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(71) Applicant: MERCK SHARP & DOHME CORP.

[US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(72) Inventors; and

(71) Applicants (for US only): MITCHELL, Helen [GB/US]; 770 Sumneytown Pike, West Point, Pennsylvania 19486 (US). FRALEY, Mark, E. [US/US]; 770 Sumneytown Pike, West Point, Pennsylvania 19486 (US). COOKE, Andrew, J. [GB/US]; 770 Sumneytown Pike, West Point, Pennsylvania 19486 (US). STUMP, Craig, A. [US/US]; 770 Sumneytown Pike, West Point, Pennsylvania 19486 (US). CHEN, Yi Heng [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). BESHORE, Douglas, C. [US/US]; 770 Sumneytown Pike, West Point, Pennsylvania 19486 (US). ZHANG, Xu-Fang [US/US]; 1473 Golden Drive, Dresher, Pennsylvania 19025 (US). MCCOMAS, Casey, C. [US/US]; 470 Springview Lane, Phoenixville, Pennsylvania 19460 (US). SCHIRIPA, Kathy [US/US]; 770 Sumneytown Pike, West Point, Pennsylvania 19486 (US). MCWHERTER, Melody [US/US]; 2 Park Road, Boyertown, New Jersey 19512 (US). MERCER, Swati, P. [US/US]; 770 Sumneytown Pike, West Point, Pennsylvania 19486 (US). MOORE, Keith, P. [US/US]; 770 Sumneytown Pike, West Point, Pennsylvania 19486 (US). LIU, Ping [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). WOOD, Harold, B. [US/US]; 126 East Lincoln Avenue,

Rahway, New Jersey 07065-0907 (US). LI, Chun Sing [CA/CN]; No. 1 Building, 288 Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai 200131 (CN). MAO, Qinghua [CN/CN]; No. 1 Building, Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai 200131 (CN).

(74) Common Representative: MERCK SHARP & DOHME

CORP.; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

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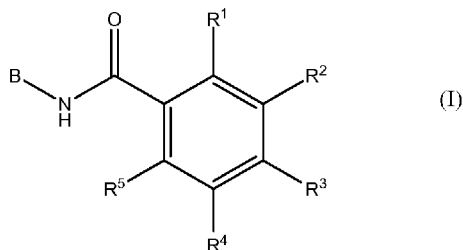
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(54) Title: TrkA KINASE INHIBITORS, COMPOSITIONS AND METHODS THEREOF



(57) Abstract: The present invention is directed to a bicyclic 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.

TITLE OF THE INVENTION

TrkA KINASE INHIBITORS, COMPOSITIONS AND METHODS THEREOF

The invention is directed to a class of bicyclic 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 bicyclic 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/neurotrophin 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 be useful in the treatment of cancer, inflammation, neurodegenerative diseases and certain infectious diseases.

SUMMARY OF THE INVENTION

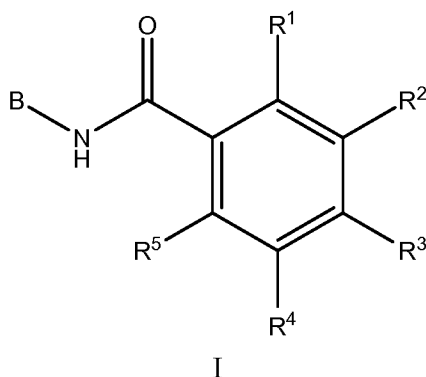
5 The present invention is directed to compounds of generic formula (I) below or pharmaceutically acceptable salts thereof that are useful as a Trk kinase mediator of NGF driven biological responses, an inhibitor of TrkA as well as other Trk kinases.

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.

10 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
15 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

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



25 or a pharmaceutically acceptable salt thereof, wherein
B is selected from the group consisting of a bicyclic heteroaryl having at least one nitrogen heteroatom, said heteroaryl optionally substituted with 1 to 3 groups of R^a;

R is selected from the group consisting of hydrogen, OH, or -C₁₋₆alkyl;

30 R¹ and R⁵ are independently selected from the group consisting of hydrogen, CN, OH, C₁₋₆alkyl, and halogen;

R² and R⁴ are independently selected from the group consisting of hydrogen, halogen, C₁₋₄ haloalkyl, C₁₋₆ alkyl, (CHR)_nC₆₋₁₀ aryl and (CHR)_nC₅₋₁₀ heterocycle, said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of R^a,

5

R³ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₁₋₄ haloalkyl, -OC₁₋₄ haloalkyl, and halogen;

10 R^a is selected from the group consisting of -CN, NO₂, -C₁₋₄haloalkyl, -OC₁₋₄haloalkyl, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -(CHR)_nC₆₋₁₀ aryl, -(CHR)_nC₄₋₁₀ heterocycle, -(CHR)_nC(O)(CHR)_nC₄₋₁₀ heterocycle, -O-(CH₂)_nC₆₋₁₀ aryl, -O-(CH₂)_nC₄₋₁₀ heterocycle - O-, -(CH₂)_nN(R^d)₂, -(CH₂)_nC(O)NH(CH₂)_nC₄₋₁₀ heterocycle, SO₂R^d, SO₂N(R^d)₂, -C(O)CF₃, COR, -(CH₂)_nhalo, -(CH₂)_nNHC(O)R^d, -(CH₂)_nNHC(O)NHR^d, -(CH₂)_nNHC(O)OR^d, -(CHR)_nC(O)N(R^d)₂, -O-C₁₋₆alkyl, and -OH, said alkyl, aryl and
15 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 form a 4-8 membered heterocycle that is optionally substituted with 1 to 3 groups of R^f;

20 R^b is selected from the group consisting of -C₁₋₆alkyl, -C₁₋₆alkylOR, -C₁₋₄haloalkyl, -(CH₂)_nC₃₋₆cycloalkyl, -(CH₂)_nN(R^d)₂, -(CH₂)_nOR^c, -O-, halogen, -CN, S(O)(NH)R^g, -SO₂R, -SO₂N(R^d)₂, -O-(CH₂)_nC₄₋₁₀ heterocycle, -(CH₂)_nC(O)N(R^d)₂, -(CH₂)_nNHC(O)R^d, -C₁₋₆alkylN(R^d)₂, and halo, said cycloalkyl optionally substituted with 1 to 3 groups of R^f, and wherein when two R^d groups are attached to a nitrogen atom they may combine with that nitrogen to form a 4-8 membered heterocycle that is optionally substituted with
25 1 to 3 groups of R^f;

R^c is selected from the group consisting of hydrogen, -C₁₋₆alkylOR^g, -C₁₋₄haloalkyl and -C₁₋₆alkyl;

30 R^d is independently selected from the group consisting of hydrogen, -C₁₋₄haloalkyl -C₁₋₆alkyl, -(CH₂)_nNR^fC₄₋₁₀ heterocycle, -(CH₂)_nC₃₋₆cycloalkyl, and -(CH₂)_nC₄₋₁₀heterocycle said alkyl, cycloalkyl and heterocycle optionally substituted with 1 to 3 groups of R^f;

35 R^f is selected from the group consisting of hydrogen, OR^c, CN, -N(R^c)₂, C(O)N(R^g)₂, C(O)C₁₋₆alkyl, -SO₂R^g, -O-, -C₁₋₆alkylSO₂R^g, -C₁₋₆alkylOR^g, -C₁₋₆alkylN(R^g)₂,

R^g is selected from the group consisting of hydrogen, and -C₁₋₆alkyl; and

n represents 0-6.

An embodiment of the invention of formula I is realized when B is a bicyclic heteroaryl selected from the group consisting of unsubstituted or substituted quinoxaliny, indolyl, imidazopyridinyl, imidazothiazolyl, imidazopyrimidinyl, imidazopyridazinyl, and imidazothiadiazolyl.

Another embodiment of the invention of formula I is realized when B is pyrazolopyridinyl that is represented by structural formula (d) found below.

Another embodiment of the invention of formula I is realized when the five membered portion the bicycle of B is attached through a carbon atom to the benzamide.

Another embodiment of the invention of formula I is realized when B is unsubstituted or substituted imidazopyridinyl. Another embodiment of the invention of formula I is realized when B is unsubstituted or substituted imidazothiazolyl. Another embodiment of the invention of formula I is realized when B is unsubstituted or substituted imidazopyrimidinyl. Still another embodiment of the invention of formula I is realized when B is unsubstituted or substituted imidazopyridazinyl. Another embodiment of the invention of formula I is realized when B is unsubstituted or substituted imidazothiadiazolyl. Yet another embodiment of the invention of formula I is realized when B is unsubstituted or substituted quinoxaliny. Another embodiment of the invention of formula I is realized when B is unsubstituted or substituted pyrazolopyridinyl that is represented by structural formula (d).

Another embodiment of the invention of formula I is realized when R^a is selected from CN, -C₁₋₄haloalkyl, -OC₁₋₄haloalkyl, -C₁₋₆alkyl, -(CHR)_nC₆₋₁₀ aryl, -(CHR)_nC₅₋₁₀ heterocycle, -C(O)(CHR)_nC₅₋₁₀ heterocycle, -C(O)CF₃, C(O)R, C(O)N(R)₂, -(CH₂)_nN(R)₂, SO₂R, SO₂N(R)₂, -(CH₂)_nhalogen, 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 is selected from CN, -C₁₋₄haloalkyl, -C₁₋₆alkyl, -(CHR)_nC₆₋₁₀ aryl, -(CHR)_nC₅₋₁₀ heterocycle, -C(O)(CHR)_nC₅₋₁₀ heterocycle, halogen, and -OR said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of R^b. Still a further aspect of the invention of formula I is realized when R^a is selected from CN, and optionally substituted -C₁₋₆alkyl, CH₂azetidiny, C(O)azetidiny, phenyl, thiazolyl, pyridyl, isoxazolyl and oxazolyl, alkyl, azetidiny, phenyl, thiazolyl, pyridyl, isoxazolyl and oxazolyl 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 -C₁₋₆alkyl, OR^c, and halogen.

Still another embodiment of the invention of formula I is realized when R¹ and R⁵ are both hydrogen. Another embodiment of the invention of formula I is realized when one of R¹ and R⁵ is hydrogen and the other is halogen. Another embodiment of the invention of formula I is realized when one of R¹ and R⁵ is hydrogen and the other is CN, OH, or C₁₋₆alkyl Yet

another embodiment of the invention of formula I is realized when one of R¹ and R⁵ hydrogen and the other is -C₁₋₆alkyl. Yet another embodiment of the invention of formula I is realized when one of R¹ and R⁵ hydrogen and the other is OH.

5 Another embodiment of the invention of formula I is realized when at least one of R² and R⁴ is (CHR)_nC₅₋₁₀ heterocycle optionally substituted with 1 to 3 groups of R^a.

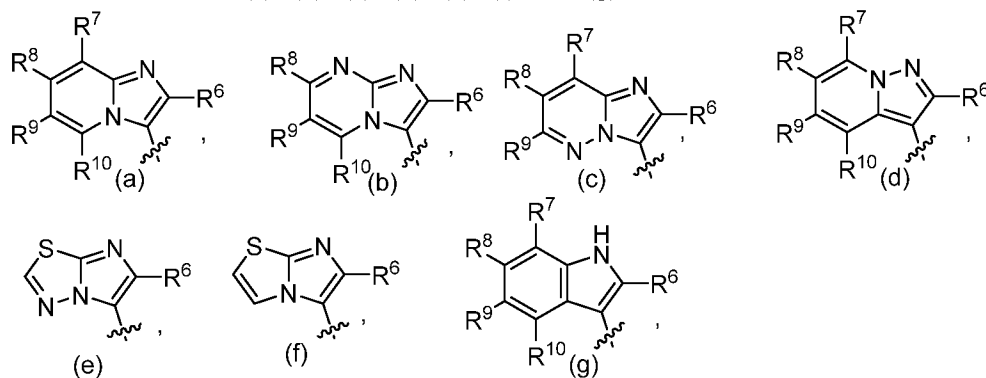
Another embodiment of the invention of formula I is realized when one of R² and R⁴ is hydrogen and the other is (CHR)_nC₅₋₁₀ heterocycle, said heterocycle optionally substituted with 1 to 3 groups of R^a. A subembodiment of this aspect of the invention is realized when the n in (CHR)_nC₅₋₁₀ heterocycle of R² and R⁴ is zero. Another subembodiment of this aspect of the invention is realized when the optionally substituted heterocycle of R² and R⁴ 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 of R² and R⁴ 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 of R² and R⁴ 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 of R² and R⁴ is selected from the group consisting of pyrazolyl, pyridyl, thiazolyl, oxazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiadiazolyl, oxadiazolyl, and triazolyl, said groups optionally substituted. Another subembodiment of this aspect of the invention is realized when the heterocycle of R² and R⁴ is optionally substituted pyrazolyl. Another subembodiment of this aspect of the invention is realized when the heterocycle of R² and R⁴ is substituted pyrazolyl. Still another subembodiment of this aspect of the invention is realized when the heterocycle of R² and R⁴ is optionally substituted thiazolyl. Yet another subembodiment of this aspect of the invention is realized when the heterocycle of R² and R⁴ is optionally substituted pyridyl. Yet another subembodiment of this aspect of the invention is realized when the heterocycle of R² and R⁴ is optionally substituted oxadiazolyl. Yet another subembodiment of this aspect of the invention is realized when the heterocycle of R² and R⁴ is optionally substituted oxazolyl. Yet another subembodiment of this aspect of the invention is realized when the heterocycle of R² and R⁴ is optionally substituted pyrimidinyl. Yet another subembodiment of this aspect of the invention is realized when the heterocycle of R² and R⁴ is optionally substituted triazolyl. Another subembodiment of this aspect of the invention is realized when the heterocycle of R² and R⁴ is optionally substituted pyridazinyl. Another subembodiment of this aspect of the invention is realized when the heterocycle of R² and R⁴ is optionally substituted pyrazinyl. Another subembodiment of this aspect of the invention is realized when the heterocycle of R² and R⁴ is optionally substituted thiadiazolyl. Still another subembodiment of this aspect of the invention is realized when the heterocycle of

R² and R⁴ is optionally substituted with 1 to 3 groups of R^a selected from CN, -C₁-4haloalkyl, -C₁-6alkyl, -(CHR)_nC₆₋₁₀ aryl, -(CHR)_nC₅₋₁₀ heterocycle, -C(O)(CHR)_nC₅₋₁₀ heterocycle, halogen, and -OR said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of R^b.

5 Another embodiment of the invention of formula I is realized when R² and R⁴ both are hydrogen. Another embodiment of the invention of formula I is realized when one of R² and R⁴ is hydrogen and the other is CF₃ or halogen.

Another embodiment of the invention of formula I is realized when R³ is selected from the group consisting of hydrogen, CF₃, OCF₃, CH₃, chlorine, and fluorine. A subembodiment of this aspect of the invention is realized when R³ is CF₃. Still another subembodiment of this aspect of the invention is realized when R³ is OCF₃. Yet another subembodiment of this aspect of the invention is realized when R³ is chlorine or fluorine.

Another embodiment of the invention of formula I is realized when B is represented by structural formulas (a), (b), (c), (d), (e), (f), and (g):



wherein:

R⁶ represents (CH₂)_nC₆₋₁₀aryl, or (CH₂)_nC₅₋₁₀heterocycle, said aryl, and heterocycle optionally substituted with 1 to 3 groups of R^a; and

R⁷, R⁸, R⁹ and R¹⁰ independently represent hydrogen, halogen, CN, C₁-6alkyl, C(O)N(R)₂, C(O)(CH₂)_nC₅₋₁₀heterocycle, (CH₂)_nC₆₋₁₀aryl, or (CH₂)_nC₅₋₁₀heterocycle, said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of R^a. A subembodiment of this aspect of the invention is realized when the R^a substituents are selected from OR, halogen, C₁-6alkyl, and N(R)₂.

A subembodiment of the invention of formula I wherein B is represented by structural formulas (a), (b), (c), (d), (e), (f), or (g) is realized when R⁶ is selected from the group

consisting of unsubstituted or substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazoly, oxazolyl, and pyrimidinyl.

Another subembodiment of the invention of formula I wherein B is represented by structural formulas (a), (b), (c), (d), (e), (f), or (g) is realized when R⁸ and R⁹ are independently selected from hydrogen, halogen, CN, CH₂OH, C(O)N(R)₂, optionally substituted C₁₋₆alkyl, phenyl, pyrazolyl, isoxazolyl, oxazolyl, (CH₂)_nazetidiny, and C(O)NHazetidiny.

Another subembodiment of the invention of formula I wherein B is represented by structural formulas (a), (b), (c), (d), (e), (f), or (g) is realized when R⁷ and R¹⁰ are independently selected from hydrogen, C₁₋₆alkyl, and halogen, said alkyl optionally substituted with 1 to 3 groups of R^a. A subembodiment of this aspect of the invention is realized when the R^a substituents are selected from OR, halogen, C₁₋₆alkyl, and N(R)₂.

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

Still another embodiment of the invention of formula I wherein B is imidazopyridinyl represented by structural formula (a) is realized when R⁶ is unsubstituted or substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazoly, oxazolyl, and pyrimidinyl. A subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted phenyl. Another subembodiment of this aspect of the invention is realized when R⁶ is substituted phenyl. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted thiazolyl. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted pyrazoly. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted pyridyl. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted pyrimidinyl. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted isoxazolyl. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted oxazolyl.

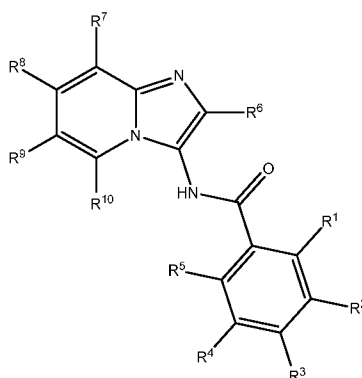
Another embodiment of the invention of formula I wherein B is imidazopyridinyl represented by structural formula (a) is realized when R⁸ and R⁹ are independently selected from hydrogen, halogen, CN, CH₂OH, C(O)N(R)₂, optionally substituted C₁₋₆alkyl, phenyl, pyrazolyl, isoxazolyl, oxazolyl, (CH₂)_nazetidiny, and C(O)NHazetidiny. A subembodiment of this aspect of the invention is realized when R⁸ and R⁹ are both hydrogen. Another subembodiment of this aspect of the invention is realized when one of R⁸ and R⁹ is hydrogen and the other is halogen, CN, CH₂OH, C(O)N(R)₂, optionally substituted C₁₋₆alkyl, phenyl, pyrazolyl, isoxazolyl, oxazolyl, (CH₂)_nazetidiny, or C(O)NHazetidiny.

Another embodiment of the invention of formula I wherein B is imidazopyridinyl represented by structural formula (a) is realized when R⁷ and R¹⁰ are independently selected

from hydrogen, C₁₋₆alkyl, and halogen, said alkyl optionally substituted with 1 to 3 groups of R^b. A subembodiment of this invention is realized when both R⁷ and R¹⁰ are hydrogen.

Another embodiment of the invention of formula I wherein B is imidazopyridinyl represented by structural formula (a) is realized when R⁷, R⁸, R⁹ and R¹⁰ are all hydrogen.

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



II

or a pharmaceutically acceptable salt thereof, wherein:

R¹ and R⁵ are as originally described, R⁶ is unsubstituted or substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazolyl, oxazolyl, or pyrimidinyl, R⁸ and R⁹ are independently selected from hydrogen, halogen, CN, CH₂OH, C(O)N(R)₂, optionally substituted C₁₋₆alkyl, phenyl, pyrazolyl, isoxazolyl, oxazolyl, (CH₂)_nazetidiny, and C(O)NHazetidiny, R⁷ and R¹⁰ are independently selected from hydrogen, C₁₋₆alkyl, and halogen, said alkyl optionally substituted with 1 to 3 groups selected from OR, halogen, C₁₋₆alkyl, and N(R)₂, R³ is selected from the group consisting of hydrogen, CF₃, OCF₃, CH₃, chlorine, and fluorine, and one of R² and R⁴ is hydrogen and the other is (CHR)_nC₅₋₁₀ heterocycle, said heterocycle optionally substituted with 1 to 3 groups of R^a. A subembodiment of the invention of formula II is realized when R³ is CF₃, one of R² and R⁴ is hydrogen and the other is a (CHR)_nC₅₋₁₀ heterocycle that is a five or six membered ring containing one or more heteroatoms at least one of which is nitrogen. Still another subembodiment of the invention of formula II is realized when the optionally substituted heterocycle of R² and R⁴ is selected from the group consisting of pyrazolyl, pyridyl, thiazolyl, oxazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiadiazolyl, oxadiazolyl, and triazolyl, said groups optionally substituted. Yet another subembodiment of the invention of formula II is realized when the optionally substituted heterocycle of R² and R⁴ is pyrazolyl, R⁶ is optionally substituted phenyl and R³ is CF₃.

Another embodiment of the invention of formula I is realized when B is optionally imidazopyrimidinyl represented by structural formula (b).

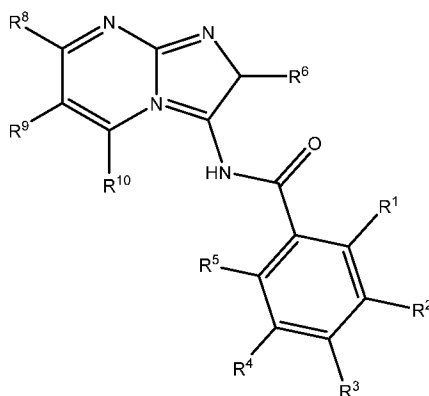
Still another embodiment of the invention of formula I wherein B is imidazopyrimidinyl represented by structural formula (b) is realized when R⁶ is unsubstituted or substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazolyl, oxazolyl, and pyrimidinyl. A subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted phenyl. Another subembodiment of this aspect of the invention is realized when R⁶ is substituted phenyl. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted thiazolyl. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted pyrazolyl. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted pyridyl. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted pyrimidinyl. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted isoxazolyl. Another subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted oxazolyl.

Another embodiment of the invention of formula I wherein B is imidazopyrimidinyl represented by structural formula (b) is realized when R⁸ and R⁹ are independently selected from hydrogen, halogen, CN, CH₂OH, C(O)N(R)₂, optionally substituted C₁-6alkyl, phenyl, pyrazolyl, isoxazolyl, oxazolyl, (CH₂)_nazetidiny, and C(O)NHazetidiny. A subembodiment of this aspect of the invention is realized when R⁸ and R⁹ are both hydrogen. Another subembodiment of this aspect of the invention is realized when one of R⁸ and R⁹ is hydrogen and the other is halogen, CN, CH₂OH, C(O)N(R)₂, optionally substituted C₁-6alkyl, phenyl, pyrazolyl, isoxazolyl, oxazolyl, (CH₂)_nazetidiny, or C(O)NHazetidiny.

Another embodiment of the invention of formula I wherein B is imidazopyrimidinyl represented by structural formula (b) is realized when R⁷ and R¹⁰ are independently selected from hydrogen, C₁-6alkyl, and halogen, said alkyl optionally substituted with 1 to 3 groups of R^b. A subembodiment of this invention is realized when both R⁷ and R¹⁰ are hydrogen.

Another embodiment of the invention of formula I wherein B is imidazopyrimidinyl represented by structural formula (b) is realized when R⁷, R⁸, R⁹ and R¹⁰ are all hydrogen.

Another embodiment of the invention of formula I is represented by structural formula III when B is imidazopyrimidinyl:



III

or a pharmaceutically acceptable salt thereof, wherein R¹ and R⁵ are as originally described, R⁶ is unsubstituted or substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazolyl, oxazolyl, or pyrimidinyl, R⁸ and R⁹ are independently selected from hydrogen, halogen, CN, CH₂OH, C(O)N(R)₂, optionally substituted C₁₋₆alkyl, phenyl, pyrazolyl, isoxazolyl, oxazolyl, (CH₂)_nazetidiny, and C(O)NHazetidiny, R⁷ and R¹⁰ are independently selected from hydrogen, C₁₋₆alkyl, and halogen, said alkyl optionally substituted with 1 to 3 groups selected from OR, halogen, C₁₋₆alkyl, and N(R)₂, R³ is selected from the group consisting of hydrogen, CF₃, OCF₃, CH₃, chlorine, and fluorine, and one of R² and R⁴ is hydrogen and the other is (CHR)_nC₅₋₁₀ heterocycle, said heterocycle optionally substituted with 1 to 3 groups of R^a.

Another subembodiment of this aspect of the invention of formula III is realized when R³ is CF₃, one of R² and R⁴ is hydrogen and the other is a (CHR)_nC₅₋₁₀ heterocycle that 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 of formula III is realized when the optionally substituted heterocycle of R² and R⁴ is selected from the group consisting of pyrazolyl, pyridyl, thiazolyl, oxazolyl, pyrimidinyl, and triazolyl, said groups optionally substituted. Yet another subembodiment of this aspect of the invention of formula III is realized when the optionally substituted heterocycle of R² and R⁴ is pyrazolyl, R⁶ is optionally substituted phenyl and R³ is CF₃.

Another embodiment of the invention of formula I is realized when B is imidazopyridazinyl represented by structural formula (c). A subembodiment of this aspect of the invention of formula I when B is imidazopyridazinyl is realized when R⁶ is unsubstituted or substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazolyl, oxazolyl, or pyrimidinyl, R⁸ and R⁹ are independently selected from hydrogen, halogen, CN, CH₂OH, C(O)N(R)₂, optionally substituted C₁₋₆alkyl, phenyl, pyrazolyl, isoxazolyl, oxazolyl, (CH₂)_nazetidiny, and C(O)NHazetidiny, R⁷ is selected from hydrogen, C₁₋₆alkyl, and halogen, said alkyl optionally substituted with 1 to 3 groups of R^b, R³ is selected from the group consisting of hydrogen, CF₃, OCF₃, CH₃, and fluorine, and one of R² and R⁴ is hydrogen and the other is (CHR)_nC₅₋₁₀ heterocycle, said heterocycle optionally substituted with 1 to 3 groups of R^a. Another subembodiment of this aspect of the invention of formula I when B is imidazopyridazinyl is realized when R³ is CF₃, one of R² and R⁴ is hydrogen and the other is a (CHR)_nC₅₋₁₀ heterocycle that 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 of formula I when B is imidazopyridazinyl is realized when the optionally substituted heterocycle of R² and R⁴ is selected from the group consisting of pyrazolyl, pyridyl, thiazolyl, oxazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiadiazolyl, oxadiazolyl, and triazolyl, said groups optionally substituted. Yet another subembodiment of this aspect of the invention of formula I when B is

imidazopyridazinyl is realized when the optionally substituted heterocycle of R² and R⁴ is pyrazolyl, R⁶ is optionally substituted phenyl and R³ is CF₃.

