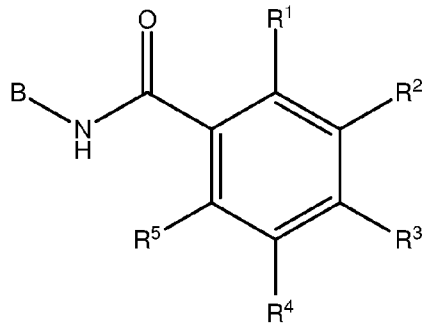
(54) Title: TrkA KINASE INHIBITORS,COMPOSITIONS AND METHODS THEREOF



(I)

(57) Abstract: The present invention is directed to six membered heteroaryl benzamide compounds of formula (I) which are tropomyosin-related kinase (Trk) family protein kinase inhibitors, and hence are useful in the treatment of pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA.

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TrkA KINASE INHIBITORS, COMPOSITIONS AND METHODS THEREOF

FIELD OF THE INVENTION

The invention is directed to a class of substituted six membered aryl or heteroaryl benzamide compounds, their salts, pharmaceutical compositions comprising them and their use in therapy of the human body. In particular, the invention is directed to a class of substituted heteroaryl benzamide compounds, which are tropomyosin-related kinase (Trk) family protein kinase inhibitors, and hence are useful in the treatment of pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA.

BACKGROUND OF THE INVENTION

Trk's are high affinity binding protein kinase receptors that are activated by Neurotrophins (NT), a group of soluble growth factors including Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF) and Neurotrophin 3-5 (NT 3-5). The Trk's consist of three family members TrkA, TrkB and TrkC that bind to and mediate the signal transduction derived from the Neurotrophins. NGF activates TrkA, BDNF and NT-4/5 activate TrkB and NT3 activates TrkC.

Inhibitors of the Trk/neutrophin pathway have been demonstrated to be highly effective in numerous pre-clinical animal models of pain. Antagonistic NGF and TrkA antibodies have been shown to be efficacious in inflammatory and neuropathic pain animal models and in human clinical trials. See Woolf, C.J. et al. (1994) *Neuroscience* 62, 327-331; Zahn, P.K. et al. (2004) *J. Pain* 5, 157-163; McMahon, S. B. et al., (1995) *Nat. Med.* 1, 774-780; Ma, Q.P. and Woolf, C. J. (1997) *Neuroreport* 8, 807-810; Shelton, D. L. et al. (2005) *Pain* 116, 8-16; Delafoy, L. et al. (2003) *Pain* 105, 489-497; Lamb, K. et al. (2003) *Neurogastroenterol. Motil.* 15, 355-361; and Jaggar, S. I. et al. (199) *Br. J. Anaesth.* 83, 442-448. Through gene disruption studies in mice the TrkA-NGF interaction was found to be required for the survival of certain peripheral neuron populations involved in mediating pain signaling in the case of pancreatic cancer - an increase in the expression of TrkA was shown to correlate with an increase level of pain signaling (Zhu et al., *Journal of Clinical oncology*, 17:2419-2428 (1999)). Increased expression of NGF and TrkA was also observed in human osteoarthritis chondrocytes (Iannone et al, *Rheumatology* 41:1413-1418 (2002)). In particular, anti-TrkA antibodies and anti-NGF antibodies have been demonstrated to be effective analgesics in in vivo models of inflammatory and neuropathic pain. See WO2006/131952, WO2005/061540, EP1181318 and WO01/78698, WO2004/058184 and WO2005/019266, respectively. See also WO2004/096122 and WO2006/137106 which describe the use of an anti-TrkA antibody in combination with an opioid analgesic for the treatment or prevention of pain.

Trk inhibitors that can induce apoptosis of proliferating osteoblast may be useful in treating diseases related to an imbalance of the regulation of bone remodeling, such as osteoporosis, rheumatoid arthritis and bone metastases. The expression of TrKA and TrkC receptors in the bone forming area in mouse models of bone fracture and localization of NGF in almost all bone forming cells have been observed (K. Asaumi, et al., Bone (2000) 26(6) 625-633). See also Exper Opin. Ther. Patents (2009) 19(3)), WO2006/115452 and WO2006/087538, WO6123113, WO10033941, WO10077680, WO2005110994, *Investigational New Drugs* (2004), 22, 449-458 and R. Tripathy, et al., *Bioorg.Med. Chem. Lett.*, 2008, 18, 3551-3555. The association between overexpression, activation, amplification and/or mutation of Trks and several cancers as seen with studies conduct on neuroblastoma (Brodeur, G. M., Nat. Rev. Cancer 2003, 3, 203-216), ovarian cancer (Kruettgen et al., *Brain Pathology* 2006, 16: 304-310), prostate cancer (Dionne et al., Clin. Cancer Res. 1998, 4(8): 1887-1898), pancreatic cancer (Dang et al., *J of Gastroenterology and Hepatology* 2006, 21(5): 850-858), large cell neuroendocrine tumors (Marchetti et al., *Human Mutation* 2008, 29(5), 609-616, and colorectal cancer (Bardelli, A., *Science* 2003, 300, 949) support the reasoning that therapeutic implications of an effective Trk inhibitor may extend far beyond pain therapy. See also WO2005/030128, WO2012158413, WO07013673, WO07025540, WO08052734, WO2012028579, WO2012159565, WO2012107434, WO2012003387, WO2010111653, WO2008124610, WO2004098518, EP1388341, WO2012028579, WO2008003770, WO2012161879, WO2012100223, WO2009046802, WO2009003999, WO2007042321, US2005143384, WO2009003998, WO2007069773, WO2005/030128, US2010120862.

Also promising is the utility of Trk inhibitors in the treatment of inflammatory lung diseases such as asthma (Freund-Michel, V; et al., *Pharmacology & Therapeutics* (2008), 117(1), 52-76), interstitial cystitis (Hu Vivian Y; et . al., *J of Urology* (2005, 173(3), 1016-21), inflammatory bowel disease including ulcerative colitis and Chron's disease (Di Mola, F. F., et al., *Gut* (2000), 46(5), 670-678 and inflammatory skin diseases such as atopic dermatitis (Dou, Y.C., et. Al., *Archives of Dermatological Research* (2006), 298(1), 31-37, eczema and psoriasis (Raychaudhuri, S. P. et. al., *J of Investigative Dermatology* (2004), 122(3), 812-819).

Modulation of the neutrophin/Trk pathway also has been shown to have an effect in the etiology of neurodegenerative diseases including multiple sclerosis, Parkinson's disease and Alzheimer's disease (Sohrabji, et. al., *Neuroendocrinology* (2006), 27(4), 404-414).

Thus, the compounds of the invention, which are Trk inhibitors, are believed to be useful in the treatment of multiple types of acute and chronic pain including but not limited to inflammatory pain, neuropathic pain, and pain associated with cancer, surgery and bone fracture. The compounds may also useful in the treatment of cancer, inflammation, neurodegenerative diseases and certain infectious diseases.

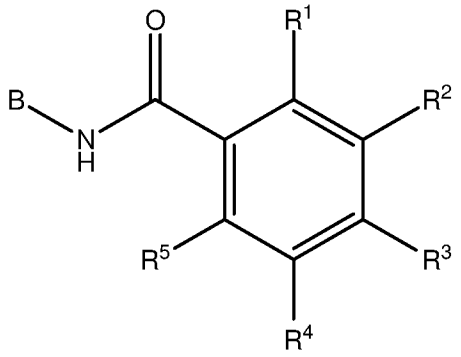
SUMMARY OF THE INVENTION

The present invention is directed to compounds of generic formula (I) below or pharmaceutically acceptable salts thereof that are useful as a Trk kinase mediator of NGF driven biological responses, an inhibitor of TrkA as well as other Trk kinases.

The invention is further directed to methods of treating a patient (preferably a human) for diseases or disorders in which the NGF receptor Trk kinases are involved, in particular TrkA. The invention further involves use of the compounds as NGF receptor TrkA inhibitor and/or antagonist for the preparation of a medicament for the treatment and/or prevention of diseases associated with inhibiting TrkA, which includes pain, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, or a disease, disorder, or injury relating to dysmyelination or demyelination. The invention is also directed to pharmaceutical compositions which include an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, and the use of the compounds and pharmaceutical compositions of the invention in the treatment of such diseases.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the invention is directed to compounds of general formula (I)



I

or pharmaceutically acceptable salts thereof, wherein:

B represents phenyl, or a six membered heteroaryl having at least one heteroatom that is nitrogen, said phenyl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R represents hydrogen, OH, or -C_{1-6}alkyl;

R^1 and R^5 are independently selected from the group consisting of hydrogen, CN, OH, -C_{1-6}alkyl and halogen;

R^2 and R^4 are independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, $(CHR)_nC_{6-10}$ aryl and $(CHR)_nC_{5-10}$ heterocycle, said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of R^a,

R^3 represents hydrogen, C_{1-6} alkyl, C_{1-4} haloalkyl, $-OC_{1-4}$ haloalkyl, and halogen;

R^a is selected from the group consisting of –CN, NO_2, $-C_{1-4}$haloalkyl, $-OC_{1-4}$haloalkyl, $-C_{1-6}$alkyl, $-C_{1-6}$alkenyl, $-C_{1-6}$alkynyl, $-(CHR)_nC_{6-10}$ aryl, $-(CHR)_nC_{4-10}$ heterocycle, $-C(O)(CHR)_nC_{4-10}$ heterocycle, $-O-(CH_2)_nC_{6-10}$ aryl, $-O-(CH_2)_nC_{4-10}$ heterocycle, -O-, $-(CH_2)_nN(R^d)_2$, $-(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$ heterocycle, SO_2R^d, $(CH_2)_nNHSO_2R^d$, $SO_2N(R^d)_2$, S(O)(NH)Rg, $-C(O)CF_3$, COR, $-(CH_2)_n$halo, $-(CH_2)_nNHC(O)R^d$, $-(CH_2)_nNHC(O)NHR^d$, $-(CH_2)_nNHC(O)OR^d$, $-(CHR)_nC(O)N(R^d)_2$ $-OC_{1-6}$alkyl, and –OH, said alkyl, aryl and heterocycle optionally substituted with 1 to 3 groups of R^b, wherein when two R^d groups are attached to a nitrogen atom they may combine with that nitrogen to from a 4-8 membered heterocyle that is optionally substituted with 1 to 3 groups of R^f;

R^b is selected from the group consisting of halogen, $-C_{1-6}$alkyl, $-C_{1-6}$alkylOR, $-C_{1-4}$haloalkyl, $-(CH_2)_nN(R^d)_2$, $-OR^c$, -O-, -CN, S(O)(NH)Rg, $-SO_2R$, $-SO_2N(R^d)_2$, $-(CH_2)_nC(O)N(R^d)_2$, $-(CH_2)_nNHC(O)R^d$, $-O-(CH_2)_nC_{4-10}$ heterocycle, and $-C_{1-6}$alkylN$(R^d)_2$, wherein when two R^d groups are attached to a nitrogen atom they may combine with that nitrogen to from a 4-8 membered heterocyle that is optionally substituted with 1 to 3 groups of R^f;

R^c is selected from the group consisting of hydrogen, $-C_{1-6}$alkylORg, $-C_{1-4}$haloalkyl and $-C_{1-6}$alkyl;

R^d is independently selected from the group consisting of hydrogen, halogen, $-C_{1-4}$haloalkyl $-C_{1-6}$alkyl, $-(CH_2)_nNR^fC_{4-10}$ heterocycle, $-(CH_2)_nC_{3-6}$cycloalkyl, $-(CH_2)_nC_{4-10}$heterocycle said alkyl, cycloalkyl and heterocycle optionally substituted with 1 to 3 groups of Rf

R^f is selected from the group consisting of hydrogen, OR^c, CN, $-N(R^c)_2$, $C(O)N(Rg)_2$, $C(O)C_{1-6}$alkyl, $-SO_2Rg$, -O-, $-C_{1-6}$alkylSO_2Rg, $-C_{1-6}$alkylORg, $-C_{1-6}$alkylN$(Rg)_2$,

Rg is selected from the group consisting of hydrogen, $-C_{1-6}$alkyl; and

n represents 0-6.

An embodiment of the invention of formula I is realized when B is unsubstituted or substituted phenyl. A subembodiment of this aspect of the invention is realized when B is unsubstituted phenyl. Another subembodiment of this aspect of the invention is realized when B is substituted phenyl.

An embodiment of the invention of formula I is realized when B is an optionally substituted six membered heteroaryl selected from the group consisting of pyridyl, pyrimidinyl and pyrazinyl. An embodiment of the invention of this aspect of formula I is realized when B is substituted pyridyl. A further embodiment of this aspect of the invention of formula I is realized when B is unsubstituted pyridyl. Still another embodiment of this aspect of the invention of formula I is realized when B is substituted pyrimidinyl. Another embodiment of the invention of formula I is realized when B is unsubstituted pyrimidinyl. Yet another embodiment of the invention of formula I is realized when B is optionally substituted pyrazinyl. Another embodiment of the invention of formula I is realized when B is unsubstituted pyrazinyl.

Another embodiment of the invention of formula I is realized when R^a selected from from the group consisting of -C_{1-4}haloalkyl, -OC_{1-4}haloalkyl, -C_{1-6}alkyl, -$(CHR)_nC_{6-10}$ aryl, -$(CHR)_nC_{4-10}$ heterocycle, -C(O)$(CHR)_nC_{4-10}$ heterocycle, -O-$(CH_2)_nC_{6-10}$ aryl, -O-$(CH_2)_nC_{4-10}$ heterocycle, -O-, -$(CH_2)_nN(R^d)_2$, -$(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$ heterocycle, COR, -$(CH_2)_n$halo, -$(CH_2)_nNHC(O)R^d$, -$(CH_2)_nNHC(O)NHR^d$, -$(CHR)_nC(O)N(R^d)_2$ -$(CH_2)_nNHSO_2R^d$, and –OR, said alkyl, aryl and heterocycle optionally substituted with 1 to 3 groups of R^b. A subembodiment of this aspect of the invention is realized when R^a selected from from the group consisting of -C_{1-4}haloalkyl, -OC_{1-4}haloalkyl, -C_{1-6}alkyl, -$(CHR)_nC_{6-10}$ aryl, -$(CHR)_nC_{4-10}$ heterocycle, -$(CH_2)_nN(R^d)_2$, COR, -$(CH_2)_n$halo, and –OR, said alkyl, aryl and heterocycle optionally substituted with 1 to 3 groups of R^b.

Another embodiment of the invention of formula I is realized when R^b is selected from the group consisting of halogen, -C_{1-6}alkyl, -C_{1-6}alkylOR, -C_{1-4}haloalkyl, -$(CH_2)_nN(R^d)_2$, -OR^c, -$(CH_2)_nC(O)N(R^d)_2$, -$(CH_2)_nNHC(O)R^d$.

Still another embodiment of the invention of formula I is realized when R^1 and R^5 are both hydrogen. Another embodiment of the invention of formula I is realized when one of R^1 and R^5 is hydrogen and the other is halogen. Still another embodiment of the invention of formula I is realized when R^1 and R^5 are both halogen. Still another embodiment of the invention of formula I is realized when one of R^1 and R^5 hydrogen and the other is chlorine, fluorine, CN, OH, or -C_{1-6}alkyl. Yet another embodiment of the invention of formula I is realized when one of R^1 and R^5 hydrogen and the other is -C_{1-6}alkyl. Yet another embodiment of the invention of formula I is realized when one of R^1 and R^5 hydrogen and the other is chlorine, or fluorine.

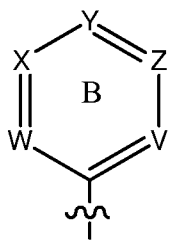
Another embodiment of the invention of formula I is realized when both R^2 and R^4 are hydrogen.

Another embodiment of the invention of formula I is realized when one of R^2 and R^4 is hydrogen and the other is $(CHR)_nC_{5-10}$ heterocycle, said heterocycle unsubstituted or substituted with 1 to 3 groups of R^a. A subembodiment of this aspect of the invention is realized when the n in $(CHR)_nC_{5-10}$ heterocycle is zero. Another subembodiment of this aspect of the invention is realized when the optionally substituted heterocycle is a five or six membered ring

containing one or more heteroatoms at least one of which is nitrogen. Still another subembodiment of this aspect of the invention is realized when the optionally substituted heterocycle is a five membered ring containing one or more heteroatoms at least one of which is nitrogen. Still another subembodiment of this aspect of the invention is realized when the optionally substituted heterocycle is a six membered ring containing one or more heteroatoms at least one of which is nitrogen. Another subembodiment of this aspect of the invention is realized when the heterocycle is selected from the group consisting of pyrazolyl, pyridyl, thiazolyl, triazolyl, oxazolyl, oxadiazolyl, and pyrimidinyl, said groups optionally substituted. Another subembodiment of this aspect of the invention is realized when the heterocycle is optionally substituted pyrazolyl. Another subembodiment of this aspect of the invention is realized when the heterocycle is substituted pyrazolyl. Still another subembodiment of this aspect of the invention is realized when the heterocycle is optionally substituted thiazolyl. Yet another subembodiment of this aspect of the invention is realized when the heterocycle is optionally substituted pyridyl. Yet another subembodiment of this aspect of the invention is realized when the heterocycle is optionally substituted oxadiazolyl. Yet another subembodiment of this aspect of the invention is realized when the heterocycle is optionally substituted oxazolyl. Yet another subembodiment of this aspect of the invention is realized when the heterocycle is optionally substituted triazolyl. Yet another subembodiment of this aspect of the invention is realized when the heterocycle is optionally substituted pyrimidinyl. Still another subembodiment of this aspect of the invention is realized when the heterocycle is optionally substituted with 1 to 3 groups of R^a selected from -C_{1-4}haloalkyl, -OC_{1-4}haloalkyl, -C_{1-6}alkyl, -C(O)CF_3, C(O)R, C(O)N$(R)_2$, -$(CH_2)_n$halo, and –OR.

Another embodiment of the invention of formula I is realized when R^3 is selected from the group consisting of hydrogen, CF_3, OCF_3, CH_3, bromine, chlorine, and fluorine. A subembodiment of this aspect of the invention is realized when R^3 is CF_3. Still another subembodiment of this aspect of the invention is realized when R^3 is OCF_3. Yet another subembodiment of this aspect of the invention is realized when R^3 is CH_3. Yet another subembodiment of this aspect of the invention is realized when R^3 is hydrogen.

Another embodiment of the invention of formula I is realized when B is represented by structural formula (a):



(a)

wherein:

V, W, X, Y, and Z are all CR^{10},
one of V, W, X, Y, and Z is N and the others are CR^{10},
X and V are both N and W, Y, and Z are all CR^{10},
W and Z are both N and V, X, and Y are all CR^{10},
X and Z are both N and Y, W, and V are all CR^{10},
W and Y are both N and X, Z, and V are all CR^{10}, or
Y and V are both N and Z, X, and W are all CR^{10}.

R^{10} is selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CHR)_n(C(O))_{0-1}N(R^d)_2$, $(CH_2)_nC_{6-10}$aryl, $C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, $(CH_2)_nC(O)NH(CH_2)_nC_{5-10}$heterocycle, $-(CH_2)_nOR$, $NH(CH_2)_nOR$, $-(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$heterocycle, SO_2R^d, $SO_2N(R^d)_2$, $S(O)(NH)R^g$, $-C(O)CF_3$, COR, $-(CH_2)_n$halo, $-(CH_2)_nNHC(O)R^d$, $-(CH_2)_nNHC(O)NHR^d$, $-(CH_2)_nNHC(O)OR^d$, $-O-C_{5-10}$heterocycle, and –OR said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of R^b andR, and R^b is as originally described.

Another embodiment of the invention of formula I is realized when B is a pyrimidinyl wherein X and Z are both N and Y, W, and V are all CR^{10}. A subembodiment of this aspect of the invention is realized when R^{10} of W and V are selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, halogen, and $-(CH_2)_nOR$, wherein n=0-2 and the alkyl, aryl and heterocycle is optionally substituted. Another embodiment of the invention of formula I wherein B is pyrimidinyl is realized when W and V are selected from hydrogen, C_{1-6}alkyl, halogen, CH_2OH, $C(O)NH_2$, and optionally substituted aryl or heterocycle selected from phenyl, pyrazolyl, isoxazolyl, oxazolyl, and imidazolyl. A further subembodiment of this aspect of the invention is realized when R^{10} of W and V are selected from the group consisting of halogen, CH_2OH, CH_3, chloro, and optionally substituted phenyl or pyrazolyl. Another embodiment of this aspect of the invention is realized when R^{10} of Y is selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $(CH_2)_nC_{5-10}$heterocycle, $-(CH_2)_nOR$, $NH(CH_2)_nOR$, $(CH_2)_n(C(O))_{0-1}N(R^d)_2$, $-(CH_2)_nNHC(O)OR^d$, $-(CH_2)_nNHC(O)R^d$, $-(CH_2)_nNHSO_2R^d$, wherein n=0-2, and the alkyl, aryl and heterocycle is optionally substituted. A further aspect of this invention is realized when Y is an aryl or heterocycle substituent and n=0. A further embodiment of this aspect of the invention is realized when X and Z are both N, W is optionally substituted phenyl, and Y, and V are both CR^{10}. Still a further embodiment of this aspect of the invention is realized when X and Z are both N, W is optionally substituted phenyl, Y is optionally substituted methyl, and V is CR^{10}. Yet a further embodiment of this aspect of the invention is realized when X and Z are both N, W is optionally substituted phenyl, Y is optionally substituted methyl, and V is hydrogen.

Another embodiment of the invention of formula I is realized when B is pyridyl and R^{10} of CR^{10} is selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl,

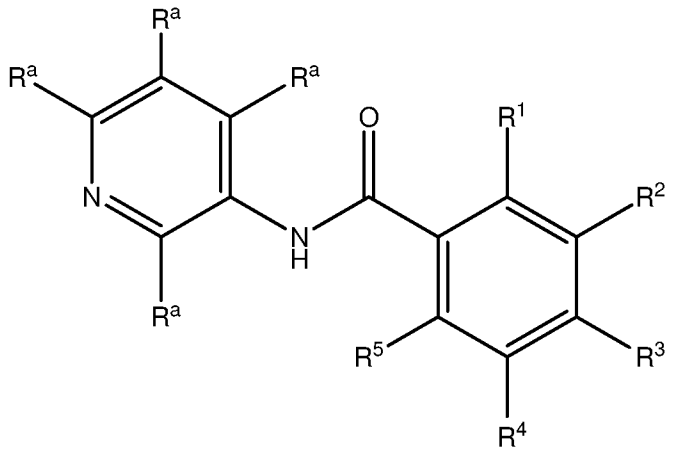
$C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, halogen, -O-C_{5-10}heterocycle, -$(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$heterocycle, $(CHR)_n(C(O))_{0-1}N(R^d)_2$, and -$(CH_2)_n$OR, wherein n=0-2 and the alkyl, aryl and heterocycle is optionally substituted. A further aspect of this invention is realized when R^{10} is an aryl or heterocycle substituent and n=0. A further embodiment of this aspect of the invention is realized when R^{10} is selected from hydrogen, C_{1-6}alkyl, $C(O)NH_2$, C(O)NHazetidinyl, pyridyl, isoxazolyl, oxazolyl, C(O)morpholinyl, pyrazolyl, and phenyl, $C(O)NH(CH_2)_n$pyridyl, said azetidinyl, pyridyl, isoxazolyl, oxazolyl, morpholinyl, pyrazolyl and phenyl optionally substituted with 1 to 3 groups of R^b.

Another embodiment of the invention of formula I is realized when B is phenyl and R^{10} of CR^{10} is selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, halogen, -O-C_{5-10}heterocycle, -$(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$heterocycle, $(CHR)_n(C(O))_{0-1}N(R^d)_2$, and -$(CH_2)_n$OR, wherein n=0-2 and the alkyl, aryl and heterocycle is optionally substituted. A further aspect of this invention is realized when R^{10} is selected from hydrogen, C_{1-6}alkyl, CF_3, $C(O)NH_2$, oxadiazolyl, isoxazolyl, oxazolyl, pyrazolyl, and phenyl, said oxadiazolyl, isoxazolyl, oxazolyl, pyrazolyl and phenyl optionally substituted with 1 to 3 groups of R^b.

Another embodiment of the invention of formula I is realized when B is pyrazinyl and R^{10} of CR^{10} is selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, halogen, -O-C_{5-10}heterocycle, -$(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$heterocycle, $(CHR)_n(C(O))_{0-1}N(R^d)_2$, and -$(CH_2)_n$OR, wherein n=0-2 and the alkyl, aryl and heterocycle is optionally substituted. A further aspect of this invention is realized when R^{10} is an aryl or heterocycle substituent and n=0.

An embodiment of the invention of formula I is wherein B is pyridyl represented by structural formula (a) and one of V, W, X, Y, and Z is N and the others are CR^{10} and R^{10} is selected from hydrogen, C_{1-6}alkyl, $C(O)NH_2$, C(O)NHazetidinyl, pyridyl, isoxazolyl, oxazolyl, C(O)morpholinyl, pyrazolyl, and phenyl, $C(O)NH(CH_2)_n$pyridyl, said azetidinyl, pyridyl, isoxazolyl, oxazolyl, morpholinyl, pyrazolyl and phenyl optionally substituted with 1 to 3 groups of R^b, R^1 and R^5 are independently selected from hydrogen and halogen, R^3 is CF_3, or halogen and one of R^2 and R^4 is hydrogen and the other is $(CHR)_nC_{5-10}$ heterocycle. A subembodiment of this aspect of the invention is realized when the heterocycle of R^2 and R^4 is optionally substituted oxodiazolyl, pyrazolyl, pyridyl, thiazolyl, oxazolyl, and pyrimidinyl. A subembodiment of this aspect of the invention is realized when the R^{10} on at least one of V, W, X Y, or Z that is CR^{10} is optionally substituted phenyl.

