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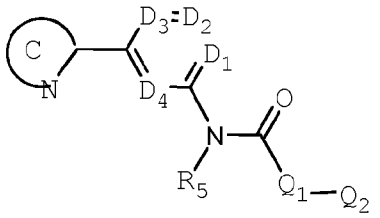

(I)

(57) Abstract: Disclosed are novel N-(3-heteroarylaryl)-4-arylarylcarboxamides and analogs thereof, represented by the Formula I: wherein C cyclic group, D_1-D_4, Q_1, Q_2, R_5 are defined herein. Compounds having Formula (I) are hedgehog pathway inhibitors. Therefore, compounds of the invention may be used to treat clinical conditions that are responsive to the inhibition of hedgehog activity, such as cancer.

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N-(3-HETEROARYLARYL)-4-ARYLARYLCARBOXAMTDES AND ANALOGS AS HEDGEHOG PATHWAY INHIBITORS AND USE THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention is in the field of medicinal chemistry. In particular, the invention relates to N-(3-heteroarylaryl)-4-arylarylcarboxamides and analogs, and the use of these compounds as hedgehog pathway inhibitors and anti-cancer drugs.

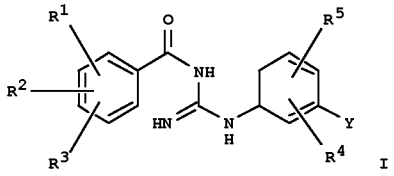
Related Art

[0002] The hedgehog (Hh) proteins, a highly conserved protein family, were originally discovered in Drosophila and play a paramount role in the proper development of the embryo. Regarding to human, the mammalian homologues of Hh proteins include mainly three genes, Sonic hedgehog (Shh), Indian hedgehog (Ihh) and Desert hedgehog (Dhh). Of these, Shh not only is important in embryonic development, but also has been suggested to be involved in tumor genesis including basal cell carcinoma (BCC) (Caro, I. and Low, J.A., Clin Cancer Res, 2010, 16(13): 3335-9). Shh protein is produced from an approximately 45 kDa precursor. After processing, a 20 kDa N-terminal fragment is produced and this N-terminal fragment has all of the known biological activity of Shh. Although the detailed mechanism to cause cancer has not been fully understood, it is known that Shh can activate intracellular hedgehog signaling pathway that includes the following components, patched (PTCH), a 7-transmembrane G-protein coupled receptor Smoothened (SMO) as well as transcription factor Gli, etc. (Bale, A.E. and Yu, K.P., Hum Mol Genet, 2001, 10(7): 757-62). The results from mutation analysis of the Hh signal pathway in basal cell carcinoma indicate that most of the mutations occur at PTCH-1 and SMO (Von Hoff, D.D.; et al., N Engl J Med, 2009, 361(12): 1164-72). PTCH-1 is a membrane protein with a 12-transmembrane structure and it is the direct receptor of Shh. In the absence of Shh, PTCH-1 interacts with SMO and inhibits the biological activity of SMO. The binding of Shh to PTCH-1 leads to the dissociation of PTCH-1 from SMO, resulting in a dis-inhibition of SMO. The transcription factor Gli is under the control of SMO and plays an important role in turning on a transcription event. Three most important members of the Gli family include Gli1, Gli2 and Gli3. The Hh signal pathway is critically important for embryonic development. Interference of the Hh signal pathway would result in severe birth defect such as

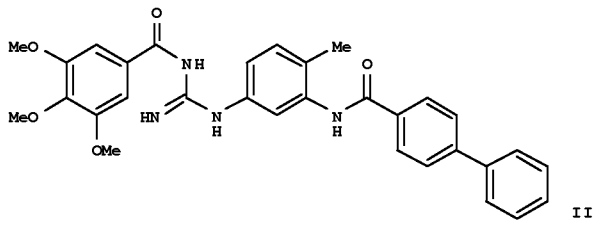
cyclopia. For example, a natural teratogenic compound cyclopamine is an Hh signal pathway inhibitor. Under normal condition, the Hh concentration is very low in adult human. Due to the low concentration of Hh, PTCH-1 binds to SMO and inhibits the activity of SMO. Therefore, the Hh signalling pathway has very low activity. When cells start to produce Hh, the secreted Hh binds to its receptor PTCH-1 and results a dissociation of PTCH-1 from SMO to remove the inhibition on SMO. The activated SMO, in turn activates transcription factor Gli-1 that regulates gene transcription and cell growth. More and more evidence indicate that most of the basal cell carcinoma is caused by mutations or other changes that cause high activity of the hedgehog signaling pathway. Therefore, inhibition of hedgehog signaling pathway may stop the growth of cancer cells, resulting to a therapeutic treatment of basal cell carcinoma and other cancers caused by similar mechanism. Series of scientific and clinic evidence indicate that hedgehog pathway inhibitors can be effectively used to treat cancers. The most recent clinical results have shown that hedgehog pathway inhibitor GDC-0449 can be used to treat basal cell carcinoma, meduloblastoma (Lorusso, P.M.; et al., Clin Cancer Res, 2011, 17(8): 2502-11) or other cancers that are caused by similar mechanisms such as basal cell nevus syndrome (BCNS) effectively (Goldberg, L.H.; et al., Arch Dermatol, 2011, 147(7): 839-41). On March of 2012, FDA approved GDC-0449 as a new targeted therapy to treat basal cell carcinoma, which validated the feasibility of using hedgehog pathway inhibitors to treat cancer. The results from biochemical research suggest that GDC-0449 interacts with SMO directly to inhibit the activity of SMO that leads to the inhibition of the entire hedgehog signaling pathway, therefore the inhibition of cancer cell growth. In addition to basal cell carcinoma and medulloblastoma there are many other cancers that are caused by high activity in hedgehog signaling pathway, such as pancreatic, gastro-intestinal, colorectal, ovarian, prostate cancers and some blood abnormality (De Smaele, E.; et al., Curr Opin Investig Drugs, 2010, 11(6): 707-18). Therefore, development of hedgehog pathway inhibitors as new type of therapeutic treatment of cancer has a great future.

[0003] Hedgehog signaling pathway is critically important for the pluripotent mesenchymal mouse embryonic cell C3H10T1/2 to differentiate into osteoblastic cells. The differentiation of C3H10T1/2 cells into osteoblastic cells accompanies with a dramatic increase in intracellular alkaline phosphatase activity which can be readily measured. Inhibition of the hedgehog signaling pathway activity can be measured as a decrease in alkaline phosphatase activity. Therefore, stimulating the hedgehog signaling pathway and measuring the alkaline phosphatase activity can be used to screen hedgehog pathway inhibitors (Peukert, S. and Miller-Moslin, K., Chem Med Chem, 2010, 5(4): 500-12; Tremblay, M.R.; et al., J Med Chem, 2009, 52(14): 4400-18).

[0004] WO2011010013 disclosed compound I [R^{1-3} independently are hydrogen, halo, hydroxy, fluoroalkyl and the like; Y = monocyclic or polycyclic heteroaryl, $NHCOR^6$, $CONHR^6$, $NHCONHR^6$; R^6 = alkyl, optionally substituted monocyclic or polycyclic heteroaryl, aryl and the like; R^{4-5} independently are hydrogen, halo, alkoxy, alkylthio, nitro and the like], such as compound II, as hedgehog pathway inhibitors.

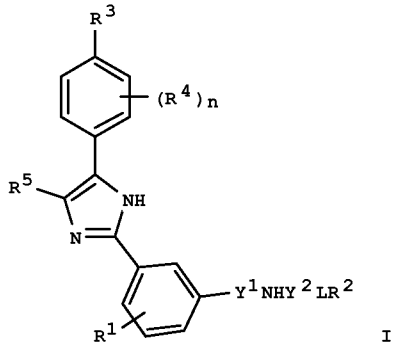


I



II

[0005] WO2008014291 disclosed compound I [n = 0−2; Y^1 = bond, CO; Y^2 = bond, CO, SO_2; R^1 = hydrogen, halo, cyano, alkyl, haloalkyl; R^2 = hydrogen, halo, cyano, alkyl, alkoxy, haloalkyl, haloalkoxy, (substituted) aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, PhO; R^3, R^4 = hydrogen, halo, cyano, alkyl, alkoxy, haloalkyl; R^5 = hydrogen, alkyl; L = phenylene, pyridinylene, naphthyridinylene, thiazolylene, (iso)quinolylene, benzothiazolylene, benzoxazolylene, benzisoxazolylene and the like] as hedgehog pathway inhibitors.



I

SUMMARY OF THE INVENTION

[0006] The invention provides novel N-(3-heteroarylaryl)-4-arylarylcarboxamides and analogs, as represented in Formulae I, II, III and IV. These compounds have hedgehog pathway inhibitory activities.

[0007] The present invention also provides pharmaceutical compositions comprising a compound of Formula I, II, III or IV in an effective amount for the treatment of cancer.

[0008] The invention also provides a pharmaceutical composition useful for the treatment of cancer, containing an effective amount of a compound of one of the Formula I, II, III or IV in admixture with one or more pharmaceutically acceptable carriers or diluents.

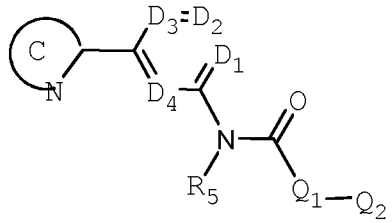
[0009] The invention also provides a pharmaceutical composition useful for the treatment of cancer, containing an effective amount of a compound of one of the Formula I, II, III or IV, in combination with at least one known anticancer drug or its pharmaceutically acceptable salts.

[0010] The invention also is directed to methods for the preparation of novel compounds of Formulae I, II, III and IV.

DETAILED DESCRIPTION OF THE INVENTION

[0011] The novel hedgehog pathway inhibitors of the present invention include N-(3-heteroarylaryl)-4-arylarylcarboxamides and analogs, as represented in Formulae I, II, III and IV.

[0012] Specifically, compounds of the present invention are represented by Formula I:



(I)

or pharmaceutically acceptable salts or prodrugs thereof, wherein:

C cyclic group is an optionally substituted nitrogen-containing heteroaryl;

D_1 is N or CR_6; D_2 is N or CR_7; D_3 is N or CR_8; D_4 is N or CR_9;

Q_1 and Q_2 independently are optionally substituted aryl, heteraryl, a carbocyclic group, or a heterocyclic group;

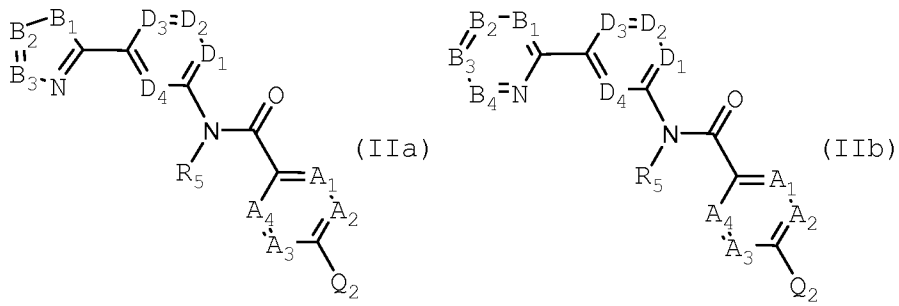
R_6-R_9 independently are hydrogen, halo, optionally substituted amino, alkoxy, C_{1-10} alkyl, C_{3-8} cycloalkyl, haloalkyl, aryl, a carbocyclic group, a heterocyclic group, heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, carboxyalkoxy, nitro, cyano, acylamino, aminocarbonyl, hydroxy, thiol, acyloxy, azido, carboxy, hydroxyacylamino, alkylsulfonyl, aminosulfonyl, dialkylaminosulfonyl, alkylsulfinyl, or alkylthiol;

R_5 is hydrogen or C_{1-10} alkyl, or R_5 is taken together with the N atom to which it is attached to, and other groups such as the carbon atom in C(=O) and an atom of Q_1 to form a heterocyclic ring.

One group of preferred compounds of Formula I includes compounds wherein the C cyclic group is an optionally substituted monocyclic or bicyclic nitrogen-containing heteroaryl.