Another embodiment of the invention of formula I is realized when B is

pyrazolopyridinyl represented by structural formula (d). A subembodiment of this aspect of the

invention of formula I when B is pyrazolopyridinyl of structural formula (d) is realized when R⁶

is unsubstituted or substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazolyl, oxazolyl, or

pyrimidinyl, R⁸ and R⁹ are independently selected from hydrogen, halogen, CN, CH₂OH,

C(O)N(R)₂, optionally substituted C₁-6alkyl, phenyl, pyrazolyl, isoxazolyl, oxazolyl,

(CH₂)_nazetidiny, and C(O)NHazetidiny, R¹⁰ is selected from hydrogen, C₁-6alkyl, and

halogen, said alkyl optionally substituted with 1 to 3 groups of R^b, R³ is selected from the group

consisting of hydrogen, CF₃, OCF₃, CH₃, and fluorine, and one of R² and R⁴ is hydrogen and

the other is (CHR)_nC₅₋₁₀ heterocycle, said heterocycle optionally substituted with 1 to 3 groups

of R^a. Another subembodiment of this aspect of the invention of formula I when B is

pyrazolopyridinyl of structural formula (d) is realized when R³ is CF₃, one of R² and R⁴ is

hydrogen and the other is a (CHR)_nC₅₋₁₀ heterocycle that 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 of formula I when B is pyrazolopyridinyl of structural formula (d) is realized when the optionally substituted heterocycle of R² and R⁴ is

selected from the group consisting of pyrazolyl, pyridyl, thiazolyl, oxazolyl, pyrimidinyl,

pyridazinyl, pyrazinyl, thiadiazolyl, oxadiazolyl, and triazolyl, said groups optionally

substituted. Yet another subembodiment of this aspect of the invention of formula I when B is

pyrazolopyridinyl of structural formula (d) is realized when the optionally substituted

heterocycle of R² and R⁴ is pyrazolyl, R⁶ is optionally substituted phenyl and R³ is CF₃.

Another embodiment of the invention of formula I is realized when B is

imidazothiadiazolyl represented by structural formula (e). A subembodiment of this aspect of

the invention of formula I when B is imidazothiadiazolyl is realized when R⁶ is unsubstituted or

substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazolyl, oxazolyl, or pyrimidinyl, R³ is

selected from the group consisting of hydrogen, CF₃, OCF₃, CH₃, and fluorine, and one of R²

and R⁴ is hydrogen and the other is (CHR)_nC₅₋₁₀ heterocycle, said heterocycle optionally

substituted with 1 to 3 groups of R^a. Another subembodiment of this aspect of the invention of

formula I when B is imidazothiadiazolyl is realized when R³ is CF₃, one of R² and R⁴ is

hydrogen and the other is a (CHR)_nC₅₋₁₀ heterocycle that 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 of formula I when B is imidazothiadiazolyl is

realized when the optionally substituted heterocycle of R² and R⁴ is selected from the group

consisting of pyrazolyl, pyridyl, thiazolyl, oxazolyl, pyrimidinyl, pyridazinyl, pyrazinyl,

thiadiazolyl, oxadiazolyl, and triazolyl, said groups optionally substituted. Yet another

subembodiment of this aspect of the invention of formula I when B is imidazothiadiazolyl is realized when the optionally substituted heterocycle of R² and R⁴ is pyrazolyl, R⁶ is optionally substituted phenyl and R³ is CF₃.

5 Another embodiment of the invention of formula I is realized when B is imidazothiazolyl represented by structural formula (f). A subembodiment of this aspect of the invention is realized when R⁶ is unsubstituted or substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazolyl, oxazolyl, or pyrimidinyl. Another subembodiment of this aspect of the invention of formula I when B is imidazothiazolyl is realized when R³ is CF₃, one of R² and R⁴ is hydrogen and the
10 other is a (CHR)_nC₅₋₁₀ heterocycle that 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 of formula I when B is imidazothiazolyl is realized when the optionally substituted heterocycle of R² and R⁴ is selected from the group consisting of pyrazolyl, pyridyl, thiazolyl, oxazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiadiazolyl, oxadiazolyl, and triazolyl, said
15 groups optionally substituted. Yet another subembodiment of this aspect of the invention of formula I when B is imidazothiazolyl is realized when the optionally substituted heterocycle of R² and R⁴ is pyrazolyl, R⁶ is optionally substituted phenyl and R³ is CF₃.

Another embodiment of the invention of formula I is realized when B is indolyl represented by structural formula (g). A subembodiment of this aspect of the invention of
20 formula I when B is indolyl is realized when R⁶ is unsubstituted or substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazolyl, oxazolyl, or pyrimidinyl, R³ is selected from the group consisting of hydrogen, CF₃, OCF₃, CH₃, and fluorine, and one of R² and R⁴ is hydrogen and the other is (CHR)_nC₅₋₁₀ heterocycle, said heterocycle optionally substituted with 1 to 3 groups of R^a.

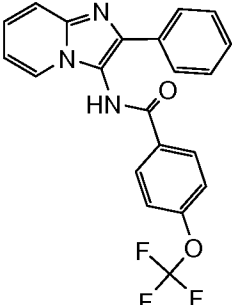
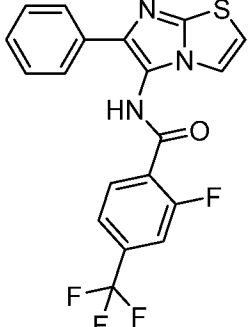
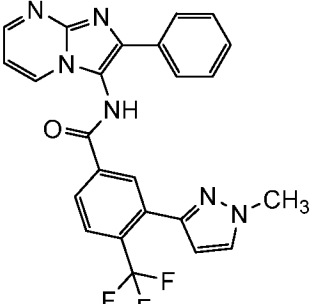
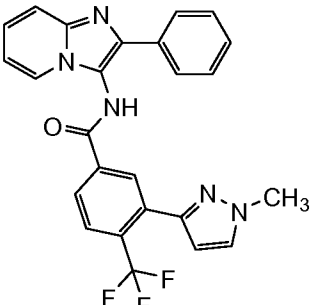
Another subembodiment of this aspect of the invention of formula I when B is indolyl is realized
25 when R³ is CF₃, one of R² and R⁴ is hydrogen and the other is a (CHR)_nC₅₋₁₀ heterocycle that is a five or six membered ring containing one or more heteroatoms at least one of which is nitrogen. Still another subembodiment of this aspect of the invention of formula I when B is indolyl is realized when the optionally substituted heterocycle of R² and R⁴ is selected from the group consisting of pyrazolyl, pyridyl, thiazolyl, oxazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiadiazolyl, oxadiazolyl, and triazolyl, said groups optionally substituted. Yet another
30 subembodiment of this aspect of the invention of formula I when B is indolyl is realized when the optionally substituted heterocycle of R² and R⁴ is pyrazolyl, R⁶ is optionally substituted phenyl and R³ is CF₃.

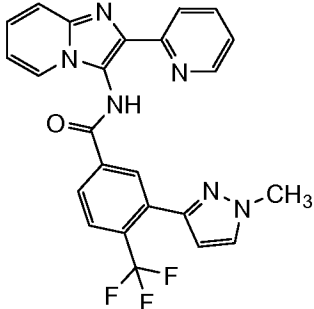
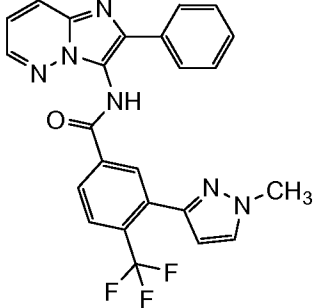
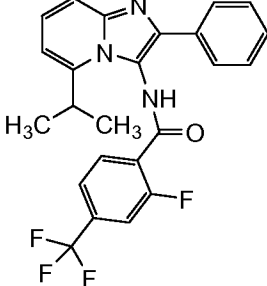
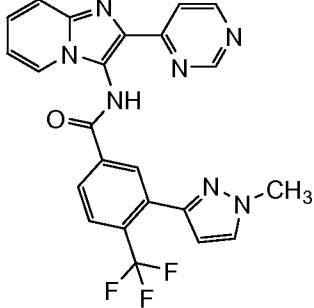
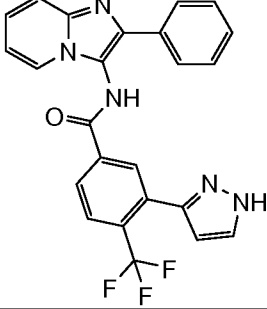
Examples of compounds of this invention include those in Table 1:

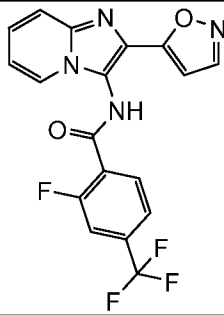
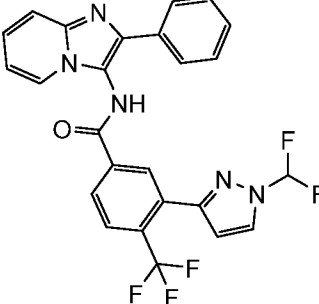
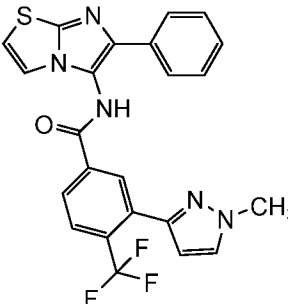
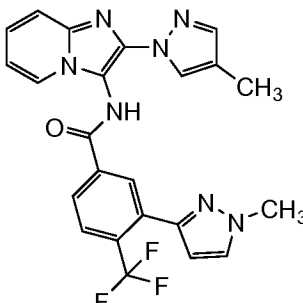
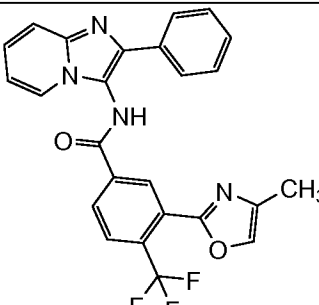
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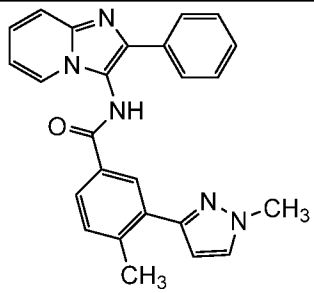
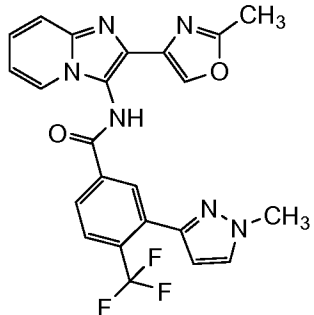
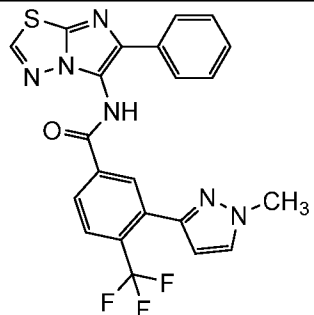
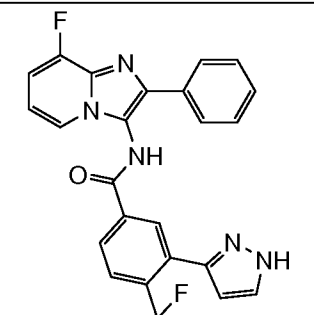
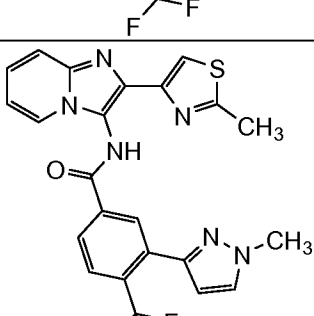
Table 1

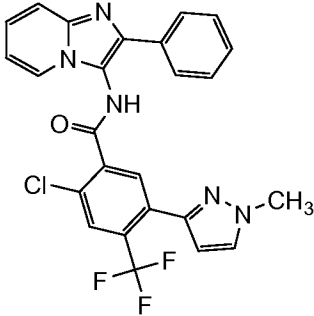
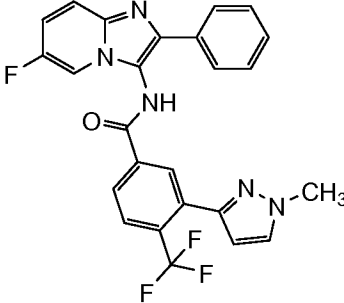
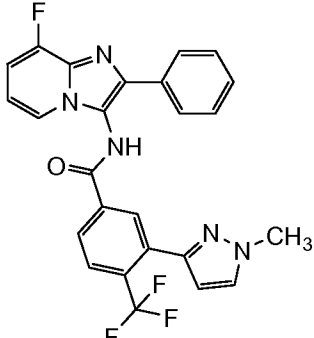
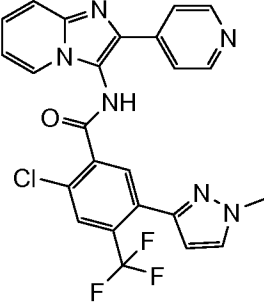
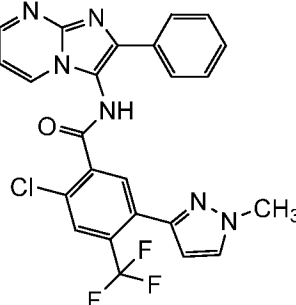
Com	Structure	Compound Name	LCMS
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pound Number			(M+1)
1		N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethoxy)benzamide	398.3
2		2-fluoro-N-(6-phenylimidazo[2,1-b][1,3]thiazol-5-yl)-4-(trifluoromethyl)benzamide	406.2
3		3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyrimidin-3-yl)-4-(trifluoromethyl)benzamide	463.1
4		3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	462.2

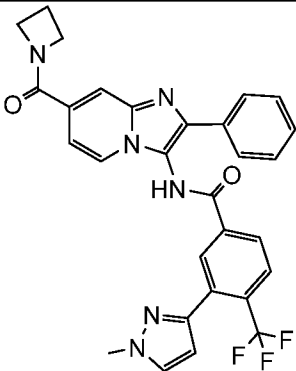
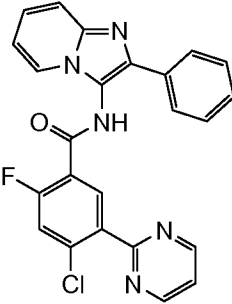
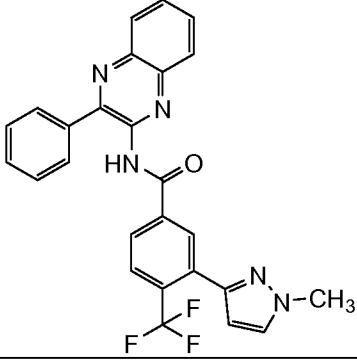
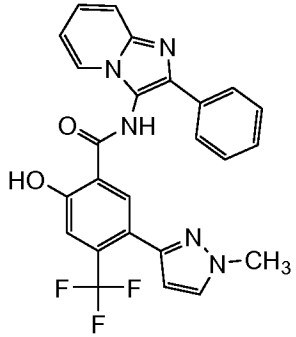
5		3-(1-methyl-1H-pyrazol-3-yl)-N-(2-pyridin-2-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	463.0
6		3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-b]pyridazin-3-yl)-4-(trifluoromethyl)benzamide	463.1
7		2-fluoro-N-[5-(1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	442.1
8		3-(1-methyl-1H-pyrazol-3-yl)-N-(2-pyrimidin-4-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	464.0
9		N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	448.0

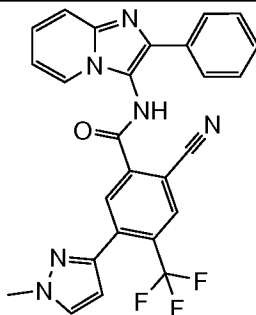
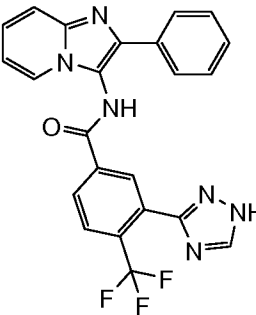
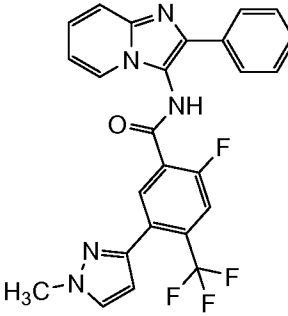
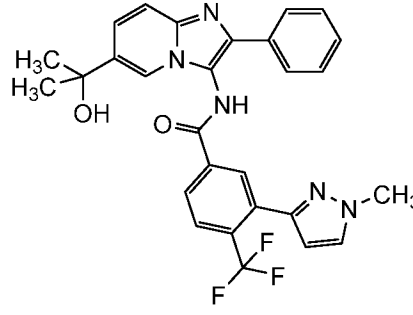
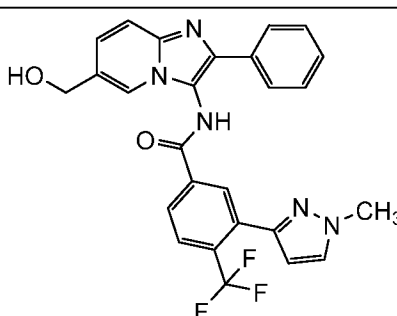
10		2-fluoro-N-(2-isoxazol-5-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	391.2
11		3-[1-(difluoromethyl)-1H-pyrazol-3-yl]-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	498.0
12		3-(1-methyl-1H-pyrazol-3-yl)-N-(6-phenylimidazo[2,1-b][1,3]thiazol-5-yl)-4-(trifluoromethyl)benzamide	468.0
13		3-(1-methyl-1H-pyrazol-3-yl)-N-[2-(4-methyl-1H-pyrazol-1-yl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	466.0
14		3-(4-methyl-1,3-oxazol-2-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	463.0

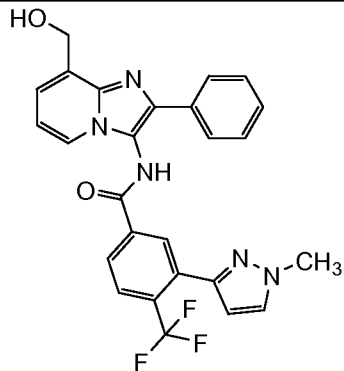
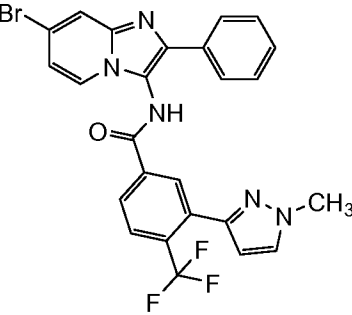
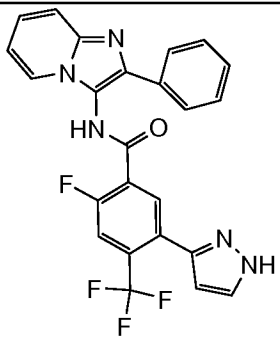
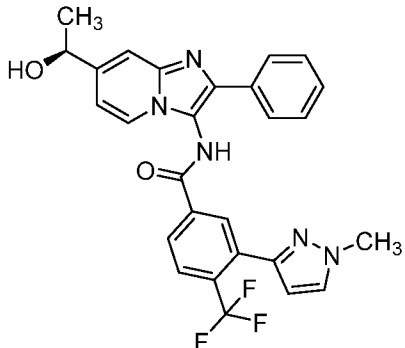
15		4-methyl-3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)benzamide	408.0
16		N-[2-(2-methyl-1,3-oxazol-4-yl)imidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	467.0
17		3-(1-methyl-1H-pyrazol-3-yl)-N-(6-phenylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)-4-(trifluoromethyl)benzamide	469.1
18		N-(8-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	466.1
19		3-(1-methyl-1H-pyrazol-3-yl)-N-[2-(2-methyl-1,3-thiazol-4-yl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	483.1

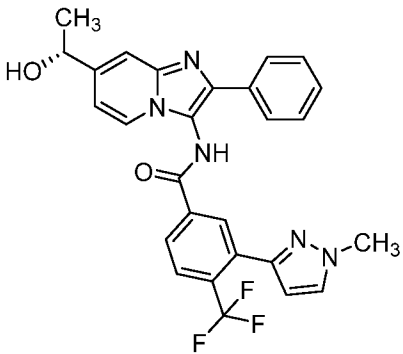
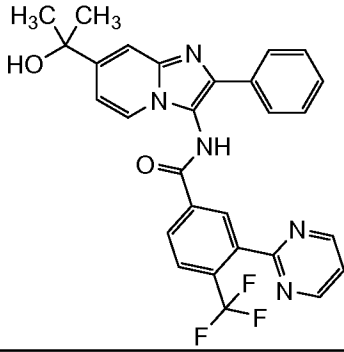
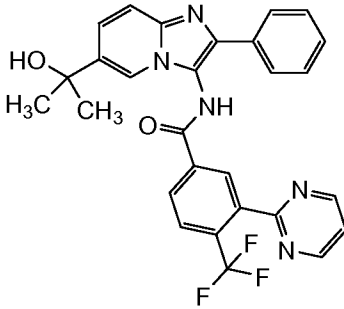
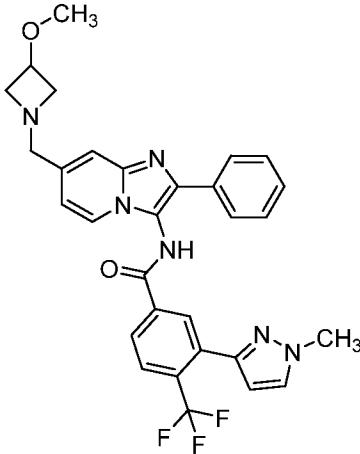
20		2-chloro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	496.1
21		N-(6-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	480.1
22		N-(8-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	480.2
23		2-chloro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-pyridin-4-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	497.1
24		2-chloro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyrimidin-3-yl)-4-(trifluoromethyl)benzamide	497.1

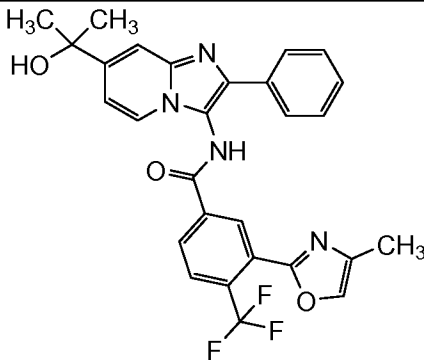
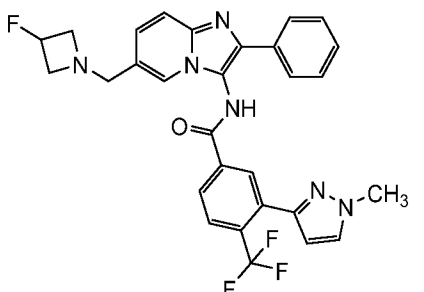
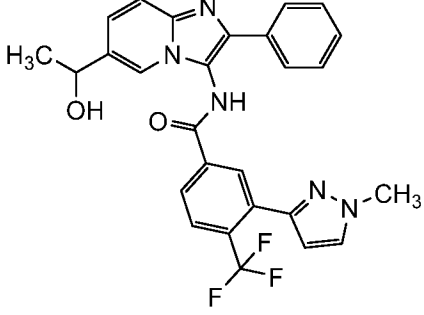
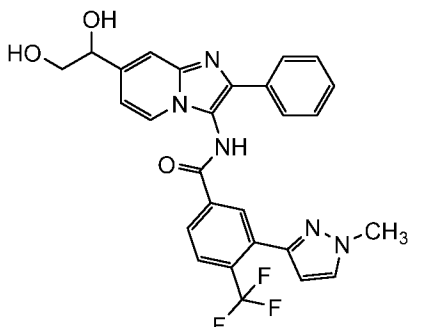
25		N-methyl-3-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-2-phenylimidazo[1,2-a]pyridine-7-carboxamide	519.4
26		N-[7-(hydroxymethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	492.2
27		N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	520.2
28		N,N-dimethyl-3-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-2-phenylimidazo[1,2-a]pyridine-7-carboxamide	533.4

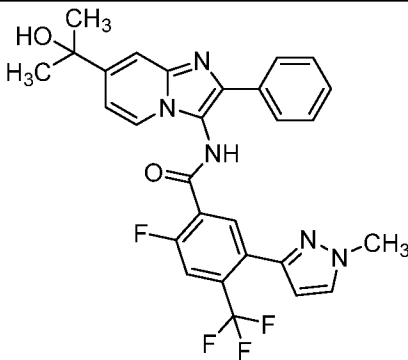
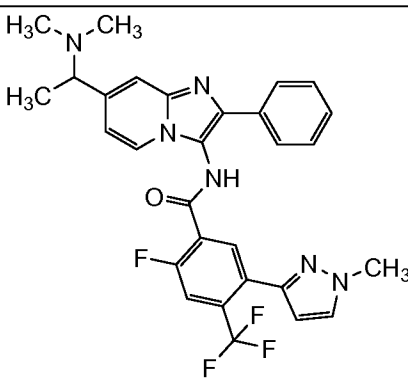
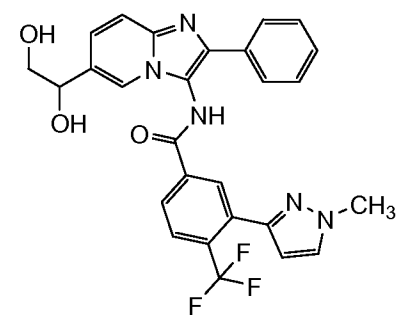
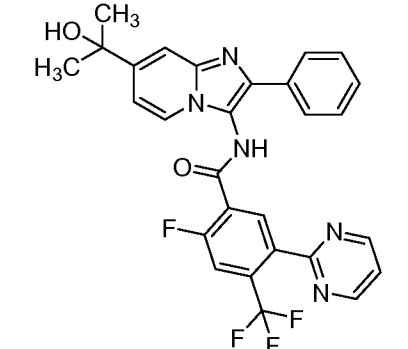
29		N-[7-(azetidin-1-ylcarbonyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	545.4
30		4-chloro-2-fluoro-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-5-pyrimidin-2-ylbenzamide	444.0
31		3-(1-methyl-1H-pyrazol-3-yl)-N-(3-phenylquinoxalin-2-yl)-4-(trifluoromethyl)benzamide	474.2
32		2-hydroxy-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	478.2