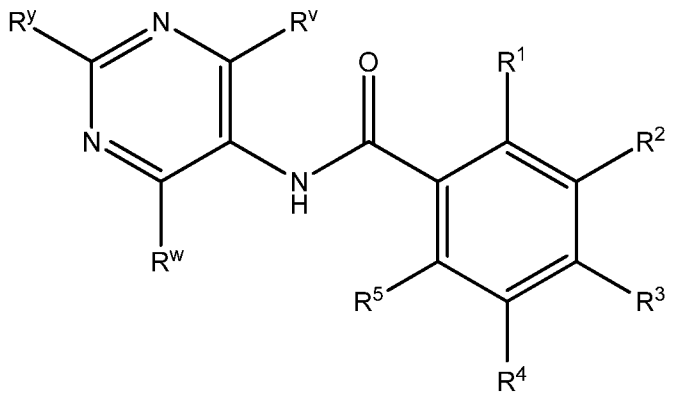
Still another embodiment of the invention of formula I is represented by structural formula Ia:



Ia

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and R^a are as originally described. A subembodiment of the invention of formula Ia is realized when R^a is selected from hydrogen, C_{1-6}alkyl, $C(O)NH_2$, C(O)NHazetidinyl, pyridyl, isoxazolyl, oxazolyl, C(O)morpholinyl, pyrazolyl, and phenyl, $C(O)NH(CH_2)_n$pyridyl, said azetidinyl, pyridyl, isoxazolyl, oxazolyl, morpholinyl, pyrazolyl and phenyl optionally substituted with 1 to 3 groups of R^b. Another subembodiment of the invention of formula Ia is realized when at two R^a groups on the pryidyl are hydrogen. Another subembodiment of the invention of formula Ia is realized when two R^a on the pyridyl are hydrogen and two are not hydrogen. Another subembodiment of the invention of formula Ia is realized when R^1 and R^5 are independently selected from hydrogen and halogen, R^3 is CF_3, or halogen and one of R^2 and R^4 is hydrogen and the other is $(CHR)_nC_{5-10}$ heterocycle. Another subembodiment of the invention of formula Ia is realized when the heterocycle of R^2 and R^4 is optionally substituted oxodiazolyl, pyrazolyl, pyridyl, thiazolyl, oxazolyl, and pyrimidinyl. Another subembodiment of the invention of formula Ia is realized when the R^a on at least one of V, W, X Y, or Z is optionally substituted phenyl.

Still another embodiment of the invention of formula I is represented by structural formula II:



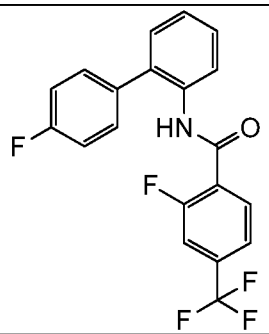
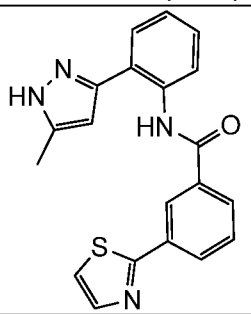
II

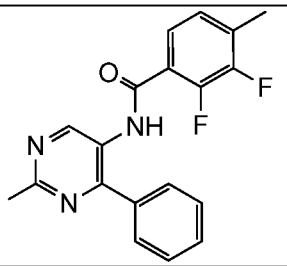
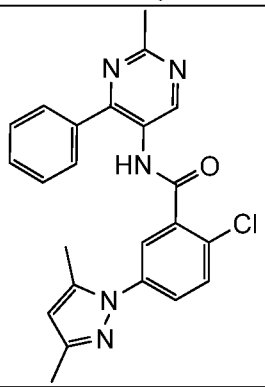
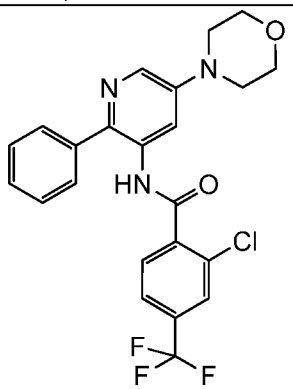
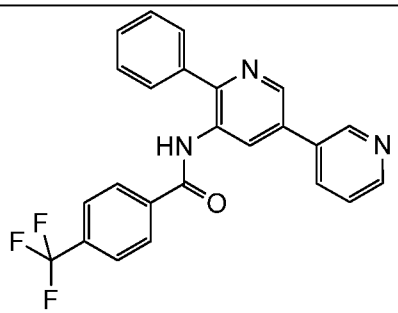
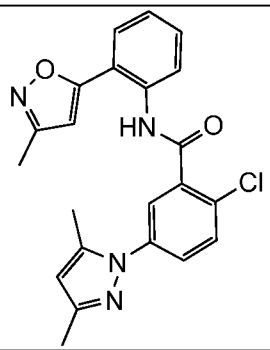
or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, and R^5 are as originally described, and R^w, R^v and R^y=R^{10}. A subembodiment of the invention of formula II is realized

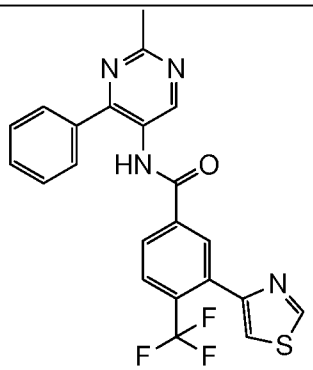
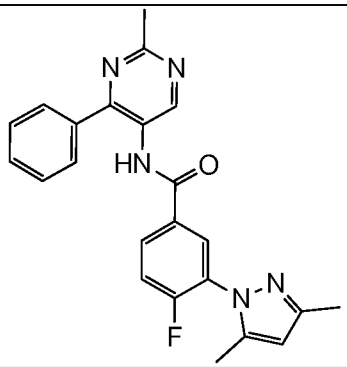
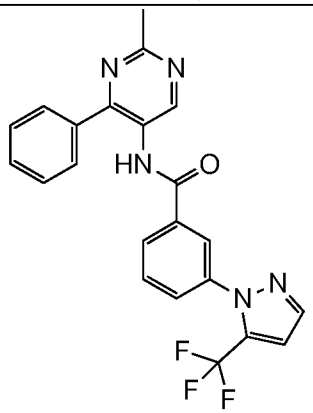
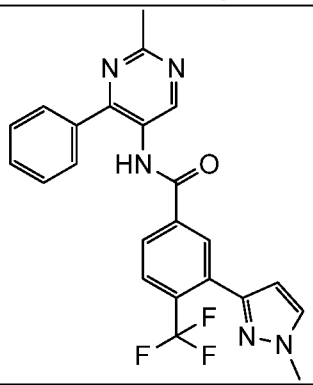
when R^1 and R^5 are independently selected from hydrogen and halogen, R^3 is CF_3, OCF_3, or halogen, R^W and R^V are selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, halogen, and $-(CH_2)_nOR$, wherein n=0-2 and the alkyl, aryl and heterocycle is optionally substituted and R^Y is selected from hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $(CH_2)_nC_{5-10}$heterocycle, $-(CH_2)_nOR$, $NH(CH_2)_nOR$, $(CH_2)_n(C(O))_{0-1}N(R^d)_2$, $-(CH_2)_nNHC(O)OR^d$, $-(CH_2)_nNHC(O)R^d$, $-(CH_2)_nNHSO_2R^d$, wherein n=0-2, and the alkyl, aryl and heterocycle is optionally substituted. Another subembodiment of the invention of formula II is realized when one of R^W, R^Y, and R^V is hydrogen and the other is not hydrogen. A subembodiment of the invention of formula II is realized when R^2 and R^4 both are hydrogen. Another subembodiment of the invention of formula II is realized when one of R^2 and R^4 is hydrogen and the other is $(CHR)_nC_{5-10}$ heterocycle, said heterocycle unsubstituted or substituted with 1 to 3 groups of R^a. An embodiment of this aspect of the invention of formula II is realized when the heterocycle of R^2 and R^4 is selected from the group consisting of oxodiazolyl, pyrazolyl, pyridyl, thiazolyl, oxazolyl, and pyrimidinyl, said groups optionally substituted. Still another subembodiment of this aspect of the invention is realize when the heterocycle of R^2 and R^4 is optionally substituted pyrazolyl or pyrimidinyl and R^3 is CF_3. A subembodiment of the invention of formula II is realized when at least one of R^W and R^V is optionally substituted phenyl.

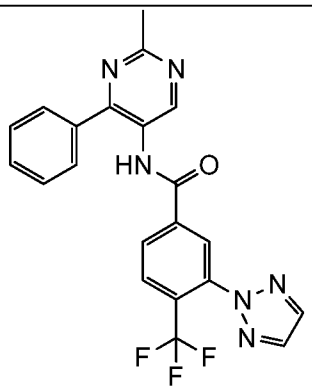
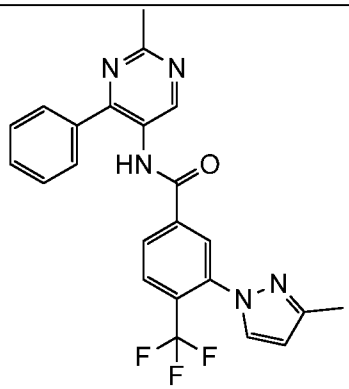
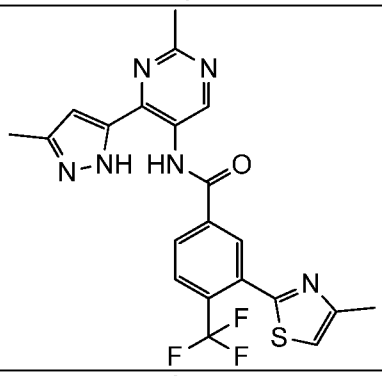
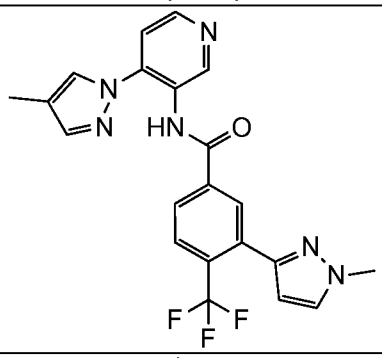
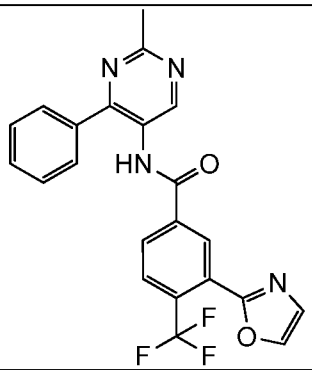
Examples of compounds of this invention include those in Table 1:

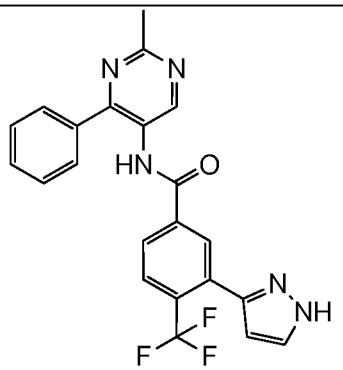
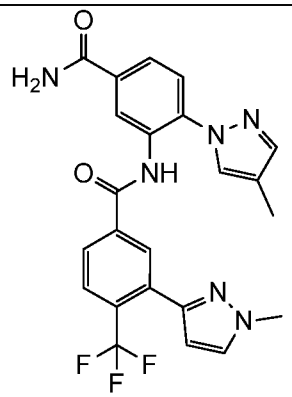
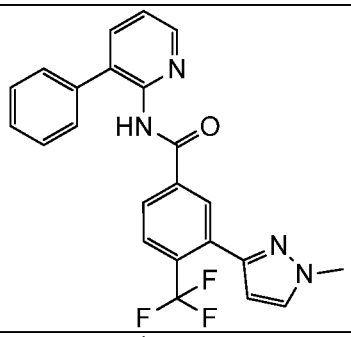
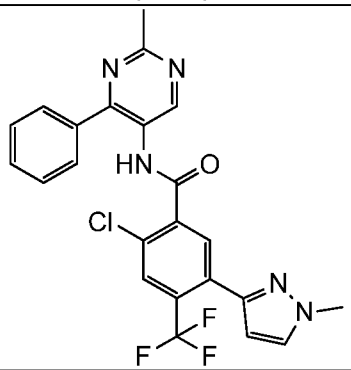
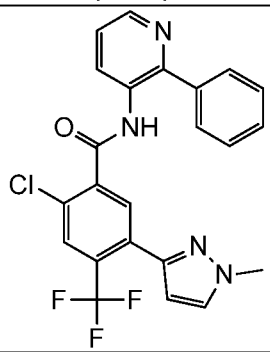
Table 1

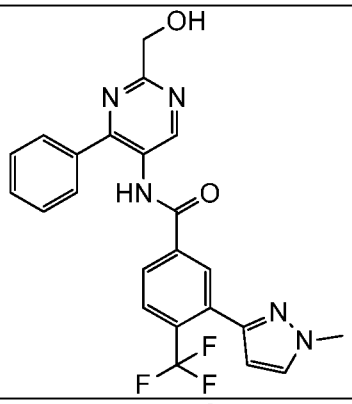
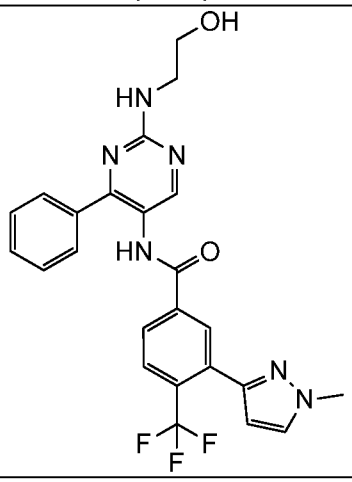
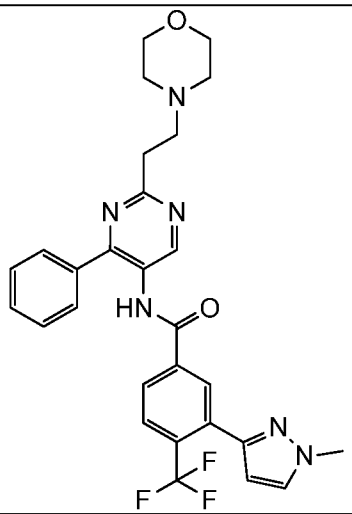
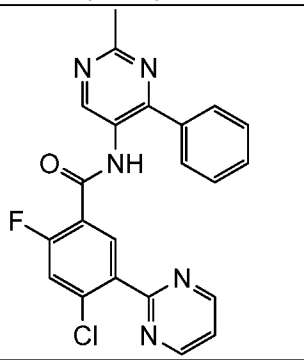
Compound number	Structure	Compound Name	LCMS (M+1)
1		2-fluoro-N-(4'-fluorobiphenyl-2-yl)-4-(trifluoromethyl)benzamide	378
2		N-[2-(5-methyl-1H-pyrazol-3-yl)phenyl]-3-(1,3-thiazol-2-yl)benzamide	361.1

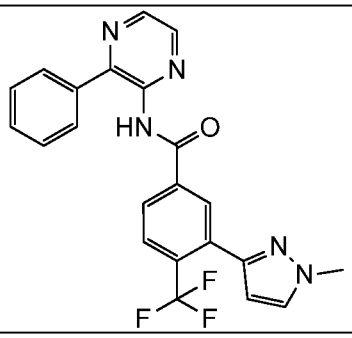
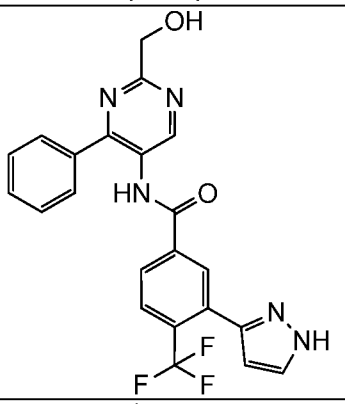
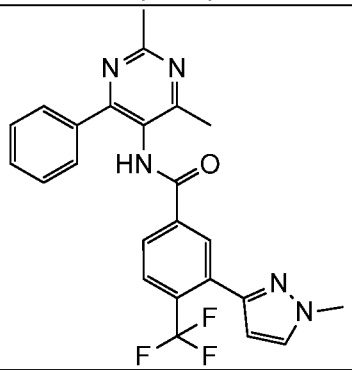
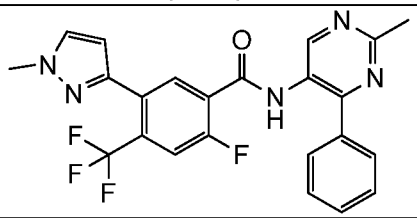
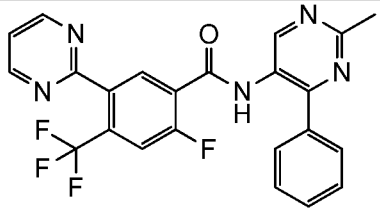
3		2,3-difluoro-4-methyl-N-(2-methyl-4-phenylpyrimidin-5-yl)benzamide	340.1
4		2-chloro-5-(3,5-dimethyl-1H-pyrazol-1-yl)-N-(2-methyl-4-phenylpyrimidin-5-yl)benzamide	418.1
5		2-chloro-N-(5-morpholin-4-yl-2-phenylpyridin-3-yl)-4-(trifluoromethyl)benzamide	462
6		N-(6-phenyl-3,3'-bipyridin-5-yl)-4-(trifluoromethyl)benzamide	420
7		2-chloro-5-(3,5-dimethyl-1H-pyrazol-1-yl)-N-[2-(3-methylisoxazol-5-yl)phenyl]benzamide	407.1

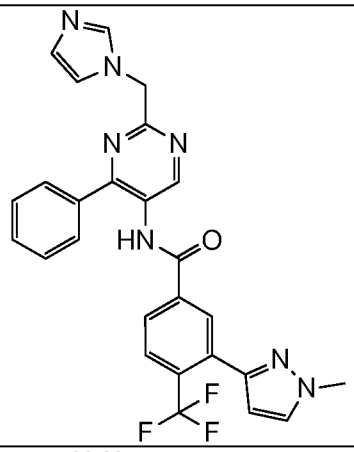
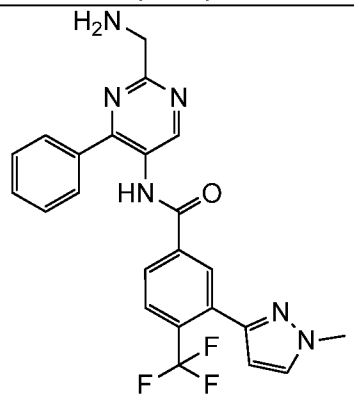
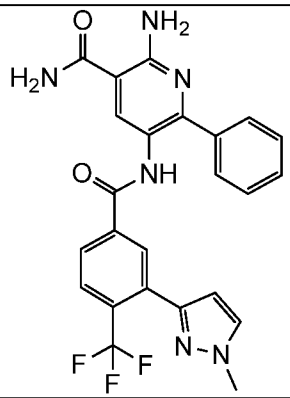
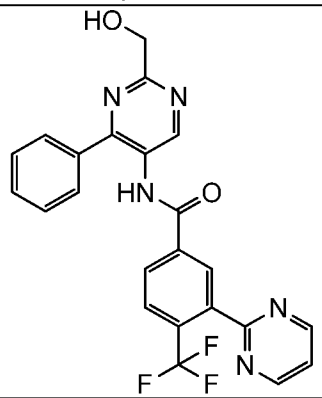
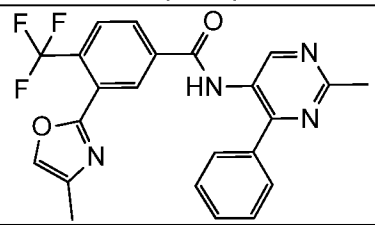
8		N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(1,3-thiazol-4-yl)-4-(trifluoromethyl)benzamide	441.1
9		3-(3,5-dimethyl-1H-pyrazol-1-yl)-4-fluoro-N-(2-methyl-4-phenylpyrimidin-5-yl)benzamide	402.2
10		N-(2-methyl-4-phenylpyrimidin-5-yl)-3-[5-(trifluoromethyl)-1H-pyrazol-1-yl]benzamide	424.1
11		N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	438.2

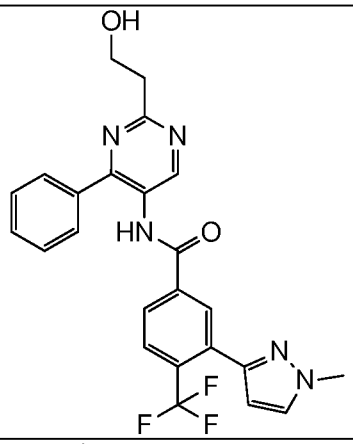
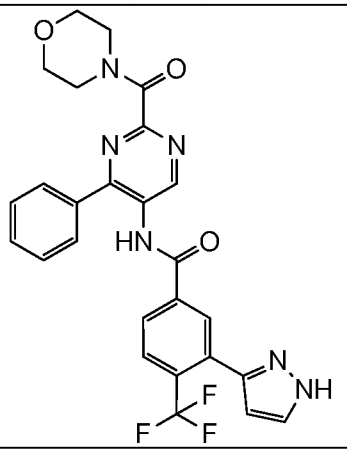
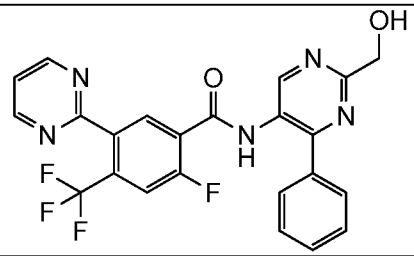
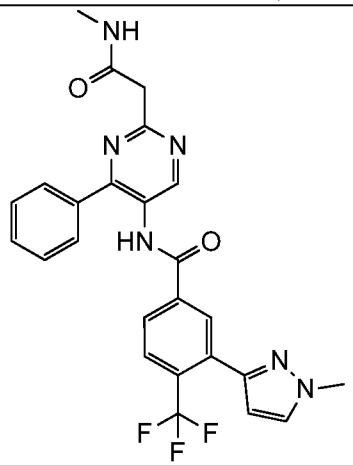
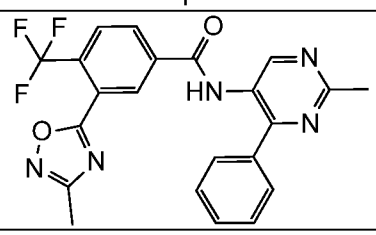
12		N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(2H-1,2,3-triazol-2-yl)-4-(trifluoromethyl)benzamide	425.1
13		N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(3-methyl-1H-pyrazol-1-yl)-4-(trifluoromethyl)benzamide	438.2
14		N-[2-methyl-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-5-yl]-3-(4-methyl-1,3-thiazol-2-yl)-4-(trifluoromethyl)benzamide	459
15		3-(1-methyl-1H-pyrazol-3-yl)-N-[4-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl]-4-(trifluoromethyl)benzamide	427
16		N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(1,3-oxazol-2-yl)-4-(trifluoromethyl)benzamide	425

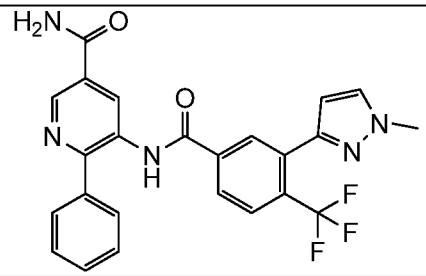
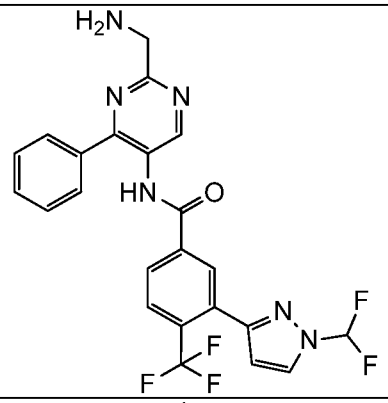
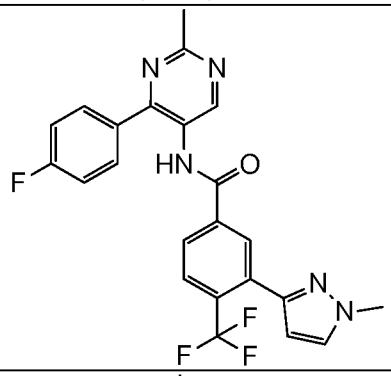
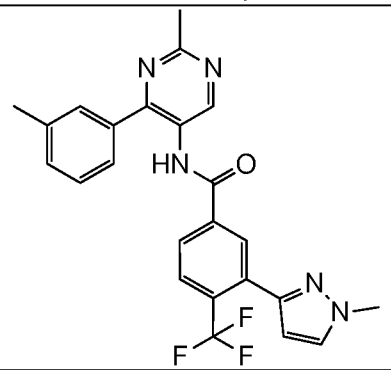
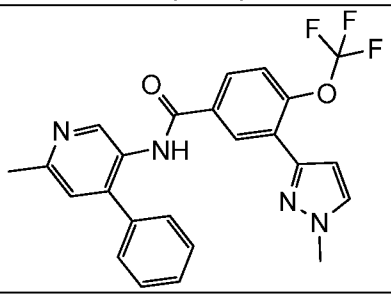
17		N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	424
18		N-[5-carbamoyl-2-(4-methyl-1H-pyrazol-1-yl)phenyl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	469
19		3-(1-methyl-1H-pyrazol-3-yl)-N-(3-phenylpyridin-2-yl)-4-(trifluoromethyl)benzamide	423
20		2-chloro-N-(2-methyl-4-phenylpyrimidin-5-yl)-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	472.1
21		2-chloro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylpyridin-3-yl)-4-(trifluoromethyl)benzamide	457.1