Another group of preferred compounds of Formula I includes compounds wherein the C cyclic group is an optionally substituted benzothiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, 3H-indolyl, indolizinyl, indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, oxazolyl, isoxazolyl, furazanyl, phenoxazinyl, 1,2-benzisoxazol-3-yl, imidazolyl, benzimidazolyl, 2-oxindolyl, thiadiazolyl, imidazo[4,5-c]pyridin-2-yl, [1,2,4]triazolo[4,3-a]pyridin-3-yl, [1,2,4]triazolo[4,3-a]pyrimidin-3-yl, [1,2,4]triazolo[4,3-a]pyrazin-3-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazol[1,2-a]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-2-yl or 2-oxobenzimidazolyl. Another group of preferred compounds of Formula I includes compounds wherein the C cyclic group is an optionally substituted imidazolyl, including phenylimidazolyl, pyridinylimidazolyl, furylimidazolyl, thienylimidazolyl, thiazolylimidazolyl, pyrrolylimidazolyl, alkylimidazolyl and cycloalkylimidazolyl, wherein said phenyl, pyridinyl, furyl, thienyl, thiazolyl, pyrrolyl, alkyl and cycloakyl may be optionally substituted. Another group of preferred compounds of Formula I includes compounds wherein the C cyclic group is an optionally substituted thienoimidazolyl and imidazothiazolyl. Another group of preferred compounds of Formula I includes compounds wherein one of D_1, D_2, D_3 and D_4 is N. One group of preferred compounds of Formula I includes compounds wherein the cyclic group containing D_1-D_4 is an optionally substituted phenyl or pyridinyl, of which the substituent preferably is alkyl, halo, haloalkyl and the like. Another group of preferred compounds of Formula I includes compounds wherein Q_1 is an optionally substituted phenyl, pyridinyl or cycloalkyl. Another group of preferred compounds of Formula I includes compounds wherein Q_2 is an optionally substituted phenyl, pyridinyl, pyrimidinyl, furyl, thienyl, morpholinyl, piperazinyl or piperidinyl.

[0013] One group of preferred compounds of the present invention are represented by Formulae IIa and IIb (Formula II):



or pharmaceutically acceptable salts or prodrugs thereof, wherein:

D_1-D_4 and Q_2 are defined as in Formula I;

A_1 is N or CR_1; A_2 is N or CR_2; A_3 is N or CR_3; A_4 is N or CR_4;

B_1 is O, S, CR_{10} or NR_{14}; B_2 is O, S, CR_{11} or NR_{15}; B_3 is O, S, CR_{12} or NR_{16} for Formula IIa;

B_1 is N or CR_{10}; B_2 is N or CR_{11}; B_3 is N or CR_{12}, B_4 is N or CR_{13} for Formula IIb;

R_1-R_4 and R_{10}-R_{13} independently are hydrogen, halo, optionally substituted amino, alkoxy, C_{1-10} alkyl, C_{3-8} cycloalkyl, haloalkyl, optionally substituted aryl, a carbocyclic group, a heterocyclic group, optionally substituted heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, carboxyalkoxy, nitro, cyano, acylamino, aminocarbonyl, hydroxy, thiol, acyloxy, azido, carboxy, hydroxyacylamino, alkylsulfonyl, aminosulfonyl, acyl, dialkylaminosulfonyl, alkylsulfinyl, or alkylthiol;

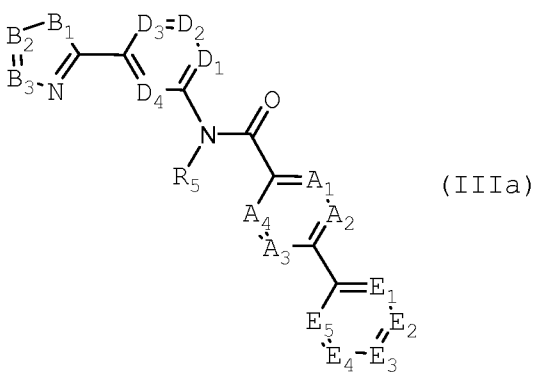
R_5 is hydrogen, C_{1-10} alkyl, or R_5 and R_1 or R_4 are taken together with other atoms, such as the carbon atom in the C(=O) group, to which they are attached to form a heterocyclic ring;

R_{14}-R_{16} independently are hydrogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, haloalkyl, optionally substituted aryl, a carbocyclic group, a heterocyclic group, optionally substituted heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl; or

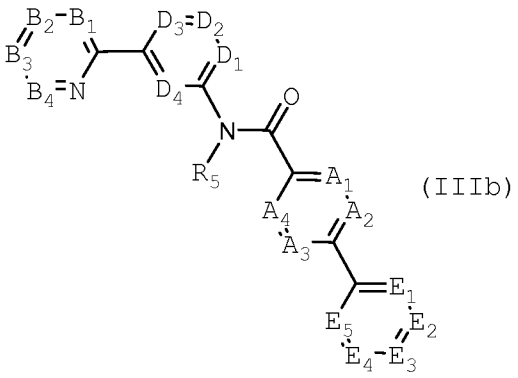
R_{10} or R_{14} and R_{11} or R_{15}, R_{11} or R_{15} and R_{12} or R_{16}, or R_{12} and R_{13}, are taken together with the C or N atom to which they are attached to form a five- or six-member aryl or heteroaryl.

One group of preferred compounds of Formulae IIa and IIb includes compounds wherein Q_2 is an optionally substituted phenyl, pyridyl, pyrimidinyl, furyl, thienyl, morpholinyl, piperazinyl, or piperidyl. Another group of preferred compounds of Formula IIa includes compounds wherein B_1 is NR_{14}; B_2 is CR_{11}; R_{11} is an optionally substituted aryl, heteroaryl, heterocyclic group, alkyl or cycloalkyl, including phenyl, pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, thiazolyl, methyl, ethyl, propyl, isopropyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0014] One group of preferred compounds of the present invention are represented by Formulae IIIa and IIIb (Formula III):



(IIIa)



(IIIb)

or pharmaceutically acceptable salts or prodrugs thereof, wherein:

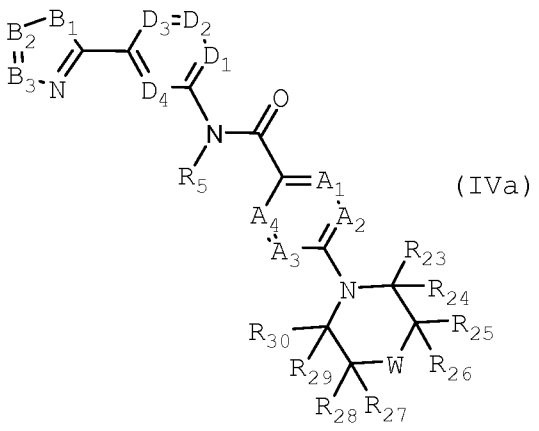
A_1-A_4, D_1-D_4, B_1-B_4 and R_5 are defined as in Formulae I, IIa and IIb;

E_1 is N or CR_{18}; E_2 is N or CR_{19}; E_3 is N or CR_{20}; E_4 is N or CR_{21}; E_5 is N or CR_{22};

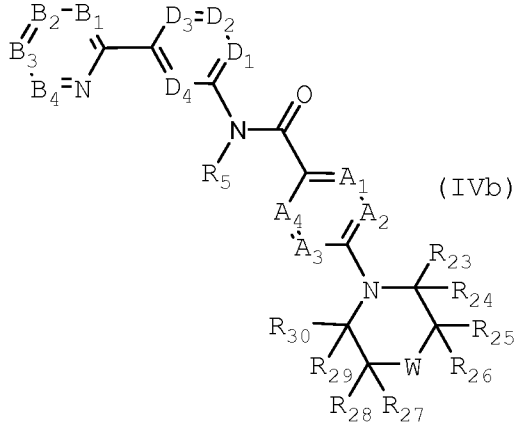
R_{18}-R_{22} independently are hydrogen, halo, optionally substituted amino, alkoxy, C_{1-10} alkyl, C_{3-8} cycloalkyl, haloalkyl, aryl, a carbocyclic group, a heterocyclic group, heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, carboxyalkoxyl, nitro, cyano, acylamino, aminocarbonyl, hydroxy, thiol, acyloxy, azido, carboxy, hydroxyacylamino, alkylsulfonyl, aminosulfonyl, acyl, dialkylaminosulfonyl, alkylsulfinyl, or alkylthiol.

One group of preferred compounds of Formula IIIa includes compounds wherein B_1 is NR_{14}; B_2 is CR_{11}; R_{11} is optionally substituted aryl, heteroaryl, heterocyclic group, alkyl or cycloalkyl, including phenyl, pyridyl, pyrimidinyl, furyl, pyrazinyl, thienyl, thiazolyl, pyrrolyl, methyl, ethyl, propyl, isopropyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Another group of preferred compounds of Formula IIIa includes compounds wherein B_1 is NR_{14}; B_2 is CR_{11}; B_3 is CR_{12}; R_{11} and R_{12} are taken together with the C atoms to which they are attached to form an optionally substituted five- or six-member aryl or heteroaryl, including phenyl, pyridinyl, pyrimidinyl, furyl and thienyl.

[0015] One group of preferred compounds of the present invention are represented by Formulae IVa and IVb (Formula IV):



(IVa)



(IVb)

or pharmaceutically acceptable salts or prodrugs thereof, wherein:

A_1-A_4, D_1-D_4, B_1-B_4 and R_5 are defined as in Formulae I, IIa and IIb;

W is O, S, $CR_{31}R_{32}$ or NR_{33};

R_{23}-R_{32} independently are hydrogen, halo, optionally substituted amino, alkoxy, C_{1-10} alkyl, C_{3-8} cycloalkyl, haloalkyl, aryl, a carbocyclic group, a heterocyclic group, heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, carboxyalkoxyl, nitro, cyano, acylamino, aminocarbonyl, hydroxy, thiol, acyloxy, azido, carboxy, hydroxyacylamino, alkylsulfonyl, aminosulfonyl, acyl, dialkylaminosulfonyl, alkylsulfinyl, or alkylthiol;

R_{33} is optionally substituted C_{1-10} alkyl, haloalkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, a carbocyclic group, a heterocyclic group, alkenyl, alkynyl, acyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl, aminocarbonyl, alkylsulfonyl, cycloalkylsulfonyl, or aminosulfonyl.

One group of preferred compounds of Formula IV includes compounds wherein the W-containing heterocyclic group is an optionally substituted morpholinyl, piperazinyl or piperidyl. Another group of preferred compounds of Formula IV includes compounds wherein W is O or NR_{33}, R_{33} is an optionally substituted C_{1-10} alkyl, preferably C_{1-3} alkyl. Another group of preferred compounds of Formula IV includes compounds wherein the W-containing heterocyclic group is an optionally substituted (2S,6R)-2,6-dimethylmorpholinyl or (2S,6R)-2,6-dimethylpiperazinyl.

One group of compounds of Formulae I, II, III and IV of the present invention include compounds wherein R_5 is taken together with the N atom to which it is attached, other groups such as the carbon atom in the C(=O) group, and an atom of Q_1 to form a quinazolinyl, benzoxazinyl or dihydroisoquinolyl.

One group of compounds of Formulae I, II, III and IV of the present invention include compounds wherein the group corresponding to the C group (that is the C cyclic group of Formula I, and the cyclic group containing B_1-B_3 or B_1-B_4 of Formulae IIa, IIb, IIIa, IIIb, IVa and IVb) is an unsubstituted or substituted benzimidazolyl or thienoimidazolyl, or imidazolyl substituted by aryl, heteroaryl, a carbocyclic group, alkyl, cycloalkyl or a heterocyclic group; the cyclic group containing D_1-D_4 is phenyl or pyridinyl, which is optionally substituted by halo, alkyl and haloalkyl; Q_1 or the cyclic group containing A_1-A_4 is phenyl, pyridinyl or cycloalkyl, which is optionally substituted by alkyl, halo, nitro and amino; Q_2 or the cyclic group

containing E_1-E_5 is phenyl, morpholinyl, pyrimidinyl, pyridinyl, piperidinyl, furyl, piperazinyl and thienyl, which is optionally substituted by alkyl, alkoxy, halo, alkylsulfonyl, cyano, nitro, acyl, haloalkyl and amino; or Q_2 or the W-containing cyclic group is morpholinyl, piperazinyl or piperidinyl, which is optionally substituted by alkyl, halo and haloalkyl; R_5 is H。

In some embodiments, compounds of the above formulae include compounds wherein the group corresponding to C group (that is the C cyclic group of Formula I, and the cyclic group containing B_1-B_3 or B_1-B_4 of Formulae IIa, IIb, IIIa, IIIb, IVa and IVb) is an unsubstituted or substituted benzimidazolyl, wherein Q_1 or the cyclic group containing A_1-A_4 and Q_2 or the cyclic group containing E_1-E_5 are not substituted by alkyl and haloalkyl at the same time. Another group of preferred compounds of Formulae I, II, III and IV of the present invention include compounds wherein at least one of D_1, D_2, D_3 and D_4 is N. Another group of preferred compounds of Formulae II, III and IV of the present invention include compounds wherein at least one of A_1, A_2, A_3 and A_4 is N. Another group of preferred compounds of Formula IV of the present invention include compounds wherein the W-containing heterocyclic group is an optionally substituted morpholinyl, piperazinyl or piperidinyl. Another group of preferred compound of Formula IV of the present invention include compounds wherein W is O or NR_{33}, R_{33} is optionally substituted $C_{1\text{-}10}$ alkyl, preferably $C_{1\text{-}3}$ alkyl. Another group of preferred compounds of Formula IV of the present invention include compounds wherein the W-containing heterocyclic group is optionally substituted (2S,6R)-2,6-dimethylpiperazinyl.