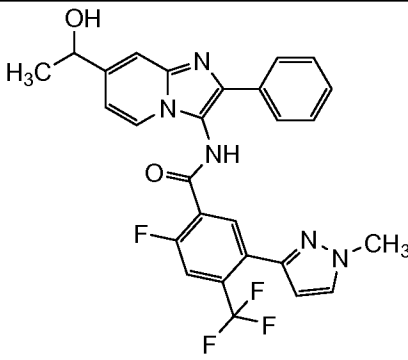
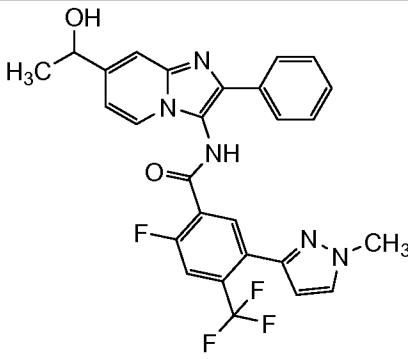
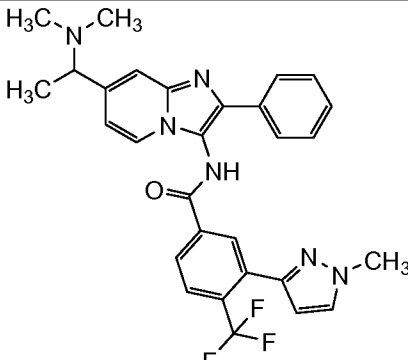
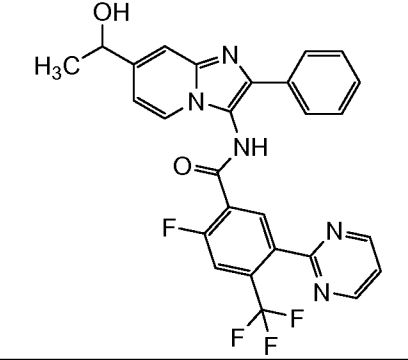
33		2-cyano-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	487.2
34		N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)benzamide	449.2
35		2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	480.2
36		N-[6-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	520.2
37		N-[6-(hydroxymethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	492.2

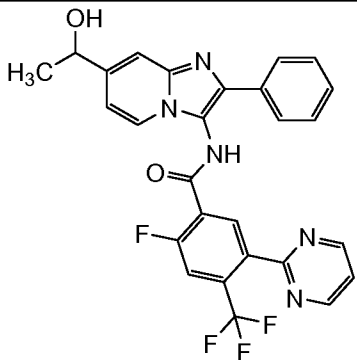
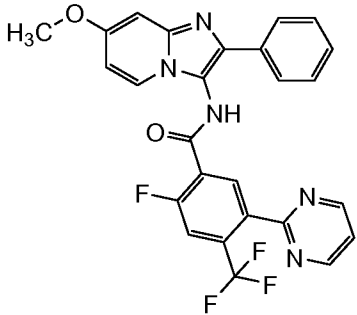
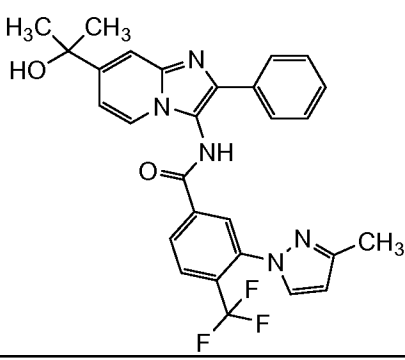
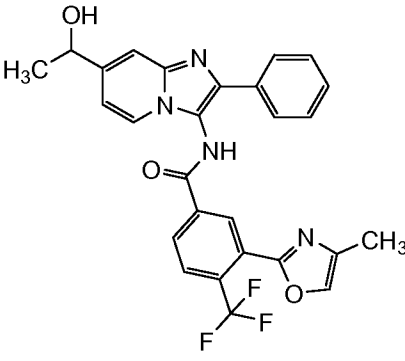
38		N-[8-(hydroxymethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	492.2
39		N-(7-bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	541.8
40		2-fluoro-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	466.2
41		N-{7-[(1S)-1-hydroxyethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	506.2

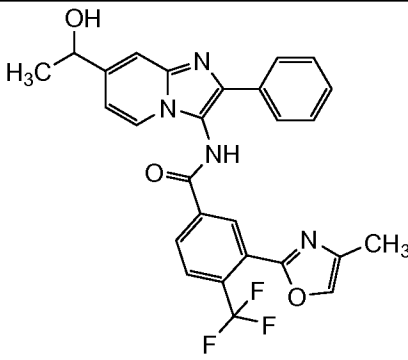
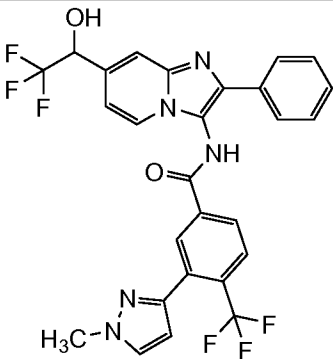
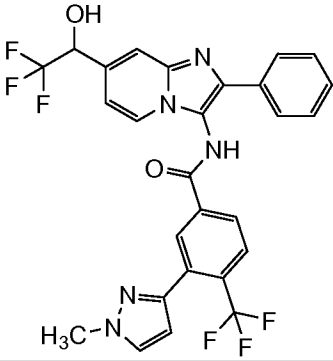
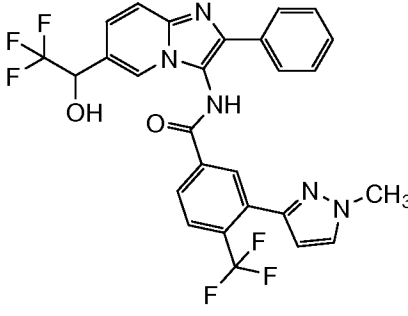
42		N-{7-[(1R)-1-hydroxyethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	506.2
43		N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	518.2
44		N-[6-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	518.2
45		N-{7-[(3-methoxyazetidin-1-yl)methyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	561.1

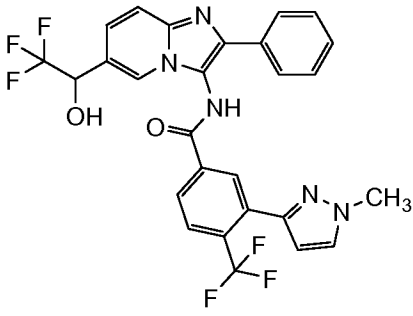
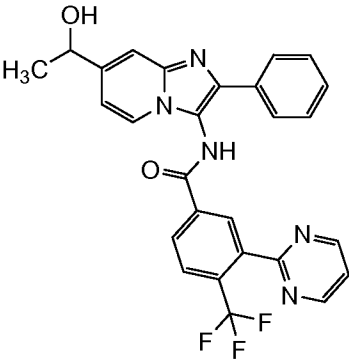
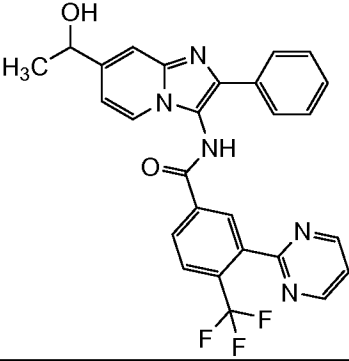
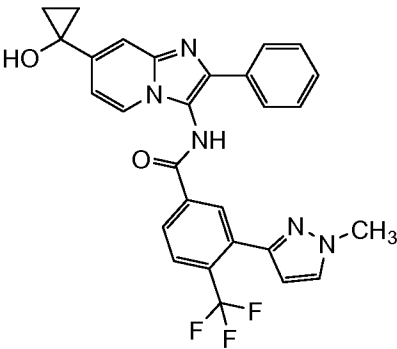
46		N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(4-methyl-1,3-oxazol-2-yl)-4-(trifluoromethyl)benzamide	521.2
47		N-{6-[(3-fluoroazetidin-1-yl)methyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	549.1
48		(R or S)-N-[6-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	506.0
49		(R or S)-N-[7-(1,2-dihydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	522.0

50		2-fluoro-N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	538.1
51		(R or S)-N-{7-[1-(dimethylamino)ethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	551.2
52		(R or S)-N-[6-(1,2-dihydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	522.2
53		2-fluoro-N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	536.2

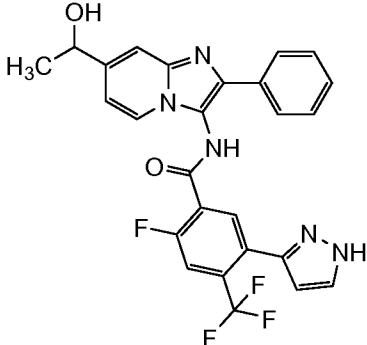
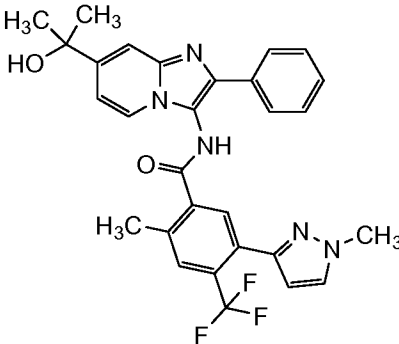
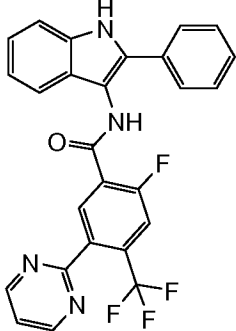
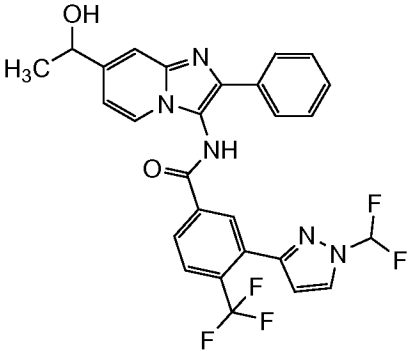
54		(R or S)-2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	524.2
55		(R or S)-2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	524.2
56		(R or S)-N-{7-[1-(dimethylamino)ethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	533.2
57		(R or S)-2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	522.2

58		(R or S)-2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	522.2
59		2-fluoro-N-(7-methoxy-2-phenylimidazo[1,2-a]pyridin-3-yl)-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	508.1
60		N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(3-methyl-1H-pyrazol-1-yl)-4-(trifluoromethyl)benzamide	520.4
61		(R or S)-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(4-methyl-1,3-oxazol-2-yl)-4-(trifluoromethyl)benzamide	507.4

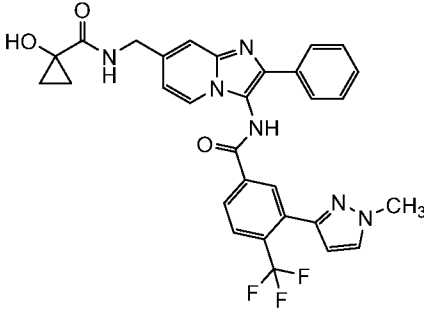
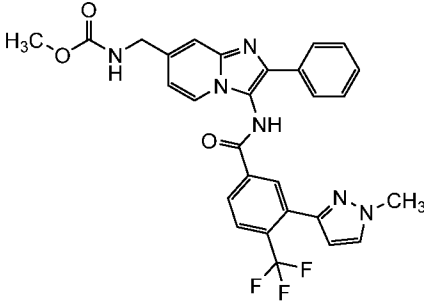
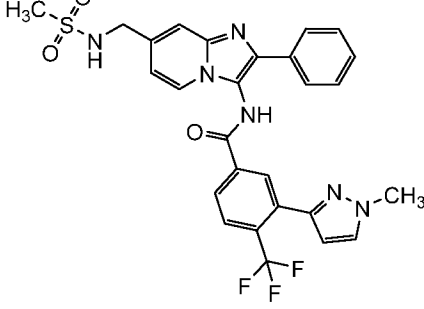
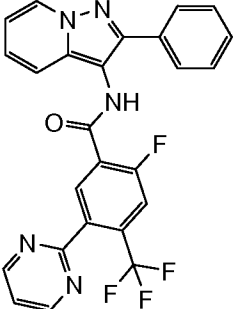
62		(R or S)-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(4-methyl-1,3-oxazol-2-yl)-4-(trifluoromethyl)benzamide	507.4
63		(R or S)-3-(1-methyl-1H-pyrazol-3-yl)-N-[2-phenyl-7-(2,2,2-trifluoro-1-hydroxyethyl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	560.3
64		(R or S)-3-(1-methyl-1H-pyrazol-3-yl)-N-[2-phenyl-7-(2,2,2-trifluoro-1-hydroxyethyl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	560.3
65		(R or S)-3-(1-methyl-1H-pyrazol-3-yl)-N-[2-phenyl-6-(2,2,2-trifluoro-1-hydroxyethyl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	560.3

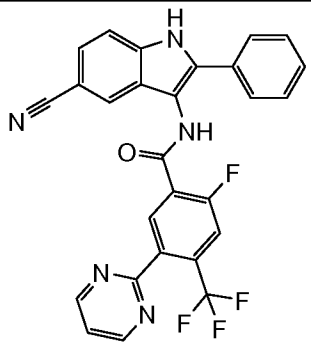
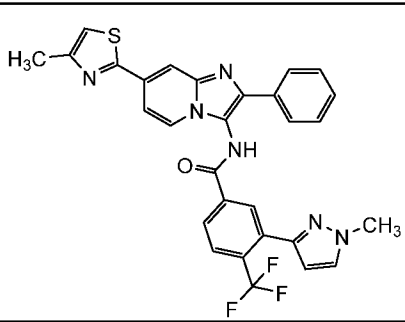
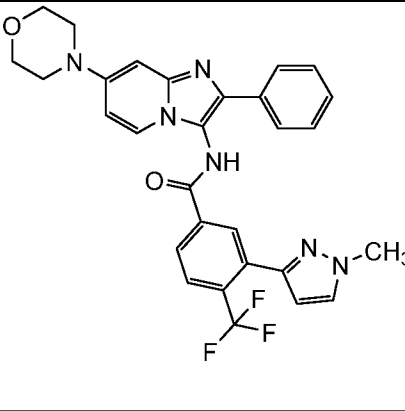
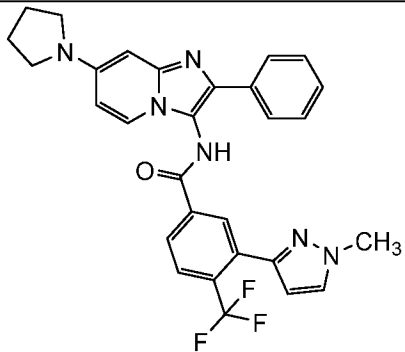
66		(R or S)-3-(1-methyl-1H-pyrazol-3-yl)-N-[2-phenyl-6-(2,2,2-trifluoro-1-hydroxyethyl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	560.3
67		(R or S)-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	504.4
68		(R or S)-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	504.4
69		N-[7-(1-hydroxycyclopropyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	518.2

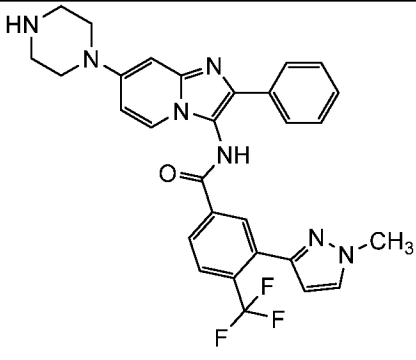
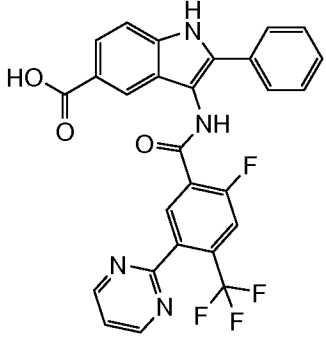
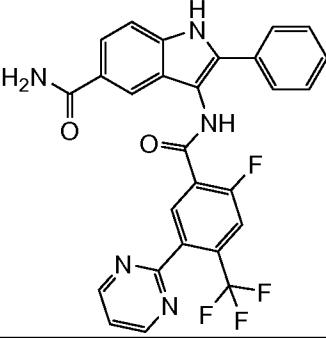
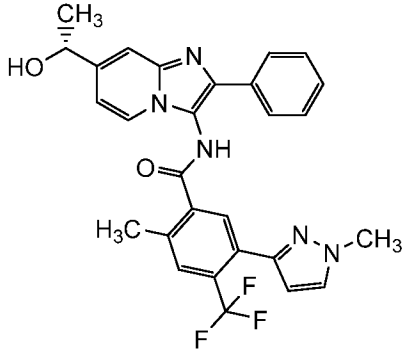
70		2-chloro-N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	554.3
71		2-chloro-N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(4-methylpyrimidin-2-yl)-4-(trifluoromethyl)benzamide	566.1
72		2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenyl-1H-indol-3-yl)-4-(trifluoromethyl)benzamide	479.9
73		(R or S)-2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	510.2

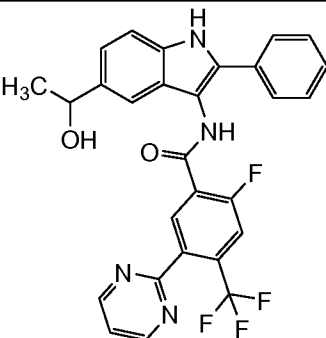
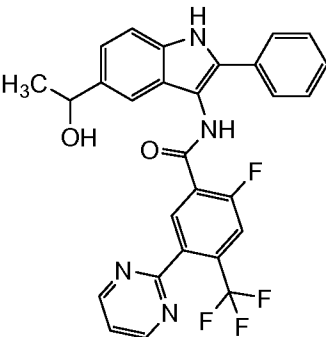
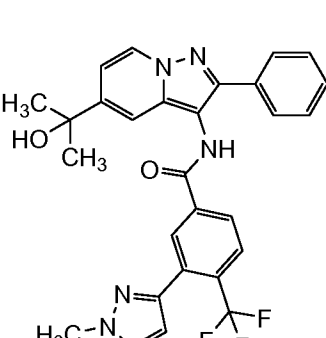
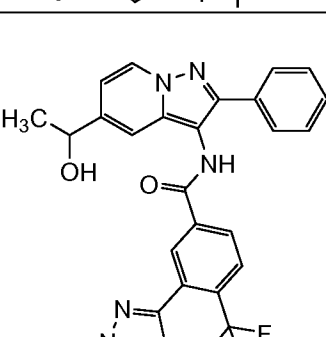
74		(R or S)-2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	510.2
75		N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-2-methyl-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	534.3
76		2-fluoro-N-(2-phenyl-1H-indol-3-yl)-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	476.9
77		(R or S)-3-[1-(difluoromethyl)-1H-pyrazol-3-yl]-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	542.2

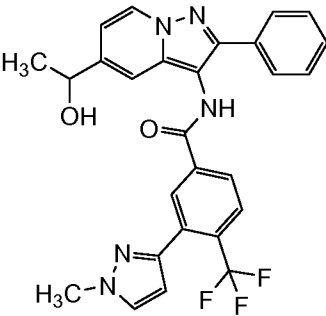
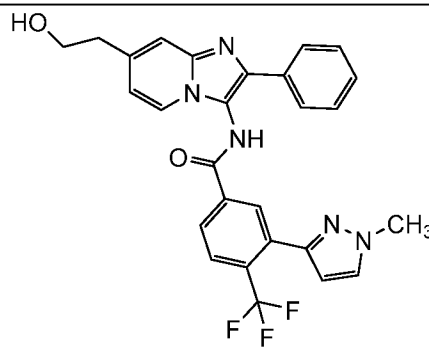
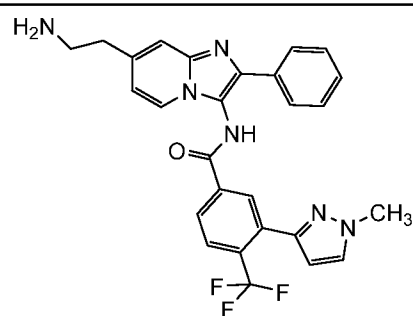
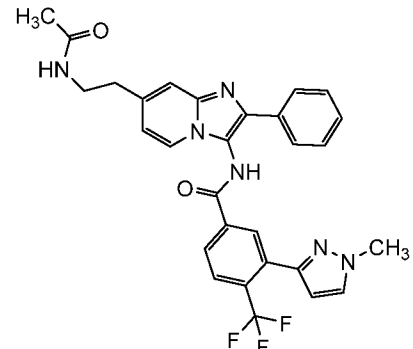
78		(R or S)-3-[1-(difluoromethyl)-1H-pyrazol-3-yl]-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	542.3
79		N-{7-[(acetylamino)methyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	533.2
80		N-(7-{[(hydroxyacetyl)amino]methyl}-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	549.3
81		N-(7-{[(methylcarbamoyl)amino]methyl}-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	548.4

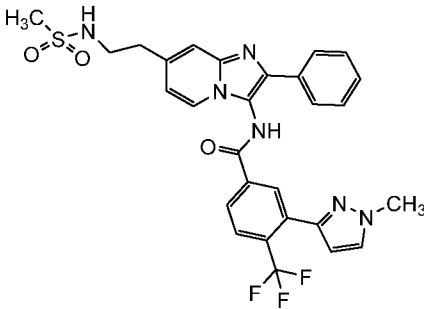
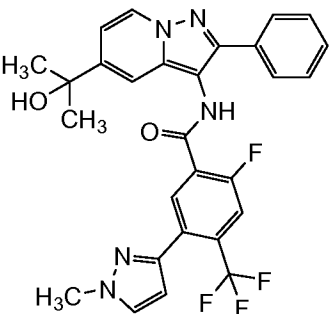
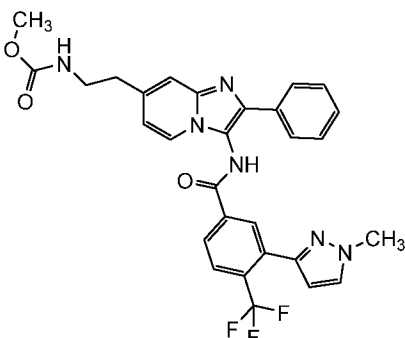
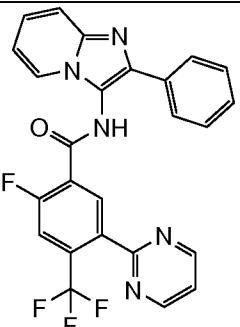
82		N-[7-({[(1-hydroxycyclopropyl)carbonyl]amino} methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	575.3
83		methyl {[3-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl} amino)-2-phenylimidazo[1,2-a]pyridin-7-yl]methyl}carbamate	549.2
84		3-(1-methyl-1H-pyrazol-3-yl)-N-(7-{{[(methylsulfonyl)amino]methyl}-2-phenylimidazo[1,2-a]pyridin-3-yl}-4-(trifluoromethyl)benzamide	569.3
85		2-fluoro-N-(2-phenylpyrazolo[1,5-a]pyridin-3-yl)-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	477.9

86		N-(5-cyano-2-phenyl-1H-indol-3-yl)-2-fluoro-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	501.9
87		3-(1-methyl-1H-pyrazol-3-yl)-N-[7-(4-methyl-1,3-thiazol-2-yl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	559.3
88		3-(1-methyl-1H-pyrazol-3-yl)-N-(7-morpholin-4-yl-2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	547.3
89		3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenyl-7-pyrrolidin-1-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	531.3

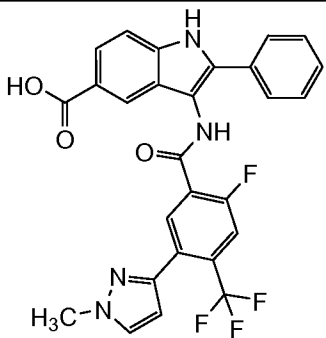
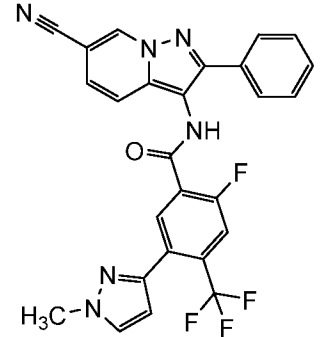
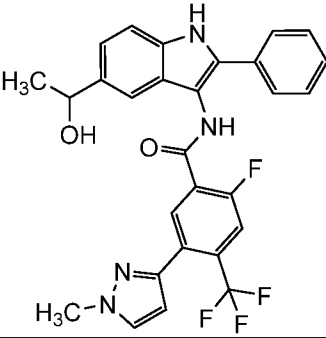
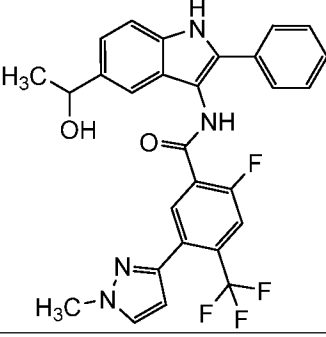
90		3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenyl-7-piperazin-1-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	546.3
91		3-({[2-fluoro-5-pyrimidin-2-yl-4-(trifluoromethyl)phenyl]carbonyl}amino)-2-phenyl-1H-indole-5-carboxylic acid	520.1
92		3-({[2-fluoro-5-pyrimidin-2-yl-4-(trifluoromethyl)phenyl]carbonyl}amino)-2-phenyl-1H-indole-5-carboxamide	520.1
93		N-{7-[(1R)-1-hydroxyethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-2-methyl-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	520.3

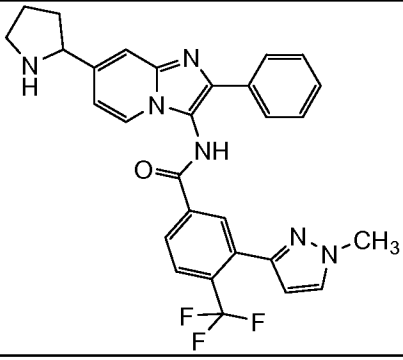
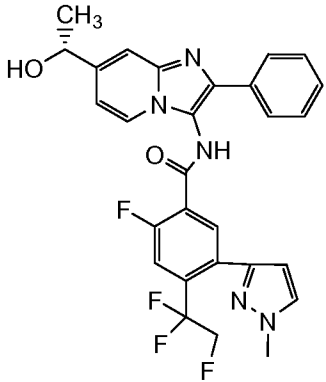
94		(R or S)-2-fluoro-N-[5-(1-hydroxyethyl)-2-phenyl-1H-indol-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	521.1
95		(R or S)-2-fluoro-N-[5-(1-hydroxyethyl)-2-phenyl-1H-indol-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	521.1
96		N-[5-(1-hydroxy-1-methylethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	520.1
97		(R or S)-N-[5-(1-hydroxyethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	506.1

98		(R or S)-N-[5-(1-hydroxyethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	506.1
99		N-[7-(2-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	506.2
100		N-[7-(2-aminoethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	505.2
101		N-{7-[2-(acetylamino)ethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	547.2

102		3-(1-methyl-1H-pyrazol-3-yl)-N-(7-{2-[(methylsulfonyl)amino]ethyl}-2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	583.1
103		2-fluoro-N-[5-(1-hydroxy-1-methylethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	538.1
104		methyl {2-[3-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-2-phenylimidazo[1,2-a]pyridin-7-yl]ethyl} carbamate	563.2
105		2-fluoro-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	478.3

106		(R or S)-2-fluoro-N-[(1-hydroxyethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	524.2
107		(R or S)-2-fluoro-N-[(1-hydroxyethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	524.2
108		N-(5-cyano-2-phenyl-1H-indol-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	504.1
109		N-{7-[2-(methylamino)ethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	519.2

110		3-({[2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-2-phenyl-1H-indole-5-carboxylic acid	522.2
111		N-(6-cyano-2-phenylpyrazolo[1,5-a]pyridin-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	505.8
112		(R or S)-2-fluoro-N-[5-(1-hydroxyethyl)-2-phenyl-1H-indol-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	521.1
113		(R or S)-2-fluoro-N-[5-(1-hydroxyethyl)-2-phenyl-1H-indol-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	521.1

114		(R or S)-3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenyl-7-pyrrolidin-2-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	531.2
115		2-fluoro-N-{7-[(1R)-1-hydroxyethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-5-(1-methyl-1H-pyrazol-3-yl)-4-(1,1,2-trifluoroethyl)benzamide	538.0

or pharmaceutically acceptable salts thereof.