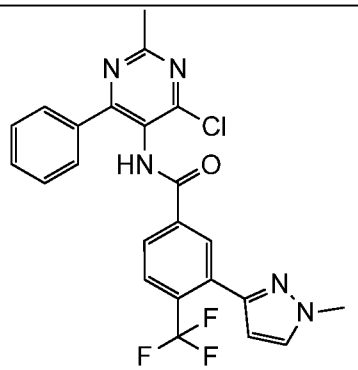
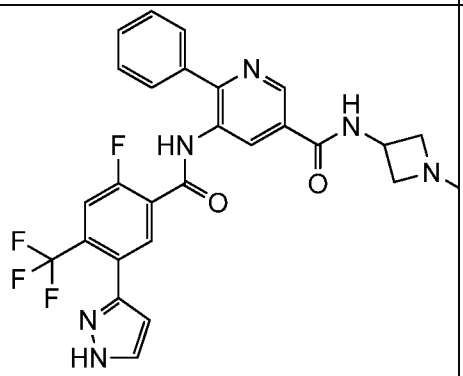
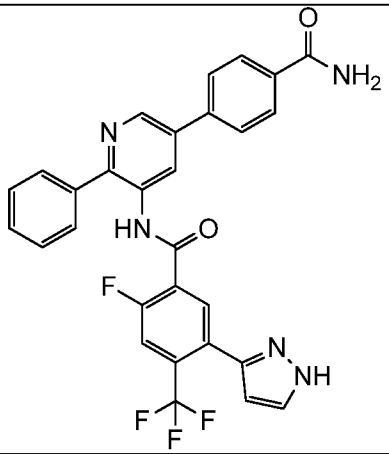
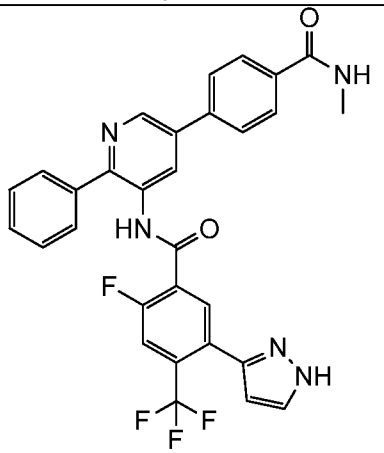
22		N-[2-(hydroxymethyl)-4-phenylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	454.1
23		N-{2-[(2-hydroxyethyl)amino]-4-phenylpyrimidin-5-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	483.2
24		3-(1-methyl-1H-pyrazol-3-yl)-N-[2-(2-morpholin-4-ylethyl)-4-phenylpyrimidin-5-yl]-4-(trifluoromethyl)benzamide	537.2
25		4-chloro-2-fluoro-N-(2-methyl-4-phenylpyrimidin-5-yl)-5-pyrimidin-2-ylbenzamide	420.1

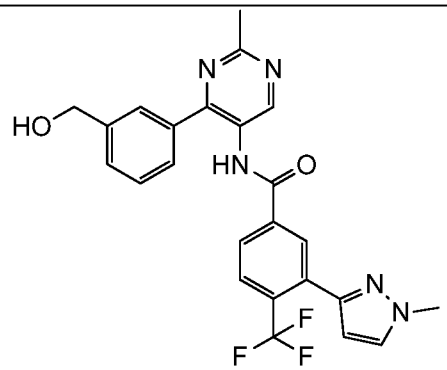
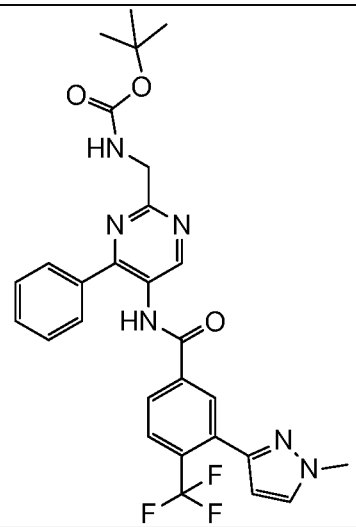
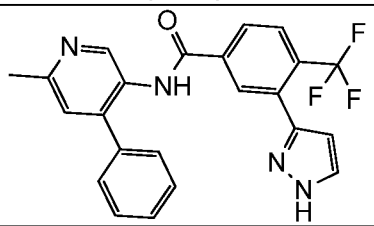
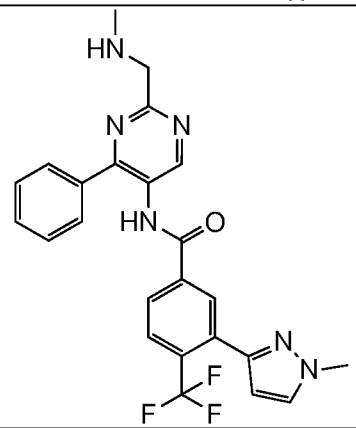
26		3-(1-methyl-1H-pyrazol-3-yl)-N-(3-phenylpyrazin-2-yl)-4-(trifluoromethyl)benzamide	424.2
27		N-[2-(hydroxymethyl)-4-phenylpyrimidin-5-yl]-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	440
28		N-(2,4-dimethyl-6-phenylpyrimidin-5-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	452.2
29		2-fluoro-N-(2-methyl-4-phenylpyrimidin-5-yl)-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	457.1
30		2-fluoro-N-(2-methyl-4-phenylpyrimidin-5-yl)-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	454.2

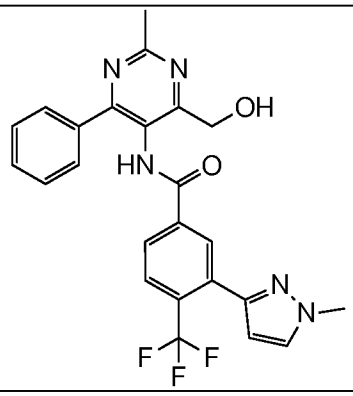
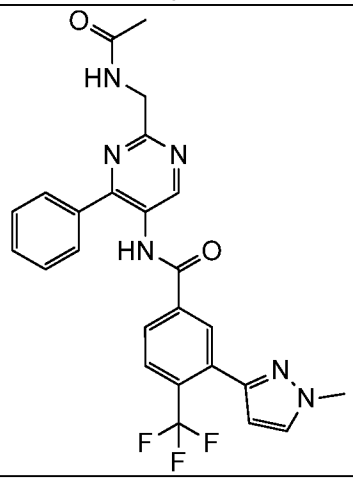
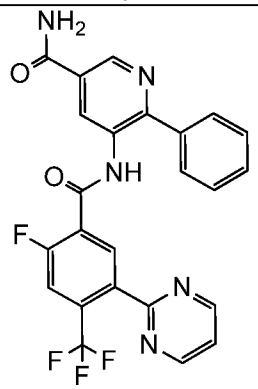
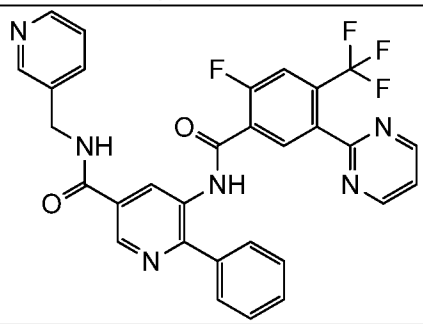
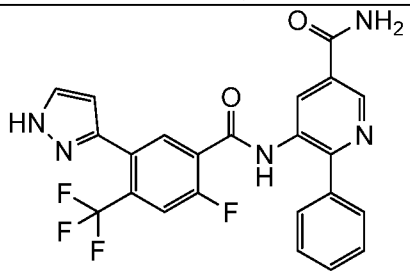
31		N-[2-(1H-imidazol-1-ylmethyl)-4-phenylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	504.2
32		N-[2-(aminomethyl)-4-phenylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	453.2
33		2-amino-5-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-6-phenylpyridine-3-carboxamide	481.2
34		N-[2-(hydroxymethyl)-4-phenylpyrimidin-5-yl]-3-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	452.2
35		3-(4-methyl-1,3-oxazol-2-yl)-N-(2-methyl-4-phenylpyrimidin-5-yl)-4-(trifluoromethyl)benzamide	439

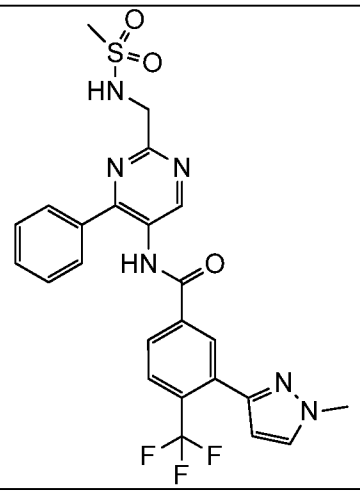
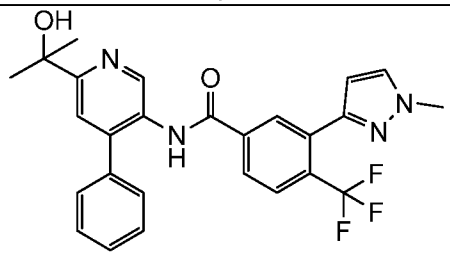
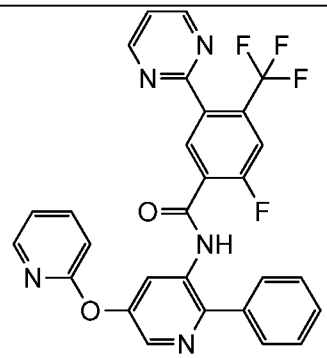
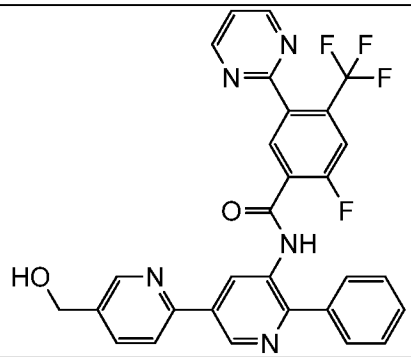
36		N-[2-(2-hydroxyethyl)-4-phenylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	468.2
37		N-[2-(morpholin-4-ylcarbonyl)-4-phenylpyrimidin-5-yl]-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	523.2
38		2-fluoro-N-[2-(hydroxymethyl)-4-phenylpyrimidin-5-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	470.2
39		N-{2-[2-(methylamino)-2-oxoethyl]-4-phenylpyrimidin-5-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	495.2
40		3-(3-methyl-1,2,4-oxadiazol-5-yl)-N-(2-methyl-4-phenylpyrimidin-5-yl)-4-(trifluoromethyl)benzamide	440

41		5-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-6-phenylpyridine-3-carboxamide	466.2
42		N-[2-(aminomethyl)-4-phenylpyrimidin-5-yl]-3-[1-(difluoromethyl)-1H-pyrazol-3-yl]-4-(trifluoromethyl)benzamide	489.2
43		N-[4-(4-fluorophenyl)-2-methylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	456.2
44		N-[2-methyl-4-(3-methylphenyl)pyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	452.3
45		N-(6-methyl-4-phenylpyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzamide	453

46		N-(4-chloro-2-methyl-6-phenylpyrimidin-5-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	472.2
47		5-({[2-fluoro-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-N-(1-methylazetidin-3-yl)-6-phenylpyridine-3-carboxamide	539.2
48		N-[5-(4-carbamoylphenyl)-2-phenylpyridin-3-yl]-2-fluoro-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	546.2
49		2-fluoro-N-{5-[4-(methylcarbamoyl)phenyl]-2-phenylpyridin-3-yl}-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	560.2

50		N-{4-[3-(hydroxymethyl)phenyl]-2-methylpyrimidin-5-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	468.2
51		tert-butyl {[5-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-4-phenylpyrimidin-2-yl]methyl}carbamate	553.3
52		N-(6-methyl-4-phenylpyridin-3-yl)-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	423
53		N-{2-[(methylamino)methyl]-4-phenylpyrimidin-5-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	467.3

54		N-[4-(hydroxymethyl)-2-methyl-6-phenylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	468.2
55		N-{2-[(acetylamino)methyl]-4-phenylpyrimidin-5-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	495.2
56		5-({[2-fluoro-5-pyrimidin-2-yl-4-(trifluoromethyl)phenyl]carbonyl}amino)-6-phenylpyridine-3-carboxamide	482.2
57		5-({[2-fluoro-5-pyrimidin-2-yl-4-(trifluoromethyl)phenyl]carbonyl}amino)-6-phenyl-N-(pyridin-3-ylmethyl)pyridine-3-carboxamide	573.2
58		5-({[2-fluoro-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-6-phenylpyridine-3-carboxamide	470.2

59		3-(1-methyl-1H-pyrazol-3-yl)-N-(2-{[(methylsulfonyl)amino]methyl}-4-phenylpyrimidin-5-yl)-4-(trifluoromethyl)benzamide	531.2
60		N-[6-(1-hydroxy-1-methylethyl)-4-phenylpyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	481.2
61		2-fluoro-N-[2-phenyl-5-(pyridin-2-yloxy)pyridin-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	532.1
62		2-fluoro-N-[5-(hydroxymethyl)-6'-phenyl-2,3'-bipyridin-5'-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	546.1

or pharmaceutically acceptable salts thereof.

The invention is also directed to methods of treating a patient (preferably a human) for diseases or disorders in which the TrkA receptor is involved, such as pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction

relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA, by administering to the patient a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

The invention is also directed to the use of a compound of the invention for treating a disease or disorder in which the TrkA receptor is involved, such as pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA, by administering to the patient a compound of the invention, or a pharmaceutically acceptable salt thereof.

The invention is also directed to medicaments or pharmaceutical compositions for the treatment of diseases or disorders in a patient (preferably a human) in which the TrkA receptor is involved, such as pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA, which comprise a compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The invention is also directed to a method for the manufacture of a medicament or a pharmaceutical composition for treating diseases in which TrkA receptor is involved, such as pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA comprising combining a compound of the invention or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier.

Where a variable occurs more than once in any formula of the invention, or in a substituent thereof, the individual occurrences of that variable are independent of each other, unless otherwise specified. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, the term "alkyl," by itself or as part of another substituent, means a saturated straight or branched chain hydrocarbon radical having the number of carbon atoms designated (*e.g.*, C_{1-10} alkyl means an alkyl group having from one to ten carbon atoms). Preferred alkyl groups for use in the invention are C_{1-6} alkyl groups, having from one to six atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, pentyl, hexyl, and the like. C_0 alkyl means a bond.

As used herein, the term "alkenyl," by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical having a single carbon-carbon double bond and the number of carbon atoms designated (*e.g.*, C_{2-10} alkenyl means an alkenyl group having from two to ten carbon atoms). Preferred alkenyl groups for use in the invention are C_{2-6} alkenyl

groups, having from two to six carbon atoms. Exemplary alkenyl groups include ethenyl and propenyl.

As used herein, the term "cycloalkyl," by itself or as part of another substituent, means a saturated cyclic hydrocarbon radical having the number of carbon atoms designated (*e.g.*, C_{3-12} cycloalkyl means a cycloalkyl group having from three to twelve carbon atoms). The term cycloalkyl as used herein includes mono-, bi- and tricyclic saturated carbocycles, spirocycles, and bridged and fused ring carbocycles as well as oxo substituted cycloalkyl groups..

Preferred cycloalkyl groups for use in the invention are monocyclic C_{3-8} cycloalkyl groups, having from three to eight carbon atoms. Exemplary monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. Exemplary bridged cycloalkyl groups include adamantyl and norbornyl. Exemplary fused cycloalkyl groups include decahydronaphthalene.

The term "heteroatom" means O, S or N, selected on an independent basis.

As used herein, the term "aryl," by itself or as part of another substituent, means an aromatic cyclic hydrocarbon radical. Preferred aryl groups have from six to ten carbons atoms. The term "aryl" includes multiple ring systems as well as single ring systems. Preferred aryl groups for use in the invention include phenyl and naphthyl.

The term "aryl" also includes fused cyclic hydrocarbon rings which are partially aromatic (i.e., one of the fused rings is aromatic and the other is non-aromatic). An exemplary aryl group which is partially aromatic is indanyl.

The term heterocyclyl, heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term heterocyclyl, heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzodioxolyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzotriazolyly, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrazolopyridinyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl, triazolyl, N-oxides and –C=O derivatives thereof.

The term "heteroaryl", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 9- to 10-membered fused bicyclic heterocyclic ring system which contains an aromatic ring, any ring of which may be saturated, such as piperidinyl, partially saturated, or unsaturated, such as pyridinyl, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heteroaryl groups include, but are not limited to, benzimidazole, benzisothiazole, benzisoxazole, benzofuran, benzothiazole, benzothiophene, benzotriazole, benzoxazole, carboline, cinnoline, furan, furazan, imidazole, indazole, indole, indolizine, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, N-oxides thereof and –C=O derivatives thereof. Suitable heteroaryl groups are imidazopyridinyl, indazolyl, imidazothiazolyl, imidazopyrimidinyl, imidazopyridazinyl, imidazothiadiazolyl, quinoxalinyl, and imidazopyrrolyl.

When a heterocyclyl group as defined herein is substituted, the substituent may be bonded to a ring carbon atom of the heteroaryl group, or on a ring heteroatom (*i.e.,* a nitrogen, oxygen or sulfur), which has a valence which permits substitution. Preferably, the substituent is bonded to a ring carbon atom. Similarly, when a heteroaryl group is defined as a substituent herein, the point of attachment may be at a ring carbon atom of the heteroaryl group, or on a ring heteroatom (*i.e.,* a nitrogen, oxygen or sulfur), which has a valence which permits attachment. Preferably, the attachment is at a ring carbon atom.

As used herein, the term “halo” or “halogen” includes fluoro, chloro, bromo and iodo.

As used herein –O- includes oxo (e.g., an annular -CH- substituted with oxo is -C(O) or carbonyl.

The compounds of the invention may have one or more asymmetric centers. Compounds with asymmetric centers give rise to enantiomers (optical isomers), diastereomers (configurational isomers) or both, and it is intended that all of the possible enantiomers and diastereomers in mixtures and as pure or partially purified compounds are included within the scope of this invention. The present invention is meant to encompass all such isomeric forms of the compounds of the invention. The present invention includes all stereoisomers of formulae (I) and pharmaceutically acceptable salts thereof.

The independent syntheses of the enantiomerically or diastereomerically enriched compounds, or their chromatographic separations, may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline

intermediates that are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers or diastereomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods using chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer or diastereomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

In the compounds of the invention the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic formulae (I). For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic formulae (I) can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

The term “substantially pure” means that the isolated material is at least 90% pure, and preferably 95% pure, and even more preferably 99% pure as assayed by analytical techniques known in the art.

As used herein, the term TrkA" refers to one of Trk's high affinity binding protein kinase receptors that are activated by Neurotrophins (NT), a group of soluble growth factors Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF) and Neurotrophin 3-5 (NT 3-5). The Trk's are made up of three family members TrkA, TrkB and TrkC that bind to and mediate the signal transduction derived from the Neurotrophins. Inhibitors of the Trk/neutrophin pathway have been demonstrated to be highly effective in numerous pre-clinical animal models of pain. The compounds of the invention are modulators of the Trk receptors, particularly TrkA.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. The compounds of the invention may be mono, di or tris salts, depending on the number of acid functionalities present in the free base form of the compound. Free bases and salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like.

Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, *N,N'*-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, trifluoroacetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, *para*-toluenesulfonic acid, and the like.

The present invention is directed to the use of the compounds of formulae (I) disclosed herein as TrkA inhibitors in a patient or subject such as a mammal in need of such activity, comprising the administration of an effective amount of the compound. In addition to humans, a variety of other mammals can be treated according to the method of the present invention.

The compounds of the present invention have utility in treating or ameliorating pain disorders (including pain associated with cancer, surgery, and bone fracture, acute pain, inflammatory pain and neuropathic pain). The compounds of formula I are also useful for treating cancers including neuroblastoma, ovarian, pancreatic and colorectal cancer. Other conditions that may be treated by the compounds of the invention include inflammation and certain infectious diseases, interstitial cystitis, painful bladder syndrome, urinary incontinence, asthma, anorexia, atopic dermatitis, and psoriasis. Treatment of demyelination and dysmyelination, by promoting myelination, neuronal survival, and oligodendrocyte differentiation via blocking Sp35-TrkA interaction may also be possible with the compounds of the present invention.

The compounds of formula I may also be useful in the treatment of bone-related diseases (e.g., those involved in bone resorption). Examples of bone-related diseases include metastatic bone disease, treatment-induce bone loss, osteoporosis, rheumatoid arthritis, ankylosing

spondylitis, Paget's disease, and periodontal disease. Another bone disorder or disease that can be treated with the compounds of the claimed invention is metastatic tumor-induced osteolysis. Cancers known to cause tumor induced osteolysis are hematological malignancies such as myeloma and lymphoma and solid tumors such as breast, prostate, lung, renal and thyroid.

Pain disorders for which the compounds of the invention may be useful include neuropathic pain (such as postherpetic neuralgia, nerve injury, the "dynias", e.g., vulvodynia, phantom limb pain, root avulsions, painful diabetic neuropathy, painful traumatic mononeuropathy, painful polyneuropathy); central pain syndromes (potentially caused by virtually any lesion at any level of the nervous system); postsurgical pain syndromes (e.g., postmastectomy syndrome, postthoracotomy syndrome, stump pain); bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia); perioperative pain (general surgery, gynecological), chronic pain, dysmennorhea, as well as pain associated with angina, and inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno- synovitis and gout), headache, migraine and cluster headache, headache, primary hyperalgesia, secondary hyperalgesia, primary allodynia, secondary allodynia, or other pain caused by central sensitization.

Compounds of the invention may also be used to treat or prevent dyskinesias. Furthermore, compounds of the invention may be used to decrease tolerance and/or dependence to opioid treatment of pain, and for treatment of withdrawal syndrome of e.g., alcohol, opioids, and cocaine.

The subject or patient to whom the compounds of the present invention is administered is generally mammals such a human being, male or female, in whom Trk-A and/or Trk-B modulation is desired. Thus, an aspect of the present invention is a method of treating diseases with an inhibitor of Trk-A and/or Trk-B comprising administering to said mammal one or more compounds of formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat or prevent said disorder. In a particular aspect of the invention is directed to a method of treating pain, cancer, inflammation, neurodegenerative disease or Typanosoma cruzi infection by administering to said mammal a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. Still another aspect of the present invention is directed to a method of treating osteolytic disease in a mammal by administering a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. For purposes of this invention mammals include dogs, cats, mice, rats, cattle, horses, sheep, rabbits, monkeys, chimpanzees or other apes or primates, for which treatment of the above noted disorders is desired.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment of diseases or conditions for which the compounds of the present invention have utility, where the combination of the drugs together are safer or more effective than either drug alone. Additionally, the compounds of the present invention may be used in combination with one or more other drugs that treat, prevent, control, ameliorate, or reduce the

risk of side effects or toxicity of the compounds of the present invention. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with the compounds of the present invention. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to the compounds of the present invention. The combinations may be administered as part of a unit dosage form combination product, or as a kit or treatment protocol wherein one or more additional drugs are administered in separate dosage forms as part of a treatment regimen.

Examples of combinations of the compounds include combinations with agents for the treatment of pain, for example steroids such as dexamethasone, cortisone, and fluticasone, non-steroidal anti-inflammatory agents, such as aspirin, diclofenac, duflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, oxaprozin, piroxicam, sulindac and tolmetin; COX-2 inhibitors, such as celecoxib, rofecoxib and valdecoxib; CB-2 agonists; VR-1 antagonists; bradykinin B l receptor antagonists; sodium channel blockers and antagonists; nitric oxide synthase (NOS) inhibitors (including iNOS and nNOS inhibitors); glycine site antagonists, including lacosamide; neuronal nicotinic agonists; NMDA antagonists; potassium channel openers; AMPA/kainate receptor antagonists; calcium channel blockers, such as ziconotide; GABA-A receptor IO modulators (e.g., a GABA- A receptor agonist); matrix metalloprotease (MMP) inhibitors; thrombolytic agents; chemotherapeutic agents, opioid analgesics such as codeine, fentanyl, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, propoxyphene; neutrophil inhibitory factor (NIF); pramipexole, ropinirole; anticholinergics; amantadine; monoamine oxidase Bl5 ("MAO-B") inhibitors; 5HT receptor agonists or antagonists; mGlu5 antagonists; alpha agonists; neuronal nicotinic agonists; NMDA receptor agonists or antagonists; NKI antagonists; selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), such as duloxetine; tricyclic antidepressant drugs, norepinephrine modulators; lithium; valproate; gabapentin; pregabalin; rizatriptan; zolmitriptan; naratriptan and sumatriptan.

Another aspecit of the present invention is directed to a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier. Still another aspect of the present invention is directed to a compound of formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition treatable with an inhibitor of Trk-A and/or Trk-B, such as the disorders, conditions and/or diseases described herein. Still another aspect is directed to use of a compound of formula I or a pharmaceutically acceptable salt thereof in the treatment of pain, cancer, inflammation, neurodegenerative disease or typanosoma cruzi infection.

The term "composition" as used herein is intended to encompass a product comprising specified ingredients in predetermined amounts or proportions, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified

amounts. This term in relation to pharmaceutical compositions is intended to encompass a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.

In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound, which is a compound of formulae (I), is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing

form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1 mg to about 500 mg of the active ingredient and each cachet or capsule preferably containing from about 0.1 mg to about 500 mg of the active ingredient.

Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Other pharmaceutical compositions include aqueous suspensions, which contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. In addition, oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Oily suspensions may also contain various excipients. The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions, which may also contain excipients such as sweetening and flavoring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension, or in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can also be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art.

By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment in a form that can be introduced into that individual's body in a therapeutically useful form and therapeutically useful amount, including, but not limited to: oral dosage forms, such as tablets, capsules, syrups,

suspensions, and the like; injectable dosage forms, such as IV, IM, or IP, and the like; transdermal dosage forms, including creams, jellies, powders, or patches; buccal dosage forms; inhalation powders, sprays, suspensions, and the like; and rectal suppositories.