Exemplary preferred compounds of Formulae I, II, III and IV include, without limitation:

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methylbiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-methoxybiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-fluorobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(methylsulfonyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-cyanobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-nitrobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-chlorobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-acetylbiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-3'-fluorobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-3'-cyanobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4'-fluorobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3'-fluorobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methoxy-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-hydroxy-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-fluoro-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-chloro-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-nitro-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3,5-dimethyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-aminobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-amino-4'-(trifluoromethyl)biphenyl-4-carboxamide;

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)quinazoline-2,4(1H,3H)-dione;

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)quinazolin-4(3H)-one;

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)-2H-benzo[e][1,3]oxazin-4(3H)-one;

2-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-phenyl-3,4-dihydroisoquinolin-1(2H)-one;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-morpholinobenzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(piperidin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-amino-4-((2S,6R)-2,6-dimethylmorpholino)benzamide;

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-((2S,6R)-2,6-dimethylmorpholino)quinazolin-4(3H)-one;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-chloro-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-5-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(2-methoxypyrimidin-5-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(pyridin-3-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(furan-3-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(thiophen-3-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(pyrimidin-5-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-phenylcyclohexanecarboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-N,3-dimethyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-imidazo[4,5-c]pyridin-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-phenyl-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-(pyridin-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-([1,2,4]triazolo[4,3-a]pyrimidin-3-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-([1,2,4]triazolo[4,3-a]pyrazin-3-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(imidazo[1,2-a]pyrimidin-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(imidazo[1,2-a]pyridin-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(imidazo[1,2-a]pyrimidin-2-yl)phenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-([1,2,4]triazolo[4,3-a]pyrazin-3-yl)-4-chlorophenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(pyridin-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(5-(1H-benzo[d]imidazol-2-yl)pyridin-3-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(4-(1H-benzo[d]imidazol-2-yl)pyridin-2-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-5-(trifluoromethyl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-5-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-2-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-2-methylphenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(6-methoxypyridin-3-yl)benzamide;

N-(3-(imidazo[1,2-a]pyridin-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-3-methyl-4'-cyanobiphenyl-4-carboxamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(6-(1H-benzo[d]imidazol-2-yl)pyridin-2-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-([1,2,4]triazolo[1,5-a]pyridin-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-fluorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-bromophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-methoxyphenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-p-tolyl-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-(4-fluorophenyl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-p-tolyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-4-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-3-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(4-methylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-4-isopropyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-(4-methylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)nicotinamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-methyl-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(piperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(1-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-isopropyl-3,5-dimethylpiperazin-1-yl)benzamide;

(S)-N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-(3,4-dimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((2S,6R)-2,6-dimethylmorpholino)benzamide;

N-(5-(6-fluoro-1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(6-chloro-1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-cyano-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-(4-methylthiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(4-methylthiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(5-chlorothiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(5-chlorothiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(4-methyl-5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-cyano-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(5-(5-methylfuran-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(5-methylfuran-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiazol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiazol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-isopropyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-(methylsulfonyl)benzamide;

N-(3-(5-(1-methyl-1H-pyrrol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(1-methyl-1H-pyrrol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(1-methyl-1H-pyrrol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-propyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-propyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-tert-butyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-tert-butyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclobutyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclobutyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopentyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopentyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclohexyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclohexyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-methyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(3H-imidazo[4,5-b]pyridin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(3H-imidazo[4,5-c]pyridin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(3H-imidazo[4,5-c]pyridin-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(quinoxalin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(imidazo[2,1-b]thiazol-6-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(benzo[d]oxazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(benzo[d]thiazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(pyridin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(pyrimidin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

and pharmaceutically acceptable salts or prodrugs thereof.

[0016] The term "alkyl" as employed herein by itself or as part of another group refers to both straight and branched chain radicals of up to ten carbons. Useful alkyl groups include straight-chained and branched C_{1-10} alkyl groups, preferably straight-chained and branched C_{1-6} alkyl groups, more preferably C_{1-3} alkyl groups. Typical C_{1-10} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, 3-pentyl, hexyl and octyl groups.

[0017] The term "alkenyl" as employed herein by itself or as part of another group means a straight or branched chain radical of 2-10 carbon atoms, including at least one double bond between two of the carbon atoms in the chain. Preferred alkenyl group is C_{2-4} alkenyl. Typical alkenyl groups include ethenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl and 2-butenyl.

[0018] The term "alkynyl" as employed herein by itself or as part of another group means a straight or branched chain radical of 2-10 carbon atoms, wherein there is at least one triple bond between two of the carbon atoms in the chain. Preferred alkynyl group is C_{2-4} alkynyl. Typical alkynyl groups include ethynyl, 1-propynyl, 1-methyl-2-propynyl, 2-propynyl, 1-butynyl and 2-butynyl.

[0019] Useful alkoxy groups include oxygen substituted by alkyl, e.g., one of the C_{1-10} alkyl groups mentioned above, preferably the C_{1-6} alkyl groups mentioned above (that is C_{1-6} alkoxy), more preferably C_{1-3} alkoxy.

[0020] Useful alkylthio groups include sulfur substituted by one of the C_{1-10} alkyl groups mentioned above, preferably C_{1-6} alkyl, more preferably C_{1-3} alkyl, which may be optionally substituted. Also included are the sulfoxides and sulfones of such alkylthio groups.

[0021] Useful amino groups include $-NH_2$, –NHR' and –NR'R'', wherein R' and R'' are C_{1-10} alkyl or C_{3-8} cycloalkyl; or R' and R'' are combined with the N to form a ring structure, such as a piperidyl; or R' and R'' are combined with the N and another group to form a ring, such as a piperazinyl, which are optionally substituted.

[0022] The groups as described herein, such as alkyl, alkoxy, alkylthio, alkenyl, alkynyl, cycloalkyl, carbocyclic, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl and heteroarylalkyl groups and heterocyclic groups, and the like, may be optionally substituted. Generally, the term "optionally substituted" used herein indicates that the group that is "optionally substituted", such as alkyl, alkoxy, alkylthio, alkenyl, alkynyl, cycloalkyl, carbocyclic and heterocyclic groups, may be optionally substituted by one or more (such as 1, 2, 3, or 4) substituents selected from the group consisting of halo, hydroxy, carboxy, amino, amido, nitro, cyano, C_1-C_6 acylamino, C_1-C_6 acyloxy, C_1-C_6 alkoxy, aryloxy, alkylthio, C_6-C_{10} aryl, C_4-C_7 cycloalkyl, C_2-C_6 alkenyl, C_6-C_{10} aryl(C_2-C_6)alkenyl, C_6-C_{10} aryl(C_2-C_6)alkynyl, saturated and unsaturated heterocyclic and heteroaryl. In one preferred embodiment, alkoxy may be substituted by one or more (such as 1~4 or 1~3) substituted selected from the group consisting of halo, morpholino, amino including alkylamino and dialkylamino, and carboxylic ester.

[0023] Optional substituents on the aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl and heteroarylalkyl groups may be one or more (such as 1, 2, 3, or 4) groups selected from the group consisting of C_1-C_6 alkyl, acyl, halo, methylenedioxy, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_4-C_7 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl(C_1-C_6)alkyl, C_6-C_{10} aryl(C_2-C_6)alkenyl, C_6-C_{10} aryl(C_2-C_6)alkynyl, C_1-C_6 hydroxyalkyl, nitro, amino, amido, ureido, cyano, C_1-C_6 acylamino, hydroxy, thiol, C_1-C_6 acyloxy, aminocarbonyl, azido, C_1-C_6 alkoxy, carboxy, di(C_1-C_{10} alkyl)amino, alkylsulfonyl, arylsulfonyl, dialkylaminosulfonyl, or alkylsulfinyl.

[0024] The term "aryl" as employed herein by itself or as part of another group refers to monocyclic, bicyclic or tricyclic aromatic groups containing from 6 to 14 carbons in the ring portion.

[0025] Useful aryl groups include $C_{6\text{-}14}$ aryl, preferably $C_{6\text{-}10}$ aryl. Typical $C_{6\text{-}14}$ aryl groups include phenyl, naphthyl, phenanthrenyl, anthracenyl, indenyl, biphenyl, biphenylene and fluorenyl groups.

[0026] The term "carbocycle" as employed herein include cycloalkyl and partially saturated carbocyclic groups. Useful cycloalkyl groups are $C_{3\text{-}8}$ cycloalkyl. Typical cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0027] Useful partially saturated carbocyclic groups are cycloalkenyl groups, such as cyclopentenyl, cycloheptenyl and cyclooctenyl.

[0028] Useful halo or halogen groups include fluorine, chlorine, bromine and iodine.

[0029] The term "arylalkyl" is used herein to mean any of the above-mentioned $C_{1\text{-}10}$ alkyl groups, preferably $C_{1\text{-}4}$ alkyl groups, substituted by any of the above-mentioned $C_{6\text{-}14}$ aryl groups. Preferably the arylalkyl group is benzyl, phenethyl or naphthylmethyl.

[0030] The term "arylalkenyl" is used herein to mean any of the above-mentioned C_{2-10} alkenyl groups, preferably C_{2-4} alkenyl groups, substituted by any of the above-mentioned C_{6-14} aryl groups.

[0031] The term "arylalkynyl" is used herein to mean any of the above-mentioned C_{2-10} alkynyl groups, preferably C_{2-4} alkynyl groups, substituted by any of the above-mentioned C_{6-14} aryl groups.

[0032] The term "aryloxy" is used herein to mean oxygen substituted by one of the above-mentioned C_{6-14} aryl groups, which may be optionally substituted. Useful aryloxy groups include phenoxy and 4-methylphenoxy.

[0033] The term "arylalkoxy" is used herein to mean any of the above mentioned C_{1-10} alkoxy groups substituted by any of the above-mentioned aryl groups, which may be optionally substituted. Useful arylalkoxy groups include benzyloxy and phenethyloxy.

[0034] Useful haloalkyl groups include C_{1-10} alkyl substituted by one or more fluorine, chlorine, bromine or iodine atoms, e.g., fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, chloromethyl, chlorofluoromethyl and trichloromethyl groups.

[0035] Acyl groups are −R−CHO groups, wherein R is C_{1-6} alkylene. Useful acyl groups include C_{1-6} acyl, e.g., formacyl, acetyl, and the like.

[0036] Useful acylamino (acylamido) groups are any C_{1-6} acyl (alkanoyl) attached to an amino nitrogen, e.g., acetamido, chloroacetamido, propionamido, butanoylamido, pentanoylamido and hexanoylamido, as well as aryl-substituted C_{1-6} acylamino groups, e.g., benzoylamido.

[0037] Useful acyloxy groups are any C_{1-6} acyl (alkanoyl) attached to an oxy (–O–) group, e.g., formyloxy, acetoxy, propionoyloxy, butanoyloxy, pentanoyloxy and hexanoyloxy.

[0038] The term heterocycle is used herein to mean a saturated or partially saturated 3−7 membered monocyclic, or 7−10 membered bicyclic ring system, which consists of carbon atoms and one to four heteroatoms independently selected from the group consisting of O, N, and S, wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, the nitrogen can be optionally quaternized. The term also includes any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring of heterocycle can be substituted on carbon or on a nitrogen atom if the resulting compound is stable.