5 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
10 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
15 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
20 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.

5 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
10 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.

15 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.*, C₁₋₁₀ alkyl means an alkyl group having from one to ten carbon atoms). Preferred alkyl groups for use in the invention are C₁₋₆ alkyl groups, having from one to six atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl,
20 *tert*-butyl, pentyl, hexyl, and the like. C₀ 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.*, C₂₋₁₀ alkenyl means an alkenyl group having from two to ten carbon atoms). Preferred alkenyl groups for use in the invention are C₂₋₆ alkenyl
25 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.*, C₃₋₁₂ cycloalkyl means a cycloalkyl group having from three to twelve carbon atoms). The term
30 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 C₃₋₈ cycloalkyl groups, having from three to eight carbon atoms. Exemplary monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. Exemplary bridged
35 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.

5 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
10 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
15 moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzodioxolyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzotriazolyl, benzoxazolyl, chromanyl, cinnolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolyl,
20 imidazolyl, indolyl, indolyl, isochromanyl, isoindolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrazolopyridinyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalyl, tetrahydrofuryl, tetrahydroisoquinolyl,
25 tetrahydroquinolyl, thiamorpholyl, thiamorpholyl sulfoxide, thiazolyl, thiazolyl, 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,
30 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
35 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 $\text{C}=\text{O}$ 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 (^1H) and deuterium (^2H). 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/neurotrophin 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 may 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 may also be 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-induced 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
5 virtually any lesion at any level of the nervous system); postsurgical pain syndromes (eg, 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, dysmenorrhea, as well as pain associated with angina, and inflammatory pain of varied origins
10 (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
15 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
20 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. 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
25 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
30 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
35 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 B1 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 B15 ("MAO-B") inhibitors; 5HT receptor agonists or antagonists; mGlu5 antagonists; alpha agonists; neuronal nicotinic agonists; NMDA receptor agonists or antagonists; NK1 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 aspect 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.

Dysregulation of Trk kinases either by mutation, overexpression, activation, and/or amplification have been shown to be associated with many cancers. Thus, an embodiment of the instant invention relates to a method of treating a patient diagnosed with a cancer having a dysregulation of TrkA, comprising administering to the patient a therapeutically effective

amount of a compound of formula I. A sub-embodiment of this aspect of the invention is realized when the dysregulation of TrkA comprises overexpression of wild-type TrkA (autocrine activation). Another sub-embodiment of this aspect of the invention is realized when the dysregulation of TrkA comprises one or more chromosome translocations or inversions resulting in TrkA gene fusions. Another sub-embodiment of this aspect of the invention is realized when the dysregulation of TrkA comprises one or more deletion, insertions or mutations in the TrkA protein. Another sub-embodiment of this aspect of the invention is realized when the dysregulation of TrkA comprises a deletion of one or more residues from the TrkA protein, resulting in constitutive activity of TrkA kinase. Another sub-embodiment of this aspect of the invention is realized when the dysregulation of TrkA comprises a splice variation in which the expressed protein is an alternatively spliced variant of TrkA having one or more residues deleted resulting in constitutive activity of TrkA kinase.

The dysregulation of TrkA has been shown to be involved with cancers such as neuroblastoma (Brodeur, G. M., *Nat. Rev. Cancer* 2003, 3, 203-216), ovarian (Davidson. B., et al., *Clin. Cancer Res.* 2003, 9, 2248-2259), colorectal cancer (Bardelli, A., *Science* 2003, 300, 949), melanoma (Truzzi, F., et al., *Dermato-Endocrinology* 2008, 3 (1), pp. 32-36), head and neck cancer (Yilmaz, T., et al., *Cancer Biology and Therapy* 2010, 10 (6), pp. 644-653), gastric carcinoma (Du, J. et al., *World Journal of Gastroenterology* 2003, 9 (7), pp. 1431-1434), lung carcinoma (Ricci A., et al., *American Journal of Respiratory Cell and Molecular Biology* 25 (4), pp. 439-446), breast cancer (Jin, W., et al., *Carcinogenesis* 2010, 31 (11), pp. 1939-1947), glioblastoma (Wadhwa, S., et al., *Journal of Biosciences* 2003, 29 (2), pp. 181-188), medulloblastoma (Gruber-Olipitz, M., et al., *Journal of Proteome Research* 2008, 7 (5), pp. 1932-1944) secretory breast cancer (Euthus D.M., et al., *Cancer Cell* 2002, 2 (5), pp. 347-348), salivary gland cancer (Li, Y. -G., et al., *Chinese Journal of Cancer Prevention and Treatment* 2009, 16 (6), pp. 428-430), papillary thyroid carcinoma (Greco, A., et al., *Molecular and Cellular Endocrinology* 2010, 321 (1), pp. 44-49); adult and/or acute myeloid leukemia (Eguchi, M., et al., *Blood* 1999, 93 (4), pp. 1355-1363); non-small cell lung cancer (Vaishnavi et al., 2013: *Nature Medicine* 19, 1469-1472); large cell neuroendocrine carcinoma (Marchetti et al., 2008: *Human Mutation* 29 (5): 609-616); prostate carcinoma (Papatsoris et al., 2007, *Expert Opinion on Inves. Drugs* 16 (3): 303-309); and pancreatic carcinoma (Zhang et al., 2005, *Oncology Reports* 14: 161-171). Non-selective inhibitors of TrkA, B and C were also found to be effective in hindering tumor growth and stopping tumor metastasis in preclinical models of cancer (Nakagawara, A. (2001) *Cancer Letters* 169:107-114; and Eric Adriaenssens, E., et al., *Cancer Res* (2008) 68: (2) pgs. 346-351.

Thus, in another embodiment of the invention a method of treating a patient diagnosed with a cancer having a dysregulation of TrkA, comprising administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable

salt thereof is realized. In another embodiment of the invention a method of treating a patient diagnosed with a cancer selected from the group consisting of non-small cell lung cancer, papillary thyroid carcinoma, glioblastoma multiforme, acute myeloid leukemia, colorectal carcinoma, large cell neuroendocrine carcinoma, prostate cancer, neuroblastoma, pancreatic carcinoma, melanoma, head and neck squamous cell carcinoma and gastric carcinoma.

In another embodiment of the invention the compounds of formula I are useful for treating cancer in combination with one or more additional therapeutic agents. A subembodiment of this aspect of the invention is realized when the additional therapeutic agents are selected from the group consisting of receptor tyrosine kinase-targeted therapeutic agents, including cabozantinib, crizotinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, pertuzumab, regorafenib, sunitinib, and trastuzumab. Another subembodiment of this aspect of the invention is realized when the additional therapeutic agents are selected from signal transduction pathway inhibitors, including sorafenib, trametinib, vemurafenib, everolimus, rapamycin, perifosine, temsirolimus and obataclax.

Still another subembodiment of this aspect of the invention is realized when the additional therapeutic agents are selected from cytotoxic chemotherapeutics, including arsenic trioxide, bleomycin, cabazitaxel, capecitabine, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, docetaxel, doxorubicin, etoposide, fluorouracil, gemcitabine, irinotecan, lomustine, methotrexate, mitomycin C, oxaliplatin, paclitaxel, pemetrexed, temozolomide, and vincristine.

Another subembodiment of this aspect of the invention is realized when the additional therapeutic agents are selected from angiogenesis-targeted therapies, including aflibercept and bevacizumab.

Another subembodiment of this aspect of the invention is realized when the additional therapeutic agents are selected from immune-targeted agents, including aldesleukin, ipilimumab, lambrolizumab, nivolumab, and sipuleucel-T.

Another subembodiment of this aspect of the invention is realized when the additional therapeutic agents are selected from agents active against the TrkA pathway, including NGF-targeted biopharmaceuticals such as NGF antibodies and pan Trk inhibitors.

Yet in another subembodiment of this aspect of the invention is realized when the additional therapeutic agent or therapy is radiotherapy, including radioiodide therapy, external-beam radiation and radium 223 therapy.

Another embodiment of the invention is realized by a method of treating cancer in a patient comprising administering to said patient a compound of formula I or a pharmaceutically acceptable salt thereof in combination with at least one of the additional therapies or therapeutic agents disclosed herein. The additional therapeutic agents may be administered with one or

more compounds of formula I as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules.

Another embodiment of the invention is realized by a composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof in combination with at least one of the additional therapies or therapeutic agents disclosed herein and optionally at least one pharmaceutically acceptable carrier.

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
5 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
10 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
15 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
20 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
25 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
30 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
35 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
5 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
10 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
15 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
20 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
25 Bu:	butyl
<i>t</i> -Bu:	<i>tert</i> -butyl
Ar:	aryl
Ph:	phenyl
Bn:	benzyl
30 Ac:	acetyl
DMF•DMA:	<i>N,N</i> -dimethylformamide dimethyl acetal
DMSO:	dimethylsulfoxide
DMF:	<i>N,N</i> -dimethylformamide
THF:	tetrahydrofuran
35 TEA:	triethylamine

	aq:	aqueous
	HPLC:	high performance liquid chromatography
	MS:	mass spectrometry
	CDI:	1,1'-carbonyldiimidazole
5	DCE:	1,2-dichloroethane
	HCl:	hydrochloric acid
	°C:	degrees Celsius
	BINAP:	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
	ATP:	adenosine triphosphate
10	<i>i</i> -Pr:	isopropyl
	Py:	pyridyl
	OAc:	acetate
	TFA:	trifluoroacetic acid
	Boc:	<i>tert</i> -butoxycarbonyl
15	BOP:	(benzotriazol-1-yloxy) <i>tris</i> (dimethylamino)phosphonium hexafluorophosphate
	DIEA:	<i>N,N</i> -diisopropylethylamine
	HOBt:	1-hydroxybenzotriazole
	EDC:	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
	PyCLU:	chlorodipyrrolidinocarbenium
20	<i>n</i> -BuLi:	<i>n</i> -butyllithium
	<i>n</i> -HexLi:	<i>n</i> -hexyllithium
	HATU:	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
	EDTA:	ethylenediaminetetraacetic acid
	HMDS:	hexamethyldisilazane
25	min:	minutes
	h:	hours
	HPLC:	high performance liquid chromatography
	LCMS:	liquid chromatography-mass spectrometry
	SFC:	supercritical fluid chromatography
30	TLC:	thin layer chromatography
	NMP:	1-methyl-2-pyrrolidinone
	MTBE:	methyl <i>tert</i> -butyl ether
	DMA:	<i>N,N</i> -dimethylacetamide
	NBS:	<i>N</i> -bromosuccinimide

	CAN:	ammonium cerium(IV) nitrate
	dppf:	1,1'- <i>bis</i> (diphenylphosphino)ferrocene
	dba:	dibenzylideneacetone
	DMAP:	4-(dimethylamino)pyridine
5	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
10	mCPBA:	3-chloroperbenzoic acid
	DABCO:	diazabicyclo[2.2.2]octane
	LDA:	lithium diisopropylamide
	HOAt:	1-hydroxy-7-azabenzotriazole
	LAH:	lithium aluminum hydride
15	AOP:	7-(azabenzotriazol-1-yloxy) <i>tris</i> (dimethylamino)phosphonium hexafluorophosphate
	PyAOP:	7-(azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
	DCM:	dichloromethane
	PE:	petroleum ether
20	TMS:	trimethylsilyl
	Conc:	concentrated

MORE EXPERIMENTALS TO BE ADDED

REACTION SCHEMES

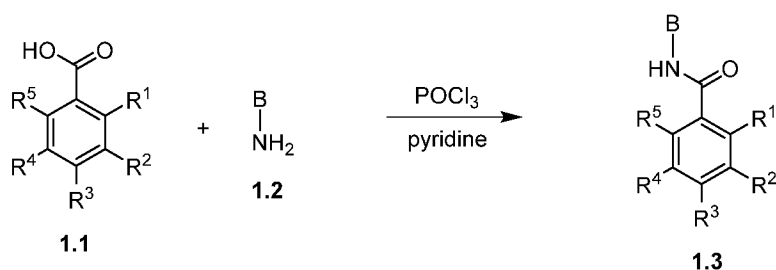
25

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.

30

Scheme 1 illustrates the general strategy for preparing the compounds of the present invention in which an carboxylic acid intermediate (**1.1**) may be activated (for example, via treatment with POCl₃, (COCl)₂, or SOCl₂ to generate the acid chloride) 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, AOP, PyAOP, CDI and the like.

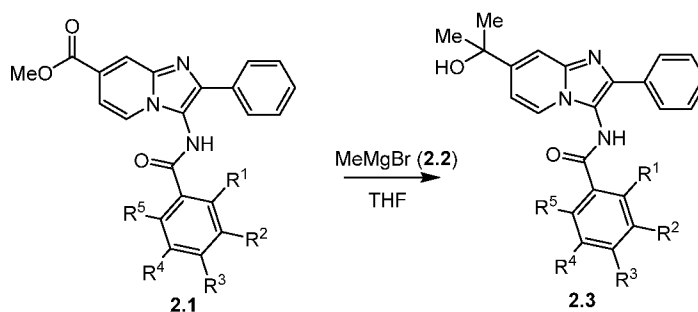
SCHEME 1



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 illustrates one of many possible methods that the target may be modified after coupling to form the amide. Treatment of ester **2.1** with a method in which a Grignard reagent (i.e. **2.2**) may be added to ester **2.1** to generate tertiary alcohol **2.3**.

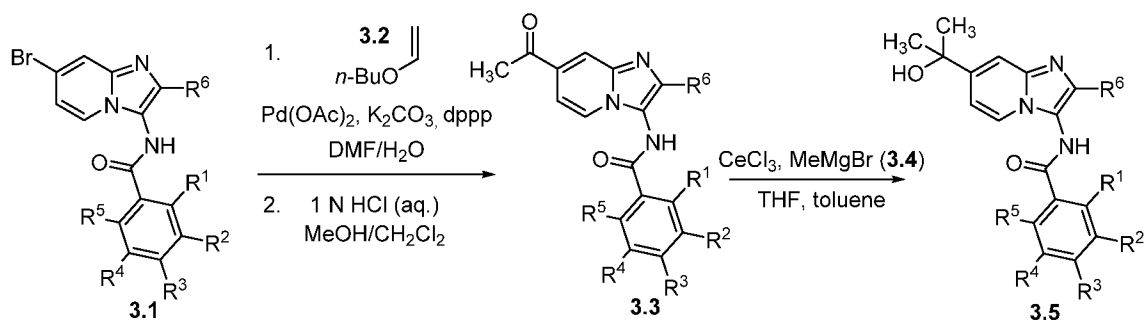
SCHEME 2



Scheme 3 describes a method in which bromide **3.1** undergoes palladium mediated cross-coupling with a vinyl enol ether (i.e. **3.2**) in the presence of a suitable catalyst and base system, followed by hydrolysis of the intermediate aryl enol by treatment with acidic

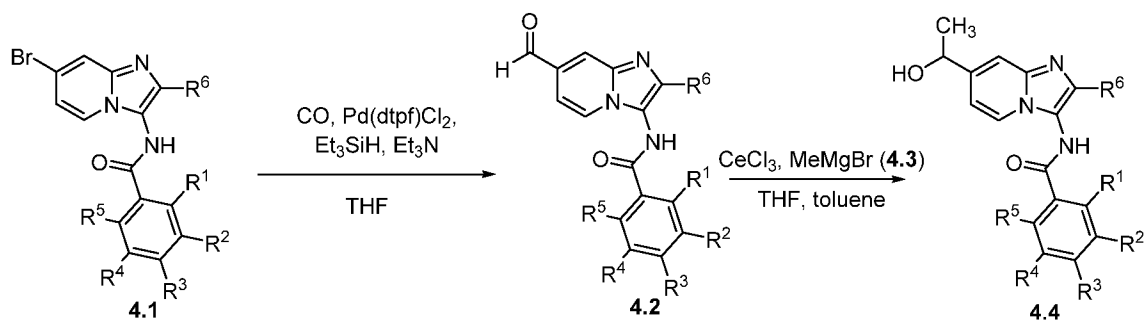
methanol to afford aryl ketone **3.3**. Exposure of ketone (**3.3**) to a Grignard reagent (**3.4**) in the presence of cerium trichloride affords the tertiary alcohol **3.5**.

SCHEME 3



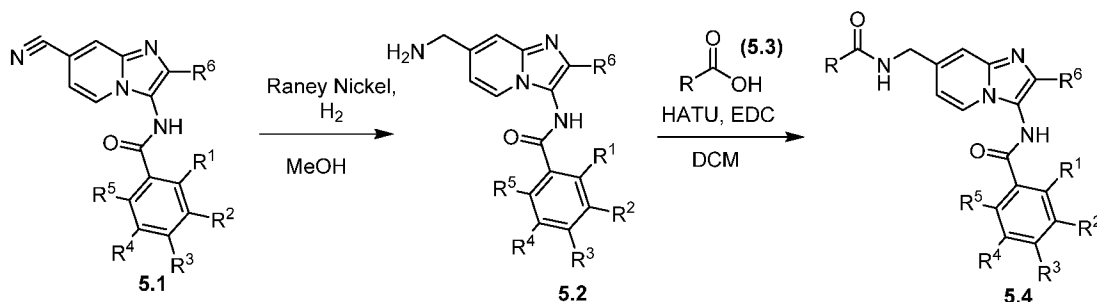
Scheme 4 describes a method in which aryl bromide **4.1** undergoes palladium mediated carbonylation under reductive conditions (triethylsilane and base) to afford aldehyde **4.2**. Grignard reagent (i.e. **4.3**) may be added to aldehyde **4.2** in the presence of cerium trichloride to generate secondary alcohol **4.4**.

SCHEME 4



Scheme 5 describes a method in which a nitrile (i.e. **5.1**) may be reduced with Raney Nickel in the presence of H_2 to generate the primary amine **5.2**. Treatment of amine **5.2** with an acid (i.e. **5.3**) in the presence of a coupling agent such as HATU and EDC affords amide **5.4**.

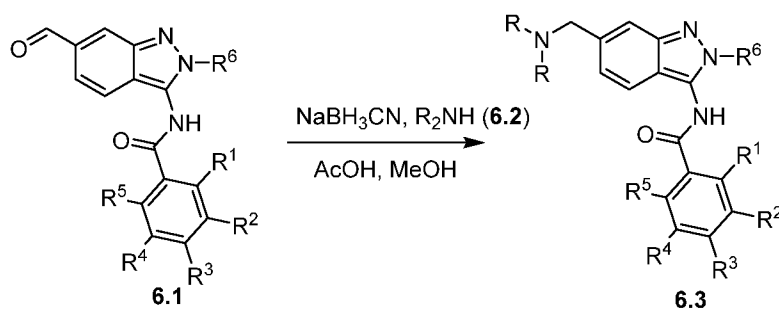
SCHEME 5



Scheme 6 describes a method in which treatment of aldehyde **6.1** with an amine (i.e. **6.2**) in the presence of a reducing agent such as sodium cyanoborohydride and acetic acid affords the amine **6.3**.

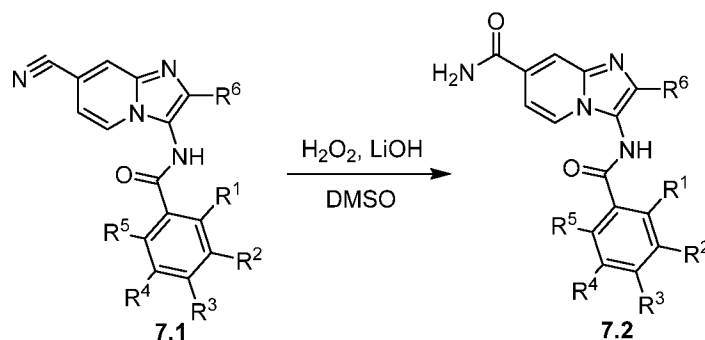
5

SCHEME 6



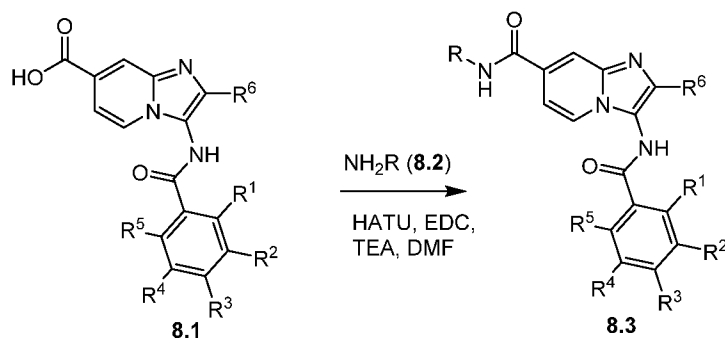
Scheme 7 describes a method in which treatment of nitrile **7.1** with hydrogen peroxide in the presence of a base such as lithium hydroxide in DMSO generates the amide **7.2**.

SCHEME 7



10

Scheme 8 describes a method in which treatment of acid **8.1** with an amine (**8.2**) in the presence of a coupling reagent such as HATU and EDC, and base, in DCM to afford the amide **8.3**.

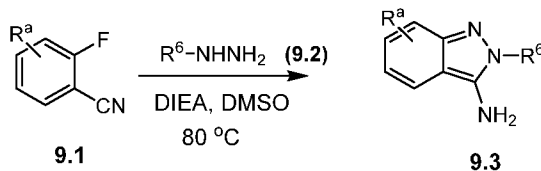


15

Alternative modifications are known to those in the art and may include, but are not limited to, ether, urea and sulfonamide, and heterocycle formation.

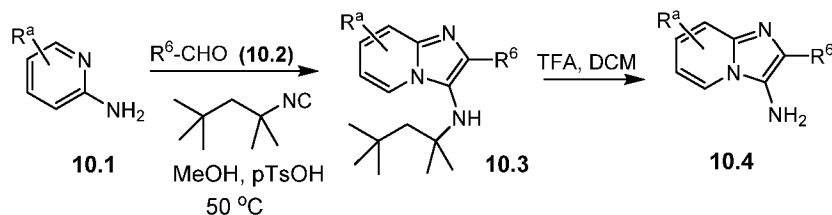
Intermediate amines and acids used in Scheme 1 may be obtained from commercial sources or synthesized using known methods. The following are examples for illustration only.

SCHEME 9



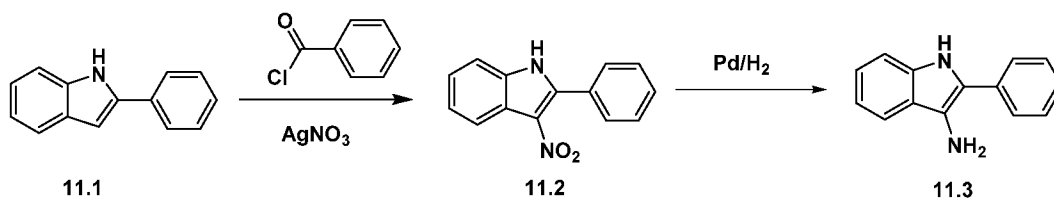
In Scheme 9, intermediate amine of the type **9.3** is described. Treatment of fluoro-nitrile **9.1** with phenyl hydrazine **9.2** in the presence of DIEA in DMSO affords indazole **9.3**.