The terms “effective amount” or “therapeutically effective amount” means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treatment" or "treating" means any administration of a compound of the present invention and includes (1) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or (2) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

The compositions containing compounds of the present invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. The term “unit dosage form” is taken to mean a single dose wherein all active and inactive ingredients are combined in a suitable system, such that the patient or person administering the drug to the patient can open a single container or package with the entire dose contained therein, and does not have to mix any components together from two or more containers or packages. Typical examples of unit dosage forms are tablets or capsules for oral administration, single dose vials for injection, or suppositories for rectal administration. This list of unit dosage forms is not intended to be limiting in any way, but merely to represent typical examples of unit dosage forms.

The compositions containing compounds of the present invention may conveniently be presented as a kit, whereby two or more components, which may be active or inactive ingredients, carriers, diluents, and the like, are provided with instructions for preparation of the actual dosage form by the patient or person administering the drug to the patient. Such kits may be provided with all necessary materials and ingredients contained therein, or they may contain instructions for using or making materials or components that must be obtained independently by the patient or person administering the drug to the patient.

When treating or ameliorating a disorder or disease for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 mg to about 100 mg per kg of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. The total daily dosage is from about 1.0 mg to about 2000 mg, preferably from about 0.1 mg to about 20 mg per kg of body weight. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 mg to about 1,400 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response. The

compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.005 mg to about 2.5 g of active agent, compounded with an appropriate and convenient amount of carrier material. Unit dosage forms will generally contain between from about 0.005 mg to about 1000 mg of the active ingredient, typically 0.005, 0.01 mg, 0.05 mg, 0.25 mg, 1 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg or 1000 mg, administered once, twice or three times a day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials and the requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures or as illustrated herein.

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are allowed under the definitions hereinabove. Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the schemes and examples herein, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures.

During any of the synthetic sequences it may be necessary or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W.McOmie, Plenum Press, 1973, and T.W. Greene & P/G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1999. The protecting groups may be removed at a convenient sequent stage using methods known from the art.

In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

The following abbreviations are used throughout the text:

Me:	methyl
Et:	ethyl
Bu:	butyl
t-Bu:	*tert*-butyl
Ar:	aryl
Ph:	phenyl
Bn:	benzyl
Ac:	acetyl
DMF•DMA:	*N,N*-dimethylformamide dimethyl acetal
DMSO:	dimethylsulfoxide
DMF:	*N,N*-dimethylformamide
THF:	tetrahydrofuran
TEA:	triethylamine
aq:	aqueous
HPLC:	high performance liquid chromatography
MS:	mass spectrometry
CDI:	1,1'-carbonyldiimidazole
DCE:	1,2-dichlorethane
HCl:	hydrochloric acid
°C:	degrees Celcius
BINAP:	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
ATP:	adenosine triphosphate
i-Pr:	isopropyl
Py:	pyridyl
OAc:	acetate
TFA:	trifluoroacetic acid
TFAA:	trifluoroacetic anhydride

Boc:	*tert*-butoxycarbonyl
BOP:	(benzotriazol-1-yloxy)*tris*(dimethylamino)phosphonium hexafluorophosphate
DIEA:	*N*,*N*-diisopropylethylamine
HOBT:	1-hydroxybenzotriazole
EDC:	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
PyCLU:	chlorodipyrrolidinocarbenium
n-BuLi:	*n*-butyllithium
HATU:	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'N'*-tetramethyluronium hexafluorophosphate
EDTA:	ethylenediaminetetraacetic acid
HMDS:	hexamethyldisilazane
min:	minutes
h:	hours
HPLC:	high performance liquid chromatography
LCMS:	liquid chromatography-mass spectrometry
SFC:	supercritical fluid chromatography
TLC:	thin layer chromatography
NMP:	1-methyl-2-pyrrolidinone
MTBE:	methyl *tert*-butyl ether
DMA:	*N*,*N*-dimethylacetamide
NBS:	*N*-bromosuccinimide
CAN:	ammonium cerium(IV) nitrate
dppf:	1,1'-*bis*(diphenylphosphino)ferrocene
dba:	dibenzylideneacetone
DMAP:	4-(dimethylamino)pyridine
PMBCl:	4-methoxybenzyl chloride
DIBAL:	diisobutylaluminum hydride
DAST:	(diethylamino)sulfur trifluoride
DBU:	1,8-diazabicyclo[5.4.0]undec-7-ene
AIBN:	2-2'-azobisisobutyronitrile
mCPBA:	3-chloroperbenzoic acid
DABCO:	diazabicyclo[2.2.2]octane
LDA:	lithium diisopropylamide
HOAt:	1-hydroxy-7-azabenzotriazole
LAH:	lithium aluminum hydride

AOP: 7-(azabenzotriazol-1-yloxy)*tris*(dimethylamino)phosphonium hexafluorophosphate

PyAOP: 7-(azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

DCM: dichloromethane

PE: petroleum ether

TMS: trimethylsilyl

Conc: concentrated

TIPS: triisopropylsilyl

OTf: trifluoromethanesulfonate

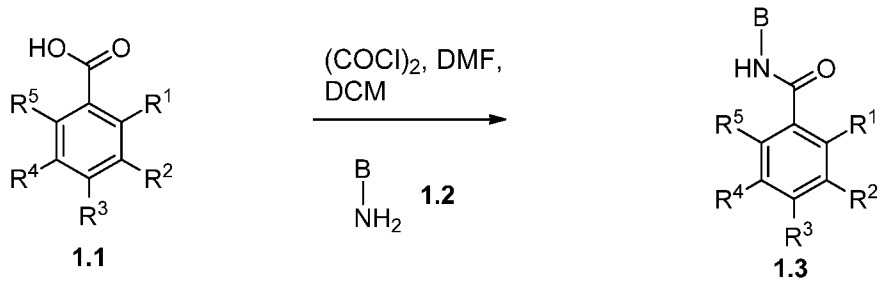
bis-pin: 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane

REACTION SCHEMES

The compounds of the present invention can be prepared readily according to the following Schemes and specific examples, or modifications thereof, using readily available starting materials, reagents and conventional synthetic procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art but are not mentioned in greater detail. The general procedures for making the compounds claimed in this invention can be readily understood and appreciated by one skilled in the art from viewing the following Schemes.

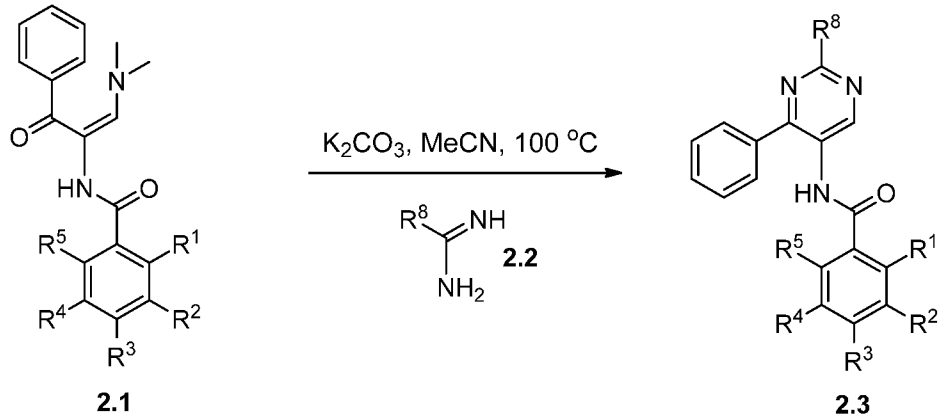
Scheme 1 illustrates a general strategy for preparing the compounds of the present invention in which an carboxylic acid intermediate (**1.1**) may be activated as an acid chloride (via treatment with $(COCl)_2$ or $POCl_3$) or anhydride, for example, followed by coupling to an amine (**1.2**) to give the desired product amide **1.3**. Various carboxylic acid intermediates, such as those described herein (*vide infra*), may be coupled to a variety of amines to give the compounds of the present invention. There are many known strategies for effecting such coupling chemistry, including use of coupling reagents, such as EDC with HOBT, PyBOP, HATU, CDI, AOP, PyAOP and the like.

SCHEME 1



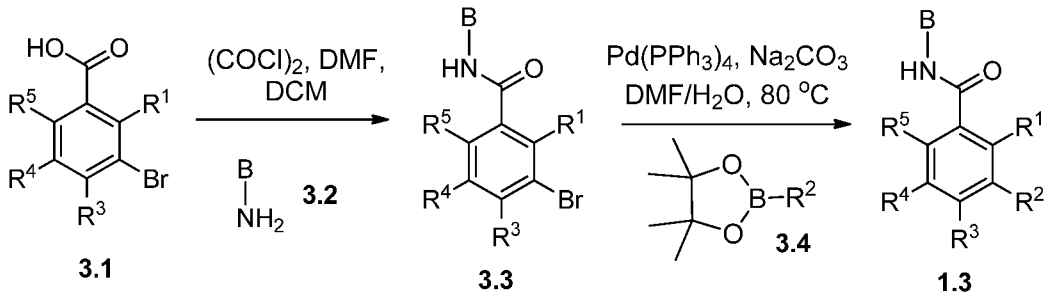
Alternatively, in cases where amine **1.2** is relatively unreactive, activation as the corresponding aluminum amide followed by reaction with an ester derivative of carboxylic acid **1.1**, may be a useful strategy to generate amides **1.3**. In some cases, various protecting group strategies familiar to one skilled in the art of organic synthesis may be employed to allow preparation of a particular compound of the present invention. This general approach may be successful for the preparation of a range of amide moieties, utilizing a variety of acids and amine intermediates.

SCHEME 2



Reaction Scheme 2 illustrates a method of preparing the compounds of the present invention in which a keto-enamine such as **2.1** is heated with amidine **2.2** in the presence of base to afford amide **2.3**.

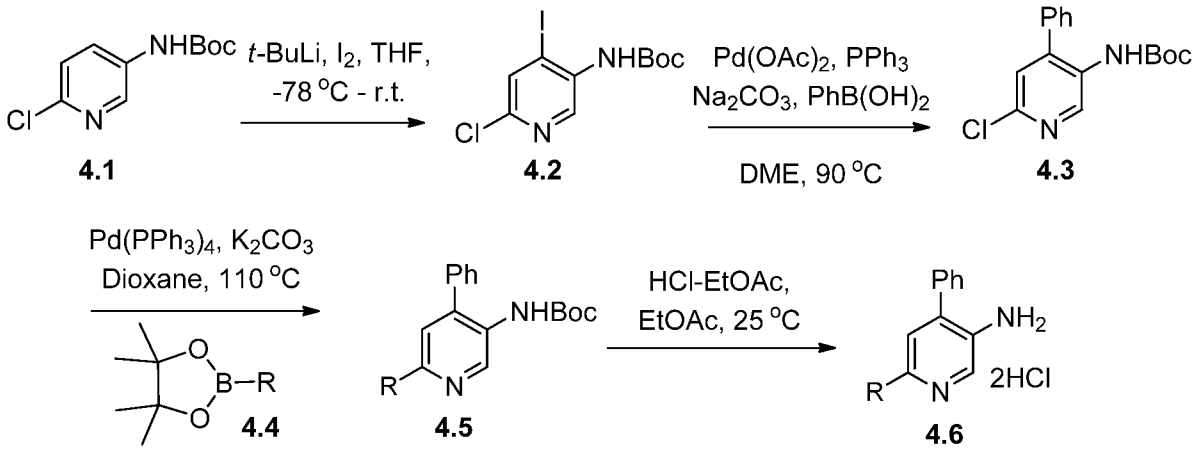
SCHEME 3



Reaction Scheme 3 illustrates a method of preparing the compounds of the present invention in which a carboxylic acid intermediate (**3.1**) may be activated as an acid chloride (via treatment with $(COCl)_2$ or $POCl_3$)) or anhydride, for example, and coupled to an amine (**3.2**) to give amide **3.3**. Cross-coupling of bromide **3.3** with an aryl or heteroarylboronic ester **3.4** (or other suitable intermediate) is mediated by heating in an aqueous solvent mixture in the presence of a suitable catalyst and base system (e.g., $Pd(PPh_3)_4$ and Na_2CO_3) to furnish amide **1.3**.

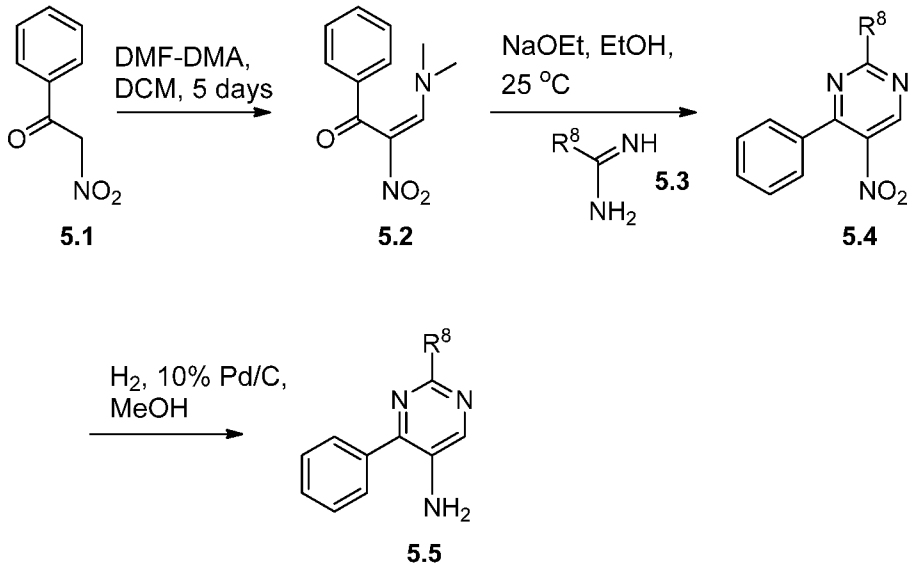
Reaction Scheme 4 through 6 illustrate the preparation of the intermediate amines of the type **1.2** which are used to prepare compounds of the invention as described above.

SCHEME 4



Reaction Scheme 4 illustrates the preparation of the intermediate amines of the type **4.6**. Pyridine **4.1** is lithiated with *t*-BuLi at low temperature followed exposure to iodine to afford iodide **4.2**. Selective cross-coupling of iodide **4.2** with phenylboronic acid (or other suitable intermediate) under Suzuki conditions in this case provides pyridine **4.3**. A subsequent cross-coupling reaction of **4.3** with an alkyl or arylboronic ester **4.4** (or other suitable intermediate) furnishes pyridine **4.5**. Removal of the Boc group is effected by exposure to HCl in EtOAc to afford amine **4.6**.

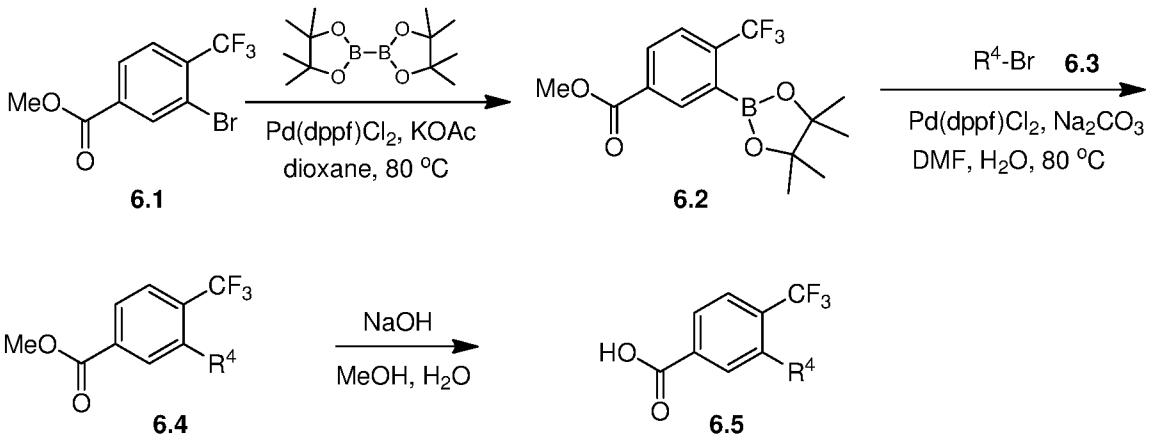
SCHEME 5



5.1 5.2 5.4 5.5

Reaction Scheme 5 illustrates the preparation of the intermediate amines of the type **5.5**. Benzoylnitromethane **5.1** is treated with *N,N*-dimethylformamide dimethylacetal to afford **5.2**. Conversion to pyrimidine **5.4** is effected by exposure of enamine **5.2** to amidine **5.3** in ethanol under basic conditions. The nitro group of **5.4** is reduced by H_2 in the presence of 10% Pd/C in MeOH to afford amine **5.5**.

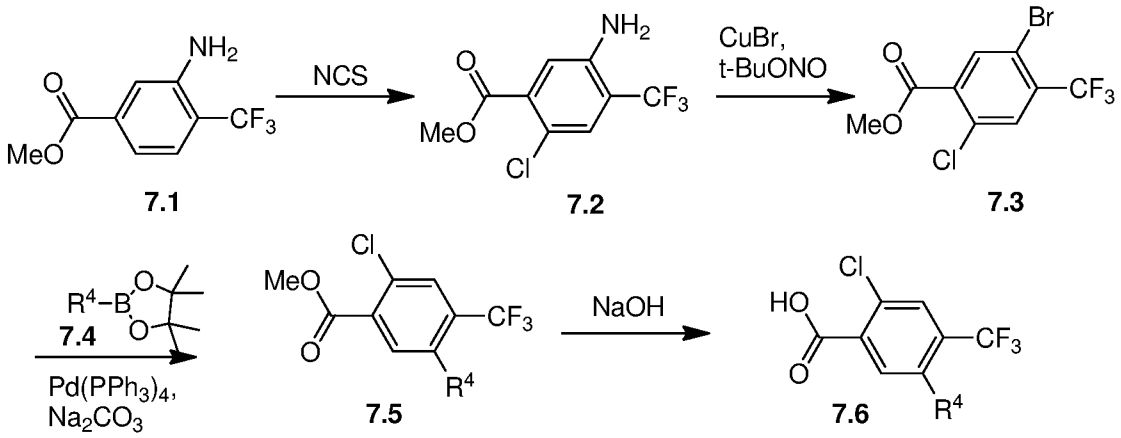
SCHEME 6



6.1 6.2 6.4 6.5

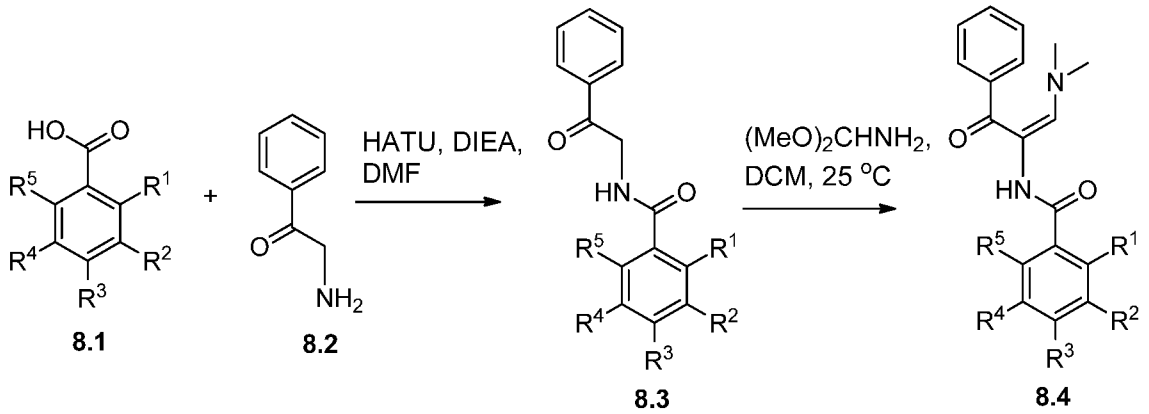
Reaction Scheme 6 illustrates the preparation of the intermediate acids of the type **6.5**. Bromide **6.1** is converted to the boronate ester with bis-pin in the presence of a suitable catalyst and base system to afford **6.2**. Palladium-catalyzed cross-coupling of the ester **6.2** with an aryl or heteroaryl bromide (**6.3**) furnishes ester **6.4**. Saponification of the ester then affords acid **6.5**.

SCHEME 7



Reaction Scheme 7 illustrates the preparation of the intermediate acids of the type **7.6**. Aniline **7.1** is treated with NCS to afford aryl chloride **7.2**, which is then converted to bromide **7.3** by exposure to *t*-butylnitrite and copper bromide. Cross-coupling of bromide **7.3** with an aryl or heteroboronic ester **7.4** (or other suitable intermediate) under Suzuki conditions provides ester **7.5**. Saponification of the ester then affords acid **7.6**.

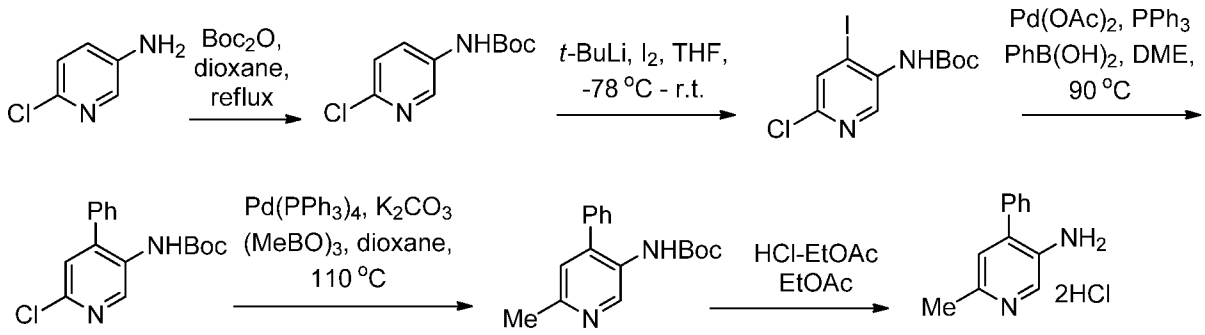
SCHEME 8



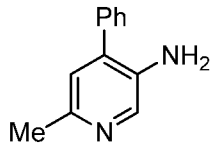
Reaction Scheme 8 illustrates the preparation of the intermediate enamines of the type **8.4** which are used to prepare compounds of the invention. Aminoacetophenone **8.2** is coupled with acid **8.1** under standard amide bond forming conditions (i.e. HATU, DIEA) to afford amide **8.3**. Ketoamide **8.3** is then treated with dimethylformamide dimethylacetal to afford enamine **8.4**.

Specific embodiments of the compounds of the invention, and methods of making them, are described in the Intermediates and Examples herein.

EXAMPLE OF SCHEME 4: INTERMEDIATE A1



INTERMEDIATE A1



6-Methyl-4-phenylpyridin-3-amine

Step A: *t*-Butyl (6-chloropyridin-3-yl)carbamate

A mixture of 6-chloropyridin-3-amine (58.0 g, 451 mmol) and Boc_2O (133 mL, 573 mmol) in dioxane (600 mL) was heated at 100 °C for 20 h. Additional Boc_2O (17 mL, 72 mmol) was added and the mixture was heated at 100 °C for 7 h. The mixture was cooled and concentrated, and the residue was partitioned between EtOAc (500 mL x 3) and water (500 mL). The combined organic layers were washed with brine (500 mL x 2), dried over Na_2SO_4 and concentrated. The residue was triturated with PE:EtOAc = 15 : 1 (400 mL x 3) and dried to give the title compound. MS: *m/z* = 223 (M + 1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 3.0 Hz, 1H), 7.95 (d, *J* = 6.3 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 6.73 (s, 1H), 1.51 (s, 9H).

Step B: *t*-Butyl (6-chloro-4-iodopyridin-3-yl)carbamate

t-Butyllithium (1.3 M in heptanes, 111 mL, 144 mmol) was added dropwise to a solution of *t*-butyl (6-chloropyridin-3-yl)carbamate (15.0 g, 65.6 mmol) in anhydrous THF (300 mL) at -78 °C over 30 min under N_2 atmosphere. The resulting mixture was stirred at -78 °C for 1 h, then at -10 °C for 1 h. The reaction mixture was cooled to -78 °C and a solution of I_2 (36.6 g, 144 mmol) in anhydrous THF (100 mL) was added. The resulting mixture was warmed to ambient temperature and stirred for 18 h. Excess *t*-butyllithium and I_2 were quenched with saturated aqueous NH_4Cl solution (150 mL) and saturated aqueous $Na_2S_2O_3$ solution (500 mL), respectively, and the resulting mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (250 mL x 2). The combined organic layers were washed with brine (250 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (EtOAc : PE : Et_3N = 2 : 98 : 1, then 2.5 : 97.5 :

1) to afford the title compound. MS: *m/z* = 355 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.72 (s, 1H), 6.64 (s, 1H), 1.53 (s, 9H).

Step C: *t*-Butyl (6-chloro-4-phenylpyridin-3-yl)carbamate

A deoxygenated mixture of *t*-butyl (6-chloro-4-iodopyridin-3-yl)carbamate (5.30 g, 14.9 mmol), phenylboronic acid (2.00 g, 16.4 mmol), $Pd(OAc)_2$ (0.168 g, 0.747 mmol), Ph_3P (0.392 g, 1.49 mmol), and aqueous Na_2CO_3 solution (2 M, 37.4 mL, 74.7 mmol) in DME (150 mL) was heated at 90 °C under N_2 atmosphere for 18 h. The mixture was cooled, silica gel (15 g) was added, and the resulting mixture was concentrated. The residue was purified by column chromatography on silica gel (PE : EtOAc : Et_3N = 95 : 5 : 1) to give the title compound. MS: *m/z* = 305 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.48-7.55 (m, 3H), 7.34-7.36 (m, 2H), 7.16 (s, 1H), 6.35 (s, 1H), 1.45 (s, 9H).