[0039] Useful saturated or partially saturated heterocyclic groups include tetrahydrofuranyl, pyranyl, piperidinyl, piperazinyl, pyrrolidinyl, imidazolidinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl, quinazoline-2,4(1H,3H)-dione, quinazolin-4(3H)-one, benzo[e][1,3]oxazin-4(3H)-one, 3,4-dihydroisoquinolin-1(2H)-one, and pyrazolinyl. A heterocyclic group also includes heteroaryl herein.

[0040] The term "heteroaryl" as employed herein refers to groups having 5 to 14 ring atoms; 6, 10 or 14 π electrons shared in a cyclic array; and containing, as ring atom, carbon atoms and 1–3 heteroatoms selected from oxygen, nitrogen and sulfur.

[0041] Useful heteroaryl groups include quinazolinyl, thienyl, benzo[b]thienyl, benzo[d]thiazolyl, benzo[d]oxazolyl, benzo[2,3-b]thienyl, thianthrenyl, furyl (furanyl), pyranyl, isobenzopyranyl, chromenyl, xanthenyl, phenoxanthiinyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl (pyridinyl, including without limitation 2-pyridyl, 3-pyridyl, and 4-pyridyl), pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, dihydroisoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7-aminoisocoumarin, pyrido[1,2-a]pyrimidin-4-one, tetrahydrocyclopenta[c]pyrazol-3-yl, imidazo[1,5-a]pyrimidinyl, imidazo[4,5-c]pyridin-2-yl, [1,2,4]triazolo[4,3-a]pyridin-3-yl, [1,2,4]triazolo[4,3-a]pyrimidin-3-yl, [1,2,4]triazolo[4,3-a]pyrazin-3-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[4,5-b]pyridin-2-yl, imidazo[2,1-b]thiazol-6-yl, benzo[e][1,3]oxazinyl, thieno[3,4-d]imidazol-2-yl, 1,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxindolyl, thiadiazolyl, quinoxalin-2-yl and 2-oxobenzimidazolyl. Where the heteroaryl group contains a nitrogen atom in a ring, such nitrogen atom may be in the form of an N-oxide, e.g., a pyridyl N-oxide, pyrazinyl N-oxide and pyrimidinyl N-oxide.

[0042] The term "heteroaryloxy" is used herein to mean oxygen substituted by one of the above-mentioned heteroaryl groups, which may be optionally substituted. Useful heteroaryloxy groups include pyridyloxy, pyrazinyloxy, pyrrolyloxy, pyrazolyloxy, imidazolyloxy and thiophenyloxy.

[0043] The term "heteroarylalkoxy" is used herein to mean any of the above-mentioned C_{1-10} alkoxy groups substituted by any of the above-mentioned heteroaryl groups, which may be optionally substituted.

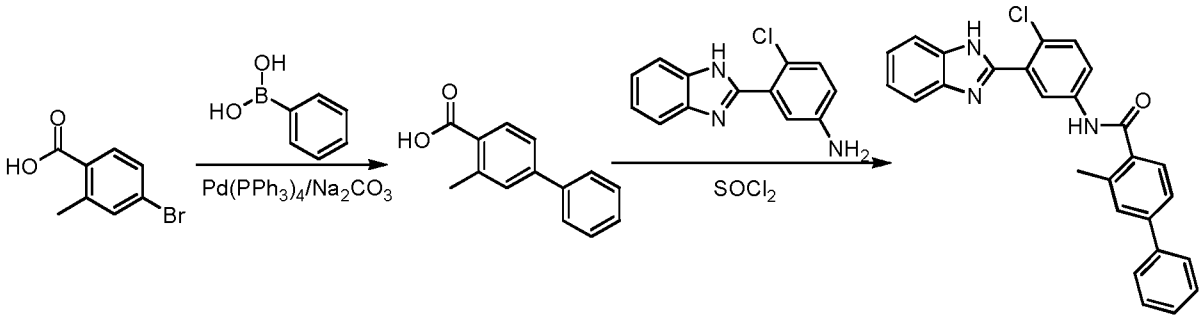
[0044] Some of the compounds of the present invention may exist as stereoisomers including optical isomers. The invention includes all stereoisomers and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are well known to those of ordinary skill in the art.

[0045] Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts, such as hydrochloride, hydrobromide, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate and oxalate; and inorganic and organic base addition salts with bases, such as sodium hydroxy, tris(hydroxymethyl)aminomethane (TRIS, tromethane) and N-methylglucamine.

[0046] Examples of prodrugs of the compounds of the invention include the simple esters of carboxylic acid containing compounds (e.g., those obtained by condensation with a C_{1-4} alcohol according to methods known in the art); esters of hydroxy containing compounds (e.g., those obtained by condensation with a C_{1-4} carboxylic acid, C_{3-8} dioic acid or anhydride thereof, such as succinic and fumaric anhydrides according to methods known in the art); imines of amino containing compounds (e.g., those obtained by condensation with a C_{1-4} aldehyde or ketone according to methods known in the art); carbamate of amino containing compounds, such as those described by Leu, *et. al.,* (*J. Med. Chem. 42*: 3623-3628 (1999)) and Greenwald, *et al.,* (*J. Med. Chem. 42*: 3657-3667 (1999)); and acetals and ketals of alcohol containing compounds (e.g., those obtained by condensation with chloromethyl methyl ether or chloromethyl ethyl ether according to methods known in the art).

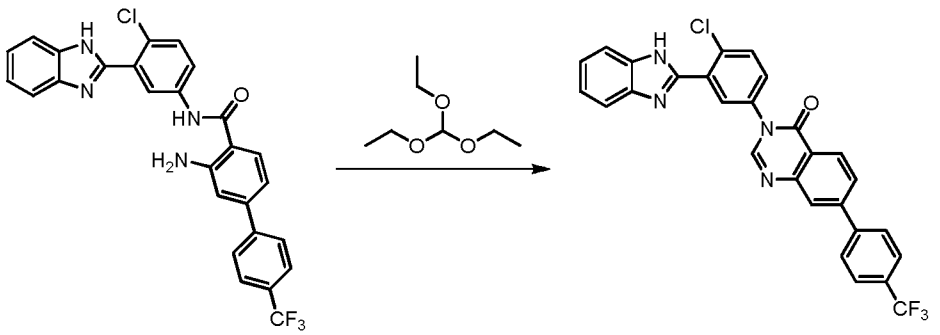
[0047] The compounds of this invention may be prepared using methods known to those skilled in the art, or the novel methods of this invention. Specifically, the compounds of this invention with Formula I, II, III or IV can be prepared as illustrated by the exemplary reaction in Scheme 1. Reaction of 4-bromo-2-methylbenzoic acid with phenylboronic acid in the presence of palladium(0)tetrakis(triphenylphosphine) and sodium carbonate in ethanol-water solution produced 3-methylbiphenyl-4-carboxylic acid. Treatment of the compound with sulfoxide chloride produced the intermediate 3-methylbiphenyl-4-carbonyl chloride. Copouling of the intermediate with 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline in the presence of sodium carbonate in DCM produced the targeted compound N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methylbiphenyl-4-carboxamide. Other related compounds can be prepared similarly. For example, replacement of 4-bromo-2-methylbenzoic acid with 4-bromobenzoic acid produced the targeted compound N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)biphenyl-4-carboxamide. Replacement of phenylboronic acid with 4-(trifluoromethyl)phenylboronic acid produced the targeted compound N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4′-(trifluoromethyl)biphenyl-4-carboxamide。Replacement of 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline with 4-chloro-3-(5-(phenyl-1H-imidazol-2-yl)aniline produced the targeted compound N-(3-(5-phenyl-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide. Replacement of 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline with 3-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-4-chloroaniline produced N-(3-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide. Replacement of 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline with 3-(imidazol[1,2-a]pyrimidin-2-yl)aniline produced the target compound N-(3-(imidazol[1,2-a]pyrimidin-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide.

Scheme 1



[0048] Similarly, compounds of this invention can be prepared as illustrated by the exemplary reaction in Scheme 2. Reaction of N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-amino-4'-(trifluoromethyl)biphenyl-4-carboxamide with triethyl orthoformate produced the target compound 3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)quinazolin-4(3H)-one. Similarly, reaction of N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-amino-4'-(trifluoromethyl)biphenyl-4-carboxamide with triphosgene in THF produced 3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)quinazoline-2,4(1H,3H)-dione. Reaction of N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4'-trifluoromethyl-3-hydroxybiphenyl-4-carboxamide with triformol and trifluoroacetic acid produced 3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)-2H-benzo[e][1,3]oxazin-4(3H)-one.

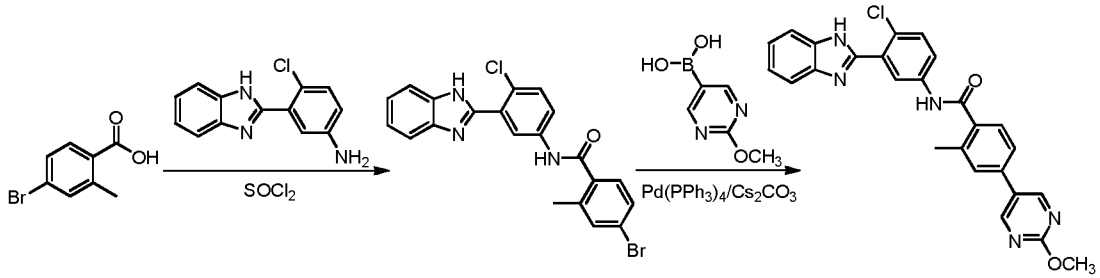
Scheme 2



[0049] Similarly, compounds of this invention can be prepared as illustrated by the exemplary reaction in Scheme 3. Reaction of 4-bromo-2-methylbenzoic acid with sulfoxide chloride produced the intermediate 4-bromo-2-methylbenzoyl chloride. Coupling of the intermediate with 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline in the presence of sodium carbonate in DCM produced N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-bromo-2-methylbenzamide. Treatment of the compound with 2-methoxypyrimidin-5-ylboronic acid in the presence of palladium(0)tetrakis(triphenylphosphine) and sodium carbonate in ethanol-water produced N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(2-methoxypyrimidin-5-yl)benzamide. Other related compounds can be prepared similarly. For

example, replacement of 2-methoxypyrimidin-5-ylboronic acid with pyridin-3-ylboronic acid produced N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(pyridin-3-yl)benzamide. Replacement of 2-methoxypyrimidin-5-ylboronic acid with furan-3-ylboronic acid produced N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(furan-3-yl)benzamide. Replacement of 2-methoxypyrimidin-5-ylboronic acid with thiophen-3-ylboronic acid produced N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(thiophen-3-yl)benzamide.

Scheme 3

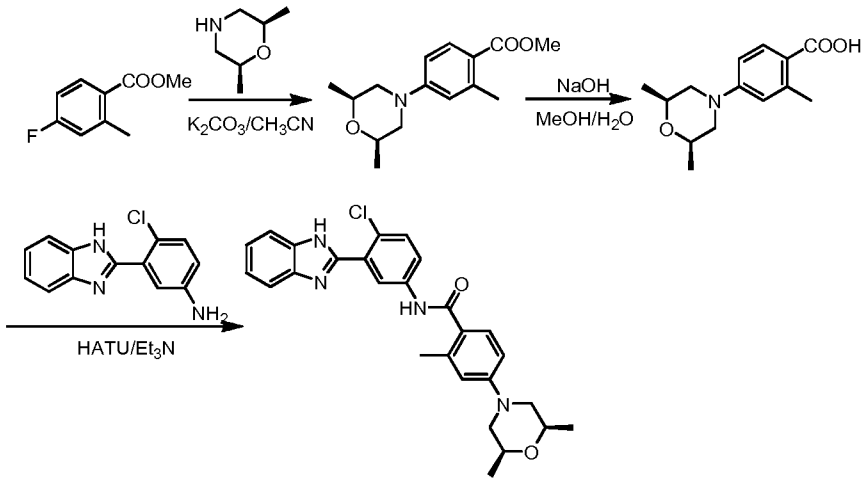


[0050] Similarly, compounds of this invention can be prepared as illustrated by the exemplary reaction in Scheme 4. Reaction of methyl 4-fluoro-2-methylbenzoate, (2S,6R)-2,6-dimethylmorpholine and potassium carbonate in ACN produced methyl 2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzoate. Hydrolysis of the ester with sodium hydroxide in methanol-water produced 2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzoic acid. Coupling of the acid with 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline in the presence of HATU and TEA in DMF produced the targeted compound N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide. Other related compounds can be prepared similarly. For example, replacement of (2S,6R)-2,6-dimethylmorpholine with morpholine produced N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-morpholinobenzamide. Replacement of (2S,6R)-2,6-dimethylmorpholine with piperidine produced N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(piperidin-4-yl)benzamide. Replacement of (2S,6R)-2,6-dimethylmorpholine with (2S,6R)-1,2,6-trimethylpiperazine produced N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide. Replacement of methyl 4-fluoro-2-methylbenzoate with ethyl 4-methyl-6-chloronicotinate produced N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide.