SCHEME 10



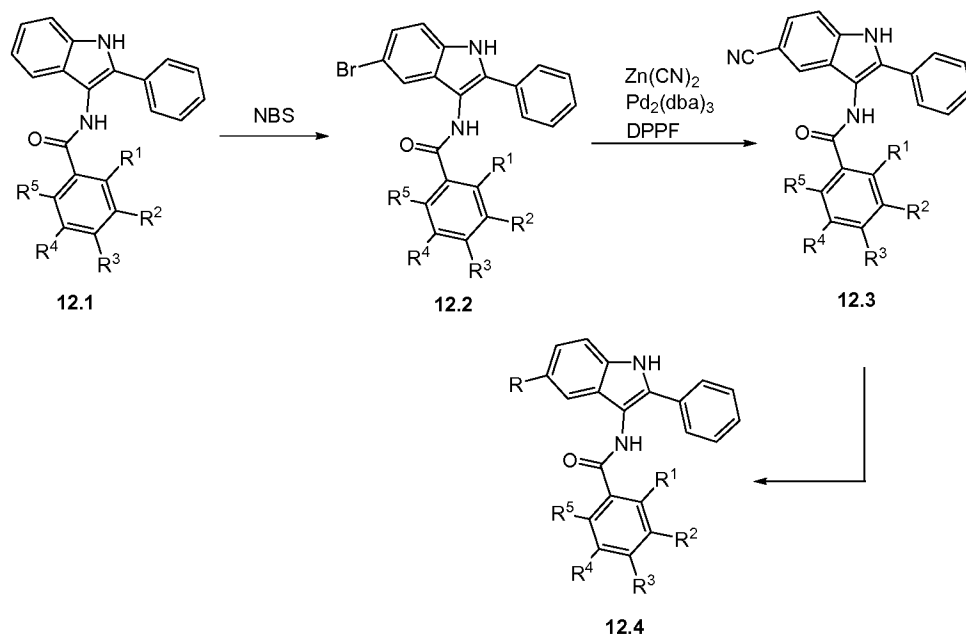
Reaction Scheme 10 illustrates the preparation of the intermediate acids of the type **10.4** which are used to prepare compounds of the invention. Aminopyridine **10.1** is converted to imidazopyridine **10.3** by heating in the presence of aldehyde **10.2**, tosic acid, and 2-isocyano-2,4,4-trimethylpentane in MeOH. Exposure of **10.3** to TFA in DCM effects removal of the 2,4,4-trimethylpentyl group to profile amine **10.4**.

SCHEME 11



Reaction Scheme 11 illustrates the preparation of the intermediate amine of the type **11.3**. Nitration of 2-phenyl-1H-indole **11.1** affords nitro indole **11.2** which is treated with Pd/H₂ to complete the synthesis of intermediate amine **11.3**.

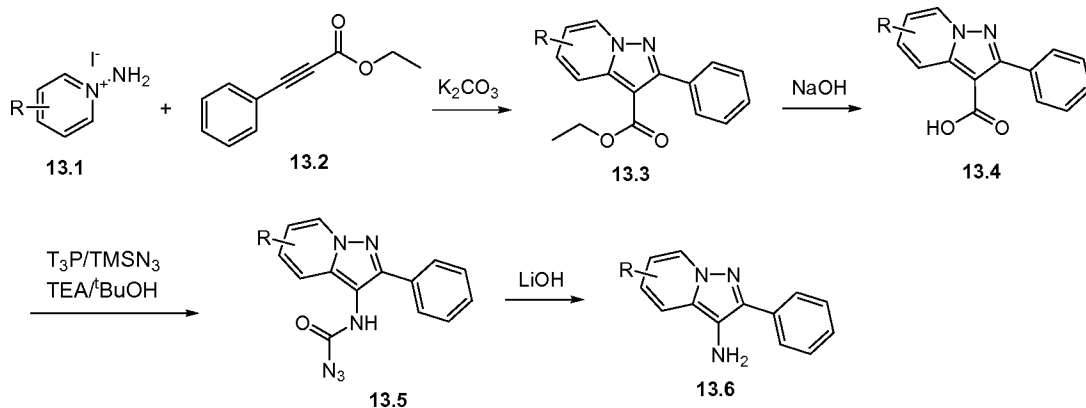
SCHEME 12



Reaction Scheme 12 illustrates the preparation of the examples of the type **12.4**.

Indole **12.1** is treated with NBS to afford bromide **12.2**, which is then converted to nitrile **12.3** by exposure to zinc cyanide, $\text{Pd}_2(\text{dba})_3$ and DPPF. Then the cyano group in **12.3** is converted to a variety of functionalities in **12.4**, where R can be carboxylic acid, methylester, primary amide, methylketone, secondary alcohol and tertiary alcohol.

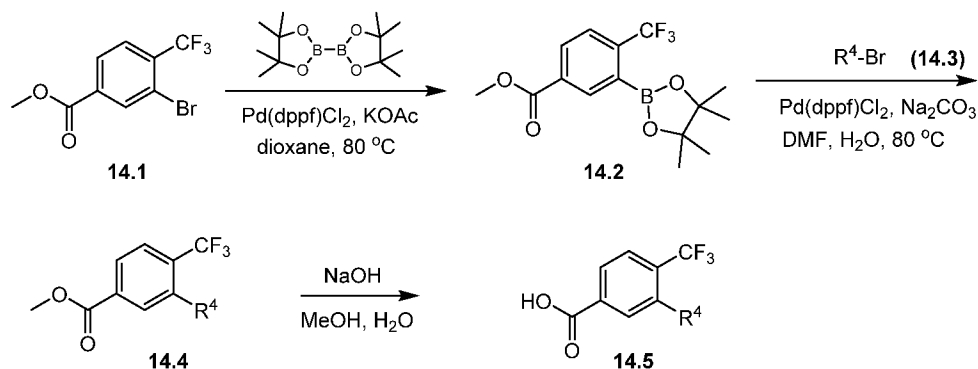
SCHEME 13



Reaction Scheme 13 illustrates the preparation of the intermediate amines of the

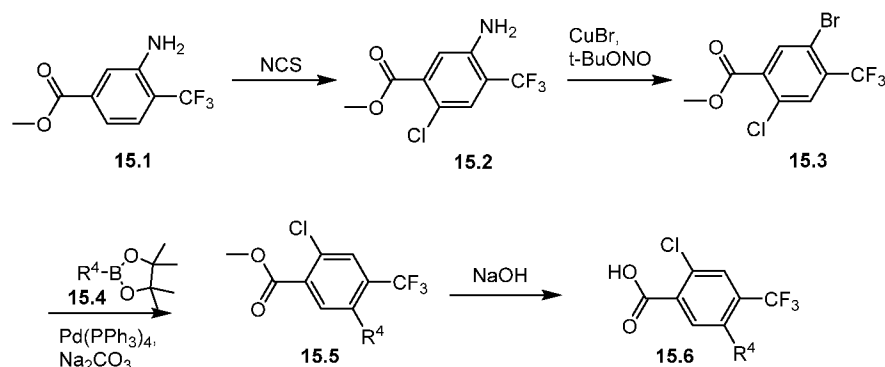
type **13.6** which are used to prepare compounds of the invention. [2+3] Cyclization between reagents **13.1** and **13.2** provides pyrazolopyridine **13.3**. After saponification of the ester in **13.3**, a Curtius type rearrangement affords an intermediate **13.5** with is treated with LiOH to give amine **13.6**.

SCHEME 14



Reaction Scheme 14 illustrates the preparation of the intermediate acids of the type **14.5**. Bromide **14.1** is converted to the boronate ester with bis-pin in the presence of a suitable catalyst and base system to afford **14.2**. Palladium-catalyzed cross-coupling of the ester **14.2** with an aryl or heteroaryl bromide (**14.3**) furnishes ester **14.4**. Saponification of the ester then affords acid **14.5**.

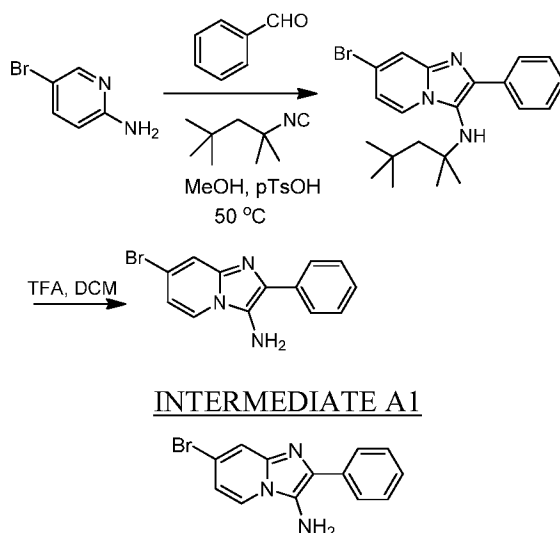
SCHEME 15



Reaction Scheme 15 illustrates the preparation of the intermediate acids of the type **15.9** which are used to prepare compounds of the invention. Amine **15.1** is treated with NCS to afford chloride **15.2**, which is then converted to bromide **15.3** by exposure to t-butyl nitrite and copper bromide. Cross-coupling of bromide **15.3** with an aryl or heteroboronic ester **15.4** (or other suitable intermediate) under Suzuki conditions provides ester **15.5**. Saponification of the ester then affords acid **15.6**.

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

REACTION SCHEME FOR INTERMEDIATE A1



7-Bromo-2-phenylimidazo[1,2-a]pyridin-3-amine

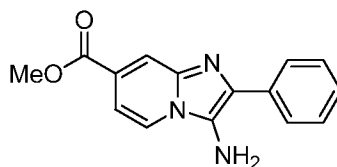
5 Step A: 7-Bromo-2-phenyl-N-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-a]pyridin-3-amine

To a solution of 4-bromopyridin-2-amine (1.5 g, 8.7 mmol) and benzaldehyde (0.88 mL, 8.7 mmol) in MeOH (32 mL) was added tosic acid (0.33 g, 1.7 mmol) and 2-isocyano-2,4,4-trimethylpentane (1.5 mL, 8.7 mmol). The resulting mixture was heated at 50 °C for 12 h, then cooled and concentrated. The residue was purified by column chromatography (0 to 100% EtOAc in hexanes) to afford the title compound. MS: m/z = 402.0 ($M + 1$). ^1H NMR (400 MHz, CDCl_3) δ 8.10-8.12 (d, J = 7.2 Hz, 1H), 7.77-7.79 (m, 2H), 7.72 (s, 1H), 7.41-7.43 (m, 2H), 7.33 - 7.35 (m, 1H), 6.86-6.88 (m, 1H), 1.01 (s, 9H), 0.92 (s, 6H), 0.90 (s, 2H).

Step B: 7-Bromo-2-phenylimidazo[1,2-a]pyridin-3-amine

15 To a solution of 7-bromo-2-phenyl-N-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-a]pyridin-3-amine (2.8 g, 7.1 mmol) in DCM (22 mL) was added TFA (22 mL, 280 mmol), and the resulting mixture was stirred for 10 min at ambient temperature. The mixture was carefully basified with saturated aqueous sodium bicarbonate solution, then concentrated. The residue was partitioned between water and a 4:1 mixture of chloroform and ethanol (3x). The combined organic layers were dried over magnesium sulfate and concentrated to afford the title compound. MS: m/z = 290.0 ($M + 1$). ^1H NMR (400 MHz, CDCl_3) δ 7.88-7.92 (m, 2H), 7.72 (s, 1H), 7.44-7.48 (m, 3H), 7.33-7.34 (m, 1H), 6.91-6.92 (d, J = 7.2 Hz, 1H).

INTERMEDIATE A2



Methyl 3-amino-2-phenylimidazo[1,2-a]pyridine-7-carboxylate

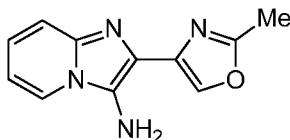
Step A: Methyl 2-phenyl-3-((2,4,4-trimethylpentan-2-yl)amino)imidazo[1,2-a]pyridine-7-carboxylate

5 To a solution of methyl 2-aminoisonicotinate (2.0 g, 13 mmol) and benzaldehyde (1.3 mL, 13 mmol) in MeOH (49 mL) was added tosic acid (0.50 g, 2.6 mmol) and 2-isocyano-2,4,4-trimethylpentane (2.3 mL, 13 mmol). The resulting mixture was heated at 50 °C for 12 h, then cooled and concentrated. The residue was purified by column chromatography on silica gel
10 (0 to 20% EtOAc in DCM) to afford the title compound. MS: m/z = 380.0 ($M + 1$). ^1H NMR (400 MHz, CDCl_3) δ 8.20 (m, 2H), 7.80-7.85 (m, 2H), 7.40-7.45 (m, 2H), 7.35-7.40 (m, 2H), 3.95 (s, 3H), 1.07 (s, 9H), 0.9 (s, 6H), 0.8 (s, 2H).

Step B: Methyl 3-amino-2-phenylimidazo[1,2-a]pyridine-7-carboxylate

15 To a solution of methyl 2-phenyl-3-((2,4,4-trimethylpentan-2-yl)amino)imidazo[1,2-a]pyridine-7-carboxylate (2.5 g, 6.6 mmol) in DCM (20 mL) was added TFA (20 mL, 260 mmol), and the resulting mixture was stirred for 10 min at ambient temperature. The mixture was carefully basified with saturated aqueous sodium bicarbonate solution and concentrated. The residue was partitioned between water and a 4:1 mixture of
20 chloroform and ethanol (3x). The combined organic layers were dried over magnesium sulfate and concentrated to afford a yellow powder. MS: m/z = 268.0 ($M + 1$). ^1H NMR (400 MHz, CDCl_3) δ 8.35 (s, 1H), 7.90-8.0 (m, 3H), 7.30-7.55 (m, 4H), 3.95 (s, 3H).

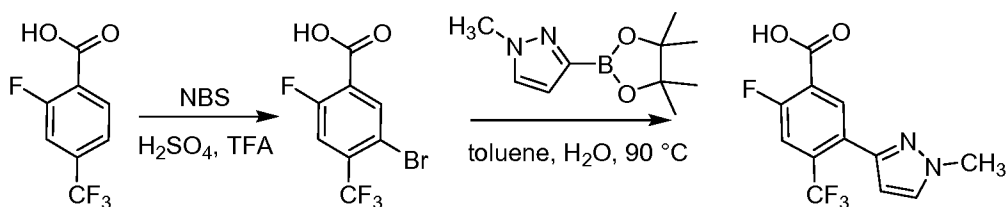
INTERMEDIATE A3



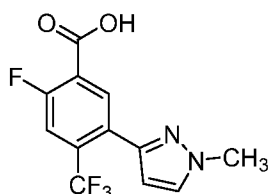
2-(2-Methyloxazol-4-yl)imidazo[1,2-a]pyridin-3-amine

A solution of pyridin-2-amine (0.15 g, 1.6 mmol), 2-methyloxazole-4-carbaldehyde (88 mg, 0.80 mmol), and *p*-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol) in MeOH (2.0 mL) was treated with TMS-CN (100 μ L, 0.80 mmol). The resulting mixture was heated at 60 °C for 18 h, then cooled and filtered, washing with MeOH (3 x 0.5 mL). The filtrate was purified by reverse-phase HPLC (5 to 50% acetonitrile + 0.1% trifluoroacetic acid in water) to yield the title compound as a trifluoroacetate salt. MS: m/z = 215.0 ($M + 1$).

REACTION SCHEME FOR INTERMEDIATE B1



INTERMEDIATE B1



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

Step A: 5-Bromo-2-fluoro-4-(trifluoromethyl)benzoic acid

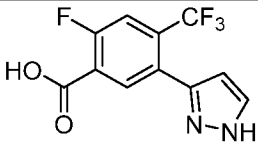
N-Bromosuccinimide (23.1 g, 130 mmol) was added portionwise to a mixture of 2-fluoro-4-(trifluoromethyl)benzoic acid (15.0 g, 72.1 mmol), sulfuric acid (9.0 mL, 170 mmol, 18 M), and TFA (50.0 mL, 650 mmol) at 50 °C and the resulting mixture was stirred at 50 °C for 18 h. Additional *N*-bromosuccinimide (3.0 g, 16 mmol) was added and the mixture was stirred at 50 °C for 4 h. The reaction mixture was cooled and water (150 mL) was added. The resulting precipitate was collected and dried to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ 9.90 (s, 1H), 8.35 (d, J = 6.3 Hz, 1H), 7.55 (d, J = 10.3 Hz, 1H).

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

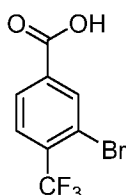
To a deoxygenated mixture of 5-bromo-2-fluoro-4-(trifluoromethyl)benzoic acid (5.0 g, 17 mmol), 1-(methyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (4.35 g, 20.9 mmol) and K₃PO₄ (11.1 g, 52.3 mmol) in toluene (55 mL) and H₂O (7 mL) was added 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (1.14 g, 1.74 mmol). The resulting mixture was heated at 90 °C for 2 h, and then stirred at 50 °C for 18 h. The mixture was cooled and filtered. The filtrate was concentrated and the residue was partitioned between water (200 mL) and EtOAc (300 mL). The aqueous layer was acidified to pH 5 with aqueous

HCl solution (1 N) and the resulting precipitate was collected and dried to give the title compound. MS: m/z = 289 ($M + 1$). ^1H NMR (400 MHz, DMSO- d_6) δ 13.85 (s, 1H), 8.11 (d, 1H), 7.82 (m, 2H), 6.45 (s, 1H), 3.92 (s, 3H).

The following intermediate was prepared in similar fashion to the procedure described above.

Compound Number	Structure	Compound Name	LCMS ($M+1$)
B2		2-fluoro-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid	275.5

INTERMEDIATE B3



3-Bromo-4-(trifluoromethyl)benzoic acid

10 Step A: Methyl 3-bromo-4-(trifluoromethyl)benzoate

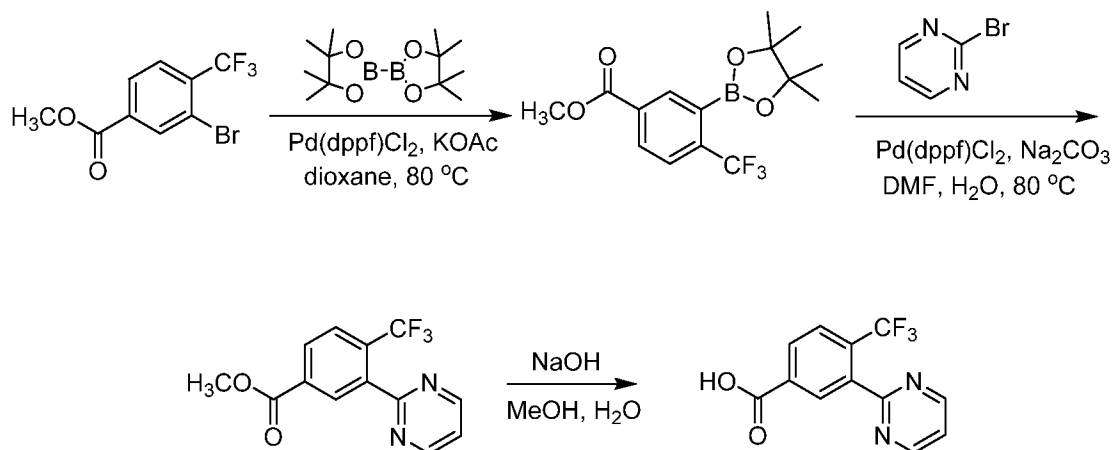
t-BuONO (79.0 g, 765 mmol) was added to a solution of methyl 3-amino-4-(trifluoromethyl)benzoate (67.0 g, 306 mmol) and CuBr (88.0 g, 612 mmol) in MeCN (1000 mL) at 0 °C, and the resulting mixture was warmed to 25 °C and stirred for 12 h. The mixture was then poured into EtOAc (600 mL) and filtered. The filtrate was washed with an aqueous HCl solution (1 M, 200 mL $\times$ 3), then brine (200 mL), dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (PE:EA = 200:1) to give the title compound. MS: m/z = 283, 285 ($M + 1$). ^1H NMR (400 MHz, CDCl₃) 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).

20 Step B: 3-Bromo-4-(trifluoromethyl)benzoic acid

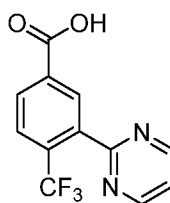
A mixture of methyl 3-bromo-4-(trifluoromethyl)benzoate (5.0 g, 17.7 mmol) in aqueous NaOH solution (1 M, 100 mL) was stirred at 25 °C for 12 h. The mixture was acidified to pH 6 with aqueous HCl solution (1 M), and the resulting aqueous mixture was extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and then concentrated to

give the title compound. MS: $m/z = 270$ ($M + 1$). ^1H NMR (400 MHz, CDCl_3) δ 8.44 (s, 1H), 8.14 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H).

REACTION SCHEME FOR INTERMEDIATE B4



INTERMEDIATE B4



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'',5,5',5'',5'''-octamethyl-1,3,2-dioxaborolane (26.9 g, 106 mmol) and potassium acetate (20.8 g, 212 mmol) in dioxane (300 mL) was added $\text{PdCl}_2(\text{dppf})$ (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 $\text{PdCl}_2(\text{dppf})$ (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 Na₂SO₄ 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).

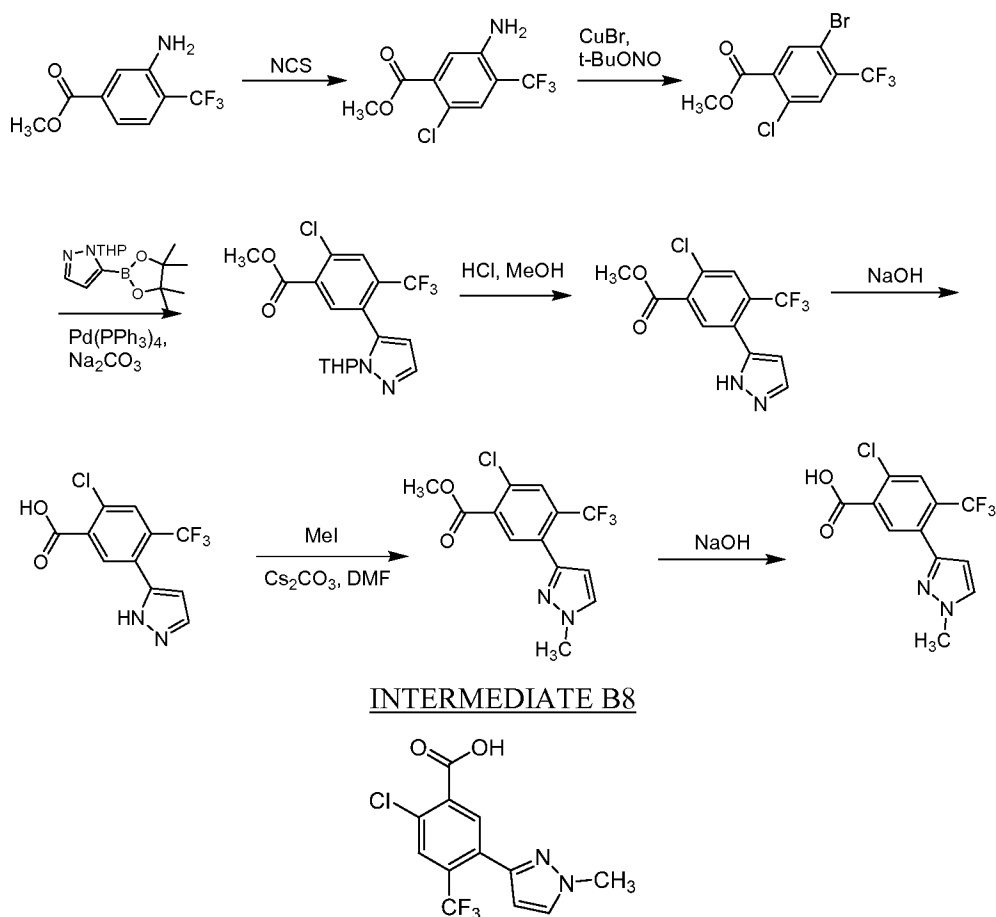
Step C: 3-(Pyrimidin-2-yl)-4-(trifluoromethyl)benzoic acid

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 H₂O (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). ¹H NMR (400 MHz, CD₃OD) 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).

The following intermediates were prepared in similar fashion to the procedure described above.

Compound Number	Structure	Compound Name	LCMS (M+1)
B5		2-fluoro-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzoic acid	301.1
B6		2-chloro-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzoic acid	303.1
B7		2-chloro-5-(4-methylpyrimidin-2-yl)-4-(trifluoromethyl)benzoic acid	317.1

REACTION SCHEME FOR INTERMEDIATE B8



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

5 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 Na₂SO₄, 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). ¹H NMR (400 MHz, CDCl₃) 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 Na₂SO₄ 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). ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 7.77 (s, 1H), 3.97 (s, 3H).

5 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 Na₂CO₃ (4.0 g, 44 mmol) in DMF (150 mL) and H₂O (24 mL)
10 was added Pd(PPh₃)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 Na₂SO₄ 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).

15 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).

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

A solution of NaOH (1.2 g, 0.030 mol) in H₂O (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
25 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

30 A mixture of 2-chloro-5-(1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoic acid (500 mg, 1.72 mmol), Cs₂CO₃ (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 H₂O (50 mL x 3), then brine (50 mL), dried over Na₂SO₄ and concentrated to give the title compound. MS: m/z = 319 (M + 1).

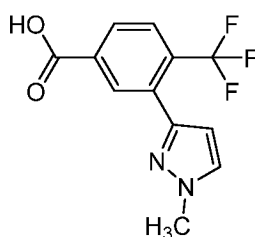
Step G: 2-Chloro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid

A solution of NaOH (414 mg, 10.4 mmol) in H₂O (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 Na₂SO₄ and concentrated. The residue was re-crystallized from MeOH (1g/5 mL) to give the title compound. MS: m/z = 305 (M + 1). ¹H NMR (400 MHz, CDCl₃) 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).

The following intermediates were prepared in similar fashion using the corresponding tributylstannane reagent in the palladium catalyzed cross-coupling reaction.