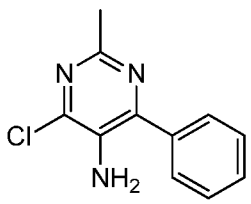
Step D: *t*-Butyl (6-methyl-4-phenylpyridin-3-yl)carbamate

A deoxygenated mixture of *t*-butyl (6-chloro-4-phenylpyridin-3-yl)carbamate (2.30 g, 7.55 mmol), $Pd(Ph_3P)_4$ (0.872 g, 0.755 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (3.79 g, 30.2 mmol), and K_2CO_3 (3.13 g, 22.6 mmol) in dioxane (30 mL) was heated at 110 °C under N_2 atmosphere for 18 h. The mixture was cooled and filtered through Celite®. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (PE : EtOAc : Et_3N = 90:10:1, then 80:20:1) to give the title compound. MS: *m/z* = 285 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.43-7.51 (m, 3H), 7.34-7.36 (m, 2H), 6.99 (s, 1H), 6.26 (s, 1H), 2.53 (s, 3H), 1.44 (s, 9H).

Step E: 6-Methyl-4-phenylpyridin-3-amine

A solution of HCl in EtOAc (4 M, 11.3 mL, 45.0 mmol) was added to a solution of *t*-butyl (6-methyl-4-phenylpyridin-3-yl)carbamate (1.28 g, 4.50 mmol) in EtOAc (15 mL). The resulting mixture was stirred at ambient temperature for 18 h, and then concentrated to give the title compound as an HCl salt. MS: *m/z* = 185 (M + 1).

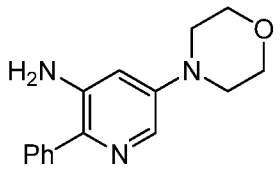
INTERMEDIATE A2



4-Chloro-2-methyl-6-phenylpyrimidin-5-amine

A deoxygenated mixture of 4,6-dichloro-2-methylpyrimidin-5-amine (536 mg, 3.01 mmol), phenylboronic acid (404 mg, 3.31 mmol), $Pd(Ph_3P)_4$ (174 mg, 0.151 mmol), and aqueous sodium carbonate solution (2 M, 3.0 mL, 6.0 mmol) in DMF (9 mL) was heated at 110 °C under microwave irradiation for 1 h. The mixture was cooled and partitioned between water (100 mL) and Et_2O (3 x 70 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (EtOAc:Hexanes = 0:100 to 50:50) to afford the title compound. MS: *m/z* = 220.2 (M + 1).

INTERMEDIATE A3



5-Morpholino-2-phenylpyridin-3-amine

Step A: 5-Chloro-3-*N'N*-diboc-amine-2-phenylpyridine

A mixture of 5-chloro-2-phenylpyridin-3-amine (3.0 g, 15 mmol), Boc_2O (3.5 g, 16 mmol), TEA (4.0 mL, 29 mmol), and DMAP (122 mg, 1.00 mmol) in DCM (50 mL) was heated at 30 °C for 16 h, and then concentrated. The residue was partitioned between DCM (100 mL) and water (30 mL x 2), and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc = 15:1) to give the title compound. MS: *m/z* = 405 (M + 1). ^{1}H NMR (400 MHz, DMSO) δ 8.72 (d, *J* = 2.4 Hz, 1H), 8.19 (d, *J* = 2.4 Hz, 1H), 7.49 (m, 5H), 1.41 (s, 18H).

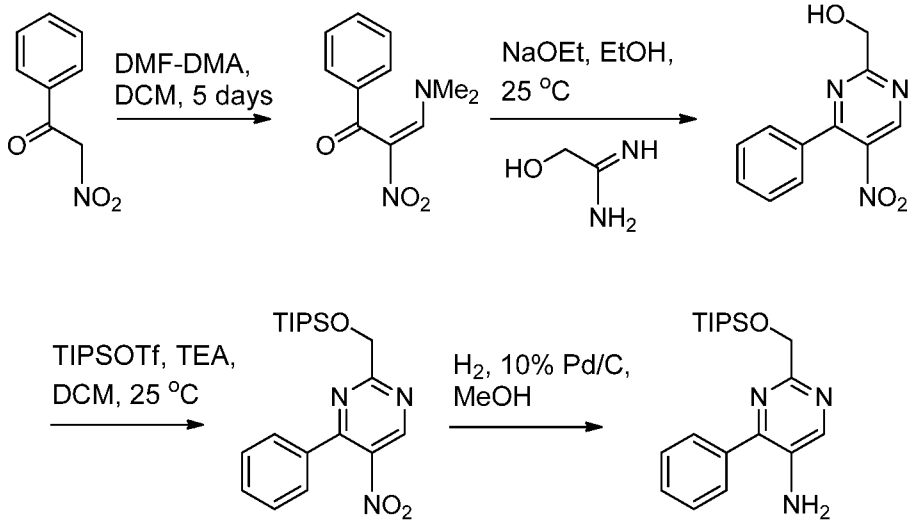
Step B: *t*-Butyl (5-morpholino-2-phenylpyridin-3-yl)carbamate

A deoxygenated mixture of 5-chloro-3-*N'N*-diboc-amine-2-phenylpyridine (2.0 g, 4.9 mmol), morpholine (0.435 mL, 5.00 mmol), *t*-BuONa (768 mg, 8.00 mmol) and $Pd_2(dba)_3$ (100 mg, 0.11 mmol) in dioxane (20 mL) was heated at 80 °C for 16 h, and then concentrated. The residue was partitioned between DCM and H_2O (50 mL x 3), and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (PE/EA = 3:1) to give the title compound. MS: *m/z* = 356 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.98 (d, *J* = 2.4 Hz, 1H), 7.52 (m, 5H), 7.44 (s, 1H), 3.87 (m, 4H), 3.29 (m, 4H) 1.47 (s, 9H).

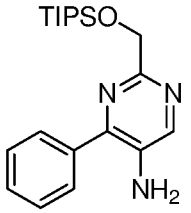
Step C: 5-Morpholino-2-phenylpyridin-3-amine

A solution of HCl in EtOAc (4 M, 5 mL, 20 mmol) was added to a solution of *t*-butyl (5-morpholino-2-phenylpyridin-3-yl)carbamate (160 mg, 0.40 mmol) in EtOAc (2 mL), and the resulting mixture was stirred at 25 °C for 2 h. The mixture was concentrated and the residue was partitioned between DCM (50 mL) and water (10 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (PE:EtOAc = 3:1) to give the title compound. MS: *m/z* = 256 (M + 1).

EXAMPLE OF SCHEME 5: INTERMEDIATE A4



INTERMEDIATE A4



4-Phenyl-2-(((triisopropylsilyl)oxy)methyl)pyrimidin-5-amine

Step A: 3-(Dimethylamino)-2-nitro-1-phenylprop-2-en-1-one

A suspension of benzoylnitromethane (1.00 g, 6.06 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (0.877 mL, 6.60 mmol) in DCM (12 mL) was stirred at ambient temperature for 5 days. The mixture was concentrated and the residue was purified by column chromatography on silica gel (EtOAc:Hexanes = 0:100 to 100:0) to yield the title compound. MS: *m/z* = 221.2 (M + 1).

Step B: (5-Nitro-4-phenylpyrimidin-2-yl)methanol

A mixture of 3-(dimethylamino)-2-nitro-1-phenylprop-2-en-1-one (2.99 g, 13.6 mmol), 2-hydroxyacetimidamide hydrochloride (1.95 g, 17.6 mmol), and sodium ethanolate (2.77 g, 40.7 mmol) in EtOH (27 mL) was stirred at ambient temperature for 3 h. The reaction mixture was partitioned between water (50 mL) and DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (EtOAc:Hexanes = 0:100 to 100:0) to yield the title compound. MS: *m/z* = 232.1 (M + 1).

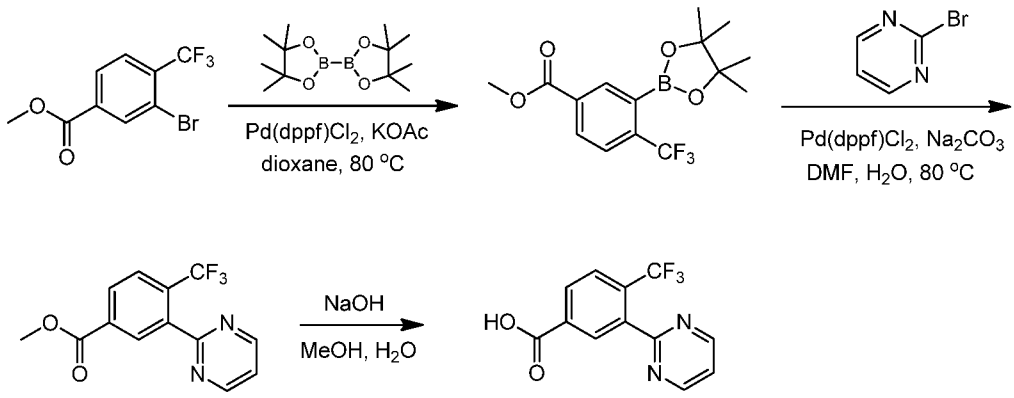
Step C: 5-Nitro-4-phenyl-2-(((triisopropylsilyl)oxy)methyl)pyrimidine

TIPSOTf (1.29 mL, 4.76 mmol) was added to a solution of (5-nitro-4-phenylpyrimidin-2-yl)methanol (1.00 g, 4.33 mmol) and TEA (1.21 mL, 8.65 mmol) in DCM (10 mL) and the resulting mixture was stirred at ambient temperature for 0.5 h. The reaction mixture was purified directly by column chromatography on silica gel (EtOAc:Hexanes = 0:100 to 30:70) to yield the title compound. MS: *m/z* = 388.3 (M + 1).

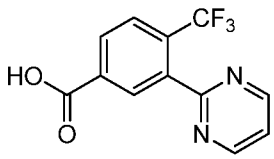
Step D: 4-Phenyl-2-(((triisopropylsilyl)oxy)methyl)pyrimidin-5-amine

To a solution of 5-nitro-4-phenyl-2-(((triisopropylsilyl)oxy)methyl)pyrimidine (117 mg, 0.302 mmol) in MeOH (3 mL) was added a slurry of 10% Pd/C (10 mg, 10 wt%) in EtOAc (~0.2 mL) and the resulting mixture was stirred under H_2 at ambient temperature for 3 h. The suspension was filtered through Celite®, washing with MeOH (0.5 mL), and the filtrate was concentrated to yield the title compound. MS: *m/z* = 358.3 (M + 1).

EXAMPLE OF SCHEME 6: INTERMEDIATE B1



INTERMEDIATE B1



3-(Pyrimidin-2-yl)-4-(trifluoromethyl)benzoyl chloride

Step A: Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)benzoate

To a deoxygenated mixture of methyl 3-bromo-4-(trifluoromethyl)benzoate (20.0 g, 70.7 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (26.9 g, 106 mmol) and potassium acetate (20.8 g, 212 mmol) in dioxane (300 mL) was added $PdCl_2$(dppf) (2.59 g, 3.50 mmol), and the resulting mixture was heated at 80 °C for 5 h. The mixture was cooled and filtered. The filtrate was concentrated and the residue was partitioned between water (100 mL) and EtOAc (200 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc = 15:1) to give the title compound. MS: *m/z* = 331 (M + 1).

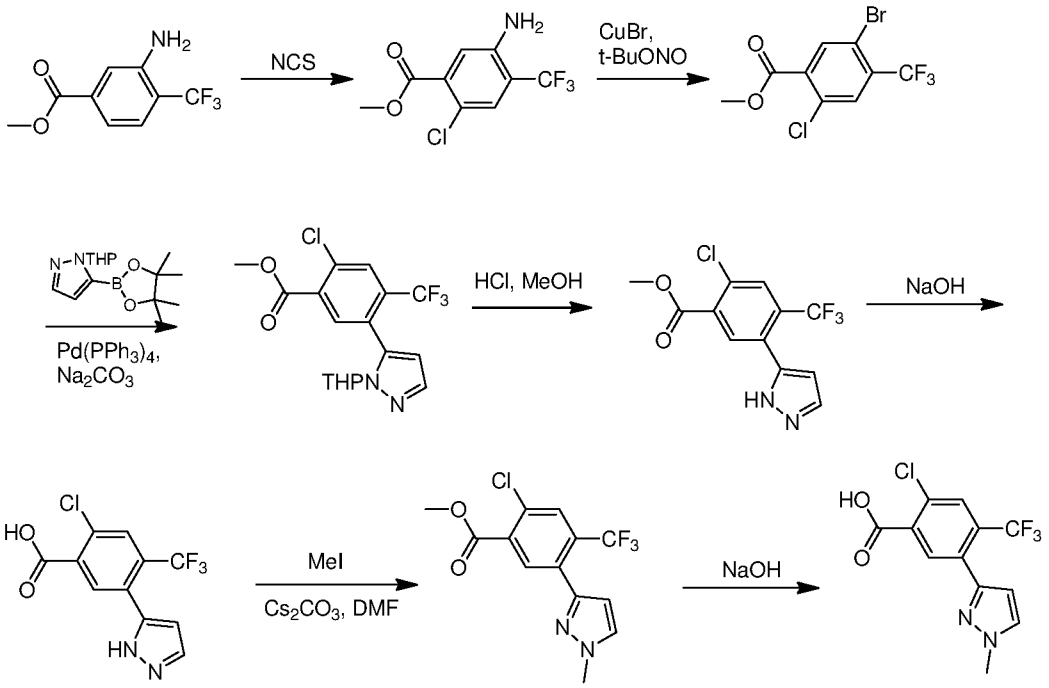
Step B: Methyl 3-(pyrimidin-2-yl)-4-(trifluoromethyl)benzoate

To a deoxygenated mixture of methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)benzoate (12.0 g, 36.4 mmol), 2-bromopyrimidine (8.67 g, 54.5 mmol) and sodium carbonate (11.6 g, 109 mmol) in DMF (450 mL) and water (60 mL) was added $PdCl_2$(dppf) (1.3 g, 1.8 mmol), and the resulting mixture was heated at 80 °C for 5 h. The mixture was cooled and filtered. The filtrate was concentrated and the residue was partitioned between water (100 mL) and EtOAc (200 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc = 5:1) to give the title compound. MS: *m/z* = 283 (M + 1).

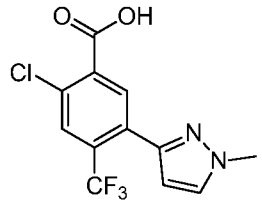
Step C: 3-(Pyrimidin-2-yl)-4-(trifluoromethyl)benzoic acid

A mixture of methyl 3-(pyrimidin-2-yl)-4-(trifluoromethyl)benzoate (7.0 g, 25 mmol) and NaOH (3.0 g, 74 mmol) in a 3:1 mixture of MeOH and H_2O (120 mL) was heated at 30 °C for 16 h. The reaction mixture was cooled and then partitioned between water (30 mL) and MTBE (2 x 60 mL). The aqueous layer was acidified to pH 4 with aqueous HCl solution (2 N). The precipitate was filtered, washed with water and dried to afford the title compound. MS: *m/z* = 269 (M + 1). ^{1}H NMR (400 MHz, MeOD) δ 8.92 (d, *J* = 5.0 Hz, 1H), 8.30 (m, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 4.9 Hz, 1H).

EXAMPLE OF SCHEME 7: INTERMEDIATE B2



INTERMEDIATE B2



2-Chloro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid

Step A: Methyl 5-amino-2-chloro-4-(trifluoromethyl)benzoate

N-Chlorosuccinimide (8.2 g, 61 mmol) was added to a solution of methyl 3-amino-4-(trifluoromethyl)benzoate (13.2 g, 60.0 mmol) in acetonitrile (200 mL), and the resulting mixture was heated at 80 °C for 20 h. After cooling, the mixture was partitioned between water (500 mL) and EtOAc (2 x 300 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc = 6:1) to afford the title compound. MS: *m/z* = 254 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.17 (s, 1H), 3.92 (s, 3H).

Step B: Methyl 5-bromo-2-chloro-4-(trifluoromethyl)benzoate

t-Butyl nitrite (4.60 g, 44.5 mmol) and methyl 5-amino-2-chloro-4-(trifluoromethyl)benzoate (4.50 g, 17.8 mmol) were added portionwise to a suspension of copper(I) bromide (5.10 g, 35.6 mmol) in DCM (100 mL). The resulting mixture was heated at 60 °C for 2 h. After cooling, the mixture was diluted with water (50 mL) and aqueous HCl solution (2 M, 50 mL) and then extracted with EtOAc (80 mL x 2). The combined organic

layers were washed with water (100 mL), then brine (80 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica (PE:EtOAc from 50:1 to 30:1) to afford the title compound. MS: *m/z* = 319 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.77 (s, 1H), 3.97 (s, 3H).

Step C: Methyl-2-chloro-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate

To a deoxygenated mixture of methyl 5-bromo-2-chloro-4-(trifluoromethyl)benzoate (4.6 g, 14 mmol), 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (4.86 g, 17.5 mmol) and Na_2CO_3 (4.0 g, 44 mmol) in DMF (150 mL) and H_2O (24 mL) was added $Pd(PPh_3)_4$ (686 mg, 0.58 mmol). The resulting mixture was heated at 80 °C for 5 h, then cooled and filtered. The filtrate was concentrated and the residue was partitioned between water (200 mL) and EtOAc (300 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 10/1) to give the title compound. MS: *m/z* = 389 (M + 1).

Step D: Methyl 2-chloro-5-(1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate

A solution of methyl-2-chloro-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-4- (trifluoromethyl)benzoate (2.5 g, 6.4 mmol) in a solution of HCl in MeOH (4 M, 50 mL) was stirred at 15 °C for 1 h and then concentrated to give the title compound. MS: *m/z* = 305 (M + 1)

Step E: 2-Chloro-5-(1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoic acid

A solution of NaOH (1.2 g, 0.030 mol) in H_2O (15 mL) was added to a solution of methyl 2-chloro-5-(1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate (2.3 g, 7.6 mmol) in MeOH (45 mL), and the resulting mixture was stirred at 15 °C for 16 h. The majority of the MeOH was removed under reduced pressure and the remaining aqueous mixture was partitioned between MTBE (50 mL) and water (50 mL). The aqueous layer was acidified to pH 5 with aqueous HCl solution (3 N). The precipitate was filtered, washed with water (50 mL x 2) and dried to give the title compound. MS: *m/z* = 291 (M + 1).

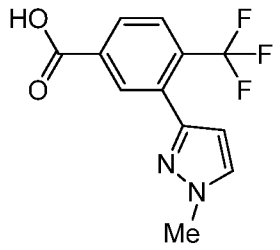
Step F: Methyl 2-chloro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoate and methyl 2-chloro-5-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate

A mixture of 2-chloro-5-(1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoic acid (500 mg, 1.72 mmol), Cs_2CO_3 (1.7 g, 5.2 mmol) and iodomethane (0.54 mL, 8.6 mmol) in DMF (15 mL) was heated at 80 °C for 2 h. The reaction mixture was cooled and filtered, and the filtrate was concentrated. The residue was partitioned between water (50 mL) and EtOAc (30 mL x 3). The combined organic layers were washed with H_2O (50 mL x 3), then brine (50 mL), dried over Na_2SO_4 and concentrated to give the title compound. MS: *m/z* = 319 (M + 1).

Step G: 2-Chloro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid

A solution of NaOH (414 mg, 10.4 mmol) in H_2O (5 mL) was added to a mixture of methyl 2-chloro-5-(1-methyl-1H-pyrazol- 3-yl)-4-(trifluoromethyl)benzoate and methyl 2-chloro-5-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate (550 mg, 3.5 mmol) in MeOH (15 mL). The resulting mixture was stirred at 15 °C for 16 h. The majority of the MeOH was removed under reduced pressure and the resulting aqueous solution was partitioned between MTBE (30 mL) and water (30 mL). The aqueous layer was acidified to pH 4 with an aqueous HCl solution (3 N). The resulting suspension was then extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was re-crystallized from MeOH (1g/5 mL) to give the title compound. MS: *m/z* = 305 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.86 (s, 1H), 7.48 (d, *J* = 2.3 Hz, 1H), 6.59 (s, 1H), 4.15 (s, 3H).

INTERMEDIATE B3



3-(1-Methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid

Step A: 4-Bromo-3-nitrobenzoic acid

4-Bromobenzoic acid (100 g, 0.5 mol) was added portionwise to aqueous HNO_3 solution (16 M, 200 mL), keeping the temperature between 0 and 25 °C, followed by the dropwise addition of aqueous H_2SO_4 solution (18 M, 240 mL) at ambient temperature. The resulting mixture was stirred at ambient temperature for 4 h, and then carefully diluted with 1.5 L of water. The precipitate was filtered, washed with water, and dried to give the title compound. MS: *m/z* = 246.0, 248.0 (M + 1). ^{1}H NMR (400 MHz, DMSO) δ 8.42 (s, 1H), 8.04 (s, 2H).

Step B: Methyl 4-bromo-3-nitrobenzoate

To a solution of 4-bromo-3-nitrobenzoic acid (115 g, 47.0 mmol) in MeOH (600 mL) was added aqueous H_2SO_4 solution (18 M, 200 mL) at ambient temperature. The mixture was heated at reflux for 2 h, and then cooled and filtered. The filtered solid was washed with water and dried to give the title compound. MS: *m/z* = 260, 262 (M + 1). ^{1}H NMR (400 MHz, DMSO) δ 8.48 (s, 3H), 8.09 (s, 2H), 3.91 (s, 3H).

Step C: Methyl 3-nitro-4-(trifluoromethyl)benzoate

To a solution of methyl 4-bromo-3-nitrobenzoate (175 g, 0.670 mol) in anhydrous DMF (1.0 L) was added CuI (140 g, 0.73 mol) under N_2 atmosphere. After stirring at ambient temperature for 10 min, $FSO_2CF_2CO_2CH_3$ (185 mL, 0.730 mol) was added and the vented mixture was heated at 110 °C for 3 h until gas evolution ceased. The mixture was then cooled and filtered through Celite®, washing with EtOAc. The filtrate was concentrated and the residue was partitioned between water (400 mL) and MTBE. The organic layer was washed with water, then brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was recrystallized from DCM/MeOH (5/1) to give the title compound. The mother liquor was concentrated and the residue purified by silica gel column chromatography (PE/EtOAc = 20/1) to give additional title compound. MS: *m/z* = 250.0 (M + 1). ^{1}H NMR (400 MHz, DMSO) δ 8.55 (br s, 1H), 8.39 (d, *J* = 7.5 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 3.88-3.99 (m, 3H).

Step D: Methyl 3-amino-4-(trifluoromethyl)benzoate

A solution of methyl 3-nitro-4-(trifluoromethyl)benzoate (102 g, 0.410 mol) and 10% Pd/C (10 g, 10 wt %) in MeOH (1.0 L) was stirred under H_2 (35 psi) at 30 °C for 12 h. The suspension was filtered through Celite®, washing with MeOH (30 mL x 3). The filtrate was concentrated to give the title compound. MS: *m/z* = 220.0 (M + 1). ^{1}H NMR (400 MHz, DMSO) δ 7.40-7.50 (m, 2H), 7.09-7.15 (m, 1H), 5.92 (s, 2H), 3.82 (s, 3H).

Step E: Methyl 3-bromo-4-(trifluoromethyl)benzoate

Methyl 3-amino-4-(trifluoromethyl)benzoate (40 g, 180 mmol) was added portionwise to a suspension of CuBr (53.0 g, 365 mmol) and *t*-BuONO (47 g, 460 mmol) in acetonitrile (600 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h, and then warmed to 25 °C and stirred for 16 h. The mixture was partitioned between EtOAc and aqueous HCl solution (1 M, 200 mL x 4). The organic layer was washed with brine (200 mL), dried over Na_2SO_4 and concentrated.

The residue was purified by column chromatography on silica gel (PE/EtOAc = 200/1) to afford the title compound. MS: *m/z* = 283, 285 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 3.97 (s, 3H).

Step F: Methyl 3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-4-(trifluoromethyl) benzoate

A deoxygenated mixture of methyl 3-bromo-4-(trifluoromethyl)benzoate (5.0 g, 17 mmol), 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (5.9 g, 21 mmol), $Pd(PPh_3)_4$ (0.80 g, 0.69 mmol), and aqueous Na_2CO_3 solution (2 M, 26 mL, 53 mmol) in DMF (150 mL) was heated at 70 °C under N_2 for 2 h. The mixture was concentrated and the residue was partitioned between EtOAc (200 mL) and water (100 mL). The organic layer was washed with brine (100 mL), then dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 10/1) to give the title compound. MS: *m/z* = 355.0 (M + 1). ^{1}H NMR (400 MHz, DMSO) δ 8.37 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 3.97 (s, 3H).

Step G: Methyl 3-(1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate

To a solution of methyl 3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate (5.0 g, 14 mmol) in MeOH (100 mL) was added a solution of HCl in MeOH (40 mL, 4 M). The mixture was stirred at 10 °C for 0.5 h, then concentrated to give the title compound. MS: *m/z* = 271.0 (M + 1).

Step H: Methyl 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoate and methyl 3-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate

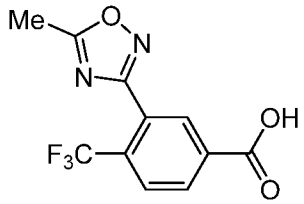
To a solution of methyl 3-(1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate (7.0 g, 26 mmol) in DMF (150 mL) was added Cs_2CO_3 (17 g, 52 mmol) and CH_3I (4.8 mL, 78 mmol). The reaction mixture was heated at 80 °C for 2 h, then cooled and concentrated. The residue was partitioned between water (150 mL) and EtOAc (100 mL x 3). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4 and concentrated to give a mixture of methyl 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoate and methyl 3-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate. MS: *m/z* = 285.0 (M + 1).