Replacement of 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline with 5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-amine, 3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chloroaniline, 3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chloroaniline, 3-(5-(1-methyl-1H-pyrrol-2-yl)-1H-imidazol-2-yl)-4-chloroaniline, 3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chloroaniline, 3-(5-isopropyl-1H-

imidazol-2-yl)-4-chloroaniline, and 3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chloroaniline, produced N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide, N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide, N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide, N-(3-(5-(1-methyl-1H-pyrrol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide, N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide, N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide, and N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide, respectively.

Scheme 4



[0051] An important aspect of the present invention is the discovery that compounds having Formula I, II, III or IV are hedgehog pathway inhibitors. Therefore, these compounds are useful for the treatment of a variety of clinical conditions responsive to the inhibition of hedgehog activity, such as cancer.

[0052] The present invention also includes a therapeutic method comprising administering to a mammal an effective amount of a compound of Formula I, II, III or IV, or a pharmaceutically acceptable salt or prodrug thereof, wherein said therapeutic method is useful for the treatment of diseases due to abnormal hedgehog activity (that is hedgehog mediated diseases), such as cancer.

[0053] Various diseases that are responsive to the inhibition of hedgehog activity or hedgehog mediated diseases include cancer, but are not limited to, basal cell carcinoma, myelogenous cancer, basal cell nevus syndrome (BCNS), liver cancer, melanoma, Hodgkin's disease, non-Hodgkin's lymphomas, acute or chronic lymphocytic leukemia, multiple myeloma, neuroblastoma, breast carcinoma, ovarian carcinoma, lung carcinoma, Wilms' tumor, cervical

carcinoma, testicular carcinoma, soft-tissue sarcoma, primary macroglobulinemia, bladder carcinoma, chronic granulocytic leukemia, primary brain carcinoma, malignant melanoma, small-cell lung carcinoma, stomach carcinoma, colon carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, choriocarcinoma, mycosis fungoide, head or neck carcinoma, osteogenic sarcoma, pancreatic carcinoma, acute granulocytic leukemia, hairy cell leukemia, rhabdomyosarcoma, Kaposi's sarcoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, malignant hypercalcemia, cervical hyperplasia, renal cell carcinoma, endometrial carcinoma, polycythemia vera, essential thrombocytosis, adrenal cortex carcinoma, skin cancer, and prostatic carcinoma. Preferably, diseases mentioned above are basal cell carcinoma, myelogenous cancer or basal cell nevus syndrome.

[0054] In practicing the therapeutic methods, effective amounts of compositions containing therapeutically effective concentrations of the compounds of Formula I, II, III or IV formulated for oral, intravenous, local or topical application, for the treatment of neoplastic diseases and other diseases, are administered to an individual exhibiting the symptoms of one or more of these disorders. The amounts are effective to ameliorate or eliminate one or more symptoms of the disorders. An effective amount of a compound for treating a particular disease is an amount that is sufficient to ameliorate, or in some manner reduce, the symptoms associated with the disease. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective. The amount may cure the disease but, typically, is administered in order to ameliorate the symptoms of the disease. Typically, repeated administration is required to achieve the desired amelioration of symptom.

[0055] The present invention also includes the use of the compounds of Formula I, II, III or IV of the subject invention in the manufacture of a medicament for treating or preventing a disorder responsive to the inhibition of hedgehog activity, including cancer. In preferred embodiment, the above-mentioned diseases are selected from cancer. In more preferred embodiment, the above-mentioned diseases are selected from basal cell carcinoma, myelogenous cancer, basal cell nevus syndrome. In another embodiment, the above-mentioned drugs may also include other known anti-cancer drugs, but not limited to the various known anti-cancer drugs described herein.

[0056] In another embodiment, a pharmaceutical composition comprising a compound of Formula I, II, III or IV or a pharmaceutically acceptable salt thereof, which functions as hedgehog pathway inhibitor, in combination with a pharmaceutically acceptable vehicle, is provided.

[0057] Another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound of Formula I, II, III or IV, or a pharmaceutically

acceptable salt or prodrug thereof, which functions as a hedgehog inhibitor, in combination with at least one known anticancer agent or a pharmaceutically acceptable salt thereof. Examples of known anticancer agents which may be used for combination therapy include, but not are limited to DNA damaging chemotherapy anti-cancer drugs, including alkylating agents, such as busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide, temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin and carboplatin; topoisomerase I inhibitors, such as camptothecin, irinotecan and topotecan; topoisomerase II inhibitors, such as doxorubicin, epirubicin, aclarubicin, mitoxantrone, elliptinium and etoposide; RNA/DNA antimetabolites, such as 5-azacytidine, gemcitabine, 5-fluorouracil and methotrexate; DNA antimetabolites, such as 5-fluoro-2'-deoxyuridine, fludarabine, nelarabine, ara-C, alanosine, pralatrexate, pemetrexed, hydroxyurea and thioguanine; antimitotic agents, such as colchicine, vinblastine, vincristine, vinorelbine, paclitaxel, ixabepilone, cabazitaxel, and docetaxel; antibodies, such as campath, Panitumumab, Ofatumumab, Avastin, Herceptin® and Rituxan®; kinase inhibitors such as imatinib, gefitinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, temsirolimus and everolimus; HDAC inhibitors such as vorinostat and romidepsin. Other known anticancer agents which may be used for combination therapy include tamoxifen, letrozole, fulvestrant, mitoguazone, octreotide, retinoic acid, arsenic trioxide, zoledronic acid, bortezomib, thalidomide and lenalidomide.

[0058] In practicing the methods of the present invention, the compound of the invention may be administered together with at least one known anticancer agent as part of a unitary pharmaceutical composition. Alternatively, the compound of the invention may be administered apart from at least one known anticancer agent. In one embodiment, the compound of the invention and at least one known anticancer agent are administered substantially simultaneously, i.e. the compounds are administered at the same time or one after the other, so long as the compounds reach therapeutic levels in the blood at the same time. In another embodiment, the compound of the invention and at least one known anticancer agent are administered according to their individual dose schedule, so long as the compounds reach therapeutic levels in the blood.

[0059] Another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a bioconjugate of a compound described herein, in bioconjugation with at least one known therapeutically useful antibody, such as Herceptin® or Rituxan®, or growth factors, such as DGF or NGF, or cytokines, such as IL-2 or IL-4, or any molecule that binds to the cell surface. The antibodies and other molecules will deliver a compound described herein to its targets and make it an effective anticancer agent. The bioconjugates could also

enhance the anticancer effect of the therapeutically useful antibodies, such as Herceptin® or Rituxan®.

[0060] Another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound of Formula I, II, III or IV, or its pharmaceutically acceptable salt or prodrug, which functions as a hedgehog pathway inhibitor, in combination with radiation therapy. In this embodiment, the compound of the invention may be administered at the same time as the radiation therapy is administered or at a different time.

[0061] Yet another embodiment of the present invention is directed to a composition effective for post-surgical treatment of cancer, comprising a compound of Formula I, II or III, or its pharmaceutically acceptable salt or prodrug, which functions as a hedgehog pathway inhibitor. The invention also relates to a method of treating cancer by surgically removing the cancer and then treating the mammal with one of the pharmaceutical compositions described herein.

[0062] Pharmaceutical compositions within the scope of this invention may also include the bioconjugate of the present invention as an active ingredient. The above-mentioned bioconjugate may form from the compound of Formula I, II or III of the subject invention with a therapeutically useful antibody. The pharmaceutical composition may also contain a pharmaceutically acceptable carrier.

[0063] Pharmaceutical compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount that is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the compounds may be administered to mammals, orally at a dose of 0.0025 to 50 mg/kg of body weight, per day, or an equivalent amount of the pharmaceutically acceptable salt thereof, to a mammal being treated. Preferably, approximately 0.01 to approximately 10 mg/kg of body weight is orally administered. If a known anticancer agent is also administered, it is administered in an amount that is effective to achieve its intended purpose. The amounts of such known anticancer agents effective for cancer are well known to those skilled in the art.

[0064] The unit oral dose may comprise from approximately 0.01 to approximately 50 mg, preferably approximately 0.1 to approximately 10 mg of the compound of the invention. The unit dose may be administered one or more times daily, as one or more tablets, each containing from approximately 0.1 to approximately 50 mg, conveniently approximately 0.25 to 10 mg of the compound or its solvates.

[0065] In a topical formulation, the compound may be present at a concentration of approximately 0.01 to 100 mg per gram of carrier.

[0066] In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the compounds into preparations that may be used pharmaceutically. Preferably, the preparations, particularly those preparations which may be administered orally and that may be used for the preferred type of administration, such as tablets, dragees, and capsules, as well as suitable solutions for administration by injection or orally, contain from approximately 0.01 to 99 percent, preferably from approximately 0.25 to 75 percent of active compound(s), together with the excipient.

[0067] Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. Acid addition salts are formed by mixing a solution of the compounds of the present invention with a solution of a pharmaceutically acceptable non-toxic acid, such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, and the like. Base addition salts are formed by mixing a solution of the compounds of the present invention with a solution of a pharmaceutically acceptable non-toxic base, such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, Tris, N-methylglucamine and the like.

[0068] The pharmaceutical compositions of the invention may be administered to any mammal, which may experience the beneficial effects of the compounds of the invention. Foremost among such mammals are humans and veterinary animals, although the invention is not intended to be so limited.

[0069] The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, intrathecal, intracranial, intranasal or topical routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

[0070] The pharmaceutical preparations of the present invention are manufactured in a manner, which is itself known, e.g., by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use may be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[0071] Suitable excipients are, in particular fillers, such as saccharides, e.g. lactose or sucrose, mannitol or sorbitol; cellulose preparations or calcium phosphates, e.g. tricalcium phosphate or calcium hydrogen phosphate; as well as binders, such as starch paste, using, e.g., maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, or polyvinyl pyrrolidone. If desired, disintegrating agents may be added, such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, e.g., silica, talc, stearic acid or salts thereof, such as magnesium stearate, calcium stearate, stearic acid or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, e.g., for identification or in order to characterize combinations of active compound doses.

[0072] Other pharmaceutical preparations, which may be used orally, include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active compounds in the form of granules, which may be mixed with fillers, such as lactose; binders, such as starches; and/or lubricants, such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

[0073] Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, e.g., water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, e.g., sesame oil, or synthetic fatty acid esters, e.g., ethyl oleate, or triglycerides or polyethylene glycol-400, or cremophor, or cyclodextrins. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, e.g., sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain stabilizers.

[0074] The topical compositions of this invention are formulated preferably as oils, creams, lotions, ointments and the like by choice of appropriate carriers. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils,

animal fats and high molecular weight alcohol (greater than C_{12}). The preferred carriers are those in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included, as well as agents imparting color or fragrance, if desired. Additionally, transdermal penetration enhancers may be employed in these topical formulations. Examples of such enhancers are found in U.S. Patent Nos. 3,989,816 and 4,444,762.

[0075] Creams are preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture of the active ingredient, dissolved in a small amount of an oil, such as almond oil, is admixed. A typical example of such a cream is one which includes approximately 40 parts water, approximately 20 parts beeswax, approximately 40 parts mineral oil and approximately 1 part almond oil.

[0076] Ointments may be formulated by mixing a solution of the active ingredient in a vegetable oil, such as almond oil, with warm soft paraffin and allowing the mixture to cool. A typical example of such an ointment is one which includes approximately 30% almond oil and approximately 70% white soft paraffin by weight.