Compound Number	Structure	Compound Name	LCMS (M+1)
B9		2-chloro-5-(pyridin-2-yl)-4-(trifluoromethyl)benzoic acid	302
B10		2-fluoro-5-(pyridin-2-yl)-4-(trifluoromethyl)benzoic acid	286.0

INTERMEDIATE B11



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 HNO₃ solution (16 M, 200 mL), keeping the temperature between 0 and 25 °C, followed by the dropwise addition of aqueous H₂SO₄ 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 ($M + 1$). ¹H 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 H₂SO₄ 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 ($M + 1$). ¹H 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 N₂ atmosphere. After stirring at ambient temperature for 10 min, FSO₂CF₂CO₂CH₃ (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 Na₂SO₄ 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 ($M + 1$). ¹H 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 H₂ (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 ($M + 1$). ¹H 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 Na₂SO₄ 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 ($M + 1$). ¹H NMR (400 MHz, CDCl₃) 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(PPh₃)₄ (0.80 g, 0.69 mmol), and aqueous Na₂CO₃ solution (2 M, 26 mL, 53 mmol) in DMF (150 mL) was heated at 70 °C under N₂ 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 Na₂SO₄ 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 ($M + 1$). ¹H 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 ($M + 1$).

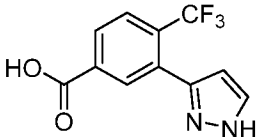
Step H: Methyl 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoate and methyl 3-(1-methyl-1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate

To a solution of methyl 3-(1H-pyrazol-5-yl)-4-(trifluoromethyl)benzoate (7.0 g, 26 mmol) in DMF (150 mL) was added Cs₂CO₃ (17 g, 52 mmol) and CH₃I (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 Na₂SO₄ 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 ($M + 1$).

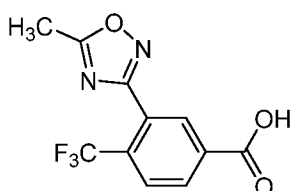
Step I: 3-(1-Methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid

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 Na₂SO₄ 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). ¹H 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).

The following intermediate was prepared in similar fashion to the procedure described above.

Compound Number	Structure	Compound Name	LCMS (M+1)
B12		3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid	257.1

INTERMEDIATE B13



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 H₂O (100 mL) at 0 °C was added dropwise a solution of NaNO₂ (5.5 g, 0.080 mol) in H₂O (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 H₂O (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 Na₂SO₄ 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 ($M + 1$). ¹H NMR (400 MHz, CDCl₃) 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 NaHCO₃ (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 ($M + 1$). ¹H NMR (400 MHz, CDCl₃) 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 ($M + 1$).

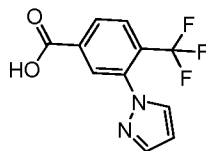
Step D: Methyl 3-(5-methyl-1,2,4-oxadiazol-3-yl)-4-(trifluoromethyl)benzoate

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 ($M + 1$). ¹H NMR (400 MHz, CDCl₃) 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 Na₂SO₄ and concentrated to give the title compound. MS: m/z = 273.0 ($M + 1$). ¹H NMR (400 MHz, CDCl₃) 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 B14

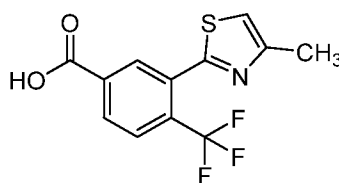


3-(1H-Pyrazol-1-yl)-4-(trifluoromethyl)benzoic acidStep A: Methyl 3-(1H-pyrazol-1-yl)-4-(trifluoromethyl)benzoate

A mixture of methyl 3-bromo-4-(trifluoromethyl)benzoate (0.50 g, 1.8 mmol), pyrazole (0.18 g, 2.6 mmol), Cs₂CO₃ (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 Na₂SO₄ and concentrated to give the title compound. MS: m/z = 257.0 (M + 1). ¹H 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 B153-(4-Methylthiazol-2-yl)-4-(trifluoromethyl)benzoic acidStep 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 H₂ 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). ¹H 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 H₂SO₄ 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 Na₂SO₄ and concentrated to afford the title compound. MS: m/z = 220.0 (M + 1). ¹H NMR (400 MHz, CDCl₃) 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 NaNO₂ (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 × 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to afford the title compound. MS: m/z = 230 (M + 1). ¹H NMR (400 MHz, CDCl₃) 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

H₂S 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 Na₂SO₄ 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). ¹H NMR (400 MHz, CDCl₃) 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

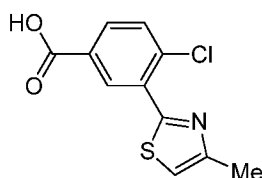
A mixture of methyl 3-carbamothioyl-4-(trifluoromethyl)benzoate (100 mg, 0.38 mmol), TEA (0.20 mL, 1.4 mmol) and 1-chloropropan-2-one (0.033 mL, 0.42 mmol) in DMF (3.0 mL) was heated at 120 °C for 4 h, then concentrated. The residue was partitioned between water and EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over

Na₂SO₄ 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 Na₂SO₄ and then concentrated to afford the title compound. MS: m/z = 288.0 (M + 1). ¹H NMR (400 MHz, CDCl₃) 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 B16



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 NaNO₂ (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 Na₂SO₄ and then concentrated to afford the title compound. MS: m/z = 196.0 (M + 1). ¹H NMR (400 MHz, CDCl₃) 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

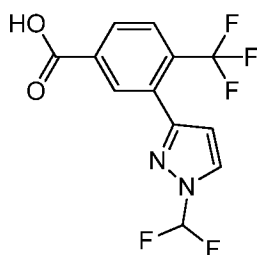
H₂S gas was bubbled through a solution of methyl 4-chloro-3-cyanobenzoate (3.0 g, 15 mmol) and TEA (2.13 mL, 15.3 mmol) in pyridine (15 mL) at ambient temperature for 1 h. The reaction mixture was concentrated and the residue was purified by column chromatography (PE:EtOAc = 10:1) to give the title compound. MS: m/z = 230.0 (M + 1). ¹H NMR (400 MHz, CDCl₃) 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 Na₂SO₄ 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). ¹H NMR (400 MHz, CDCl₃) 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).

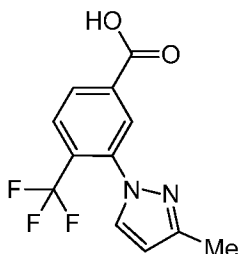
Step D: 4-Chloro-3-(4-methylthiazol-2-yl)benzoic acid

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 Na₂SO₄ and then concentrated to afford the title compound. MS: m/z = 254.0 (M + 1).

INTERMEDIATE B173-(1-(Difluoromethyl)-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid

A solution of methyl 3-(1H-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).

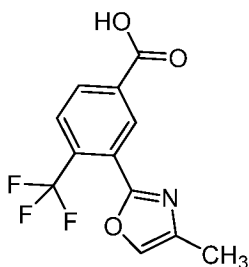
INTERMEDIATE B18



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

A deoxygenated solution of 3-methyl-1H-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 B19



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, H₂O:CH₃CN:CF₃CO₂H = 95:5:0.1 to 5:95:0.1) to give the title compound. MS: m/z = 272.0 ($M + 1$).

INTERMEDIATE B20



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 HNO₃ solution (15 M, 75 mL) at 25 °C. Aqueous H₂SO₄ solution (18 M, 90 mL) was added and the resulting mixture was stirred for 18 h. The reaction mixture was carefully
5 diluted with water (300 mL) and the precipitate was filtered, washed with water, and dried to give the title compound. MS: m/z = 252 ($M + 1$). ¹H NMR (400 MHz, DMSO-d₆) 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 H₂SO₄ solution (18 M, 60 mL) was added dropwise to a solution of 3-
10 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 NaHCO₃ solution (100 mL x 3), and brine. The organic layer was dried over Na₂SO₄ and concentrated to give the title
15 compound. MS: m/z : 266 ($M + 1$). ¹H NMR (400 MHz, DMSO-d₆) 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 H₂ (50 psi) at 15 °C for 24 h. The suspension was filtered and the filtrate was concentrated. The residue was purified by
20 column chromatography on silica gel (PE:EtOAc = 5:1) to give the title compound. MS: m/z = 236 ($M + 1$). ¹H NMR (400 MHz, DMSO-d₆) δ 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
25 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
30 over Na₂SO₄ 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 ($M + 1$). ¹H NMR (400 MHz, DMSO-d₆) δ 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(PPh₃)₄ (50 mg, 0.05 mmol), and Na₂CO₃ (530 mg, 5.0 mmol) in DMF (5 mL) was heated at 100 °C under N₂ 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 Na₂SO₄ 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).

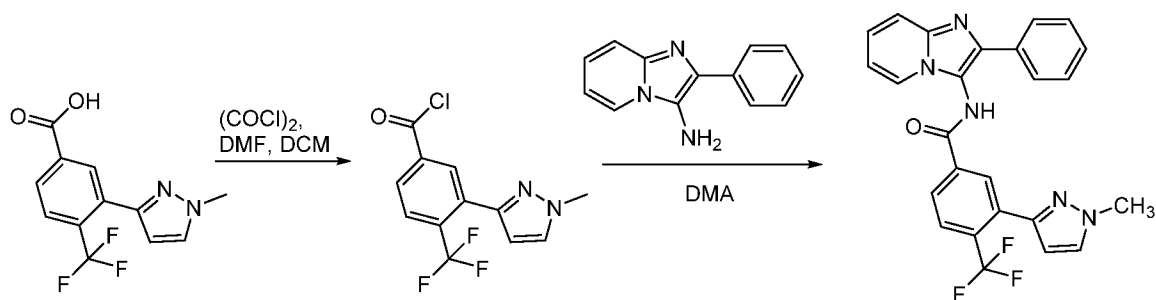
Step G: Methyl 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzoate

A mixture of methyl 3-(1H-pyrazol-5-yl)-4-(trifluoromethoxy)benzoate (220 mg, 0.81 mmol), CH₃I (0.292 mL, 4.00 mmol), and Cs₂CO₃ (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 Na₂SO₄ and concentrated. The residue was purified by preparative TLC (PE:EtOAc = 2:1) to give the title compound. MS: m/z = 301 (M + 1).

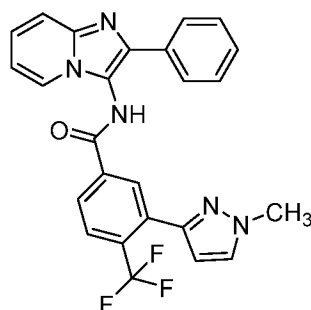
Step H: 3-(1-Methyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzoic acid

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 Na₂SO₄ and concentrated to give the title compound. MS: m/z = 287 (M + 1).

REACTION SCHEME FOR EXAMPLE 4



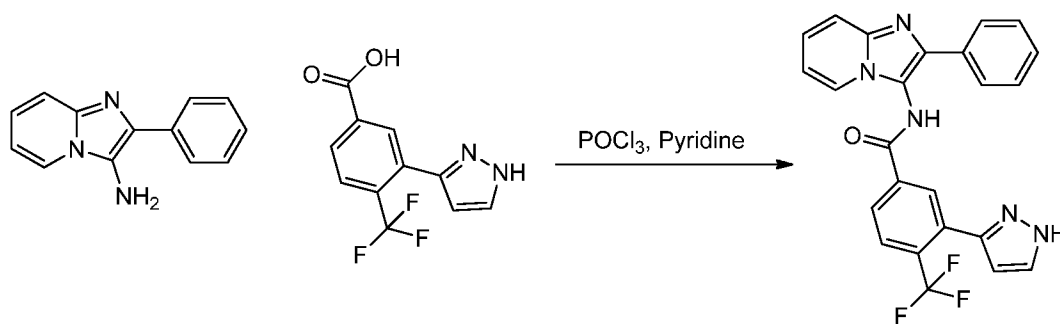
EXAMPLE 4



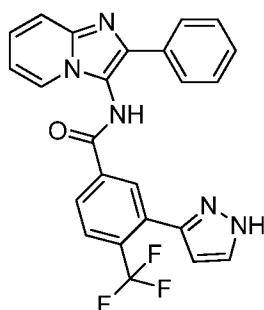
5 3-(1-Methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-
(trifluoromethyl)benzamide

(COCl)₂ (1.1 mL, 2.2 mmol) was added to a solution of 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (0.50 g, 1.9 mmol) and DMF (0.014 mL, 0.19 mmol) in DCM (20 mL), and the resulting mixture was stirred at ambient temperature for 0.5 h. The mixture was concentrated and dried under vacuum. The residue was dissolved in DMA (4 mL) and 2-phenylimidazo[1,2-a]pyridin-3-amine (0.45 g, 2.1 mmol) was added. The resulting mixture was stirred at ambient temperature for 2 h and then concentrated. 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* = 462.1 (M + 1). ¹H NMR (400 MHz, CDCl₃) δ 8.51 (s, 1H), 8.31 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.91-7.84 (m, 5H), 7.64 (d, *J* = 9.1 Hz, 1H), 7.43-7.32 (m, 3H), 7.28-7.25 (m, 1H), 6.87-6.84 (m, 1H), 6.55 (s, 1H), 3.91 (s, 3H).

REACTION SCHEME FOR EXAMPLE 9



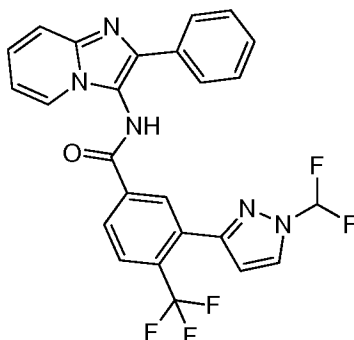
EXAMPLE 9



5 N-(2-Phenylimidazo[1,2-a]pyridin-3-yl)-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

POCl₃ (0.20 mL, 2.2 mmol) was added to a suspension of 2-phenylimidazo[1,2-a]pyridin-3-amine (0.23 g, 1.1 mmol) and 3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (0.28 g, 1.1 mmol) in pyridine (0.3 mL), and the resulting mixture was stirred at ambient
 10 temperature for 1.5 h. Water (0.3 mL) was added and stirring was continued for an additional 2 h. The product mixture was purified by reverse-phase HPLC (5-95% acetonitrile + 0.1% trifluoroacetic acid in water) to provide the title compound as a trifluoroacetate salt. MS: *m/z* = 448.0 (*M* + 1). ¹H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 8.42-8.32 (m, 2H), 8.23 (d, *J* = 7.7 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.83 (s, 1H), 7.78-7.70 (m, 1H), 7.58-
 15 7.32 (m, 4H), 7.15-7.08 (m, 1H), 6.53 (s, 1H).

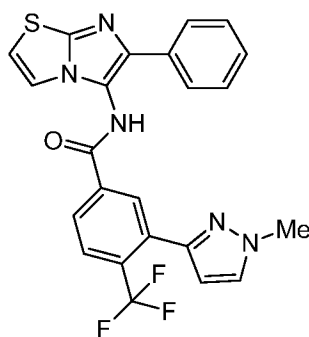
EXAMPLE 11



3-(1-(Difluoromethyl)-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide

POCl₃ (0.019 mL, 0.201 mmol) was added to a suspension of 2-phenylimidazo[1,2-a]pyridin-3-amine (14 mg, 0.069 mmol) and 3-(1-(difluoromethyl)-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (21 mg, 0.069 mmol) in pyridine (0.3 mL), and the resulting mixture was stirred at ambient temperature for 72 h. The product mixture was diluted with DMF (1 mL) and purified by reverse-phase HPLC (5-95% acetonitrile + 0.1% trifluoroacetic acid in water) to yield the title compound as a trifluoroacetate salt. MS: *m/z* = 498.0 (*M* + 1). ¹H NMR (400 MHz, CDCl₃) δ 11.39 (s, 1H), 8.49-8.42 (m, 2H), 8.07 (d, *J* = 6.8 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 2.7 Hz, 1H), 7.66-7.58 (m, 2H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.46-7.41 (m, 1H), 7.18-7.06 (m, 5H), 6.75 (d, *J* = 2.1 Hz, 1H).

EXAMPLE 12

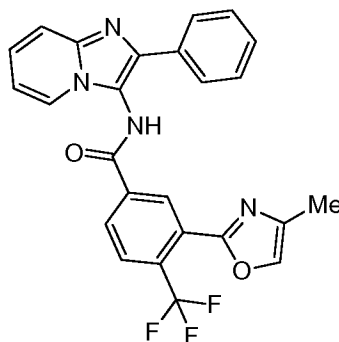


3-(1-Methyl-1H-pyrazol-3-yl)-N-(6-phenylimidazo[2,1-b]thiazol-5-yl)-4-(trifluoromethyl)benzamide

A solution of 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (25 mg, 0.093 mmol), PYAOP (58 mg, 0.11 mmol), DIEA (0.049 mL, 0.28 mmol), and 6-phenylimidazo[2,1-b]thiazol-5-amine (20 mg, 0.093 mmol) in DMF (1 mL) was heated at 60 °C for 18 h. The product mixture was cooled and then purified by reverse-phase HPLC (5-95%

acetonitrile + 0.1% trifluoroacetic acid in water). The combined desired fractions were partitioned between aqueous NaOH solution (1 N, 10 mL) and DCM (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to provide the title compound. MS: m/z = 468.0 (M + 1). ¹H NMR (400 MHz, CDCl₃) δ 8.65 (s, 1H), 8.22 (s, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.82-7.79 (m, 3H), 7.41-7.37 (m, 4H), 7.30 (t, J = 7.3 Hz, 1H), 6.85 (d, J = 4.5 Hz, 1H), 6.52 (s, 1 H), 3.86 (s, 3 H).

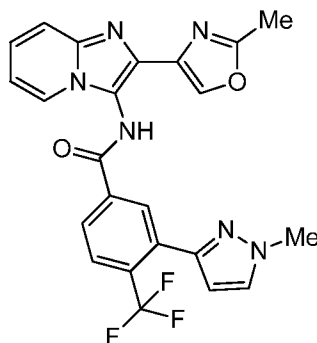
EXAMPLE 14



3-(4-Methyloxazol-2-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide

POCl₃ (1.5 μL, 0.016 mmol) was added to a suspension of 2-phenylimidazo[1,2-a]pyridin-3-amine (1.7 mg, 0.008 mmol) and 3-(4-methyloxazol-2-yl)-4-(trifluoromethyl)benzoic acid (2.2 mg, 0.008 mmol) in pyridine (0.1 mL), and the resulting mixture was stirred at ambient temperature for 18 h. The product mixture was diluted with DMF (1 mL) and purified by reverse-phase HPLC (5-95% acetonitrile + 0.1% trifluoroacetic acid in water) to give the title compound as a trifluoroacetate salt. MS: m/z = 463.0 (M + 1). ¹H NMR (400 MHz, CDCl₃) δ 11.19 (s, 1H), 8.82 (s, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 6.8 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.65-7.60 (m, 3H), 7.58 (d, J = 9.0 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.20-7.08 (m, 4H), 2.30 (d, J = 1.0 Hz, 3H).

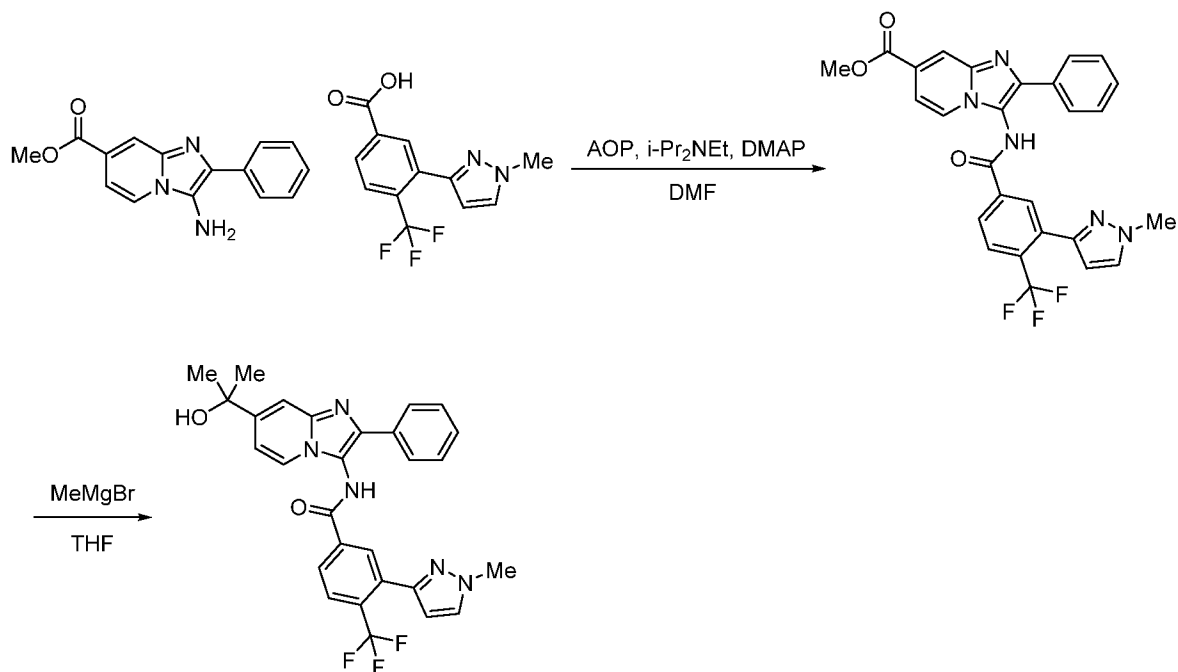
EXAMPLE 16



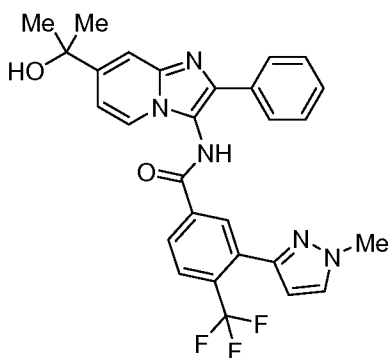
3-(1-Methyl-1H-pyrazol-3-yl)-N-(2-(2-methyloxazol-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide

A solution of 2-(2-methyloxazol-4-yl)imidazo[1,2-a]pyridin-3-amine (40 mg, 0.12 mmol), 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (33 mg, 0.12 mmol), 7-azabenzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (65 mg, 0.15 mmol), DMAP (1.5 mg, 0.012 mmol), and DIEA (0.064 mL, 0.37 mmol) in DMF (1.0 mL) was heated at 60 °C for 21 h. The product mixture was cooled and then purified by reverse-phase HPLC (5-95% acetonitrile + 0.1% trifluoroacetic acid in water) to yield the title compound as a trifluoroacetate salt. MS: $m/z = 467$ ($M + 1$). ^1H NMR (400 MHz, CDCl_3) δ 10.19 (s, 1H), 8.45 (s, 1H), 8.38 (s, 1H), 8.21 (t, $J = 7.2$ Hz, 2H), 8.06 (d, $J = 9.0$ Hz, 1H), 7.93 (d, $J = 8.2$ Hz, 1H), 7.66 (t, $J = 8.1$ Hz, 1H), 7.45 (d, $J = 2.3$ Hz, 1H), 7.23 (t, $J = 6.9$ Hz, 1H), 6.55 (d, $J = 1.2$ Hz, 1H), 3.99 (s, 3H), 2.38 (s, 3H).

REACTION SCHEME FOR EXAMPLE 27



EXAMPLE 27



5

N-(7-(2-hydroxypropan-2-yl)-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

Step A: Methyl 3-(3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamido)-2-phenylimidazo[1,2-a]pyridine-7-carboxylate

10

Methyl 3-amino-2-phenylimidazo[1,2-a]pyridine-7-carboxylate (400 mg, 1.50 mmol) and 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (404 mg, 1.50 mmol) were dissolved in DMF (3.3 mL). AOP (1.33 g, 2.99 mmol), diisopropylethylamine (0.78 mL, 4.49 mmol), and DMAP (18.3 mg, 0.15 mmol) were added, and the mixture was stirred at 30 °C for

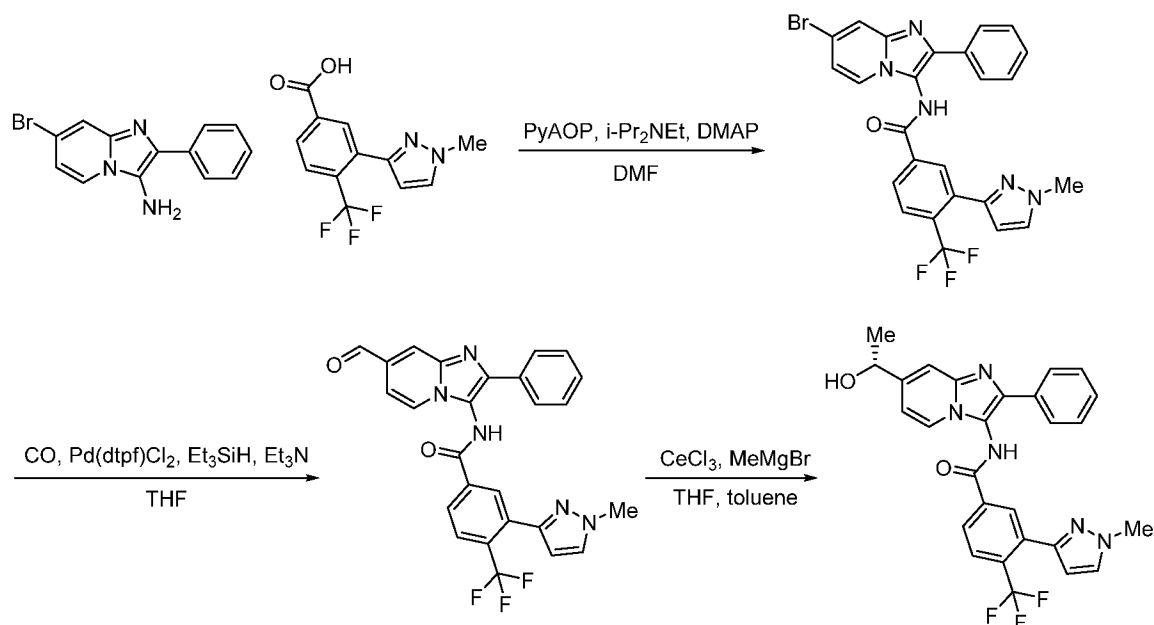
16 h. The mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (20 mL), dried over MgSO₄, and concentrated. The crude product was purified by SiO₂ flash column chromatography, eluting with 0-10% MeOH/EtOAc to give the title compound. MS: m/z = 520.5 (M + 1).