Step I: 3-(1-Methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid

To a solution of methyl 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoate and methyl 3-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate

(6.5 g, 23 mmol) in MeOH (100 mL) was added aqueous NaOH solution (35 mL, 2 M). The mixture was heated at 50 °C for 50 min, then cooled. The majority of the MeOH was removed under reduced pressure and the resulting aqueous solution was partitioned between EtOAc (100 mL) and water (150 mL). The aqueous layer was acidified to pH 5 with aqueous HCl solution (1 N) and then further extracted with EtOAc (150 mL x 2). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by recrystallization from MeOH (1g/5 mL) to provide the title compound. MS: *m/z* = 271.0 (M + 1). ^{1}H NMR (400 MHz, DMSO) δ 13.43-13.68 (m, 1H) 8.18-8.24 (m, 1H), 8.05-8.12 (m, 1H), 7.92-7.99 (m, 1H), 7.77-7.84 (m, 1H), 6.43-6.52 (m, 1H), 3.93 (s, 3H).

INTERMEDIATE B4



3-(5-Methyl-1,2,4-oxadiazol-3-yl)-4-(trifluoromethyl)benzoic acid

Step A: Methyl 3-cyano-4-(trifluoromethyl)benzoate

To a mixture of methyl 3-amino-4-(trifluoromethyl)benzoate (15 g, 0.073 mol) and aqueous HCl solution (12 M, 24 mL) in H_2O (100 mL) at 0 °C was added dropwise a solution of $NaNO_2$ (5.5 g, 0.080 mol) in H_2O (30 mL). The reaction was stirred at 0 °C for 30 min and then added dropwise to a slurry of CuCN (7.1 g, 0.080 mol) and KCN (8.4 g, 0.13 mol) in H_2O (200 mL), while maintaining the internal temperature between 5-10 °C. After the addition was complete, the reaction was heated at 80 °C for 1 h. The mixture was cooled and the solution was extracted with EtOAc (200 mL x 4). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (2% EtOAc in PE) to afford the title compound. MS: *m/z* = 230.0 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46-8.53 (m, 1H), 8.33-8.42 (m, 1H), 7.87-7.95 (m, 1H), 4.01 (s, 3H).

Step B: Methyl 3-(N'-hydroxycarbamimidoyl)-4-(trifluoromethyl)benzoate

To a mixture of methyl 3-cyano-4-(trifluoromethyl)benzoate (1.6 g, 7.0 mmol) and hydroxylamine hydrochloride (0.98 g, 14 mmol) in MeOH (20 mL) was added $NaHCO_3$ (2.3 g, 28 mmol). The resulting mixture was heated at 85 °C for 5 h, then cooled and concentrated. The residue was purified by column chromatography on silica gel (40% EtOAc in PE) to afford

the title compound. MS: *m/z* = 263.0 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.18-8.21 (d, *J* = 8.4 Hz, 1H), 7.80-7.83 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 4.89 (s, 2H), 3.96 (s, 3H).

Step C: Methyl 3-(N-acetyl-N'-hydroxycarbamimidoyl)-4-(trifluoromethyl) benzoate

To a solution of methyl 3-(N'-hydroxycarbamimidoyl)-4-(trifluoromethyl) benzoate (282 mg, 1.07 mmol) and TEA (0.30 mL, 2.14 mmol) in anhydrous DCM (20 mL) at 25 °C was added AcCl (0.083 mL, 1.18 mmol). The resulting mixture was heated at 30 °C for 20 min, then cooled and concentrated to give the title compound. MS: *m/z* = 305.0 (M + 1).

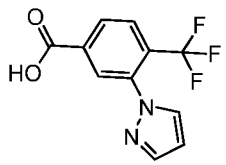
Step D: Methyl 3-(5-methyl-1,2,4-oxadiazol-3-yl)-4-(trifluoromethyl)benzoate

A solution of methyl 3-(N-acetyl-N'-hydroxycarbamimidoyl)-4-(trifluoromethyl) benzoate (0.28 g, 0.93 mmol) in toluene (10 mL) was heated at 110 °C for 2 h, then cooled and concentrated. The residue was purified by column chromatography on silica gel (30% EtOAc in PE) to afford the title compound. MS: *m/z* = 287.0 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37-8.49 (m, 1H), 8.22-8.32 (m, 1H), 7.87-7.99 (m, 1H), 3.96 (s, 3H), 2.70 (s, 3H).

Step E: 3-(5-Methyl-1,2,4-oxadiazol-3-yl)-4-(trifluoromethyl)benzoic acid

To a solution of methyl 3-(5-methyl-1,2,4-oxadiazol-3-yl)-4-(trifluoromethyl) benzoate (0.13 g, 0.45 mmol) in MeOH (2.0 mL) was added aqueous NaOH solution (2.0 mL, 1 M). The resulting mixture was heated at 50 °C for 1 h, and then cooled and acidified to pH 5 with aqueous HCl solution (1 M). The aqueous mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give the title compound. MS: *m/z* = 273.0 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 2.69 (s, 3H).

INTERMEDIATE B5



3-(1H-Pyrazol-1-yl)-4-(trifluoromethyl)benzoic acid

Step A: Methyl 3-(1H-pyrazol-1-yl)-4-(trifluoromethyl)benzoate

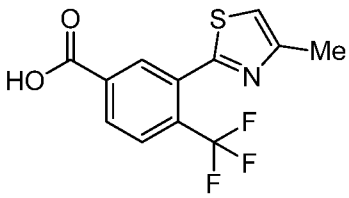
A mixture of methyl 3-bromo-4-(trifluoromethyl)benzoate (0.50 g, 1.8 mmol), pyrazole (0.18 g, 2.6 mmol), Cs_2CO_3 (1.4 g, 4.4 mmol), CuI (670 mg, 3.52 mmol) and 1,10-phenanthroline (0.13 g, 0.70 mmol) in anhydrous toluene (15 mL) was heated at 140 °C for 1 h under microwave irradiation. After cooling, the reaction mixture was diluted with EtOAc (50

mL) and filtered. The filtrate was concentrated and the residue was purified by preparative TLC (PE/EA = 5/1) to give the title compound. MS: *m/z* = 271.0 (M + 1).

Step B: 3-(1H-Pyrazol-1-yl)-4-(trifluoromethyl)benzoic acid

To a solution of methyl 3-(1H-pyrazol-1-yl)-4-(trifluoromethyl)benzoate (0.20 g, 0.74 mmol) in MeOH (15 mL) was added aqueous NaOH solution (3.0 mL, 2 M). The mixture was heated at 50 °C for 10 min. The majority of the MeOH was removed under reduced pressure and the resulting aqueous solution was partitioned between EtOAc (30 mL) and water (20 mL). The aqueous layer was acidified to pH 5 with aqueous HCl solution (1 M) and then extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated to give the title compound. MS: *m/z* = 257.0 (M + 1). ^{1}H NMR (400 MHz, DMSO) δ 8.19 (m, 1H), 8.13 (m, 1H), 8.07 (m, 1H), 7.97 (m, 1H), 7.78 (m, 1H), 6.55 (m, 1H).

INTERMEDIATE B6



3-(4-Methylthiazol-2-yl)-4-(trifluoromethyl)benzoic acid

Step A: 3-Amino-4-(trifluoromethyl)benzoic acid

A mixture of 3-nitro-4-(trifluoromethyl)benzoic acid (1.0 g, 4.3 mmol) and 10% Pd/C (0.20 g, 5% wt) in MeOH (20 mL) was stirred under H_2 atmosphere (15 psi) at ambient temperature for 12 h. The catalyst was filtered and the filtrate concentrated to afford the title compound. MS: *m/z* = 206.0 (M + 1). ^{1}H NMR (400 MHz, DMSO) δ 7.46 (s, 1H), 7.38-7.45 (m, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 5.84 (s, 2H).

Step B: Methyl 3-amino-4-(trifluoromethyl)benzoate

A mixture of 3-amino-4-(trifluoromethyl)benzoic acid (3.4 g, 16 mmol) and aqueous H_2SO_4 solution (18 M, 2.0 mL) in MeOH (20 mL) was heated at reflux until the starting material was consumed. The mixture was cooled, then neutralized to pH 7 by the addition of aqueous NaOH solution (1N). The aqueous mixture was extracted with EtOAc (10 mL × 3), and the combined organic combined layers were washed with brine, dried over Na_2SO_4 and concentrated to afford the title compound. MS: *m/z* = 220.0 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.52 (m, 1H), 7.42 (s, 2H), 4.30 (br s, 2H), 3.92 (s, 3H).

Step C: Methyl 3-cyano-4-(trifluoromethyl)benzoate

To a mixture of methyl 3-amino-4-(trifluoromethyl)benzoate (3.2 g, 15 mmol) and aqueous HCl solution (12 M, 3.5 mL) in water (20 mL) was added dropwise a solution of $NaNO_2$ (1.2 g, 17 mmol) in water (7.0 mL) at 5 °C. The resulting mixture was stirred for 30 min at 5 °C and then added dropwise to a slurry of CuCN (1.3 g, 15 mmol) and KCN (1.6 g, 25 mmol) in water (4 mL), while maintaining the internal temperature between 5-10 °C. The mixture was stirred at 10 °C for 30 min and then heated at 80 °C for 1 h. After cooling, the mixture was extracted with DCM (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to afford the title compound. MS: *m/z* = 230 (M +1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45-8.53 (m, 1H), 8.33-8.40 (m, 1H), 7.91 (d, 1H, *J* = 8.5 Hz), 4.01 (s, 3H).

Step D: Methyl 3-carbamothioyl-4-(trifluoromethyl)benzoate

H_2S gas was bubbled through a solution of methyl 3-cyano-4-(trifluoromethyl)benzoate (0.10 g, 0.61 mmol) and TEA (0.20 mL, 1.4 mmol) in pyridine (10 mL) at ambient temperature for 30 min. The mixture was concentrated, and the residue was partitioned between water and EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc = 5:1) to afford the title compound. MS: *m/z* = 264.0 (M +1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.31 (m, 1H), 8.09-8.17 (m, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 4.45-4.68 (m, 2H), 3.96 (s, 3H).

Step E: Methyl 3-(4-hydroxy-4-methyl-4,5-dihydrothiazol-2-yl)-4-(trifluoromethyl)benzoate

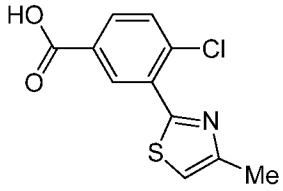
A mixture of methyl 3-carbamothioyl-4-(trifluoromethyl)benzoate (100 mg, 0.38 mmol), TEA (0.20 mL, 1.4 mmol) and 1-chloropropan-2-one (0.033 mL, 0.42 mmol) in DMF (3.0 mL) was heated at 120 °C for 4 h, then concentrated. The residue was partitioned between water and EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE:EA = 3:1) to afford the title compound. MS: *m/z* = 320.0 (M +1).

Step F: 3-(4-Methylthiazol-2-yl)-4-(trifluoromethyl)benzoic acid

A solution of methyl 3-(4-hydroxy-4-methyl-4,5-dihydrothiazol-2-yl)-4-(trifluoromethyl)-benzoate in aqueous NaOH solution (1 M, 10 mL) was stirred at ambient

temperature for 8 h. The mixture was acidified to pH 5 with aqueous HCl solution (1 M), then extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated to afford the title compound. MS: *m/z* = 288.0 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23-8.34 (m, 1H), 8.06-8.17 (m, 1H), 7.68-7.83 (m, 1H), 6.97-7.10 (m, 1H), 2.50 (s, 3H).

INTERMEDIATE B7



4-Chloro-3-(4-methylthiazol-2-yl)benzoic acid

Step A: Methyl 4-chloro-3-cyanobenzoate

To a mixture of methyl 3-amino-4-chlorobenzoate (10 g, 54 mmol) and aqueous HCl solution (12 M, 15 mL) in water (80 mL) at 0 °C was added dropwise a solution of $NaNO_2$ (4.5 g, 60 mmol) in water (18 mL) at 0 °C. The reaction was stirred for 30 min at 0 °C and then added dropwise to a slurry of CuCN (4.9 g, 54 mmol) and KCN (6.0 g, 92 mmol) in water (40 mL), while maintaining the temperature between 5-10 °C. The reaction mixture was stirred at 10 °C for 30 min and then heated at 80 °C for 1 h. After cooling, the mixture was extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated to afford the title compound. MS: *m/z* = 196.0 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 2.0 Hz, 1H), 8.17-8.20 (m, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 3.96 (s, 3H).

Step B: Methyl 3-carbamothioyl-4-chlorobenzoate

H_2S gas was bubbled through a solution of methyl 4-chloro-3-cyanobenzoate (3.0 g, 15 mmol) and TEA (2.13 mL, 15.3 mmol) in pyridine (15 mL) at ambient temperature for 1 h. The reaction mixture was concentrated and the residue was purified by column chromatography (PE:EtOAc = 10:1) to give the title compound. MS: *m/z* = 230.0 (M +1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 1.6 Hz, 1H), 7.95-7.97 (m, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.26 (s, 1H), 3.92 (s, 3H).

Step C: Methyl 4-chloro-3-(4-methylthiazol-2-yl)benzoate

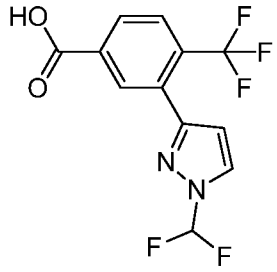
A mixture of methyl 3-carbamothioyl-4-(trifluoromethyl)benzoate (1.0 g, 4.3 mmol), TEA (0.20 mL, 1.4 mmol) and 1-chloropropan-2-one (0.80 g, 8.6 mmol) in DMF (10 mL) was heated at 120 °C for 4 h, then concentrated. The residue was partitioned between water and EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4

and concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc = 3:1) to afford the title compound. MS: *m/z* = 268.0 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 2.0 Hz, 1H), 7.97-8.00 (m, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.09 (s, 1H), 3.92 (s, 3H), 2.56 (s, 3H).

Step D: 4-Chloro-3-(4-methylthiazol-2-yl)benzoic acid

A mixture of methyl 4-chloro-3-(4-methylthiazol-2-yl)benzoate (0.40 g, 2.0 mmol) in aqueous NaOH solution (1 M, 10 mL) was stirred at ambient temperature for 8 h. The mixture was acidified to pH 5 with aqueous HCl solution (2 M) and then extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated to afford the title compound. MS: *m/z* = 254.0 (M + 1).

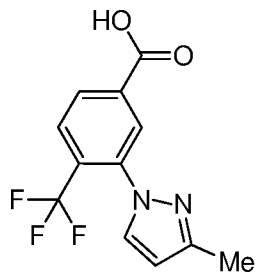
INTERMEDIATE B8



3-(1-(Difluoromethyl)-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid

A solution of methyl 3-(1*H*-pyrazol-5-yl)-4-(trifluoromethyl)benzoate (50 mg, 0.18 mmol), sodium chlorodifluoroacetate (34 mg, 0.22 mmol), and 18-crown-6 (9.8 mg, 0.037 mmol) in acetonitrile (1 mL) was heated at reflux for 40 h. Additional sodium chlorodifluoroacetate (34 mg, 0.22 mmol) was added after 18 and 22 h. The reaction mixture was cooled to ambient temperature and aqueous NaOH solution (10 M, 0.056 mL, 0.55 mmol) was added. The resulting mixture was heated at 50 °C for 2 h. The mixture was cooled and then filtered, washing with acetonitrile (1 mL) and DMF (1 mL). The filtrate was purified by reverse-phase HPLC (5-95% acetonitrile + 0.1% trifluoroacetic acid in water) to provide the title compound. MS: *m/z* = 307.0 (M + 1).

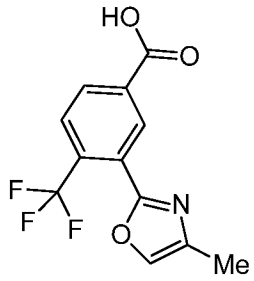
INTERMEDIATE B9



3-(3-Methyl-1*H*-pyrazol-1-yl)-4-(trifluoromethyl)benzoic acid

A deoxygenated solution of 3-methyl-1*H*-pyrazole (0.120 mL, 1.49 mmol), 3-bromo-4-(trifluoromethyl)benzoic acid (0.20 g, 0.74 mmol), copper(I) iodide (28 mg, 0.15 mmol), cesium carbonate (0.48 g, 1.5 mmol), and *trans*-*N*,*N*'-dimethylcyclohexane-1,2-diamine (0.023 mL, 0.15 mmol) in dioxane (1.0 mL) was heated at reflux for 18 h. The mixture was cooled and filtered, washing with DMF (1.5 mL). The filtrate was purified by reverse-phase HPLC (5-95% acetonitrile + 0.1% trifluoroacetic acid in water) to afford the title compound. MS: *m*/*z* = 271.0 (M + 1).

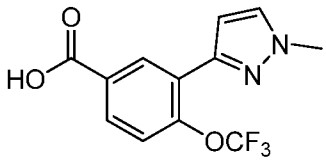
INTERMEDIATE B10



3-(4-Methyloxazol-2-yl)-4-(trifluoromethyl)benzoic acid

A deoxygenated mixture of 3-bromo-4-(trifluoromethyl)benzoic acid (100 mg, 0.372 mmol), 4-methyloxazole (0.061 mL, 0.74 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butyl ether adduct (15.4 mg, 0.019 mmol), and sodium *tert*-butoxide (107 mg, 1.12 mmol) in DMA (1.5 mL) was heated under microwave irradiation at 110 °C for 18 h. The mixture was cooled and filtered, and the filtrate was purified by reverse-phase HPLC (C18 column, H_2O:CH_3CN:CF_3CO_2H = 95:5:0.1 to 5:95:0.1) to give the title compound. MS: *m*/*z* = 272.0 (M + 1).

INTERMEDIATE B11



3-(1-Methyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzoic acid

Step A: 3-Nitro-4-(trifluoromethoxy)benzoic acid

4-(Trifluoromethoxy)benzoic acid (37.4 g, 0.181 mol) was added portionwise to an aqueous HNO_3 solution (15 M, 75 mL) at 25 °C. Aqueous H_2SO_4 solution (18 M, 90 mL) was added and the resulting mixture was stirred for 18 h. The reaction mixture was carefully

diluted with water (300 mL) and the precipitate was filtered, washed with water, and dried to give the title compound. MS: *m/z* = 252 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H).

Step B: Methyl 3-nitro-4-(trifluoromethoxy)benzoate

Aqueous H_2SO_4 solution (18 M, 60 mL) was added dropwise to a solution of 3-nitro-4-(trifluoromethoxy)benzoic acid (33.5 g, 0.135 mol) in MeOH (400 mL) at 0 °C. The resulting mixture was heated at 80 °C for 2 h, then cooled and concentrated. The residue was diluted with EtOAc, and washed with water (100 mL x 3), aqueous $NaHCO_3$ solution (100 mL x 3), and brine. The organic layer was dried over Na_2SO_4 and concentrated to give the title compound. MS: *m/z*: 266 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H).

Step C: Methyl 3-amino-4-(trifluoromethoxy)benzoate

A mixture of methyl 3-nitro-4-(trifluoromethoxy)benzoate (14 g, 0.053 mol) and 10% Pd/C (1.0 g, 10 wt%) in MeOH (200 mL) was stirred under H_2 (50 psi) at 15 °C for 24 h. The suspension was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc = 5:1) to give the title compound. MS: *m/z* = 236 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6) 7.47 (d, *J* = 2.0 Hz, 1H), 7.19 - 7.25 (m, 1H), 7.11 - 7.17 (m, 1H), 5.71 (s, 2H), 3.82 (s, 3H).

Step D: Methyl 3-bromo-4-(trifluoromethoxy)benzoate

A mixture of CuBr (5.0 g, 34 mmol) and *t*-BuONO (5.0 g, 43 mmol) in MeCN (60 mL) was stirred at 0 °C for 15 min, and then methyl 3-amino-4-(trifluoromethoxy)benzoate (4.0 g, 17 mmol) was added. The resulting mixture was stirred at 0 °C for 2 h, and then stirred at 15 °C for 16 h. The mixture was filtered and the filter cake was washed with EtOAc. The filtrate was washed with aqueous HCl solution (1N), water, and then brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc = 20:1) to give the title compound. MS: *m/z* = 298/300 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6) 8.14 (d, *J* = 2.0 Hz, 1H), 7.96 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.55 (dd, *J* = 8.7, 1.1 Hz, 1H), 3.84 (s, 3H).

Step E: Methyl 3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-4-(trifluoro-methoxy)benzoate

A deoxygenated mixture of methyl 3-bromo-4-(trifluoromethoxy)benzoate (500 mg, 1.67 mmol), 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-

1H-pyrazole (510 mg, 1.84 mmol), $Pd(PPh_3)_4$ (50 mg, 0.05 mmol), and Na_2CO_3 (530 mg, 5.0 mmol) in DMF (5 mL) was heated at 100 °C under N_2 atmosphere for 16 h. The reaction mixture was cooled and then partitioned between water (15 mL) and EtOAc (15 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (PE:EtOAc = 3:1) to give the title compound. MS: *m/z* = 371 (M + 1).

Step F: Methyl 3-(1H-pyrazol-5-yl)-4-(trifluoromethoxy)benzoate

A solution of HCl in EtOAc (4 M, 10 mL, 40 mmol) was added to a solution of methyl 3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-4-(trifluoromethoxy)benzoate (300 mg, 1.1 mmol) in EtOAc (2 mL). The resulting mixture was stirred at 15 °C for 1 h and then concentrated to give the title compound. MS: *m/z* = 287 (M + 1).

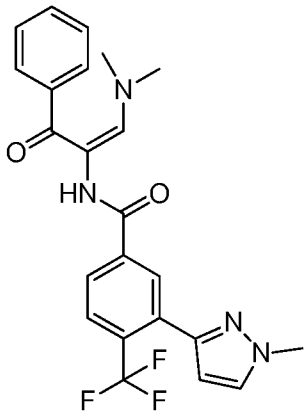
Step G: Methyl 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzoate

A mixture of methyl 3-(1H-pyrazol-5-yl)-4-(trifluoromethoxy)benzoate (220 mg, 0.81 mmol), CH_3I (0.292 mL, 4.00 mmol), and Cs_2CO_3 (780 mg, 2.4 mmol) in DMF (5 mL) was heated at 70 °C for 1 h. The mixture was cooled and then partitioned between water (10 mL) and EtOAc (10 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (PE:EtOAc = 2:1) to give the title compound. MS: *m/z* = 301 (M + 1).

Step H: 3-(1-Methyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzoic acid

A mixture of methyl 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzoate (120 mg, 0.4 mmol) and aqueous NaOH solution (2 M, 10 mmol, 5 mL) was heated at 50 °C for 30 min. The reaction mixture was cooled, acidified to pH 5 with aqueous HCl solution (1 M), and then extracted with EtOAc (10 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated to give the title compound. MS: *m/z* = 287 (M + 1).

INTERMEDIATE C1



N-(1-(Dimethylamino)-3-oxo-3-phenylprop-1-en-2-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

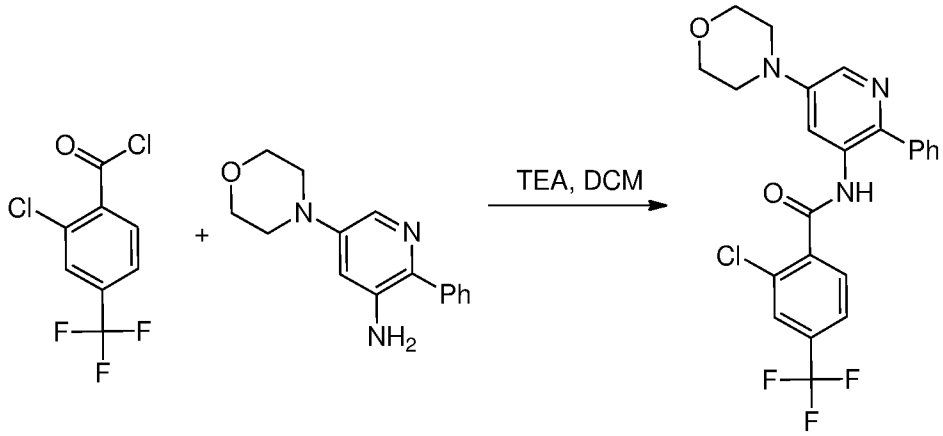
Step A: 3-(1-Methyl-1*H*-pyrazol-3-yl)-*N*-(2-oxo-2-phenylethyl)-4-(trifluoromethyl)benzamide

A mixture of 3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (500 mg, 1.85 mmol), 2-aminoacetophenone hydrochloride (349 mg, 2.04 mmol), HATU (844 mg, 2.22 mmol), and DIEA (0.970 mL, 5.55 mmol) in DMF (4 mL) was stirred at ambient temperature for 2 h. The product mixture was purified directly by column chromatography on silica gel (EtOAc:Hexanes = 0:100 to 100:0) to yield the title compound. MS: *m/z* = 388.2 (M + 1).

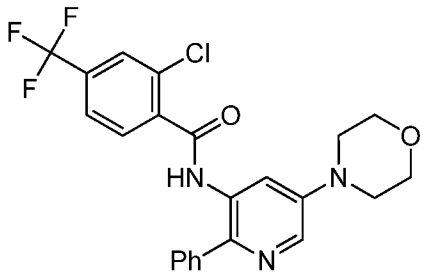
Step B: *N*-(1-(Dimethylamino)-3-oxo-3-phenylprop-1-en-2-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

A mixture of 3-(1-methyl-1*H*-pyrazol-3-yl)-*N*-(2-oxo-2-phenylethyl)-4-(trifluoromethyl)benzamide (88.0 mg, 0.227 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (0.036 mL, 0.27 mmol) in dioxane (1 mL) was stirred at ambient temperature for 16 h. The product mixture was purified directly by column chromatography on silica gel (DCM:MeOH:NH_4OH = 100:0:0 to 90:10:1) to give the title compound. MS: *m/z* = 443.2 (M + 1).