[0077] The present application also includes the use of the compounds of Formula I, II, III or IV of the subject invention in the manufacture of a composition, such as a pharmaceutical composition, for inhibiting hedgehog activity.

[0078] The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

EXAMPLES

General remarks

All reagents were of commercial quality. Solvents were dried and purified by standard methods. Mass spectrum analyses were recorded on a Platform II (Agilent 6110) quadrupole mass spectrometer fitted with an electrospray rinterface. ^{1}H NMR spectra were recorded at 300 MHz and at 300 K, on a Brücker AMX 300 apparatus. Chemical shifts were recorded as parts per million (ppm) downfield from TMS (0.00 ppm), and *J* coupling constants were reported in hertz (Hz).

Example 1

3-Methylbiphenyl-4-carboxylic acid

A mixture of 4-bromo-2-methylbenzoic acid (215 mg, 1.0 mmol) and Na_2CO_3 (425 mg, 4.0 mmol) in ethanol (5 mL) was added water (2 mL), then the mixture was heated to reflux for 30 min, cooled to room temperature, phenylboronic acid (146 mg, 1.2 mmol) and $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol) were added to the reaction mixture. Then the mixture was heated to reflux for 8 h under nitrogen. After filtered and the residue was washed with water (5 mL). The filtrate was evaporated under reduced pressure to remove ethanol. Adjusted pH to 13~14 with sodium hydroxide and then washed with CH_2Cl_2 (10 mL×3), the water layer was adjusted pH to 1~2 with diluted hydrochloric acid and a lot of solid was precipitated. Filtered, the residue was washed with water (20 mL), dried to obtain the title compound as a light-yellow solid (180 mg, 85%). MS: m/z 211.1 $[M-H]^-$.

Example 2

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methylbiphenyl-4-carboxamide

A mixture of 3-methylbiphenyl-4-carboxylic acid (44.5 mg, 0.21 mmol) in $SOCl_2$ (3 mL) was heated to reflux for 2 h, then the mixture was evaporated under reduced pressure to remove solvent to get the intermediate 3-methylbiphenyl-4-carbonyl chloride.

A mixture of 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline (51.2 mg, 0.21 mmol), Na_2CO_3 (44.5 mg, 0.42 mmol) in CH_2Cl_2 (1 mL) was stirred for 15 min in an ice-water bath. Then 3-methylbiphenyl-4-carbonyl chloride in CH_2Cl_2 was added dropwise to the mixture, the reaction mixture was stirred for 8 h at room temperature. After water (5 mL) was added, the mixture was extracted with EtOAc (10 mL×3), the combined organic solution was dried with anhydrous sulfate sodium, and then concentrated in vacuo to get the crude product, which was recrystallized from methanol, then purified through TLC (CH_2Cl_2/CH_3OH) to obtain the title compound as as an off-white solid (14.23 mg, 15.5%). ^1H NMR (DMSO-d_6): 12.72 (s, 1H), 10.65 (s, 1H), 8.40 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 8.7 and 2.4 Hz, 1H), 7.72-7.68 (m, 3H), 7.63-7.56 (m, 5H), 7.48-7.45 (m, 2H), 7.41-7.36 (m, 1H), 7.27-7.19 (m, 2H), 2.51 (s, 3H). MS: m/z 438.1 $[M+H]^+$.

The following compounds were prepared from (un)substituted 4-bromobenzoic acid, the corresponding phenylboronic aicd and 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline using a procedure similar to those described for the syntheses of compounds of Examples 1 and 2.

Example 3

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-methoxybiphenyl-4-carboxamide

Off-white solid (6.57 mg, 6.69%). ^{1}H NMR (DMSO-d_6): 12.71 (s, 1H), 10.61 (s, 1H), 8.40 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 9.2 and 2.6 Hz, 1H), 7.71-7.55 (m, 8H), 7.27-7.19 (m, 2H), 7.03 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H), 2.51 (s, 3H). MS: m/z 468.1 $[M+H]^+$.

Example 4

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-fluorobiphenyl-4-carboxamide

White solid (30.44 mg, 31.79%). ^{1}H NMR (DMSO-d_6): 12.74 (s, 1H), 10.67 (s, 1H), 8.43 (d, J = 2.4 Hz, 1H), 7.80 (dd, J = 8.9 and 2.6 Hz, 1H), 7.79-7.70 (m, 3H), 7.65-7.57 (m, 4H), 7.36-7.20 (m, 4H), 2.53 (s, 3H). MS: m/z 456.1 $[M+H]^+$.

Example 5

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(methylsulfonyl)biphenyl-4-carboxamide

Off-white solid (27.03 mg, 24.94%). ^{1}H NMR (DMSO-d_6): 12.75 (s, 1H), 10.72 (s, 1H), 8.43 (d, J = 2.4 Hz, 1H), 8.05-7.99 (m, 4H), 7.88 (dd, J = 8.7 and 2.6 Hz, 1H), 7.75-7.57 (m, 6H), 7.29-7.20 (m, 2H), 3.32 (s, 3H), 2.53 (s, 3H). MS: m/z 516.1 $[M+H]^+$.

Example 6

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-cyanobiphenyl-4-carboxamide

Off-white solid (13.28 mg, 13.66%). ^{1}H NMR (DMSO-d_6): 12.75 (s, 1H), 10.71 (s, 1H), 8.42 (d, J = 2.4 Hz, 1H), 7.99-7.93 (m, 4H), 7.88 (dd, J = 8.9 and 2.6 Hz, 1H), 7.75-7.70 (m, 3H), 7.66-7.57 (m, 3H), 7.29-7.21 (m, 2H), 2.53 (s, 3H). MS: m/z 463.1 $[M+H]^+$.

Example 7

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-nitrobiphenyl-4-carboxamide

Light-yellow solid (32.07 mg, 31.6%). ^{1}H NMR (DMSO-d_6): 12.75 (s, 1H), 10.73 (s, 1H), 8.43 (d, J = 2.4 Hz, 1H), 8.34 (d, J = 8.7 Hz, 2H), 8.03 (d, J = 8.7 Hz, 2H), 7.88 (dd, J = 9.0 and 2.6 Hz, 1H), 7.79-7.58 (m, 6H), 7.29-7.20 (m, 2H), 2.53 (s, 3H). MS: m/z 483.1 $[M+H]^+$.

Example 8

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-chlorobiphenyl-4-carboxamide

White solid (8.25 mg, 8.32%). ^{1}H NMR (DMSO-d_6): 12.72 (s, 1H), 10.66 (s, 1H), 8.41 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 8.1 and 1.8 Hz, 1H), 7.76-7.68 (m, 3H), 7.64-7.52 (m, 7H), 7.28-7.18 (m, 2H), 2.48 (s, 3H). MS: m/z 472.1 $[M+H]^+$.

Example 9

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-acetylbiphenyl-4-carboxamide

White solid (8.62 mg, 8.55%). ^{1}H NMR (DMSO-d_6): 12.73 (s, 1H), 10.68 (s, 1H), 8.41 (d, J = 2.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.85-7.83 (m, 1H), 7.72-7.54 (m, 6H), 7.27-7.19 (m, 2H), 2.61 (s, 3H), 2.48 (s, 3H). MS: m/z 480.2 $[M+H]^+$.

Example 10

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-3'-fluorobiphenyl-4-carboxamide

White solid (44.51 mg, 46.49%). ^{1}H NMR (DMSO-d_6): 12.74 (s, 1H), 10.69 (s, 1H), 8.42 (d, J = 2.4 Hz, 1H), 7.88 (dd, J = 8.7 and 2.7 Hz, 1H), 7.73-7.50 (m, 9H), 7.30-7.20 (m, 3H), 2.50 (s, 3H). MS: m/z 456.2 $[M+H]^+$.

Example 11

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-3'-cyanobiphenyl-4-carboxamide

White solid (20.47 mg, 21.06%). ^{1}H NMR (DMSO-d_6): 12.74 (s, 1H), 10.70 (s, 1H), 8.43 (d, J = 2.4 Hz, 1H), 8.25 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 2H), 7.76-7.57 (m, 7H), 7.29-7.21 (m, 2H), 2.50 (s, 3H). MS: m/z 463.1 $[M+H]^+$.

Example 12

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4'-fluorobiphenyl-4-carboxamide

White solid (39.15 mg, 42.19%). ^{1}H NMR (DMSO-d_6): 12.75 (brs, 1H), 10.61 (s, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.10 (d, J = 8.7 Hz, 2H), 8.03 (dd, J = 8.9 and 2.7 Hz, 1H), 7.87-7.81 (m, 4H), 7.73-7.57 (m, 3H), 7.35 (t, J = 8.9 Hz, 2H), 7.27-7.24 (m, 2H). MS: m/z 442.1 $[M+H]^+$.

Example 13

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3'-fluorobiphenyl-4-carboxamide

White solid (14.85 mg, 16.00%). ^{1}H NMR (DMSO-d_6): 12.74 (brs, 1H), 10.63 (s, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 7.8 Hz, 2H), 8.03 (dd, J = 8.7 and 1.2 Hz, 1H), 7.92 (d, J = 7.8 Hz, 2H), 7.73-7.52 (m, 7H), 7.31-7.21 (m, 3H). MS: m/z 442.1 $[M+H]^+$.

Example 14

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (46.58 mg, 43.8%). ^{1}H NMR (DMSO-d_6): 12.74 (s, 1H), 10.60 (s, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.04 (dd, J = 8.7 and 2.4 Hz, 1H), 7.98 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 7.5 Hz, 1H), 7.67-7.64 (m, 3H), 7.60 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.30-7.21 (m, 2H), 2.33 (s, 3H). MS: m/z 506.2 $[M+H]^+$.

Example 15

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methoxy-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (7.54 mg, 6.88%). ^{1}H NMR (DMSO-d_6): 12.75 (s, 1H), 10.48 (s, 1H), 8.38 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.92 (dd, J = 8.9 and 2.3 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.49 (s, 1H), 7.44 (dd, J = 8.1 and 1.2 Hz, 1H), 7.29-7.21 (m, 2H), 4.02 (s, 3H). MS: m/z 522.2 $[M+H]^+$.

Example 16

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-hydroxy-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (23.26 mg, 21.81%). ^{1}H NMR (DMSO-d_6): 12.76 (s, 1H), 11.88 (brs, 1H), 10.71 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.95-7.84 (m, 5H), 7.72 (d, J = 6.9 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 6.9 Hz, 1H), 7.39-7.34 (m, 2H), 7.30-7.21 (m, 2H). MS: m/z 508.1 $[M+H]^+$.

Example 17

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-fluoro-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (17.91 mg, 16.7%). ^{1}H NMR (DMSO-d_6): 12.76 (s, 1H), 10.83 (s, 1H), 8.38 (d, J = 2.4 Hz, 1H), 8.03 (d, J = 8.1 Hz, 2H), 7.92-7.82 (m, 5H), 7.78-7.58 (m, 4H), 7.30-7.21 (m, 2H). MS: m/z 510.1 $[M+H]^+$.

Example 18

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-chloro-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (19.54 mg, 17.68%). ^{1}H NMR (DMSO-d_6): 12.72 (brs, 1H), 10.88 (s, 1H), 8.37 (d, J = 2.4 Hz, 1H), 8.00-7.98 (m, 3H), 7.86-7.82 (m, 4H), 7.75 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 6.9 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.57 (d, J = 6.9 Hz, 1H), 7.28-7.19 (m, 2H). MS: m/z 526.1 $[M+H]^+$.

Example 19

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-nitro-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (250.2 mg, 51.8%). ^{1}H NMR (DMSO-d_6): 12.74 (s, 1H), 11.06 (s, 1H), 8.48 (s, 1H)， 8.32 (d, J = 2.4 Hz, 1H), 8.26 (dd, J = 8.0 and 1.7 Hz, 1H), 8.07 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.81 (dd, J = 8.7 and 2.7 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.57 (d, J = 6.9 Hz, 1H), 7.28-7.19 (m, 2H). MS: m/z 537.3 $[M+H]^+$.

Example 20

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3,5-dimethyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (20 mg, 7.7%). ^{1}H NMR (DMSO-d_6): 12.75 (s, 1H), 10.79 (s, 1H), 8.41 (d, J = 2.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.85-7.82 (m, 3H), 7.72 (d, J = 7.2 Hz, 1H), 7.64 (d, J =

9.0 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.53 (s, 2H), 7.29-7.21 (m, 2H), 2.38 (s, 6H). MS: m/z 520.2 $[M+H]^+$.