5

Step B: *N*-(7-(2-Hydroxypropan-2-yl)-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

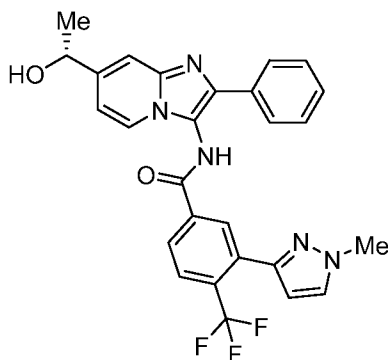
To a solution of methyl 3-(3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamido)-2-phenylimidazo[1,2-a]pyridine-7-carboxylate (25 mg, 0.048 mmol) in tetrahydrofuran (0.96 mL) at room temperature under a N₂ atmosphere was added a 3.0 M solution of methylmagnesium bromide in Et₂O (64.2 μ L, 0.193 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with ice (2 mL), and extracted with EtOAc (2 x 5 mL). Combined organic layers were washed with saturated aqueous NH₄Cl solution (5 mL), dried, and concentrated. The crude product was purified by SiO₂ flash column chromatography, eluting with 0-10% MeOH/EtOAc to give the title compound. MS: m/z = 520.4 (M + 1). ¹H NMR (400 MHz, CD₃OD): δ 8.33 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 7.2 Hz, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.88-7.90 (m, 2H), 7.67-7.70 (m, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.16 (dd, J = 7.2, 1.8 Hz, 1H), 6.53 (s, 1H), 3.98 (s, 3 H), 1.29 (s, 6H).

REACTION SCHEME FOR EXAMPLE 42



20

EXAMPLE 42



(R)-N-(7-(1-Hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

5 Step A: N-(7-Bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

7-Bromo-2-phenylimidazo[1,2-a]pyridin-3-amine (1.20 g, 4.16 mmol) and 3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (1.35 g, 5.00 mmol) were dissolved in DMF (9.2 mL). PyAOP (4.34 g, 8.33 mmol), diisopropylethylamine (3.64 mL, 20.8 mmol), and DMAP (51 mg, 0.416 mmol) were added, and the mixture was stirred at 30 °C for 3 h. Brine (20 mL) was added, and the mixture was extracted with EtOAc (2 x 20 mL). Combined organic layers were washed with brine (20 mL), dried over MgSO₄, and concentrated. The crude product was purified by SiO₂ flash column chromatography, eluting with 0-70% EtOAc/hexanes to give the title compound. MS: m/z = 540.1 (M + 1).

15 Step B: N-(7-Formyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

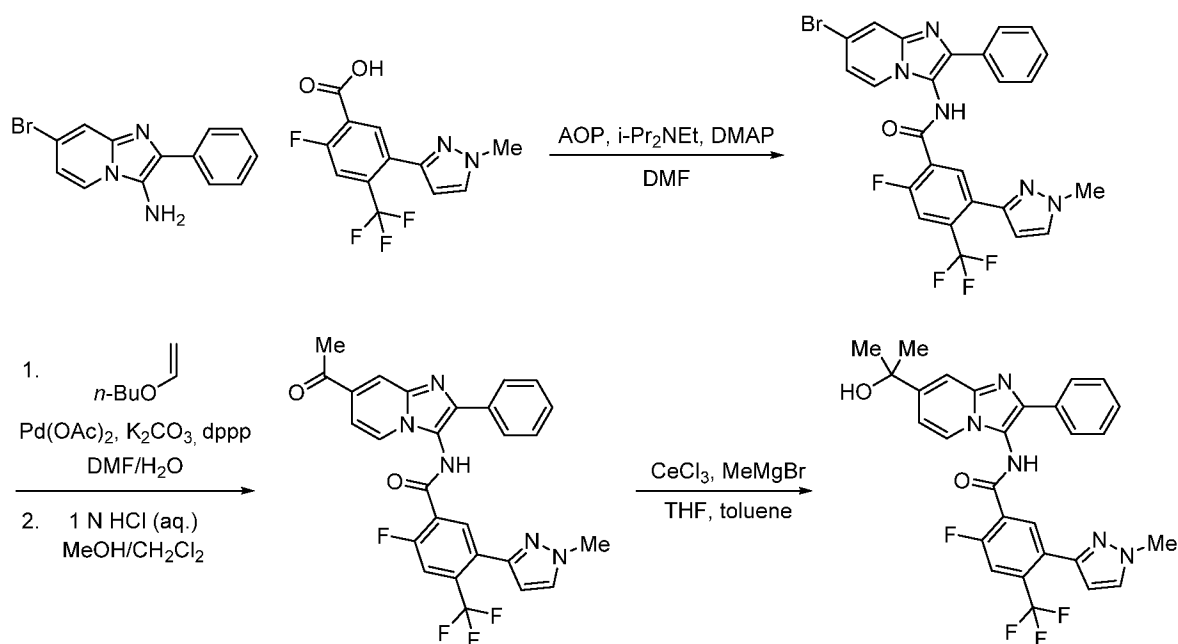
N-(7-Bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (550 mg, 1.02 mmol), Pd(dtpf)Cl₂ (66.3 mg, 0.102 mmol), triethylsilane (325 μL, 2.04 mmol), and triethylamine (142 μL, 1.02 mmol) were dissolved in THF (22.6 mL), and the solution was distributed across three 20-mL capacity vessels, which were placed under a 3-bar atmosphere of CO gas at 90 °C for 18 h. The contents of the vessels were then combined, water (20 mL) was added, and the mixture was extracted with EtOAc (2 x 30 mL). Combined organic layers were washed with brine (30 mL), dried over MgSO₄, and concentrated. The crude material was purified by SiO₂ flash column chromatography, eluting with 0-70% EtOAc/hexanes to give the title compound. MS: m/z = 490.2 (M + 1).

Step C: (R)-N-(7-(1-Hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

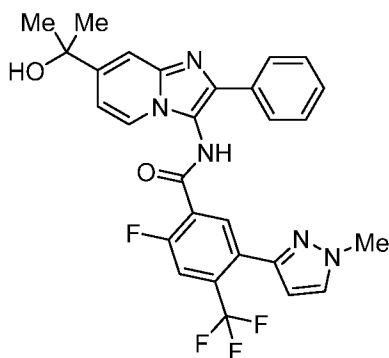
A suspension of CeCl₃ (10.1 mg, 0.041 mmol) in THF (817 µL) was cooled to 0 °C and treated with a 1.4 M solution (THF/toluene) of methylmagnesium bromide (117 µL, 0.163 mmol). After 1 h, a suspension of *N*-(7-formyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide in toluene (817 µL) was added, and the mixture was allowed to warm to room temperature. After an additional 1 h, the reaction was cooled to 0 °C and quenched with a solution of saturated aqueous NH₄Cl. The mixture was diluted with water (2 mL) and extracted EtOAc (2 x 5 mL). Combined organic layers were washed with brine (5 mL), dried over MgSO₄, filtered, concentrated. The crude material was purified by SiO₂ flash column chromatography, eluting with 0-100% EtOAc/hexanes to give the purified racemate. The racemate was purified by SFC (AD-H column), eluting with 20% EtOH (0.1% NH₄OH)/CO₂ at 100 bar to give the title compound as the second-eluting enantiomer.

MS: m/z = 506.2 (M + 1). ¹H NMR (400 MHz, CD₃OD): δ 8.33 (s, 1H), 8.23 (d, J = 8.3 Hz, 1H), 8.11 (d, J = 7.1 Hz, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 7.7 Hz, 2H), 7.69 (d, J = 2.3 Hz, 1H), 7.61 (s, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.07 (dd, J = 7.1, 1.6 Hz, 1H), 6.53 (s, 1H), 4.93 (q, J = 6.6 Hz, 1H), 3.98 (s, 3H), 1.51 (d, J = 6.6 Hz, 3H).

REACTION SCHEME FOR EXAMPLE 50



EXAMPLE 50



5

Step A: N-(7-bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

7-bromo-2-phenylimidazo[1,2-a]pyridin-3-amine (900 mg, 2.50 mmol) and 2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (720 mg, 2.50 mmol) were suspended in DMF (6.25 mL). Diisopropylethylamine (2.18 mL, 12.5 mmol) and DMAP (30.5 mg, 0.25 mmol) were added, followed by AOP (3.88 g, 8.75 mmol), and the mixture was stirred at room temperature for 3 days. The mixture was then poured into brine (100 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layers were washed with brine, dried over

MgSO₄, filtered, and concentrated. The crude material was purified by SiO₂ gel flash column

chromatography, eluting with 0-40% EtOAc/hexanes to give the title compound. MS: m/z = 558.3 ($M + 1$).

Step B: *N*-(7-Acetyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

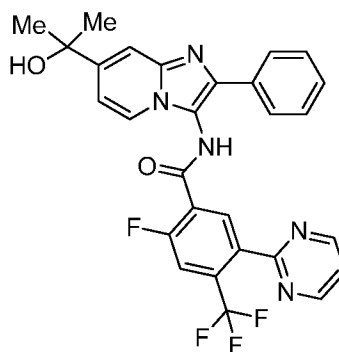
DMF (8 mL) and H₂O (1 mL) were placed in a flask and sparged with N₂ gas for 45 min. A 20-mL vessel was charged with palladium acetate (11.6 mg, 0.052 mmol), potassium carbonate (171 mg, 1.24 mmol), and 1,3-bis(diphenylphosphino)propane (46.8 mg, 0.113 mmol). 1-(vinyl-1-ethoxy)butane (334 μ L, 2.58 mmol) was added, followed by *N*-(7-bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (576 mg, 1.03 mmol). The DMF/H₂O (8:1) mixture (2.95 mL) was added to the reaction, and the vial was sealed. The vessel was evacuated and then purged with N₂ gas (5x), then heated at 80 °C for 16 h. The reaction was concentrated to dryness under a stream of N₂ gas. The crude material was purified by SiO₂ flash column chromatography, eluting with 0-80% EtOAc/hexanes to give 146 mg of the title compound and 243 mg of an enol ether intermediate. The enol ether was dissolved in MeOH (2.8 mL) and CH₂Cl₂ (2.8 mL), treated with 1 N aq. HCl, and allowed to stir for 22 h. Solvent was removed under a stream of N₂ gas, and the residue was neutralized with saturated aqueous NaHCO₃ (5 mL). The mixture was extracted with EtOAc (3 x 5 mL), and combined organic layers were dried over MgSO₄, filtered, and concentrated to give an additional 215 mg of the title compound. MS: m/z = 522.4 ($M + 1$).

Step C: 2-fluoro-*N*-(7-(2-hydroxypropan-2-yl)-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

A suspension of CeCl₃ (3.54 mg, 0.014 mmol) in THF (0.29 mL) was cooled at 0 °C and treated with a 3 M solution (Et₂O) solution of methylmagnesium bromide (33.6 μ L, 0.101 mmol). After 1 h, a solution of *N*-(7-acetyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (15 mg, 0.029 mmol) in 1:1 THF/toluene (2.0 mL) was added. The reaction was allowed to warm to room temperature and stirred for 3 h, then cooled to 0 °C and quenched with a solution of saturated aqueous NH₄Cl (2 mL). The mixture was diluted with H₂O (2 mL) and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, concentrated to give the title compound. MS: m/z = 538.1 ($M + 1$). ¹H NMR (400 MHz, CD₃OD): δ 8.11 (dd, J = 15.0, 7.1

Hz, 2H), 7.94 (d, $J = 7.7$ Hz, 2H), 7.82 (d, $J = 10.5$ Hz, 1H), 7.67-7.70 (m, 2H), 7.47 (t, $J = 7.6$ Hz, 2H), 7.37 (t, $J = 7.3$ Hz, 1H), 7.19 (d, $J = 7.3$ Hz, 1H), 6.51 (s, 1H), 3.98 (s, 3H), 1.61 (s, 6H).

5

EXAMPLE 53

2-Fluoro-N-(7-(2-hydroxypropan-2-yl)-2-phenylimidazo[1,2-a]pyridin-3-yl)-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide

10 Step A: N-(7-Bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide

To a solution of 7-bromo-2-phenylimidazo[1,2-a]pyridin-3-amine (0.15 g, 0.52 mmol) and 2-fluoro-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzoic acid (0.15 g, 0.52 mmol) in DMF (1.1 mL) was added AOP (7-azabenzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate) (0.46 g, 1.0 mmol), DMAP (6.0 mg, 0.052 mmol) and DIEA (0.45 mL, 2.6 mmol). The resulting mixture was stirred at ambient temperature for 12 h and then partitioned between EtOAc and brine. The organic layer was dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (0 to 50% EtOAc in hexanes) to afford the title compound. MS: $m/z = 558.0$ ($M + 1$).

20

Step B: N-(7-(1-Ethoxyvinyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide

Bis(tri-*t*-butylphosphine)palladium (39 mg, 0.076 mmol) and tributyl(1-ethoxyvinyl)tin (0.26 mL, 0.76 mmol) were added to a solution of *N*-(7-bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide (0.21 g, 0.379 mmol) in dioxane (1.9 mL). The resulting mixture was heated at 80 °C for 1 h, then cooled and partitioned between EtOAc and water. The organic layer was washed with

25

brine, dried over magnesium sulfate, and concentrated afford the title compound. MS: m/z = 548.0 ($M + 1$).

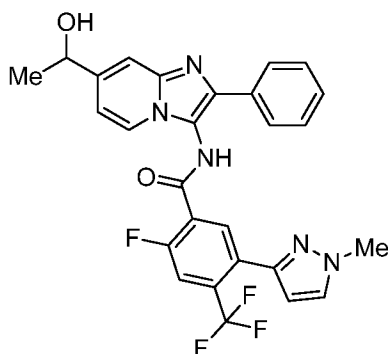
5 Step C: *N*-(7-Acetyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide

An aqueous HCl solution (1 N, 1.9 mL, 1.9 mmol) was added to a solution of *N*-(7-(1-ethoxyvinyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide (0.21 g, 0.38 mmol) in MeOH (2.5 mL), and the resulting mixture was stirred at ambient temperature for 12 h. The mixture was concentrated and the residue was
10 partitioned between a saturated aqueous sodium bicarbonate solution and EtOAc. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (0 to 100% EtOAc in hexanes) to afford the title compound as a yellow solid. MS: m/z = 520.0 ($M + 1$).

15 Step D: 2-Fluoro-*N*-(7-(2-hydroxypropan-2-yl)-2-phenylimidazo[1,2-a]pyridin-3-yl)-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide

A solution of methylmagnesium bromide in diethyl ether (3.0 M, 0.15 mL, 0.45 mmol) was added to a suspension of ultra-dry cerium chloride (0.016 g, 0.064 mmol) in THF (1.3 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h before a solution of *N*-(7-acetyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzamide (0.067 g, 0.13 mmol) in 1:1 toluene/THF (2 mL) was added
20 dropwise. The mixture was warmed to ambient temperature and stirred for 3 h. The mixture was then cooled to 0 °C, and excess MeMgBr was quenched with aqueous ammonium chloride solution. The mixture was partitioned between water and EtOAc. The organic layer was washed
25 with brine, dried over magnesium sulfate, and concentrated to afford the title compound. MS: m/z = 536.0 ($M + 1$). ^1H NMR (400 MHz, CD_3OD) δ 8.95-8.93 (d, J = 8.0 Hz, 1H) 8.30-8.28 (d, J = 8.0 Hz, 1H) 8.11-8.09 (d, J = 7.2 Hz, 1H) 7.95-7.88 (m, 3H) 7.71 (s, 1H) 7.56-7.35 (m, 5H) 7.19-7.17 (d, J = 8.0 Hz, 1H) 1.60 (s, 6H).

EXAMPLE 54



2-(R or S)-Fluoro-N-(7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

5 Step A: N-(7-Bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

To a solution of 7-bromo-2-phenylimidazo[1,2-a]pyridin-3-amine (0.10 g, 0.35 mmol) and 2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzoic acid (0.10 g, 0.35 mmol) in DMF (0.76 mL) was added AOP (7-azabenzotriazol-1-yloxytris (dimethylamino) phosphoniumhexafluorophosphate) (0.30 g, 0.69 mmol), DMAP (4.0 mg, 0.035 mmol) and DIEA (0.30 mL, 1.7 mmol). The resulting mixture was stirred at ambient temperature for 12 h and then partitioned between EtOAc and brine. The organic layer was dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (0 to 40% EtOAc in hexanes) to afford the title compound. MS: $m/z = 560.0$ ($M + 1$).

15 Step B: N-(7-(1-Ethoxyvinyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

To a deoxygenated solution of N-(7-bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (0.14 g, 0.25 mmol) in dioxane (1.2 mL) was added bis(tri-*t*-butylphosphine)palladium (25 mg, 0.049 mmol) followed by tributyl(1-ethoxyvinyl)tin (0.17 mL, 0.49 mmol). The resulting mixture was heated at 80 °C for 1 h, then cooled and partitioned between EtOAc and water. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to afford the title compound. MS: $m/z = 530.0$ ($M + 1$).

25 Step C: N-(7-Acetyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

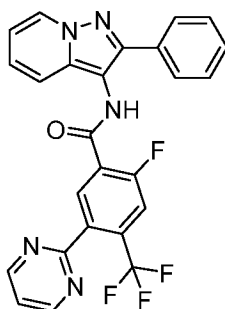
To a solution of *N*-(7-(1-ethoxyvinyl)-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (0.13 g, 0.25 mmol) in MeOH (1.6 mL) was added aqueous HCl solution (1 N, 1.2 mL, 1.2 mmol), and the resulting mixture was stirred at ambient temperature for 12 h. The mixture was concentrated and residue was partitioned between a saturated aqueous sodium bicarbonate solution and EtOAc. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (0 to 100% EtOAc in hexanes) to afford the title compound. MS: m/z = 522.0 ($M + 1$).

Step D: 2-(*R* or *S*)-Fluoro-*N*-(7-(1-hydroxyethyl)-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide

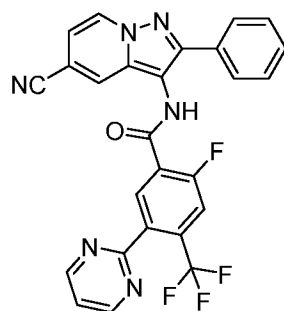
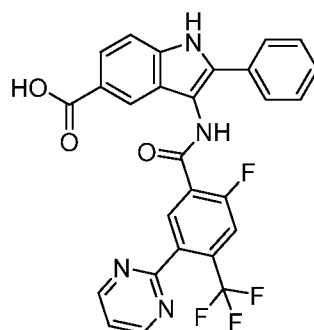
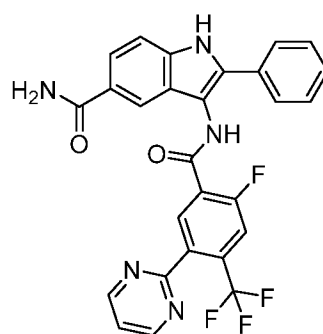
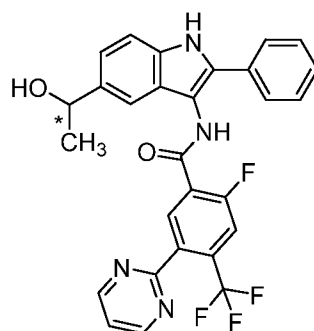
Sodium borohydride (0.020 g, 0.038 mmol) was added to a solution of *N*-(7-acetyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide (0.020 g, 0.038 mmol) in EtOH (1 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 0.5 h. The mixture was concentrated and the residue was partitioned between water and EtOAc. The organic layer was dried over magnesium sulfate and concentrated to afford the mixture of enantiomers. The enantiomers were separated using supercritical fluid chromatography (SFC) (2cm x 25cm IC column) eluting with 25% MeOH (0.1% DEA), 75% CO₂ at 50 mL/min to afford the title compound. MS: m/z = 524.0 ($M + 1$).

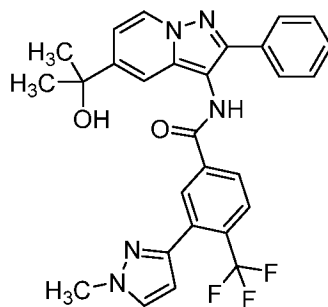
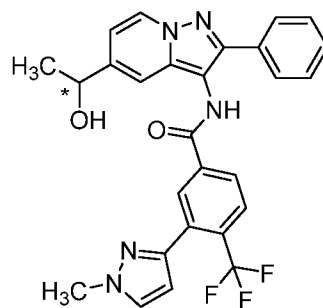
¹H NMR (400 MHz, CD₃OD) δ 8.13-8.10 (m, 2H) 7.95-7.93 (d, J = 8.0 Hz, 1H) 7.83-7.80 (d, J = 8.0 Hz, 1H) 7.68 (s, 1H) 7.60 (s, 1H) 7.48-7.44 (m, 2H) 7.39-7.37 (m, 2H) 7.09-7.07 (d, J = 8.0 Hz, 1H) 6.50 (s, 1H) 4.95-4.90 (q, J = 6.8 Hz, 1H) 3.97 (s, 3H) 1.52-1.50 (d, J = 6.8 Hz, 3H).

EXAMPLE 85

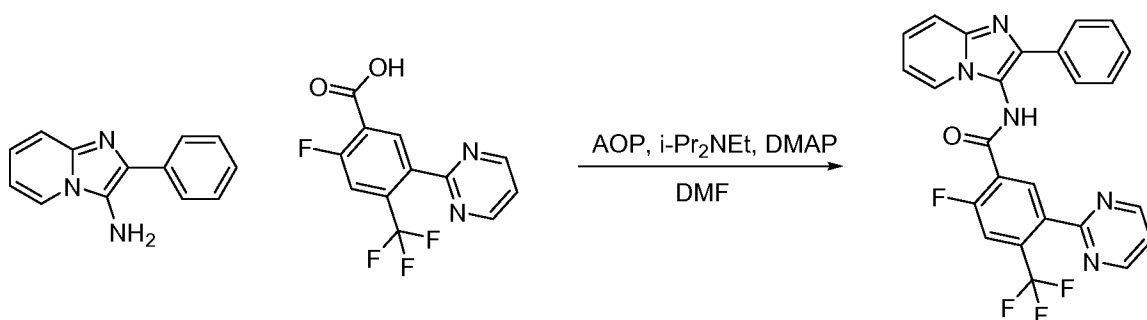
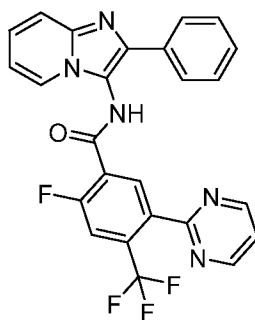


EXAMPLE 86

EXAMPLE 91EXAMPLE 92EXAMPLE 93 AND 94EXAMPLE 96

EXAMPLE 97 AND 98

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REACTION SCHEME FOR EXAMPLE 104EXAMPLE 104

2-fluoro-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-5-(pyrimidin-2-yl)-4-
(trifluoromethyl)benzamide

10

To 2-phenylimidazo[1,2-a]pyridin-3-amine (100 mg, 0.478 mmol) and 2-fluoro-5-(pyrimidin-2-yl)-4-(trifluoromethyl)benzoic acid (137 mg, 0.478 mmol) in pyridine (2.4 mL) at 0 °C was added phosphoryl trichloride in a dropwise manner (53.5 µL, 0.573 mmol). The mixture was maintained at 0 °C with stirring for 20 min. The reaction was carefully quenched with saturated aqueous NaHCO₃ solution (3 mL), and the resulting mixture was partitioned between brine (5 mL) and 3:1 EtOAc/hexane (10 mL). The organic layer was dried over MgSO₄, filtered, and concentrated. The crude material was purified by SiO₂ column chromatography, eluting with 0-70% EtOAc/hexanes to give the title compound. MS: m/z = 478.3 ($M + 1$). ¹H NMR (500 MHz, CDCl₃): δ 8.92 (m, 2H), 7.97 (d, J = 7.5 Hz, 2H), 7.87 (s, 1H), 7.76 (d, J = 11.3 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.48 (m, 2H), 7.40 (m, 2H), 7.30 (m, 2H), 6.92 (m, 1H).

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 IC₅₀ was determined using Equation 1 below.