EXAMPLE OF SCHEME 1: EXAMPLE 5



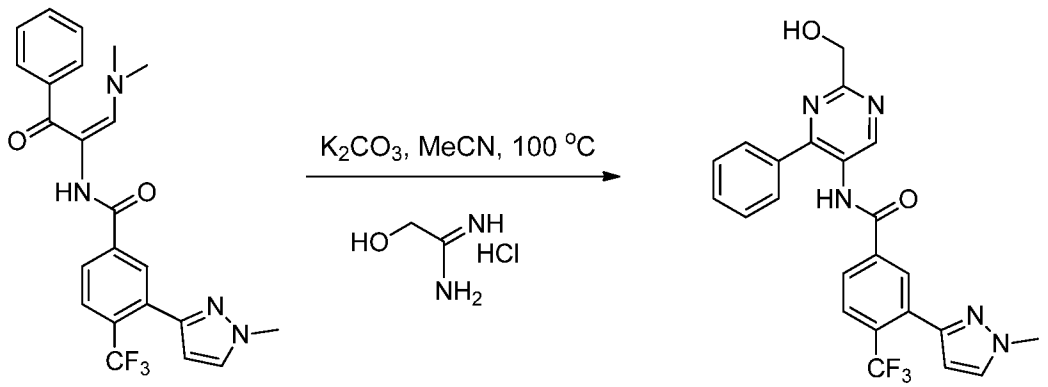
EXAMPLE 5



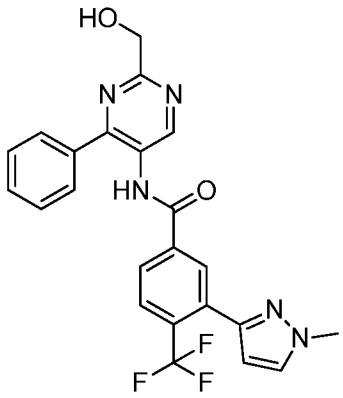
2-Chloro-*N*-(5-morpholino-2-phenylpyridin-3-yl)-4-(trifluoromethyl)benzamide

A mixture of 5-morpholino-2-phenylpyridin-3-amine (30 mg, 0.12 mmol), 2-chloro-4-(trifluoromethyl)benzoyl chloride (49 mg, 0.20 mol), and TEA (0.050 mL, 0.36 mmol) in DCM (2 mL) was stirred at 15 °C for 2 h. The reaction mixture was concentrated and the residue was partitioned between DCM (50 mL) and water (10 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by reverse-phase HPLC (10-40% acetonitrile + 0.75% trifluoroacetic acid in water) to give the title compound. MS: *m/z* = 462 (M + 1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.30-8.25 (m, 2H), 7.82 (s, 1H), 7.74-7.70 (m, 1H), 7.69-7.63 (m, 3H), 7.59 - 7.54 (m, 3H), 3.92-3.88 (m, 4H), 3.47-3.42 (m, 4H).

EXAMPLE OF SCHEME 2: EXAMPLE 22



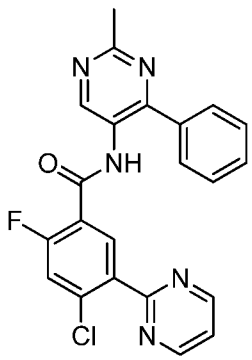
EXAMPLE 22



N-(2-(Hydroxymethyl)-4-phenylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

A mixture of *N*-(1-(dimethylamino)-3-oxo-3-phenylprop-1-en-2-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (2.04 g, 4.62 mmol), 2-hydroxyacetimidamide hydrochloride (0.818 g, 7.40 mmol), and potassium carbonate (1.92 g, 13.9 mmol) in EtOH (8 mL) was heated at 65 °C for 2 h and then at 80 °C for 18 h. The reaction mixture was cooled and then filtered, washing with EtOH and water. The filtrate was diluted with water (50 mL), and extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was purified by column chromatography on silica gel (Hexanes/EtOAc = 97:3 to 0:100) to afford the title compound. MS: *m/z* = 454.2 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.10 (s, 1H), 8.02 (s, 1H), 7.83-7.78 (m, 2H), 7.70-7.67 (m, 2H), 7.58-7.50 (m, 3H), 7.39 (d, *J* = 2.3 Hz, 1H), 6.48 (s, 1H), 4.87 (d, *J* = 4.8 Hz, 2H), 3.95 (s, 3H), 3.62 (t, *J* = 4.8 Hz, 1H).

EXAMPLE 25

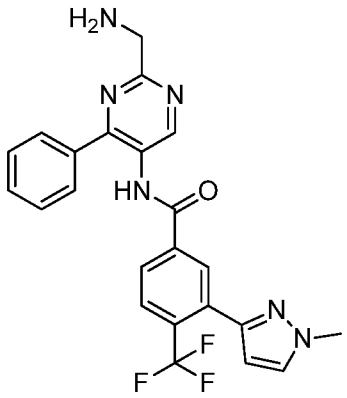


4-Chloro-2-fluoro-*N*-(2-methyl-4-phenylpyrimidin-5-yl)-5-(pyrimidin-2-yl)benzamide

A mixture of 2-methyl-4-phenylpyrimidin-5-aminium chloride (95 mg, 0.43 mmol), pyridine (46 mg, 0.58 mmol), and 4-chloro-2-fluoro-5-(pyrimidin-2-yl)benzoyl chloride (78 mg, 0.29 mmol) in DMA (2.5 mL) was stirred at 23 °C for 16 h. The reaction mixture was

filtered and then purified by reverse-phase HPLC (5-95% acetonitrile + 0.1% trifluoroacetic acid in water) to give the title compound. MS: *m/z* = 420.1 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) 9.69 (s, 1H), 8.90 (d, *J* = 4.9 Hz, 2H), 8.59 (d, *J* = 8.4 Hz, 1H), 7.66 (dd, *J* = 6.6, 2.3 Hz, 2H), 7.56-7.60 (m, 4H), 7.36 (t, *J* = 4.9 Hz, 1H), 2.80 (s, 3H).

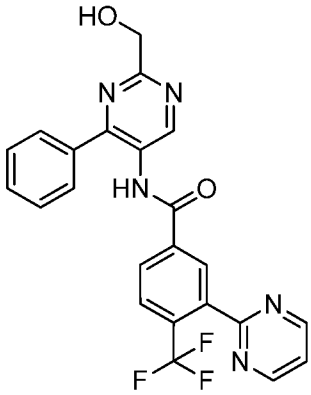
EXAMPLE 32



N-(2-(Aminomethyl)-4-phenylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

A solution of *t*-butyl ((5-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamido)-4-phenylpyrimidin-2-yl)methyl)carbamate (615 mg, 1.11 mmol) and HCl in dioxane (4 M, 5.0 mL, 20 mmol) was stirred at ambient temperature for 5 h. The mixture was concentrated to yield the title compound as the HCl salt. MS: *m/z* = 453.2 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.61 (s, 2H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.97 (s, 1H), 7.82-7.78 (m, 2H), 7.68-7.60 (m, 2H), 7.49-7.42 (m, 3H), 7.42 (d, *J* = 2.3 Hz, 1H), 6.49 (s, 1H), 4.47 (s, 2H), 3.95 (s, 3H).

EXAMPLE 34



N-(2-(Hydroxymethyl)-4-phenylpyrimidin-5-yl)-3-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide

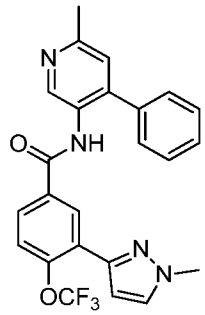
Step A: *N*-(4-Phenyl-2-(((triisopropylsilyl)oxy)methyl)pyrimidin-5-yl)-3-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide

$POCl_3$ (0.023 mL, 0.25 mmol) was added to a solution of 4-phenyl-2-(((triisopropylsilyl)oxy)methyl)pyrimidin-5-amine (58.8 mg, 0.164 mmol), 3-(pyrimidin-2-yl)-4-(trifluoromethyl)benzoic acid (44.1 mg, 0.164 mmol), and pyridine (0.080 mL, 0.99 mmol) in DCM (1 mL) at -15 °C, and the resulting mixture was stirred at ambient temperature for 4.5 h. The product mixture was purified directly by column chromatography on silica gel (EtOAc:Hexanes = 0:100 to 50:50) to give the title compound. MS: *m/z* = 608.4 (M + 1).

Step B: *N*-(2-(Hydroxymethyl)-4-phenylpyrimidin-5-yl)-3-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide

A mixture of *n*-Bu_4NF (0.118 mL, 0.118 mmol, 1.0 M in THF) and *N*-(4-phenyl-2-(((triisopropylsilyl)oxy)methyl)pyrimidin-5-yl)-3-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide (36 mg, 0.059 mmol) in THF (1 mL) and was stirred at ambient temperature for 2.5 h. The product mixture was purified by column chromatography on silica gel (EtOAc:DCM = 0:100 to 100:0) to yield the title compound. MS: *m/z* = 452.2 (M + 1). ^1H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 8.94 (d, *J* = 4.9 Hz , 2H), 8.86 (s, 1H), 8.21 (s, 1H), 8.15 (d, *J* = 8.9 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.80-7.75 (m, 2H), 7.56 (t, *J* = 4.9 Hz, 1H), 7.42-7.40 (m, 3H), 5.30 (t, *J* = 6.6 Hz, 1H), 4.64 (d, *J* = 6.3 Hz, 2H).

EXAMPLE 45



3-(1-Methyl-1*H*-pyrazol-3-yl)-*N*-(6-methyl-4-phenylpyridin-3-yl)-4-(trifluoromethoxy)benzamide

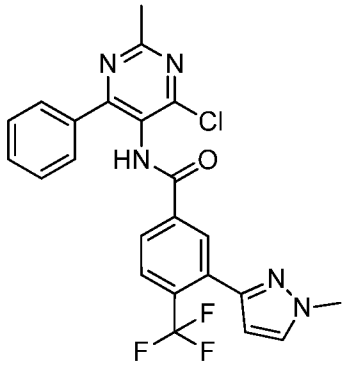
Step A: 3-(1-Methyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzoyl chloride

A mixture of 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzoic acid (85 mg, 0.30 mmol) and oxalyl chloride (1.30 mL, 14.9 mmol) in DCM (10 mL) was heated at 50 °C for 1 h. The mixture was cooled and then concentrated to give the title compound. MS: *m/z* = 301 (M + 1, Me ester from reaction with MeOH).

Step B: 3-(1-Methyl-1H-pyrazol-3-yl)-N-(6-methyl-4-phenylpyridin-3-yl)-4-(trifluoromethoxy)benzamide

A mixture of 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzoyl chloride (88 mg, 0.29 mmol), 6-methyl-4-phenylpyridin-3-amine (82 mg, 0.32 mmol), and pyridine (0.047 mL, 0.58 mmol) in DCM (10 mL) was at heated at reflux for 18 h. The reaction mixture was cooled and then partitioned between saturated $NaHCO_3$ solution (30 mL) and DCM (20 mL x 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), then dried over Na_2SO_4 and concentrated. The residue was purified by reverse-phase HPLC to give the title compound. MS: *m/z* = 453 (M + 1). ^{1}H NMR (400 MHz, MeOD) δ 9.13 (s, 1H), 8.42 (d, *J* = 2.2 Hz, 1H), 7.90 (s, 1H), 7.83 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.64-7.67 (m, 3H), 7.53-7.61 (m, 3H), 7.48 (dd, *J* = 8.6, 1.3 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 3.97 (s, 3H), 2.79 (s, 3H).

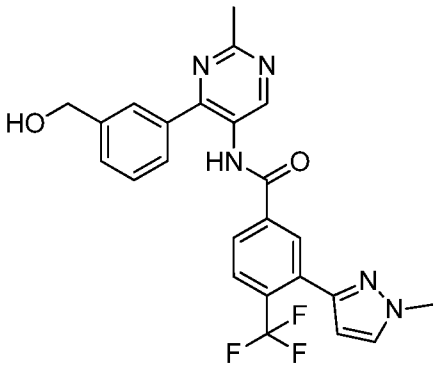
EXAMPLE 46



N-(4-Chloro-2-methyl-6-phenylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

$POCl_3$ (0.205 mL, 2.20 mmol) was added to a mixture of 4-chloro-2-methyl-6-phenylpyrimidin-5-amine (322 mg, 1.47 mmol) and 3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (396 mg, 1.47 mmol) in pyridine (3 mL) at -15 °C, and the resulting mixture was stirred at -15 °C for 2 h. The product mixture was purified directly by column chromatography on silica gel (EtOAc:Hexanes = 0:100 to 100:0) to yield the title compound. MS: *m/z* = 472.2 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.84-7.78 (m, 2H), 7.68-7.63 (m, 3H), 7.40-7.36 (m, 4H), 6.48 (s, 1H), 3.93 (s, 3H), 2.77 (s, 3H).

EXAMPLE 50



N-(4-(3-(Hydroxymethyl)phenyl)-2-methylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

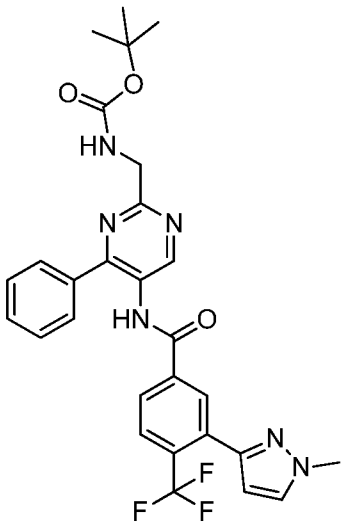
Step A: *N*-(4-chloro-2-methylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

$POCl_3$ (1.16 mL, 12.4 mmol) was added to a solution of 4-chloro-2-methylpyrimidin-5-amine (1.19 g, 8.28 mmol) and 3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (2.24 g, 8.28 mmol) in DCM (10 mL) at -15 °C, and the resulting mixture was stirred at -15 °C for 1.5 h. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (Hexanes:EtOAc = 100:0 to 0:100) to give the title compound. MS: *m/z* = 396.1 (M + 1).

Step B: *N*-(4-(3-(Hydroxymethyl)phenyl)-2-methylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

A deoxygenated mixture of *bis*(tri-*t*-butylphosphine)palladium (0.78 mg, 1.5 μmol), *N*-(4-chloro-2-methylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (12 mg, 0.030 mmol), (3-(hydroxymethyl)phenyl)boronic acid (14 mg, 0.091 mmol), and aqueous cesium carbonate solution (0.030 mL, 0.061 mmol, 2 M) in dioxane (0.4 mL) was heated at 100 °C under microwave irradiation for 0.5 h. The product mixture was purified by column chromatography on silica gel (DCM:MeOH:NH_4OH = 100:0:0 to 90:10:1) to afford the title compound. MS: *m/z* = 468.2 (M + 1). ^1H NMR (400 MHz, CD_3OD) δ 8.88 (s, 1H), 8.05 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.78 (s, 1H), 7.66-7.64 (m, 2H), 7.47-7.45 (m, 2H), 6.46 (s, 1H), 4.47 (d, *J* = 1.2 Hz, 1H), 3.96 (s, 3H), 2.76 (s, 3H).

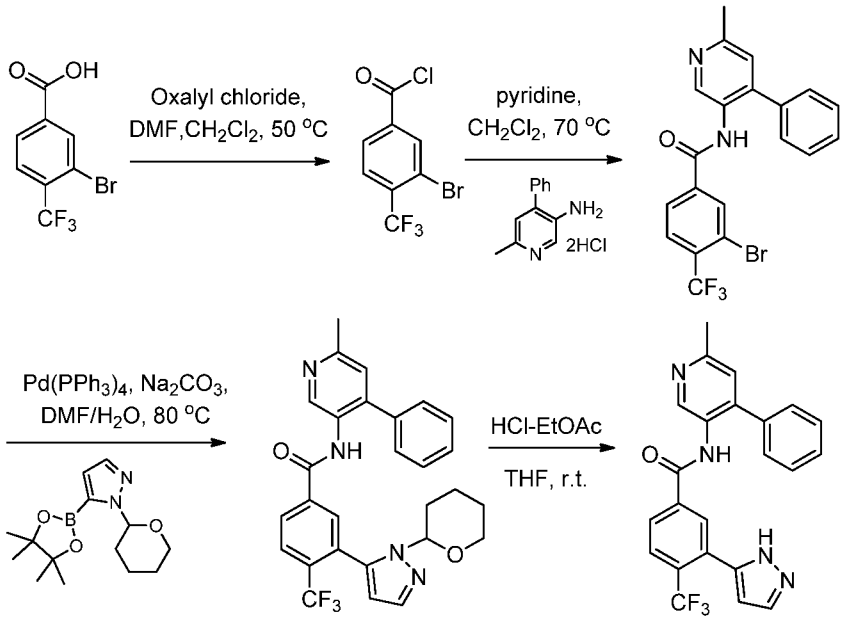
EXAMPLE 51



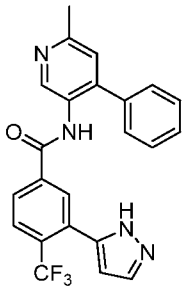
t-Butyl ((5-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamido)-4-phenylpyrimidin-2-yl)methyl)carbamate

A mixture of *N*-(1-(dimethylamino)-3-oxo-3-phenylprop-1-en-2-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (1.00 g, 2.26 mmol), *tert*-butyl (2-amino-2-iminoethyl)carbamate acetate (701 mg, 3.01 mmol), and potassium carbonate (0.937 g, 6.78 mmol) in acetonitrile (5 mL) was heated at 100 °C for 3.5 h. The reaction mixture was cooled and then filtered, washing with acetonitrile (3 x 10 mL). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (Hexanes:EtOAc = 97:3 to 0:100) to give the title compound. MS: *m/z* = 553.3 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.06 (s, 1H), 8.01 (s, 1H), 7.81-7.78 (m, 2H), 7.68 (dd, *J* = 7.3, 1.6 Hz, 2H), 7.56-7.49 (m, 3H), 7.39 (d, *J* = 2.2 Hz, 1H), 6.47 (s, 1H), 5.62 (s, 1H), 4.62 (d, *J* = 5.5 Hz, 2H), 3.95 (s, 3H), 1.46 (s, 9H).

EXAMPLE OF SCHEME 3: EXAMPLE 52



EXAMPLE 52



N-(6-Methyl-4-phenylpyridin-3-yl)-3-(1H-pyrazol-5-yl)-4-(trifluoromethyl)benzamide

Step A: 3-Bromo-4-(trifluoromethyl)benzoyl chloride

A mixture of 3-bromo-4-(trifluoromethyl)benzoic acid (400 mg, 1.49 mmol) and oxalyl chloride (1.30 mL, 14.9 mmol) in DCM (10 mL) was heated at 50 °C for 1 h and then concentrated to give the title compound. MS: *m/z* = 283/285 (M + 1, Me ester from reaction with MeOH).

Step B: 3-Bromo-*N*-(6-methyl-4-phenylpyridin-3-yl)-4-(trifluoromethyl)benzamide

A mixture of 3-bromo-4-(trifluoromethyl)benzoyl chloride (427 mg, 1.49 mmol), 6-methyl-4-phenylpyridin-3-amine (421 mg, 1.64 mmol), and pyridine (0.241 mL, 2.97 mmol) in DCM (10 mL) was heated at reflux for 18 h. The reaction mixture was cooled and then partitioned between a saturated $NaHCO_3$ solution (30 mL) and DCM (20 mL x 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), then dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc:Et_3N = 80:20:1, 70:30:1, then 50:50:1) to give the title compound. MS: *m/z* =

435/437 (M + 1). ^{1}H NMR (400 MHz, MeOD) δ 8.54 (s, 1H), 8.14 (s, 1H), 7.84-7.89 (m, 2H), 7.38-7.48 (m, 6H), 2.60 (s, 3H).

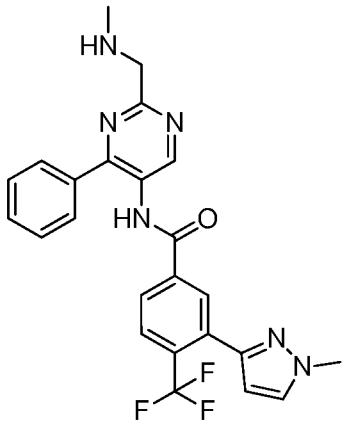
Step C: *N*-(6-Methyl-4-phenylpyridin-3-yl)-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-4-(trifluoromethyl)benzamide

A deoxygenated mixture of 3-bromo-*N*-(6-methyl-4-phenylpyridin-3-yl)-4-(trifluoromethyl)-benzamide (200 mg, 0.460 mmol), 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (192 mg, 0.689 mmol), $Pd(PPh_3)_4$ (27 mg, 0.023 mmol), and Na_2CO_3 (122 mg, 1.15 mmol) in 4:1 DMF:water (7.5 mL) was heated at 80 °C for 18 h. The reaction mixture was cooled and then partitioned between water (30 mL) and EtOAc (30 mL x 3). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated to give the title compound. MS: *m/z* = 507 (M + 1).

Step D: *N*-(6-Methyl-4-phenylpyridin-3-yl)-3-(1H-pyrazol-5-yl)-4-(trifluoromethyl)-benzamide

A solution of HCl in EtOAc (4 M, 0.9 mL, 3.6 mmol) was added to a solution of *N*-(6-methyl-4-phenylpyridin-3-yl)-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-4-(trifluoromethyl)benzamide (348 mg, 0.687 mmol) in THF (10 mL), and the resulting mixture was stirred at ambient temperature for 18 h. The mixture was concentrated and the residue was purified by reverse-phase HPLC to give the title compound. MS: *m/z* = 423 (M + 1). ^{1}H NMR (400 MHz, MeOD) δ 9.09 (s, 1H), 8.02 (s, 1H), 7.91-7.98 (m, 2H), 7.88 (s, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.61-7.64 (m, 2H), 7.50-7.57 (m, 3H), 6.50 (d, *J* = 1.3 Hz, 1H), 2.79 (s, 3H).

EXAMPLE 53



3-(1-Methyl-1*H*-pyrazol-3-yl)-*N*-(2-((methylamino)methyl)-4-phenylpyrimidin-5-yl)-4-(trifluoromethyl)benzamide

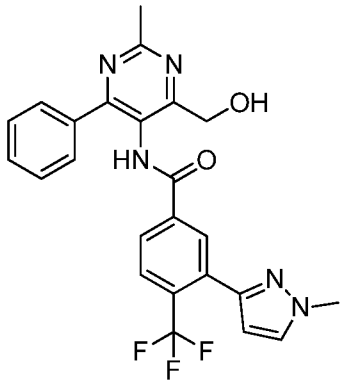
Step A: *N*-(2-Formyl-4-phenylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

A mixture of *N*-(2-(hydroxymethyl)-4-phenylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (452 mg, 0.997 mmol) and Dess-Martin Periodinane (507 mg, 1.20 mmol) in DCM (5 mL) was stirred at ambient temperature for 18 h. Additional Dess-Martin Periodinane (200 mg, 0.47 mmol) was added and the mixture was stirred for 3 h. The reaction mixture was filtered, washing with DCM. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (DCM:EtOAc = 100:0 to 0:100) to yield the title compound. MS: *m/z* = 452.2 (M + 1).

Step B: 3-(1-Methyl-1*H*-pyrazol-3-yl)-*N*-(2-((methylamino)methyl)-4-phenylpyrimidin-5-yl)-4-(trifluoromethyl)benzamide

A mixture of *N*-(2-formyl-4-phenylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (9.0 mg, 0.020 mmol), methylamine (0.030 mL, 0.060 mmol, 2 M in THF), sodium triacetoxyborohydride (5.5 mg, 0.026 mmol), and acetic acid (0.057 mL, 0.10 mmol) in DCE (1 mL) was stirred at ambient temperature for 2 h. The reaction mixture was concentrated and the residue was purified by reverse-phase HPLC (C18 column, H_2O:CH_3CN:CF_3CO_2H = 95:5:0.1 to 5:95:0.1) to yield the title compound as the TFA salt. MS: *m/z* = 467.3 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.57 (s, 1H), 7.98 (s, 1H), 7.87-7.82 (m, 2H), 7.69-7.66 (m, 2H), 7.50-7.47 (m, 3H), 7.44 (d, *J* = 2.4 Hz, 1H), 6.51 (s, 1H), 4.48 (s, 2H), 3.98 (s, 3H), 2.92 (s, 3H).

EXAMPLE 54



N-(4-(Hydroxymethyl)-2-methyl-6-phenylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

Step A: *N*-(4-(((*t*-Butyldimethylsilyl)oxy)methyl)-2-methyl-6-phenylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

A deoxygenated mixture of *N*-(4-chloro-2-methyl-6-phenylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (50.0 mg, 0.106 mmol), *t*-butyldimethyl((tributylstannyl)methoxy)silane (69.2 mg, 0.159 mmol), and tetrakis(triphenylphosphine)palladium (12.2 mg, 0.0106 mmol) in dioxane (0.6 mL) and was heated at 150 °C under microwave irradiation for 2 h. The reaction mixture was diluted with DMF (1 mL) and purified by reverse-phase HPLC (C18 column, H_2O:CH_3CN:CF_3CO_2H = 95:5:0.1 to 5:95:0.1). The desired fractions were neutralized by partitioning between saturated $NaHCO_3$ solution (10 mL) and DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to yield the title compound. MS: *m/z* = 582.3 (M + 1).

Step B: *N*-(4-(Hydroxymethyl)-2-methyl-6-phenylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

A mixture of *n*-Bu_4NF (0.108 mL, 0.108 mmol, 1 M in THF) and *N*-(4-(((*t*-butyldimethylsilyl)oxy)methyl)-2-methyl-6-phenylpyrimidin-5-yl)-3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (21 mg, 0.036 mmol) in THF (1 mL) was stirred at ambient temperature for 1 h. The product mixture was purified by column chromatography on silica gel (DCM:EtOAc = 97:3 to 0:100) to yield the title compound. MS: *m/z* = 468.2 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.84-7.78 (m, 2H), 7.76-7.63 (s, 1H), 7.60-7.55 (m, 2H), 7.42-7.36 (m, 4H), 6.47 (s, 1H), 4.69 (s, 2H), 3.92 (s, 3H), 2.81 (s, 3H).