Example 21

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

a) 3-Methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid: The title compound was prepared from 4-bromo-2-methylbenzoic acid and 4-(trifluoromethyl)phenylboronic acid using a procedure similar to those described for the synthesis of compound of Example 1. Brown solid (300 mg, 53.5 %). MS: m/z 281.1 $[M+H]^+$.

b) N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide: To a solution of 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (112 mg, 0.4 mmol) in DMF (2 mL) was added triethylamine (80 mg, 0.8 mmol), HATU (200 mg, 0.48 mmol), 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline (100 mg, 0.4 mmol) in sequence. The reaction mixture was stirred at room temperature for 8 h, and then poured into 20 mL of water, extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with 1 N hydrochloric acid (20 mL) and brine (20 mL × 3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate to give the title compound as a white solid (2 mg, 1.0%). ^{1}H NMR (CD_3OD): 8.18 (d, *J* = 2.4 Hz, 1H), 7.96 (dd, *J* = 8.7 and 1.8 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.68-7.56 (m, 6H), 7.33-7.31 (m, 2H), 2.56 (s, 3H). MS: m/z 506.1 $[M+H]^+$.

The following compounds were prepared from 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline and the corresponding 4'-(trifluoromethyl)biphenyl-4-carboxylic acid (the compound was prepared from 4-bromobenzoic acid and 4-(trifluoromethyl)phenylboronic using a procedure similar to those described for the synthesis of compound of Example 1) or biphenyl-4-carboxylic acid using a procedure similar to those described for the synthesis of compound of Example 21b.

Example 22

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (9 mg, 4.6%). ^{1}H NMR (DMSO-d_6): 12.74 (s, 1H), 10.66 (s, 1H), 8.47 (d, J = 1.8 Hz, 1H), 8.14 (d, J = 8.1 Hz, 2H), 8.05-7.93 (m, 5H), 7.87 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.28-7.20 (m, 2H). MS: m/z 492.1 $[M+H]^+$.

Example 23

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)biphenyl-4-carboxamide

White solid (10.1 mg, 6.0%). ^{1}H NMR (DMSO-d_6): 12.74 (s, 1 H), 10.61 (s, 1 H), 8.47 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 2H), 8.03 (dd, J = 8.9 and 2.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 7.2 Hz, 2H), 7.72 (d, J = 6.9 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.59 (d, J = 6.9 Hz, 1H), 7.54-7.50 (m, 2H), 7.46-7.41 (m, 1H), 7.30-7.21 (m, 2H). MS: m/z 424.1 $[M+H]^+$.

Example 24

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-aminobiphenyl-4-carboxamide

To a solution of N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-nitrobiphenyl-4-carboxamide (Example 7, 30.1 mg, 0.06 mmol) in methanol (5 mL) and water (1 mL) was added iron power (10.9 mg, 0.3 mmol) and NH_4Cl (2.1 mg, 0.04 mmol). The mixture was heated to reflux for 2 h. The cooled solution was treated with Na_2CO_3 to pH 8~9, and filtered through celite, washed with methanol (10 mL), then evaporated to remove methanol, the residue was washed with water (5 mL), and dried to give the title compound as an off-white solid (18.43 mg, 67.8%). ^{1}H NMR (DMSO-d_6): 12.72 (s, 1H), 10.56 (s, 1H), 8.41 (d, J = 2.4 Hz, 1H), 7.87 (dd, J = 8.9 and 2.6 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.65-7.62 (m, 7H), 7.29-7.20 (m, 2H), 6.65 (d, J = 8.4 Hz, 2H), 5.32 (s, 2H), 2.45 (s, 3H). MS: m/z 453.3 $[M+H]^+$.

Example 25

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-amino-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-nitro-4'-(trifluoromethyl)biphenyl-4-carboxamide (Example 19) using a procedure similar to those described for the synthesis of compound of Example 24. Light-yellow solid (200 mg, 91.7%). ^{1}H NMR (DMSO-d_6): 12.71 (brs, 1H), 10.37 (s, 1H), 8.42 (d, J = 2.7 Hz, 1H), 7.93 (dd,

J = 8.9 and 2.6 Hz, 1H), 7.88-7.82 (m, 5H), 7.73-7.56 (m, 3H), 7.26-7.25 (m, 2H), 7.13 (d, *J* = 1.5 Hz, 1H), 6.97 (dd, *J* = 8.1 and 1.5 Hz, 1H), 6.59 (s, 2H). MS: m/z 507.5 $[M+H]^+$.

Example 26

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)quinazoline-2,4(1H,3H)-dione

To a mixture of N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-amino-4'-(trifluoromethyl)biphenyl-4-carboxamide (51.1 mg, 0.1 mmol) in THF (2 mL) was added triphosgene (12.0 mg, 0.04 mmol), then the mixture was heated to reflux for 3 h, then removed the solvent in a vaccum. The residue was washed with 1N hydrochloric acid (10 mL), and purified by TLC (CH_2Cl_2/CH_3OH) to give the title compound as a white solid (3.86 mg, 7.2%). ^1H NMR (DMSO-d_6): 12.83 (brs, 1H), 11.70 (brs, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.99-7.88 (m, 5H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.62-7.56 (m, 3H), 7.52-7.49 (m, 1H), 7.30-7.20 (m, 2H). MS: m/z 533.2 $[M+H]^+$.

Example 27

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)quinazolin-4(3H)-one

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-amino-4'-(trifluoromethyl)biphenyl-4-carboxamide (101.5 mg, 0.2 mmol) was dissolved in anhydrous triethyl orthoformate (5 mL) and the mixture was heated to reflux for 3 h, then evaporated to remove the solvent, and the residue was purified through TLC (CH_2Cl_2/CH_3OH) to give the title compound as a white solid (36.71 mg, 36.2%). ^1H NMR (DMSO-d_6): 12.85 (brs, 1H), 8.51 (s, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 8.17-8.09 (m, 4H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.91-7.87 (m, 3H), 7.80-7.75 (m, 1H), 7.71-7.61 (m, 2H), 7.31-7.22 (m, 2H). MS: m/z 517.2 $[M+H]^+$.

Example 28

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)-2H-benzo[e][1,3]oxazin-4(3H)-one

A mixture of N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-hydroxy-4'-(trifluoromethyl)biphenyl-4-carboxamide (Example 16, 20 mg, 0.04 mmol) and paraformaldehyde (3.6 mg, 0.12 mmol) in TFA (1 mL) was heated at 100°C for 4 h. The TFA

was removed under vacuum, and the residue was diluted with EtOAc (10 mL), washed with $NaHCO_3$ aqueous solution (10 mL), water (10 mL) and brine (10 mL), and dried and concentrated. The residue was purified by TLC (CH_2Cl_2/CH_3OH) and then recrystallized from CH_3OH and CH_2Cl_2 to obtain the title compound as a white solid (2.99 mg, 14.38%). ^1H NMR (DMSO-d_6): 12.80 (s, 1H), 8.05-7.97 (m, 4H), 7.87 (d, J = 8.4 Hz, 2H), 7.77-7.71 (m, 2H), 7.64-7.59 (m, 4H), 7.30-7.22 (m, 2H), 5.86 (s, 2H). MS: m/z 520.1 $[M+H]^+$.

Example 29

2-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-phenyl-3,4-dihydroisoquinolin-1(2H)-one

a) 3,4-Dihydro-6-phenyl-1H-2-benzopyran-1-one: A sealed vessal equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (56 mg, 0.25 mmol) followed by Na_2CO_3 (1.6 g, 15 mmol), 4-biphenylcarboxylic acid (1 g, 5 mmol), 1,2-dichloroethane (20 mL). The reaction mixture was heated to 140°C over 36 h. After cooled to room temperature, the mixture was diluted with DCM (20 mL) and filtered through a short pad of celite. The filtrate was washed with brine, concentrated in vacuum, and the residue was purified by chromatography (PE/EA) to give the title compound as a yellow solid (90 mg, 7.96%). MS: m/z 225.1 $[M+H]^+$.
b) 2-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-phenyl-3,4-dihydroisoquinolin-1(2H)-one: A mixture of 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline (122 mg, 0.5 mmol), 3,4-dihydro-6-phenyl-1H-2-benzopyran-1-one (90 mg, 0.4 mmol) and Aluminum trichloride (26 mg, 0.2 mmol) was heated in a sealed vessel at 160°C for 16 h. After cooling, to the mixture was added 1 N hydrochloric acid (4 mL), then the mixture was extracted with DMC (5 mL × 2). The combined organic layers were washed with brine, dried, and evaporated. The residue was purified on silica gel column chromatography (DCM/MeOH, PE/EA) to give the title compound as a yellow solid (15 mg, 8.3%). ^1H NMR (DMSO-d_6): 12.78 (s, 1H), 8.04-7.99 (m, 2H), 7.78-7.70 (m, 6H), 7.66-7.58 (m, 2H), 7.51-7.40 (m, 3H), 7.27-7.23 (m, 2H), 4.09 (t, J = 6.9 Hz, 2H), 3.25 (t, J = 6.9 Hz, 2H). MS: m/z 450.2 $[M+H]^+$.

Example 30

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-morpholinobenzamide

a) Methyl 2-methyl-4-morpholinobenzoate: A clean 50 mL flask was charged with methyl 4-fluoro-2-methylbenzoate (168 mg, 1 mmol), morpholine (870 mg, 10 mmol), potassium carbonate (276 mg, 2 mmol) and acetonitrile (10 mL). The mixture was heated to reflux

overnight. After cooled to room temperature, to the suspension was added water (20 mL), filtered, and dried to give the title compound as a yellow liquid (190 mg, 80.8%). MS: m/z 236.2 $[M+H]^+$.

b) 2-Methyl-4-morpholinobenzoic acid: A mixture solution of methyl 2-methyl-4-morpholinobenzoate (190 mg, 0.8 mmol), 4 N aqueous NaOH solution (10 mL) in methanol (5 mL) was stirred at 50°C for 2 h. Then the mixture was evaporated under reduced pressure to remove methanol. To the resulting suspension was added 10 mL of water and extracted with DCM (10 mL), acidified with 3 N hydrochloric acid to pH = 3. The precipitate was filtered and dried to give the title compound as a white solid (130 mg, 73.0%). MS: m/z 222.1 $[M+H]^+$.

c) N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-morpholinobenzamide: The title compound was prepared from 3-(1H-benzo[d]imidazol-2-yl)-4-choroaniline and 2-methyl-4-morpholinobenzoic acid using a procedure similar to those described for the synthesis of compound of Example 21b. White solid (10.8 mg, 6.1%). ^{1}H NMR (DMSO-d_6): 12.72 (s, 1H), 10.36 (s, 1H), 8.38 (d, J = 2.7 Hz, 1H), 7.86 (dd, J = 8.9 and 2.6 Hz, 1H), 7.70 (d, J = 6.9 Hz, 1H), 7.61-7.56 (m, 2H), 7.45 (d, J = 9.0 Hz, 1H), 7.29-7.22 (m, 2H), 6.86-6.83 (m, 2H), 3.76-3.72 (m, 4H), 3.21-3.17 (m, 4H), 2.40 (s, 3H). MS: m/z 447.3 $[M+H]^+$.

The following compounds were prepared from methyl 4-fluoro-2-methylbenzoate, the corresponding piperidine or (2S,6R)-2,6-dimethylmorpholine, and 3-(1H-benzo[d]imidazo-2-yl)-4-chloroaniline using a procedure similar to those described for the synthesis of compound of Example 30.

Example 31

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(piperidin-1-yl)benzamide

Off-white solid (1 mg, 0.6%). ^{1}H NMR (CD_3OD): 8.11 (d, J = 2.4 Hz, 1H), 7.91 (dd, J = 8.7 and 2.7 Hz, 1H), 7.69-7.63 (m, 2H), 7.57 (d, J = 8.7 Hz, 1H), 7.43 (d, J = 9.3 Hz, 1H), 7.32-7.29 (m, 2H), 6.83-6.81 (m, 2H), 3.26-3.24 (m, 4H), 2.45 (s, 3H), 1.64-1.71 (m, 6H). MS: m/z 445.2 $[M+H]^+$.