Equation 1:
$$\% \text{ Inhibition} = \left(\text{Max} + \frac{(\text{Min} - \text{Max})}{1 + \left(\frac{\text{Conc}}{\text{IC}_{50}} \right)^n} \right)$$

- 5 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:

10

Table 2

<u>L- Number</u>	<u>Com poun d #</u>	<u>IUPAC Name</u>	<u>IC₅₀ (nM)</u>
L- 0051526 33-000R	1	N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethoxy)benzamide	550
L- 0051649 82-001D	2	2-fluoro-N-(6-phenylimidazo[2,1-b][1,3]thiazol-5-yl)-4-(trifluoromethyl)benzamide	139
L- 0052145 02-002K	3	3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyrimidin-3-yl)-4-(trifluoromethyl)benzamide	5.9
L- 0052151 08-000N	4	3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	1.4
L- 0052204 05-002M	5	3-(1-methyl-1H-pyrazol-3-yl)-N-(2-pyridin-2-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	12
L- 0052214 37-000X	6	3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-b]pyridazin-3-yl)-4-(trifluoromethyl)benzamide	3.9

L- 0052313 35-000J	7	2-fluoro-N-[5-(1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	264
L- 0052353 11-000T	8	3-(1-methyl-1H-pyrazol-3-yl)-N-(2-pyrimidin-4-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	568
L- 0052690 32-001E	9	N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	8.8
L- 0052885 17-001W	10	2-fluoro-N-(2-isoxazol-5-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	1920
L- 0052885 24-001M	11	3-[1-(difluoromethyl)-1H-pyrazol-3-yl]-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	3.2
L- 0052897 93-000M	12	3-(1-methyl-1H-pyrazol-3-yl)-N-(6-phenylimidazo[2,1-b][1,3]thiazol-5-yl)-4-(trifluoromethyl)benzamide	1.9
L- 0052904 98-001S	13	3-(1-methyl-1H-pyrazol-3-yl)-N-[2-(4-methyl-1H-pyrazol-1-yl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	17
L- 0052926 53-001M	14	3-(4-methyl-1,3-oxazol-2-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	3.3
L- 0052926 71-000C	15	4-methyl-3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-	26

		3-yl)benzamide	
L- 0052941 97-001G	16	N-[2-(2-methyl-1,3-oxazol-4-yl)imidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	556
L- 0053025 29-000B	17	3-(1-methyl-1H-pyrazol-3-yl)-N-(6-phenylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)-4-(trifluoromethyl)benzamide	9.2
L- 0053033 72-001E	18	N-(8-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	11
L- 0053051 86-001B	19	3-(1-methyl-1H-pyrazol-3-yl)-N-[2-(2-methyl-1,3-thiazol-4-yl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	14
L- 0053066 45-001S	20	2-chloro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	0.73
L- 0053066 87-000B	21	N-(6-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	3.8
L- 0053066 88-000K	22	N-(8-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	1.9
L- 0053075 55-001U	23	2-chloro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-pyridin-4-ylimidazo[1,2-a]pyridin-3-yl)-	2

		4-(trifluoromethyl)benzamide	
L- 0053107 64-001Z	24	2-chloro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyrimidin-3-yl)-4-(trifluoromethyl)benzamide	2.8
L- 0053107 86-000Z	25	N-methyl-3-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl} amino)-2-phenylimidazo[1,2-a]pyridine-7-carboxamide	1.4
L- 0053204 96-000B	26	N-[7-(hydroxymethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	1.4
L- 0053204 97-000K	27	N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	1.8
L- 0053210 22-001C	28	N,N-dimethyl-3-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl} amino)-2-phenylimidazo[1,2-a]pyridine-7-carboxamide	1.3
L- 0053210 25-001D	29	N-[7-(azetidin-1-ylcarbonyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	1.4
L- 0053228 46-001V	30	4-chloro-2-fluoro-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-5-pyrimidin-2-	40

		ylbenzamide	
L- 0053275 97-000G	31	3-(1-methyl-1H-pyrazol-3-yl)-N-(3-phenylquinoxalin-2-yl)-4-(trifluoromethyl)benzamide	27
L- 0053278 07-001G	32	2-hydroxy-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	477
L- 0053298 08-000C	33	2-cyano-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	532
L- 0053366 45-001J	34	N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)benzamide	58
L- 0053368 87-000N	35	2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	0.49
L- 0053370 92-000D	36	N-[6-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	0.34
L- 0053371 50-000B	37	N-[6-(hydroxymethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	1.8
L- 0053411	38	N-[8-(hydroxymethyl)-2-phenylimidazo[1,2-a]pyridin-	2.4

20-000W		3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	
L-0053443 13-000H	39	N-(7-bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	2.7
L-0053502 92-000P	40	2-fluoro-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	2.7
L-0053577 52-000F	41	N-{7-[(1S)-1-hydroxyethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	0.96
L-0053577 53-000P	42	N-{7-[(1R)-1-hydroxyethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	0.79
L-0053580 83-001V	43	N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	7.9
L-0053580 86-000U	44	N-[6-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	1.4
L-0053593 77-001L	45	N-{7-[(3-methoxyazetidin-1-yl)methyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-	5.0

		(trifluoromethyl)benzamide	
L- 0053593 82-000H	46	N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(4-methyl-1,3-oxazol-2-yl)-4-(trifluoromethyl)benzamide	0.44
L- 0053704 72-001E	47	N-{6-[(3-fluoroazetidin-1-yl)methyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	8.8
L- 0053728 41-000V	48	N-[6-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	1.9
L- 0053728 43-000M	49	N-[7-(1,2-dihydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	0.51
L- 0053780 00-000F	50	2-fluoro-N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	0.45
L- 0053819 10-000N	51	N-{7-[1-(dimethylamino)ethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	3.5
L- 0053819	52	N-[6-(1,2-dihydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-	4.9

15-000G		3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	
L-0053819 23-000G	53	2-fluoro-N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	1.1
L-0053819 28-000A	54	2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	0.40
L-0053819 29-000J	55	2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	0.37
L-0053819 32-000R	56	N-{7-[1-(dimethylamino)ethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	1.0
L-0053849 41-000H	57	2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	1.1
L-0053849 42-000S	58	2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	0.92
L-	59	2-fluoro-N-(7-methoxy-2-	1.7

0053984 11-001B		phenylimidazo[1,2-a]pyridin-3-yl)-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	
L- 0054101 46-000Z	60	N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(3-methyl-1H-pyrazol-1-yl)-4-(trifluoromethyl)benzamide	14
L- 0054157 24-000D	61	N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(4-methyl-1,3-oxazol-2-yl)-4-(trifluoromethyl)benzamide	2.4
L- 0054157 25-000M	62	N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(4-methyl-1,3-oxazol-2-yl)-4-(trifluoromethyl)benzamide	1.5
L- 0054238 37-000G	63	3-(1-methyl-1H-pyrazol-3-yl)-N-[2-phenyl-7-(2,2,2-trifluoro-1-hydroxyethyl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	1.6
L- 0054238 38-000R	64	3-(1-methyl-1H-pyrazol-3-yl)-N-[2-phenyl-7-(2,2,2-trifluoro-1-hydroxyethyl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	1.1
L- 0054238 39-000Z	65	3-(1-methyl-1H-pyrazol-3-yl)-N-[2-phenyl-6-(2,2,2-trifluoro-1-hydroxyethyl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	12

L- 0054238 40-000N	66	3-(1-methyl-1H-pyrazol-3-yl)-N-[2-phenyl-6-(2,2,2-trifluoro-1-hydroxyethyl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	4.5
L- 0054238 41-000X	67	N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	5.1
L- 0054238 42-000F	68	N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	4.6
L- 0054284 81-000A	69	N-[7-(1-hydroxycyclopropyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	3.4
L- 0054290 94-000Z	70	2-chloro-N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	1.2
L- 0054306 19-000A	71	2-chloro-N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(4-methylpyrimidin-2-yl)-4-(trifluoromethyl)benzamide	7.6
L- 0054310 83-001H	72	2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenyl-1H-indol-3-yl)-4-(trifluoromethyl)benzamide	4.1
L- 0054315	73	2-fluoro-N-[7-(1-hydroxyethyl)-2-	1.4

63-000V		phenylimidazo[1,2-a]pyridin-3-yl]-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	
L-0054315 64-000D	74	2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	1.8
L-0054324 97-000S	75	N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-2-methyl-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	4.5
L-0054338 53-000W	76	2-fluoro-N-(2-phenyl-1H-indol-3-yl)-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	8.2
L-0054341 20-000U	77	3-[1-(difluoromethyl)-1H-pyrazol-3-yl]-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	4.0
L-0054341 22-000L	78	3-[1-(difluoromethyl)-1H-pyrazol-3-yl]-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	4.8
L-0054341 23-001X	79	N-{7-[(acetylamino)methyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	8.2
L-0054341 26-000W	80	N-(7-{{[(hydroxyacetyl)amino]methyl}}-2-phenylimidazo[1,2-	20

		a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	
L-0054388 53-000U	81	N-(7- {[(methylcarbamoyl)amino]methyl}-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	15
L-0054426 61-001Y	82	N-[7-({[(1-hydroxycyclopropyl)carbonyl]amino}methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	4.6
L-0054426 62-001G	83	methyl {[3-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-2-phenylimidazo[1,2-a]pyridin-7-yl]methyl} carbamate	0.77
L-0054426 63-001R	84	3-(1-methyl-1H-pyrazol-3-yl)-N-(7- {[(methylsulfonyl)amino]methyl}-2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	3.1
L-0054430 20-001F	85	2-fluoro-N-(2-phenylpyrazolo[1,5-a]pyridin-3-yl)-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	5.0
L-0054439 04-000S	86	N-(5-cyano-2-phenyl-1H-indol-3-yl)-2-fluoro-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	2.6
L-	87	3-(1-methyl-1H-pyrazol-3-	0.68

0054447 88-001T		yl)-N-[7-(4-methyl-1,3-thiazol-2-yl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide	
L- 0054478 47-001H	88	3-(1-methyl-1H-pyrazol-3-yl)-N-(7-morpholin-4-yl-2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	1.2
L- 0054478 48-001S	89	3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenyl-7-pyrrolidin-1-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	5.0
L- 0054478 63-001H	90	3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenyl-7-piperazin-1-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	3.8
L- 0054510 37-000G	91	3-({[2-fluoro-5-pyrimidin-2-yl-4-(trifluoromethyl)phenyl]carbo- nyl}amino)-2-phenyl-1H-indole-5-carboxylic acid	11
L- 0054531 78-000J	92	3-({[2-fluoro-5-pyrimidin-2-yl-4-(trifluoromethyl)phenyl]carbo- nyl}amino)-2-phenyl-1H-indole-5-carboxamide	8.7
L- 0054539 97-000N	93	N-{7-[(1R)-1-hydroxyethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-2-methyl-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	4.7
L- 0054591	94	2-fluoro-N-[5-(1-hydroxyethyl)-2-phenyl-1H-	6.5

69-000T		indol-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	
L-0054591 70-000G	95	2-fluoro-N-[5-(1-hydroxyethyl)-2-phenyl-1H-indol-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	4.9
L-0054591 74-000S	96	N-[5-(1-hydroxy-1-methylethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	6.7
L-0054604 60-000G	97	N-[5-(1-hydroxyethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	1.9
L-0054604 63-000H	98	N-[5-(1-hydroxyethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	3.3
L-0054608 46-000N	99	N-[7-(2-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	2.1
L-0054614 29-000K	100	N-[7-(2-aminoethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	13
L-0054614 31-000H	101	N-{7-[2-(acetylamino)ethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	10

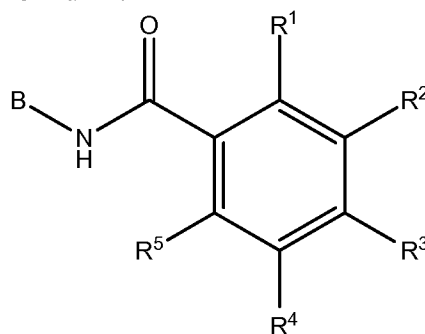
L- 0054614 32-000S	102	3-(1-methyl-1H-pyrazol-3-yl)-N-(7-{2-[(methylsulfonyl)amino]ethyl}-2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide	4.3
L- 0054616 30-000U	103	2-fluoro-N-[5-(1-hydroxy-1-methylethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	0.94
L- 0054637 98-000S	104	methyl {2-[3-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl} amino)-2-phenylimidazo[1,2-a]pyridin-7-yl]ethyl} carbamate	1.7
L- 0054644 64-000V	105	2-fluoro-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide	1.4
L- 0054655 64-000Z	106	2-fluoro-N-[5-(1-hydroxyethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	1.7
L- 0054655 65-000H	107	2-fluoro-N-[5-(1-hydroxyethyl)-2-phenylpyrazolo[1,5-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide	0.85
L- 0054655 66-000S	108	N-(5-cyano-2-phenyl-1H-indol-3-yl)-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-	1.0

		(trifluoromethyl)benzamide	
L- 0054657 00-000E	109	N-{7-[2-(methylamino)ethyl]- 2-phenylimidazo[1,2- a]pyridin-3-yl}-3-(1-methyl- 1H-pyrazol-3-yl)-4- (trifluoromethyl)benzamide	169
L- 0054663 58-000S	110	3-([2-fluoro-5-(1-methyl- 1H-pyrazol-3-yl)-4- (trifluoromethyl)phenyl]carbo nyl}amino)-2-phenyl-1H- indole-5-carboxylic acid	3.6
L- 0054693 49-000S	111	N-(6-cyano-2- phenylpyrazolo[1,5-a]pyridin- 3-yl)-2-fluoro-5-(1-methyl- 1H-pyrazol-3-yl)-4- (trifluoromethyl)benzamide	1000
L- 0054695 95-000N	112	2-fluoro-N-[5-(1- hydroxyethyl)-2-phenyl-1H- indol-3-yl]-5-(1-methyl-1H- pyrazol-3-yl)-4- (trifluoromethyl)benzamide	1.4
L- 0054696 11-000Z	113	2-fluoro-N-[5-(1- hydroxyethyl)-2-phenyl-1H- indol-3-yl]-5-(1-methyl-1H- pyrazol-3-yl)-4- (trifluoromethyl)benzamide	1.7
L- 0054757 96-000C	114	3-(1-methyl-1H-pyrazol-3- yl)-N-(2-phenyl-7-pyrrolidin- 2-ylimidazo[1,2-a]pyridin-3- yl)-4- (trifluoromethyl)benzamide	15
L- 0054816 96-000D	115	2-fluoro-N-{7-[(1R)-1- hydroxyethyl]-2- phenylimidazo[1,2-a]pyridin- 3-yl}-5-(1-methyl-1H- pyrazol-3-yl)-4-(1,1,2- trifluoroethyl)benzamide	3.7

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
5 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.

What is claimed is:

1. A compound of formula I:



I

5 or a pharmaceutically acceptable salt thereof, wherein

B is selected from the group consisting of a bicyclic heteroaryl having at least one nitrogen heteroatom, said heteroaryl optionally substituted with 1 to 3 groups of R^a ;

R is selected from the group consisting of hydrogen, OH, or $-C_{1-6}$ alkyl;

10 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_{1-4} haloalkyl, C_{1-6} alkyl, $(CHR)_n C_{6-10}$ aryl and $(CHR)_n C_{5-10}$ heterocycle, said alkyl, aryl, and
15 heterocycle optionally substituted with 1 to 3 groups of R^a ,

R^3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-4} haloalkyl, $-OC_{1-4}$ haloalkyl, and halogen;

20 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, $-(CHR)_n C_{6-10}$ aryl, $-(CHR)_n C_{4-10}$ heterocycle, $-(CHR)_n C(O)(CHR)_n C_{4-10}$ heterocycle, $-O-(CH_2)_n C_{6-10}$ aryl, $-O-(CH_2)_n C_{4-10}$ heterocycle -
O-, $-(CH_2)_n N(R^d)_2$, $-(CH_2)_n C(O)NH(CH_2)_n C_{4-10}$ heterocycle, $SO_2 R^d$, $SO_2 N(R^d)_2$, -
C(O)CF₃, COR, $-(CH_2)_n$ halo, $-(CH_2)_n NHC(O)R^d$, $-(CH_2)_n NHC(O)NHR^d$, -
25 $(CH_2)_n NHC(O)OR^d$, $-(CHR)_n C(O)N(R^d)_2$, $-O-C_{1-6}$ 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 form a 4-8 membered
heterocycle that is optionally substituted with 1 to 3 groups of R^f ;

30 R^b is selected from the group consisting of $-C_{1-6}$ alkyl, $-C_{1-6}$ alkylOR, $-C_{1-4}$ haloalkyl, $-(CH_2)_n C_{3-6}$ cycloalkyl, $-(CH_2)_n N(R^d)_2$, $-(CH_2)_n OR^c$, $-O-$, halogen, $-CN$,

S(O)(NH)R^g, -SO₂R, -SO₂N(R^d)₂, -O-(CH₂)_nC₄₋₁₀ heterocycle, -(CH₂)_nC(O)N(R^d)₂, -(CH₂)_nNHC(O)R^d, -C₁₋₆alkylN(R^d)₂, and halo, said cycloalkyl optionally substituted with 1 to 3 groups of R^f, and wherein when two R^d groups are attached to a nitrogen atom they may combine with that nitrogen to form a 4-8 membered heterocycle that is optionally substituted with 1 to 3 groups of R^f;

R^c is selected from the group consisting of hydrogen, -C₁₋₆alkylOR^g, -C₁₋₄haloalkyl and -C₁₋₆alkyl;

R^d is independently selected from the group consisting of hydrogen, -C₁₋₄haloalkyl, -C₁₋₆alkyl, -(CH₂)_nNR^fC₄₋₁₀ heterocycle, -(CH₂)_nC₃₋₆cycloalkyl, and -(CH₂)_nC₄₋₁₀heterocycle said alkyl, cycloalkyl and heterocycle optionally substituted with 1 to 3 groups of R^f;

R^f is selected from the group consisting of hydrogen, OR^c, CN, -N(R^c)₂, C(O)N(R^g)₂, C(O)C₁₋₆alkyl, -SO₂R^g, -O-, -C₁₋₆alkylSO₂R^g, -C₁₋₆alkylOR^g, -C₁₋₆alkylN(R^g)₂,

R^g is selected from the group consisting of hydrogen, and -C₁₋₆alkyl; and

n represents 0-6.

2. The compound according to claim 2 wherein B is selected from the group consisting of unsubstituted or substituted imidazopyridinyl, imidazothiazolyl, imidazopyrimidinyl, imidazopyridazinyl, imidazothiadiazolyl, quinoxalinyl.

3. The compound according to claim 3 wherein B is unsubstituted or substituted imidazopyridinyl or imidazopyrimidinyl.

4. The compound according to claim 1 wherein one of R² and R⁴ is hydrogen and the other is (CHR)_nC₅₋₁₀ heterocycle, said heterocycle optionally substituted with 1 to 3 groups of R^a and R³ is selected from the group consisting of hydrogen, CF₃, OCF₃, CH₃, chlorine, and fluorine.

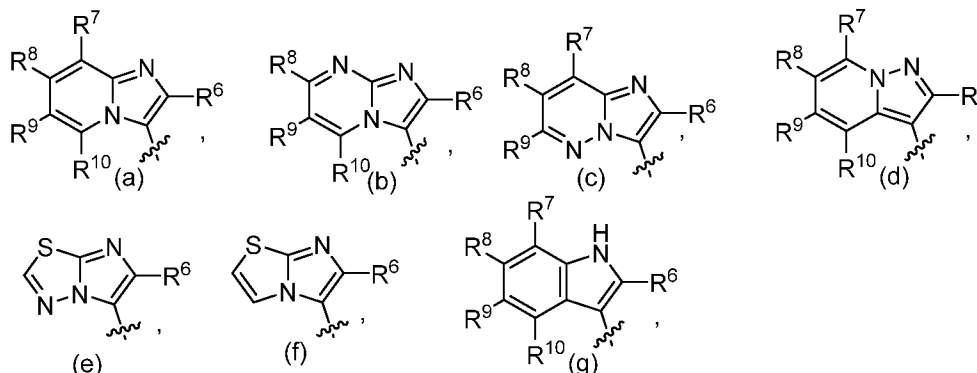
5. The compound according to claim 4 wherein the optionally substituted heterocycle of R² and R⁴ is a five or six membered ring containing one or more heteroatoms at least one of which is nitrogen.

6. The compound according to claim 1 wherein one of R² and R⁴ is hydrogen and the other is selected from the group consisting of optionally substituted pyrazolyl, pyridyl, thiazolyl, oxazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiadiazolyl, oxadiazolyl and triazolyl.

7. The compound according to claim 6 wherein the heterocycle is optionally substituted pyrazolyl.

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.

5 9. The compound according to claim 1 of formula I wherein B is represented by structural formulas (a), (b), (c), (d), (e), (f), (g), (h), or (i):



wherein:

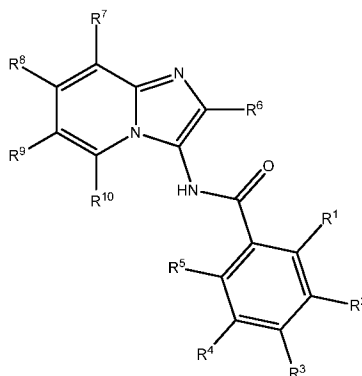
10 R^6 represents $(CH_2)_n C_{6-10}$ aryl, or $(CH_2)_n C_{5-10}$ heterocycle, said aryl, and heterocycle optionally substituted with 1 to 3 groups of R^a ; and

R^7 , R^8 , R^9 and R^{10} independently represent hydrogen, halogen, CN, C_{1-6} alkyl, $C(O)N(R)_2$, $C(O)(CH_2)_n C_{5-10}$ heterocycle, $(CH_2)_n C_{6-10}$ aryl, or $(CH_2)_n C_{5-10}$ heterocycle, said alkyl, aryl, and heterocycle optionally substituted with 1 to 3 groups of R^a .

15 10. The compound according to claim 9 wherein B is imidazopyridinyl or indazolyl represented by structural formula (a) or (b), respectively.

11. The compound according to claim 10 wherein B is imidazopyridinyl or indazolyl represented by structural formula (a) or (b), respectively, R^6 is unsubstituted or substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazolyl, oxazolyl, or pyrimidinyl, R^8 and R^9 are
 20 independently selected from hydrogen, halogen, CN, CH_2OH , $C(O)N(R)_2$, and optionally substituted C_{1-6} alkyl, phenyl, pyrazolyl, isoxazolyl, oxazolyl, $(CH_2)_n$ azetidyl, and $C(O)NH$ azetidyl and R^7 and R^{10} are independently selected from hydrogen, C_{1-6} alkyl, and halogen, said alkyl optionally substituted with 1 to 3 groups of R^b .

12. The compound of formula II according to claim 1:



II

wherein:

R⁶ is unsubstituted or substituted phenyl, thiazolyl, pyrazolyl, pyridyl, isoxazolyl, oxazolyl or pyrimidinyl, R⁸ and R⁹ are independently selected from hydrogen, halogen, CN, CH₂OH, C(O)N(R)₂, and optionally substituted C₁₋₆alkyl, phenyl, pyrazolyl, isoxazolyl, oxazolyl, (CH₂)_nazetidiny, and C(O)NHazetidiny, R⁷ and R¹⁰ are independently selected from hydrogen, C₁₋₆alkyl, and halogen, said alkyl optionally substituted with 1 to 3 groups of R^b, R³ is selected from the group consisting of hydrogen, CF₃, OCF₃, CH₃, chlorine and fluorine, and one of R² and R⁴ is hydrogen and the other is (CHR)_nC₅₋₁₀ heterocycle, said heterocycle optionally substituted with 1 to 3 groups of R^a.

13. The compound according to claim 12 wherein R¹ and R⁵ are both hydrogen or one is hydrogen and the other halogen, R³ is OCF₃, or CF₃, one of R² and R⁴ is hydrogen and the other is an optionally substituted (CHR)_nC₅₋₁₀ heterocycle that is a five or six membered ring containing one or more heteroatoms at least one of which is nitrogen.

14. The compound according to claim 13 wherein the optionally substituted heterocycle of R² and R⁴ is selected from the group consisting of pyrazolyl, pyridyl, thiazolyl, oxazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiadiazolyl, oxadiazolyl and triazolyl.

15. The compound according to claim 12 wherein one of R² and R⁴ is hydrogen and the other is is pyrazolyl, R⁶ is optionally substituted phenyl and R³ is CF₃.

16. A compound which is selected from the group consisting of

N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethoxy)benzamide;

2-fluoro-N-(6-phenylimidazo[2,1-b][1,3]thiazol-5-yl)-4-(trifluoromethyl)benzamide;

3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyrimidin-3-yl)-4-(trifluoromethyl)benzamide;

3-(1-methyl-1H-pyrazol-3-yl)-N-(2-pyridin-2-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide;

3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-b]pyridazin-3-yl)-4-(trifluoromethyl)benzamide;

- 2-fluoro-N-[5-(1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide;
 3-(1-methyl-1H-pyrazol-3-yl)-N-(2-pyrimidin-4-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide;
 5 N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
 2-fluoro-N-(2-isoxazol-5-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide;
 3-[1-(difluoromethyl)-1H-pyrazol-3-yl]-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide;
 3-(1-methyl-1H-pyrazol-3-yl)-N-(6-phenylimidazo[2,1-b][1,3]thiazol-5-yl)-4-(trifluoromethyl)benzamide;
 10 3-(1-methyl-1H-pyrazol-3-yl)-N-[2-(4-methyl-1H-pyrazol-1-yl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide;
 3-(4-methyl-1,3-oxazol-2-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide;
 15 4-methyl-3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)benzamide;
 N-[2-(2-methyl-1,3-oxazol-4-yl)imidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
 3-(1-methyl-1H-pyrazol-3-yl)-N-(6-phenylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)-4-(trifluoromethyl)benzamide;
 20 N-(8-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
 3-(1-methyl-1H-pyrazol-3-yl)-N-[2-(2-methyl-1,3-thiazol-4-yl)imidazo[1,2-a]pyridin-3-yl]-4-(trifluoromethyl)benzamide;
 N-(6-fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
 25 2-chloro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-pyridin-4-ylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide;
 2-chloro-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyrimidin-3-yl)-4-(trifluoromethyl)benzamide;
 30 N-methyl-3-({[3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]carbonyl}amino)-2-phenylimidazo[1,2-a]pyridine-7-carboxamide;
 N-[7-(azetidin-1-ylcarbonyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
 4-chloro-2-fluoro-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-5-pyrimidin-2-ylbenzamide;
 35 3-(1-methyl-1H-pyrazol-3-yl)-N-(3-phenylquinoxalin-2-yl)-4-(trifluoromethyl)benzamide;
 2-cyano-5-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide;

N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)benzamide;
N-[6-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
N-[8-(hydroxymethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
5 N-(7-bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
N-{7-[(3-methoxyazetidin-1-yl)methyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
10 N-{6-[(3-fluoroazetidin-1-yl)methyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-3-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
N-{7-[1-(dimethylamino)ethyl]-2-phenylimidazo[1,2-a]pyridin-3-yl}-2-fluoro-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
2-fluoro-N-[7-(1-hydroxy-1-methylethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-pyrimidin-2-yl-4-(trifluoromethyl)benzamide;
15 2-fluoro-N-[7-(1-hydroxyethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl]-5-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)benzamide;
2-fluoro-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide;
3-(1-methyl-1H-pyrazol-3-yl)-N-(2-phenylimidazo[1,2-a]pyridin-3-yl)-4-(trifluoromethyl)benzamide
20 or a pharmaceutically acceptable salt thereof.

17. 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.

18. 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.

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

20. 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.