Biological Utility

TrkA functional activity was measured using a DiscoverX PathHunter assay. In this assay, U2OS cells express the human TrkA receptor as a fusion with the weakly complementing fragment of B-galactosidase, which DiscoverX calls “Prolink (PK)”; additionally, Shc1 is fused with a larger fragment, which is called “Enzyme Acceptor (EA)”. Activation of the TrkA receptor, upon NGF addition, results in the kinase domain being phosphorylated, resulting in subsequent recruitment of Shc1-EA protein. That recruitment results in an active B-galactosidase enzyme that is detected by addition of a chemiluminescent substrate. The human $p75^{NTR}$ protein was also expressed as a co-receptor for NGF.

All reagents were purchased from DiscoverX, except for the receptor agonists (NGF, BDNF, NT3) which were purchased from Peprotech. Cells were expanded and frozen into cryovials, and stored in the vapor phase of liquid nitrogen, and thawed immediately before use.

Thawed cells were added to a 384-well plate at 7500 cells/well, and allowed to incubate overnight. Compound at various concentrations was added the following morning and allowed to incubate on cells for 1 h. Then, NGF was added at a concentration sufficient to elicit ~80% of a maximal response and allowed to incubate for 3 h at ambient temperature. DiscoverX PathHunter detection reagent was then added and the plate was further incubated for 1 h in the dark. The plate was then read via luminescence on the Perkin Elmer Envision.

The percent inhibition was calculated for each compound concentration, and the IC_{50} was determined using Equation 1 below.

Equation 1: $$\% \text{ Inhibition} = (Max + \frac{(Max - Min)}{1 + (\frac{Conc}{IC_{50}})^{Hill}})$$

IC50 values from the aforementioned assay for the compounds of this invention range between 20 nM to 10000 nM. IC50 values for particular compounds of this invention are provided below in Table 2 below:

Table 2

Compound Number	TrkA IC_{50} (nM)
1	4900
2	4000
3	4300
4	140
5	480
6	1600
7	7500
8	36
9	910
10	590
11	3.0
12	66
13	15
14	330
15	25
16	15
17	35
18	19
19	64

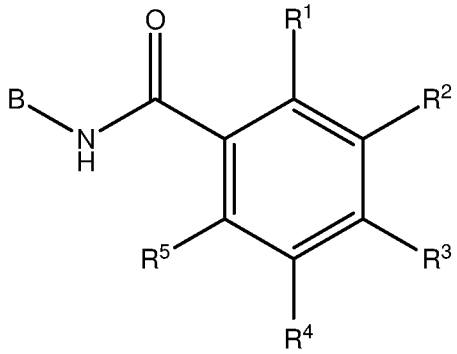
20	1.1
21	2.2
22	7.3
23	2.5
24	25
25	100
26	83
27	24
28	210
29	1.0
30	9.6
31	1.6
32	21
33	8.5
34	70
35	4.0
36	4.0
37	1200
38	12
39	4.1
40	130
41	1.5
42	55
43	5.5
44	8.3
45	54
46	160
47	80
48	2.3
49	12
50	20
51	5.0
52	14
53	16
54	24
55	3.6
56	11

57	2.2
58	5.7
59	12
60	1.3
61	24
62	0.68

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

CLAIMS

1. A compound of formula I:



I

or pharmaceutically acceptable salts thereof, wherein:

B represents phenyl, or a six membered heteroaryl having at least one heteroatom that is nitrogen, said phenyl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R represents hydrogen, OH, or -C_{1-6}alkyl;

R^1 and R^5 are independently selected from the group consisting of hydrogen, CN, OH, -C_{1-6}alkyl and halogen;

R^2 and R^4 are independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, $(CHR)_nC_{6-10}$ aryl and $(CHR)_nC_{5-10}$ heterocycle, said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of R^a,

R^3 represents hydrogen, C_{1-6} alkyl, C_{1-4} haloalkyl, -OC_{1-4} haloalkyl, and halogen;

R^a is selected from the group consisting of –CN, NO_2, -C_{1-4}haloalkyl, -OC_{1-4}haloalkyl, -C_{1-6}alkyl, -C_{1-6}alkenyl, -C_{1-6}alkynyl, -$(CHR)_nC_{6-10}$ aryl, -$(CHR)_nC_{4-10}$ heterocycle, -$C(O)(CHR)_nC_{4-10}$ heterocycle, -O-$(CH_2)_nC_{6-10}$ aryl, -O-$(CH_2)_nC_{4-10}$ heterocycle, -O-, -$(CH_2)_nN(R^d)_2$, -$(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$ heterocycle, SO_2R^d, $(CH_2)_nNHSO_2R^d$, $SO_2N(R^d)_2$, S(O)(NH)Rg, $-C(O)CF_3$, COR, -$(CH_2)_n$halo, -$(CH_2)_nNHC(O)R^d$, -$(CH_2)_nNHC(O)NHR^d$, -$(CH_2)_nNHC(O)OR^d$, -$(CHR)_nC(O)N(R^d)_2$ -OC_{1-6}alkyl, and –OH, said alkyl, aryl and heterocycle optionally substituted with 1 to 3 groups of R^b, wherein when two R^d groups are attached to a nitrogen atom they may combine with that nitrogen to from a 4-8 membered heterocyle that is optionally substituted with 1 to 3 groups of R^f;

R^b is selected from the group consisting of halogen, -C_{1-6}alkyl, -C_{1-6}alkylOR, -C_{1-4}haloalkyl, -$(CH_2)_nN(R^d)_2$, -OR^c, -O-, -CN, S(O)(NH)Rg, -SO_2R, -$SO_2N(R^d)_2$, -$(CH_2)_nC(O)N(R^d)_2$, -$(CH_2)_nNHC(O)R^d$, -O-$(CH_2)_nC_{4-10}$ heterocycle, and -C_{1-6}alkyl$N(R^d)_2$, wherein when two R^d groups are attached to a nitrogen atom they may combine with that nitrogen to from a 4-8 membered heterocyle that is optionally substituted with 1 to 3 groups of R^f;

R^c is selected from the group consisting of hydrogen, -C_{1-6}alkylORg, -C_{1-4}haloalkyl and -C_{1-6}alkyl;

R^d is independently selected from the group consisting of hydrogen, halogen, -C_{1-4}haloalkyl -C_{1-6}alkyl, -$(CH_2)_nNR^fC_{4-10}$ heterocycle, -$(CH_2)_nC_{3-6}$cycloalkyl, -$(CH_2)_nC_{4-10}$heterocycle said alkyl, cycloalkyl and heterocycle optionally substituted with 1 to 3 groups of Rf

R^f is selected from the group consisting of hydrogen, OR^c, CN, -$N(R^c)_2$, C(O)$N(Rg)_2$, C(O)C_{1-6}alkyl, -SO_2Rg, -O-, -C_{1-6}alkylSO_2Rg, -C_{1-6}alkylORg, -C_{1-6}alkyl$N(Rg)_2$,

Rg is selected from the group consisting of hydrogen, -C_{1-6}alkyl; and

n represents 0-6.

2. The compound according to claim 1 wherein B is unsubstituted or substituted phenyl.

3. The compound according to claim 1 wherein B is an unsubstituted or substituted six membered heterocycle selected from the group consisting of pyridyl, pyrimidinyl and pyrazinyl.

4. The compound according to claim 3 wherein B is unsubstituted or substituted pyridyl.

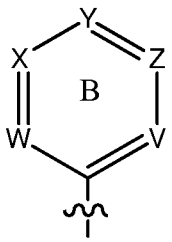
5. The compound according to claim 3 wherein B is unsubstituted or substituted pyrimidinyl.

6. The compound according to claim 1 wherein one of R^2 and R^4 is hydrogen and the other is optionally substituted $(CHR)_nC_{5-10}$ heterocycle and R^1 and R^5 are independently selected from hydrogen and halogen.

7. The compound according to claim 6 wherein the heterocycle of R^2 and R^4 is selected from the group consisting of pyrazolyl, pyridyl, thiazolyl, triazolyl, oxazolyl, oxadiazolyl, and pyrimidinyl, said groups optionally substituted.

8. The compound according to claim 1 wherein R^3 is selected from the group consisting of hydrogen, CF_3, OCF_3, CH_3, chlorine, and fluorine.

9. The compound according to claim 1 of formula I wherein B is represented by structural formula (a):



(a)

wherein:

V, W, X, Y, and Z are all CR^{10},

one of V, W, X, Y, and Z is N and the others are CR^{10},

X and V are both N and W, Y, and Z are all CR^{10},

W and Z are both N and V, X, and Y are all CR^{10},

X and Z are both N and Y, W, and V are all CR^{10},

W and Y are both N and X, Z, and V are all CR^{10}, or

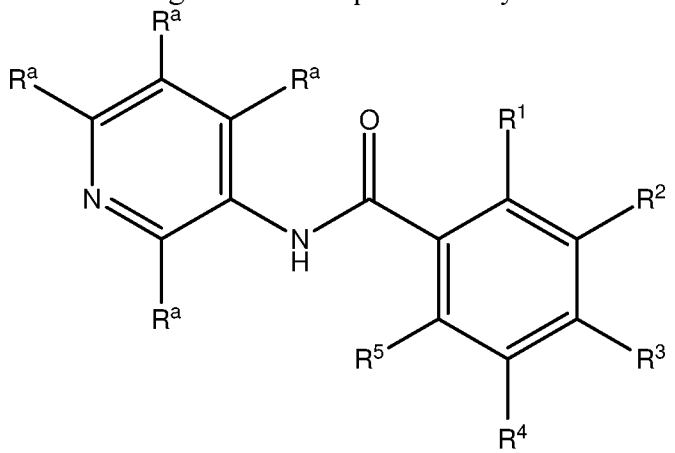
Y and V are both N and Z, X, and W are all CR^{10};

R^{10} is selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CHR)_n(C(O))_{0-1}N(R^d)_2$, $(CH_2)_nC_{6-10}$aryl, $C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, $(CH_2)_nC(O)NH(CH_2)_nC_{5-10}$heterocycle, $-(CH_2)_nOR$, $NH(CH_2)_nOR$, $-(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$heterocycle, SO_2R^d, $SO_2N(R^d)_2$, $S(O)(NH)R^g$, $-C(O)CF_3$, COR, $-(CH_2)_n$halo, $-(CH_2)_nNHC(O)R^d$, $-(CH_2)_nNHC(O)NHR^d$, $-(CH_2)_nNHC(O)OR^d$, $-O-C_{5-10}$heterocycle, $-OC_{1-6}$alkyl, and –OH said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of R^b.

10. The compound according to claim 9 wherein B is one of V, W, X, Y, and Z is N and the others are CR^{10} and R^{10} of CR^{10} is selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, halogen, $-O-C_{5-10}$heterocycle, $-(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$heterocycle, $(CHR)_n(C(O))_{0-1}N(R^d)_2$, and $-(CH_2)_nOR$, wherein n=0-2 and the alkyl, aryl and heterocycle is optionally substituted.

11. The compound according to claim 10 wherein R^{10} is selected from hydrogen, C_{1-6}alkyl, $C(O)NH_2$, C(O)NHazetidinyl, pyridyl, isoxazolyl, oxazolyl, C(O)morpholinyl, pyrazolyl, and phenyl, $C(O)NH(CH_2)_n$pyridyl, said azetidinyl, pyridyl, isoxazolyl, oxazolyl, morpholinyl, pyrazolyl and phenyl optionally substituted with 1 to 3 groups of R^b, R^1 and R^5 are independently selected from hydrogen and halogen, R^3 is CF_3, or halogen and one of R^2 and R^4 is hydrogen and the other is $(CHR)_nC_{5-10}$ heterocycle selected from optionally substituted oxodiazolyl, pyrazolyl, pyridyl, thiazolyl, oxazolyl, and pyrimidinyl.

12. The compound according to claim 1 represented by structural formula Ia:



Ia

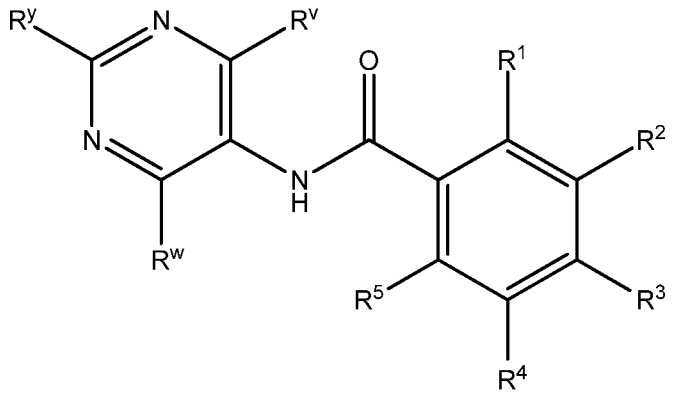
or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, and R^5 are as originally described and R^a is selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, halogen, -O-C_{5-10}heterocycle, -$(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$heterocycle, $(CHR)_n(C(O))_{0-1}N(R^d)_2$, and -$(CH_2)_nOR$, wherein n=0-2 and the alkyl, aryl and heterocycle is optionally substituted.

13. The compound according to claim 9 wherein B is V, W, X, Y, and Z are all CR^{10} and R^{10} of CR^{10} is selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, halogen, -O-C_{5-10}heterocycle, -$(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$heterocycle, $(CHR)_n(C(O))_{0-1}N(R^d)_2$, and -$(CH_2)_nOR$, wherein n=0-2 and the alkyl, aryl and heterocycle is optionally substituted.

14. The compound according to claim 13 wherein R^{10} is selected from hydrogen, C_{1-6}alkyl, CF_3, $C(O)NH_2$, oxadiazolyl, isoxazolyl, oxazolyl, pyrazolyl, and phenyl, said oxadiazolyl, isoxazolyl, oxazolyl, pyrazolyl and phenyl optionally substituted with 1 to 3 groups of R^b, R^1 and R^5 are independently selected from hydrogen and halogen, R^3 is CF_3, or halogen and one of R^2 and R^4 is hydrogen and the other is $(CHR)_nC_{5-10}$ heterocycle selected from optionally substituted oxodiazolyl, pyrazolyl, pyridyl, thiazolyl, oxazolyl, and pyrimidinyl.

15. The compound according to claim 9 wherein B is X and V are both N and W, Y, and Z are all CR^{10}, or W and Z are both N and V, X, and Y are all CR^{10} and R^{10} of CR^{10} is selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, halogen, -O-C_{5-10}heterocycle, -$(CH_2)_nC(O)NH(CH_2)_nC_{4-10}$heterocycle, $(CHR)_n(C(O))_{0-1}N(R^d)_2$, and -$(CH_2)_nOR$, wherein n=0-2 and the alkyl, aryl and heterocycle is optionally substituted.

16. The compound according to claim 9 represented by structural formula II:



II

and pharmaceutically acceptable salts thereof, wherein R^1, R^2, R^3, R^4, and R^5 are as originally described, and R^w, R^v and R^y=R^{10}.

17. The compound according to claim 16 wherein R^1 and R^5 are independently selected from hydrogen and halogen, R^3 is CF_3, OCF_3, or halogen, R^w and R^v are selected from the group consisting of hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $C(O))_{0-1}(CH_2)_nC_{5-10}$heterocycle, halogen, and $-(CH_2)_nOR$, wherein n=0-2 and the alkyl, aryl and heterocycle is optionally substituted and R^y is selected from hydrogen, C_{1-6}alkyl, $(CH_2)_nC_{6-10}$aryl, $(CH_2)_nC_{5-10}$heterocycle, $-(CH_2)_nOR$, $NH(CH_2)_nOR$, $(CH_2)_n(C(O))_{0-1}N(R^d)_2$, $-(CH_2)_nNHC(O)OR^d$, $-(CH_2)_nNHC(O)R^d$, $-(CH_2)_nNHSO_2R^d$, wherein n=0-2, and the alkyl, aryl and heterocycle is optionally substituted.

18. A compound which is selected from the group consisting of
2-fluoro-N-(4'-fluorobiphenyl-2-yl)-4-(trifluoromethyl)benzamide,
N-[2-(5-methyl-1H-pyrazol-3-yl)phenyl]-3-(1,3-thiazol-2-yl)benzamide,
2,3-difluoro-4-methyl-N-(2-methyl-4-phenylpyrimidin-5-yl)benzamide,
2-chloro-5-(3,5-dimethyl-1H-pyrazol-1-yl)-N-(2-methyl-4-phenylpyrimidin-5-yl)benzamide,
2-chloro-N-(5-morpholin-4-yl-2-phenylpyridin-3-yl)-4-(trifluoromethyl)benzamide,
N-(6-phenyl-3,3'-bipyridin-5-yl)-4-(trifluoromethyl)benzamide,
2-chloro-5-(3,5-dimethyl-1H-pyrazol-1-yl)-N-[2-(3-methylisoxazol-5-yl)phenyl]benzamide,
N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(1,3-thiazol-4-yl)-4-(trifluoromethyl)benzamide,
3-(3,5-dimethyl-1H-pyrazol-1-yl)-4-fluoro-N-(2-methyl-4-phenylpyrimidin-5-yl)benzamide,
N-(2-methyl-4-phenylpyrimidin-5-yl)-3-[5-(trifluoromethyl)-1H-pyrazol-1-yl]benzamide,
N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(2H-1,2,3-triazol-2-yl)-4-(trifluoromethyl)benzamide,
N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(3-methyl-1H-pyrazol-1-yl)-4-(trifluoromethyl)benzamide,

N-[2-methyl-4-(3-methyl-1H-pyrazol-5-yl)pyrimidin-5-yl]-3-(4-methyl-1,3-thiazol-2-yl)-4-(trifluoromethyl)benzamide,
3-(1-methyl-1H-pyrazol-3-yl)-N-[4-(4-methyl-1H-pyrazol-1-yl)pyridin-3-yl]-4-(trifluoromethyl)benzamide,
N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(1,3-oxazol-2-yl)-4-(trifluoromethyl)benzamide,
N-(2-methyl-4-phenylpyrimidin-5-yl)-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
N-[5-carbamoyl-2-(4-methyl-1H-pyrazol-1-yl)phenyl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
3-(1-methyl-1H-pyrazol-3-yl)-N-(3-phenylpyridin-2-yl)-4-(trifluoromethyl)benzamide,
2-chloro-N-(2-methyl-4-phenylpyrimidin-5-yl)-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
2-chloro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylpyridin-3-yl)-4-(trifluoromethyl)benzamide,
N-[2-(hydroxymethyl)-4-phenylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
N-{2-[(2-hydroxyethyl)amino]-4-phenylpyrimidin-5-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
3-(1-methyl-1H-pyrazol-3-yl)-N-[2-(2-morpholin-4-ylethyl)-4-phenylpyrimidin-5-yl]-4-(trifluoromethyl)benzamide,
4-chloro-2-fluoro-N-(2-methyl-4-phenylpyrimidin-5-yl)-5-pyrimidin-2-ylbenzamide,
3-(1-methyl-1H-pyrazol-3-yl)-N-(3-phenylpyrazin-2-yl)-4-(trifluoromethyl)benzamide,
N-[2-(hydroxymethyl)-4-phenylpyrimidin-5-yl]-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
N-(2,4-dimethyl-6-phenylpyrimidin-5-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
2-fluoro-N-(2-methyl-4-phenylpyrimidin-5-yl)-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
2-fluoro-N-(2-methyl-4-phenylpyrimidin-5-yl)-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide,
N-[2-(1H-imidazol-1-ylmethyl)-4-phenylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
N-[2-(aminomethyl)-4-phenylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
2-amino-5-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-6-phenylpyridine-3-carboxamide,
N-[2-(hydroxymethyl)-4-phenylpyrimidin-5-yl]-3-pyrimidin-2-yl-4-(trifluoromethyl)benzamide,
3-(4-methyl-1,3-oxazol-2-yl)-N-(2-methyl-4-phenylpyrimidin-5-yl)-4-(trifluoromethyl)benzamide,
N-[2-(2-hydroxyethyl)-4-phenylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,

N-[2-(morpholin-4-ylcarbonyl)-4-phenylpyrimidin-5-yl]-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
2-fluoro-N-[2-(hydroxymethyl)-4-phenylpyrimidin-5-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide,
N-{2-[2-(methylamino)-2-oxoethyl]-4-phenylpyrimidin-5-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
3-(3-methyl-1,2,4-oxadiazol-5-yl)-N-(2-methyl-4-phenylpyrimidin-5-yl)-4-(trifluoromethyl)benzamide,
5-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-6-phenylpyridine-3-carboxamide,
N-[2-(aminomethyl)-4-phenylpyrimidin-5-yl]-3-[1-(difluoromethyl)-1H-pyrazol-3-yl]-4-(trifluoromethyl)benzamide,
N-[4-(4-fluorophenyl)-2-methylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
N-[2-methyl-4-(3-methylphenyl)pyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
N-(6-methyl-4-phenylpyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzamide,
N-(4-chloro-2-methyl-6-phenylpyrimidin-5-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
5-({[2-fluoro-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-N-(1-methylazetidin-3-yl)-6-phenylpyridine-3-carboxamide,
N-[5-(4-carbamoylphenyl)-2-phenylpyridin-3-yl]-2-fluoro-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
2-fluoro-N-{5-[4-(methylcarbamoyl)phenyl]-2-phenylpyridin-3-yl}-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
N-{4-[3-(hydroxymethyl)phenyl]-2-methylpyrimidin-5-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
tert-butyl {[5-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-4-phenylpyrimidin-2-yl]methyl}carbamate,
N-(6-methyl-4-phenylpyridin-3-yl)-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide
N-{2-[(methylamino)methyl]-4-phenylpyrimidin-5-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
N-[4-(hydroxymethyl)-2-methyl-6-phenylpyrimidin-5-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
N-{2-[(acetylamino)methyl]-4-phenylpyrimidin-5-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide ,
5-({[2-fluoro-5-pyrimidin-2-yl-4-(trifluoromethyl)phenyl]carbonyl}amino)-6-phenylpyridine-3-carboxamide,

5-({[2-fluoro-5-pyrimidin-2-yl-4-(trifluoromethyl)phenyl]carbonyl}amino)-6-phenyl-N-(pyridin-3-ylmethyl)pyridine-3-carboxamide,
5-({[2-fluoro-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-6-phenylpyridine-3-carboxamide,
3-(1-methyl-1H-pyrazol-3-yl)-N-(2-{[(methylsulfonyl)amino]methyl}-4-phenylpyrimidin-5-yl)-4-(trifluoromethyl)benzamide,
N-[6-(1-hydroxy-1-methylethyl)-4-phenylpyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide,
2-fluoro-N-[2-phenyl-5-(pyridin-2-yloxy)pyridin-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide,
2-fluoro-N-[5-(hydroxymethyl)-6'-phenyl-2,3'-bipyridin-5'-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide,
or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

20. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, for the manufacture of a medicament for the treatment of a disease or disorder mediated by the Trk receptors, wherein said disease or disorder is selected from the group consisting of pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA.

21. The compound of claim 1 for use in therapy.

22. A method of treating a disease or disorder mediated by the TrK receptors, wherein said disease or disorder is selected from the group consisting of pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, a disease, disorder, injury, or malfunction relating to dysmyelination or demyelination or a disease or disorder associated with abnormal activities of nerve growth factor (NGF) receptor TrkA in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2014/074145

A. CLASSIFICATION OF SUBJECT MATTER

C07D 213/00(2006.01)i; C07D 221/00(2006.01)i; C07D 239/02(2006.01)i; C07D 241/02(2006.01)i; C07D 251/02(2006.01)i; C07D 265/00(2006.01)i; C07D 279/00(2006.01)i; A61K 31/16(2006.01)i; A61P 29/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D213/-; C07D221/-; C07D239/-; C07D241/-; C07D251/-; C07D265/-; C07D279/-; A61K 31/-; A61P 29/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNPAT, CNKI, EPODOC, WPI, REGISTRY(STN), CAPLUS(STN): Trk, kinase, tropomyosin, inhibitors, NGF, receptor, cancer, inflammation, pain

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010130522A1 (SYNTA PHARMACEUTICALS CORP.) 27 May 2010 (2010-05-27) description, table 1, paragraphs [0021], [0031], [0052]-[0053], [0077]-[0079], claim 1	1-22
X	CN 103534257A (PFIZER LTD.) 22 January 2014 (2014-01-22) description, paragraphs [0003]-[0009], [0024]-[0045], example 292, claims 1, 21	1-22

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 July 2014	**30 July 2014**

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2014/074145

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **22**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] The subject matter of claim 22 relates to methods for the treatment of human body by therapy as defined in PCT Rule 39.1(IV). This search has been carried out on the basis of the subject matter of the use in manufacture of medicaments for treating the alleged diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2014/074145

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
US 2010130522A1	27 May 2010	US 2014045861A1	13 February 2014
		JP 2012504605A	23 February 2012
		AU 2009300318A1	08 April 2010
		US 2012196838A1	02 August 2012
		WO 2010039238A1	08 April 2010
		TW 201018667A	16 May 2010
		AU 2009300318A8	16 June 2011
		CA 2739303A1	08 April 2010
		EP 2350006A1	03 August 2011
CN 103534257A	22 January 2014	EA 201391239A1	31 March 2014
		TW 201302757A	16 January 2013
		CA 2832291A1	11 October 2012
		CR 20130470A	16 October 2013
		UY 34004A	30 November 2012
		AR 085852A1	30 October 2013
		CO 6801740A2	29 November 2013
		DO P2013000221A	16 March 2014
		JP 2014510131A	24 April 2014
		US 2012258950A1	11 October 2012
		EP 2694509A1	12 February 2014
		AU 2012238369A1	03 October 2013
		WO 2012137089A1	11 October 2012
		SG 193513A1	30 October 2013
		MX 2013011612A	17 October 2013
		IL 228590D0	31 December 2013
		KR 20130133905A	09 December 2013
		AP 201307159D0	31 October 2013