Example 32

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide

Off-white solid (5 mg, 2.6%). ^{1}H NMR (DMSO-d_6): 12.69 (s, 1H), 10.32 (s, 1H), 8.36 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 8.9 and 2.6 Hz, 1H), 7.68 (d, J = 5.1 Hz, 1H), 7.58-7.55 (m, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.24-7.20 (m, 2H), 6.84-6.81 (m, 2H), 3.75-3.68 (m, 4H), 2.38 (s, 3H), 2.30-2.23 (m, 2H), 1.14 (d, J = 6.0 Hz, 6H). MS: m/z 475.3 $[M+H]^+$.

Example 33

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-amino-4-((2S,6R)-2,6-dimethylmorpholino)benzamide

a) Methyl 4-((2S,6R)-2,6-dimethylmorpholino)-2-nitrobenzoate: To a solution of methyl 4-bromo-2-nitrobenzoate (1 g, 3.8 mmol), (2S,6R)-2,6-dimethylmorpholine (0.88 g, 7.7 mmol) in dry dioxane (20 mL) was added cesium carbonate (2.5 g, 7.7 mmol), palladium acetatete (43 mg, 0.2 mmol), (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, 23 mg, 0.04 mmol). The mixture was heated to reflux under argon overnight. After cooling to room temperature, the reaction was filtered, and the filtrate was concentrate to give the crude title compound, which was used for the next step without further purification. MS: m/z 295.2 $[M+H]^+$.

b) 4-((2S,6R)-2,6-dimethylmorpholino)-2-nitrobenzoic acid: The title compound was prepared from methyl 4-((2S,6R)-2,6-dimethylmorpholino)-2-nitrobenzoate using a procedure similar to those described for the synthesis of compound of Example 30b. Yellow solid (0.7 g). MS: m/z 281.2 $[M+H]^+$.

c) N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-nitro-4-((2S,6R)-2,6-dimethylmorpholino)benzamide: A solution of 4-((2S,6R)-2,6-dimethylmorpholino)-2-nitrobenzoic acid (84 mg, 0.3 mmol), 1H-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP, 158 mg, 0.36 mmol) in pyridine (10 mL) was stirred at room temperature for 30 min before the addition of 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline (73 mg, 0.3 mmol). The reaction mixture was stirred at 80°C overnight, and then poured into 20 mL of water, extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with 1 N hydrochloric acid (20 mL) and brine (20 mL × 3), and dried over anhydrous sodium sulfate, concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with DCM/MeOH to give the title compound as a yellow solid (80 mg, 52.9%). MS: m/z 506.3$[M+H]^+$.

d) N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-amino-4-((2S,6R)-2,6-

dimethylmorpholino)benzamide: The title compound was prepared from N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-nitro-4-((2S,6R)-2,6-dimethylmorpholino)benzamide using a procedure similar to those described for the synthesis of compound of Example 24. Gray solid (20 mg, 26.5%). ^{1}H NMR (DMSO-d_6): 12.67 (s, 1H), 9.95 (s, 1H), 8.35 (d, J = 2.4 Hz, 1H), 7.89 (dd, J = 9.0 and 2.7 Hz, 1H), 7.72-7.55 (m, 4H), 7.28-7.20 (m, 2H), 6.51 (s, 2H), 6.28 (d, J = 7.2 Hz, 1H), 6.19 (s, 1H), 3.64-3.60 (m, 4H), 2.34-2.26 (m, 2H), 1.15 (d, J = 6.3 Hz, 6H). MS: m/z 476.2 $[M+H]^+$.

Example 34

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-((2S,6R)-2,6-dimethylmorpholino)quinazolin-4(3H)-one

The title compound was prepared from N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-amino-4-((2S,6R)-2,6-dimethylmorpholino)benzamide and triethyl orthoformate using a procedure similar to those described for the synthesis of compound of Example 27. White solid (6 mg, 12.3%). ^{1}H NMR (DMSO-d_6): 12.83 (s, 1H), 8.32 (s, 1H), 8.08 (d, J = 2.4 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.74-7.70 (m, 2H), 7.60 (dd, J = 6.8 and 1.4 Hz, 1H), 7.31-7.21 (m, 3H), 7.06 (d, J = 2.1 Hz, 1H), 3.90 (d, J = 11.1 Hz, 2H), 3.74-3.64 (m, 2H), 2.51-2.43 (m, 2H), 1.19 (d, J = 6.0 Hz, 6H). MS: m/z 486.2 $[M+H]^+$.

Example 35

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide

a) N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-chloronicotinamide: A clean flask was charged with 6-chloronicotinic acid (79 mg, 0.5 mmol), BOP (264 mg, 0.6 mmol) and pyridine (5 mL), the solution was stirred over 10 min before the addition of 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline (121 mg, 0.5 mmol). The mixture was stirred at room temperature overnight, poured into 30 mL of water, the resulting precipitate was collected by filtered, and dried to give the title compound as a yellow solid (100 mg, 52.3%). MS: m/z 384.1 $[M+H]^+$.

b) N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide: A mixture of N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-chloronicotinamide (100 mg, 0.26 mmol), (2S,6R)-2,6-dimethylmorpholine (30 mg, 0.52 mmol), Na_2CO_3 (55 mg, 0.52 mmol) in DMSO (5 mL)

was heated to 60°C for 10 h. After cooling to room temperature, the solution was poured into 30 mL of water, the solids was filtered and dried. The crude was purified by chromatography (PE/EA) to give the title compound as a white solid (15 mg, 12.5%). ^{1}H NMR (DMSO-d_6): 12.66 (s, 1H), 10.27 (s, 1H), 8.74 (d, J = 2.4 Hz, 1H), 8.38 (d, J = 2.7 Hz, 1H), 8.11 (dd, J = 9.0 and 2.7 Hz, 1H), 7.97 (d, J = 8.7 and 2.7 Hz, 1H), 7.69 (d, J = 6.9 Hz, 1H), 7.60-7.55 (m, 2H), 7.26-7.20 (m, 2H), 6.93 (d, J = 9.3 Hz, 1H), 4.30 (d, J = 12.0 Hz, 2H), 3.61-3.52 (m, 2H), 2.54-2.51 (m, 2H), 1.15 (d, J = 6.0 Hz, 6H). MS: m/z 462.3 $[M+H]^+$.

The following compounds were prepared from 4,6-dichloronicotinic acid or 6-chloro-5-methylnicotinic acid, 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline and (2S,6R)-2,6-dimethylmorpholine using a procedure similar to those described for the synthesis of compound of Example 35.

Example 36

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-chloro-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide

Gray solid (8.4 mg, 15.3%). ^{1}H NMR (DMSO-d_6): 12.75 (brs, 1H), 10.76 (s, 1H), 8.32 (d, J = 2.4 Hz, 1H), 8.21 (s, 1H), 7.84 (dd, J = 8.9 and 2.4 Hz, 1H), 7.66-7.63 (m, 3H), 7.27-7.24 (m, 2H), 7.06 (s, 1H), 3.62-3.57 (m, 2H), 3.45 (d, J = 12.3 Hz, 2H), 2.67-2.59 (m, 2H), 1.02 (d, J = 6.3 Hz, 6H). MS: m/z 496.2 $[M+H]^+$.

Example 37

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-5-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide

White solid (19 mg, 26.3%). ^{1}H NMR (DMSO-d_6): 12.69 (s, 1H), 10.42 (s, 1H), 8.67 (d, J = 2.4 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.96 (dd, J = 8.9 and 2.6 Hz, 1H), 7.70-7.68 (m, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.57 (dd, J = 6.6 and 1.8 Hz, 1H), 7.28-7.18 (m, 2H), 3.76-3.66 (m, 2H), 3.53 (d, J = 12.3 Hz, 2H), 2.54-2.49 (m, 2H), 2.30 (s, 3H), 1.12 (d, J = 6.3 Hz, 6H). MS: m/z 476.3 $[M+H]^+$.

Example 38

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide

The title compound was prepared from ethyl 6-chloro-2-methylnicotinate, (2S,6R)-2,6-dimethylmorpholine and 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline using a procedure similar to those described for the syntheses of compounds of Examples 30a, 30b and 33c. White solid (14 mg, 14.7%). ^{1}H NMR (DMSO-d_6): 12.69 (s, 1H), 10.34 (s, 1H), 8.36 (d, J = 2.4 Hz ,1H), 7.87 (dd, J = 8.7 and 2.7 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.61-7.57 (m, 2H), 7.29-7.20 (m, 2H), 6.75 (d, J = 8.7 Hz, 1H), 4.26 (d, J = 11.7 Hz, 2H), 3.64-3.55 (m, 2H), 3.29 (s, 3H), 2.45-2.40 (m, 2H), 1.16 (d, J = 6.3 Hz, 6H). MS: m/z 476.2 $[M+H]^+$.

The following compounds were prepared from 4-bromo-2-methylbenzoic acid, 3-(1H-benzo[d]midazol-2-yl)-4-chloroaniline and the corresponding phenylboronic acid using a procedure similar to those described for the syntheses of compounds of Examples 2 and 1.

Example 39

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(2-methoxypyrimidin-5-yl)benzamide

White solid (13 mg, 13.8%). ^{1}H NMR (DMSO-d_6): 12.71 (s, 1H), 10.65 (s, 1H), 8.99 (s, 2H), 8.41 (d, J = 2.4 Hz, 1H), 7.87 (dd, J = 8.9 and 2.6 Hz, 1H), 7.72-7.54 (m, 6H), 7.30-7.21 (m, 2H), 3.98 (s, 3H), 2.48 (s, 3H). MS: m/z 470.2 $[M+H]^+$.

Example 40

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(pyridin-3-yl)benzamide

White solid (30 mg, 34.2%). ^{1}H NMR (DMSO-d_6): 12.74 (s, 1H), 10.68 (s, 1H), 8.94 (d, J = 2.1 Hz, 1H), 8.61 (dd, J = 4.8 and 1.5 Hz, 1H), 8.41 (d, J = 2.4 Hz, 1H), 8.15-8.11 (m, 1H), 7.88 (dd, J = 8.7 and 2.4 Hz, 1H), 7.72-7.50 (m, 6H), 7.29-7.21 (m, 2H), 2.50 (s, 3H). MS: m/z 439.2 $[M+H]^+$.

Example 41

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(furan-3-yl)benzamide

White solid (10 mg, 11.7%). ^{1}H NMR (DMSO-d_6): 12.71 (brs, 1H), 10.57 (s, 1H), 8.40 (d, J = 2.4 Hz, 1H), 8.27 (s, 1H), 7.88 (dd, J = 8.9 and 2.6 Hz, 1H), 7.77 (t, J = 1.7 Hz, 1H), 7.70-7.52 (m, 6H), 7.26-7.24 (m, 2H), 7.03 (s, 1H), 2.45 (s, 3H). MS: m/z 428.2 $[M+H]^+$.

Example 42

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(thiophen-3-yl)benzamide

White solid (15 mg, 16.9%). ^{1}H NMR (DMSO-d_6): 12.74 (brs, 1H), 10.61 (s, 1H), 8.40 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 1.5 Hz, 1H), 7.88 (dd, J = 8.9 and 2.3 Hz, 1H), 7.70-7.54 (m, 8H), 7.26-7.23 (m, 2H), 2.46 (s, 3H). MS: m/z 444.2 $[M+H]^+$.

Example 43

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(pyrimidin-5-yl)benzamide

White solid (40 mg, 20%). ^{1}H NMR (DMSO-d_6): 12.72 (s, 1H), 10.70 (s, 1H), 9.23-9.21 (m, 3H), 8.42 (d, J = 2.7 Hz, 1H), 7.89 (dd, J = 8.7 and 2.7 Hz, 1H), 7.82-7.77 (m, 2H), 7.73-7.58 (m, 4H), 7.29-7.21 (m, 2H), 2.50 (s, 3H). MS: m/z 440.2 $[M+H]^+$.

Example 44

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-phenylcyclohexanecarboxamide

The title compound was prepared from 4-phenylcyclohexanecarboxylic acid and 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline using a procedure similar to those described for the synthesis of compound of Example 2. White solid (14.2 mg, 2.2%). ^{1}H NMR (DMSO-d_6): 12.67 (s, 1H), 10.22 (s, 1H), 8.27 (d, J = 2.7 Hz, 1H), 7.75 (dd, J = 8.9 and 2.6 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.56-7.53 (m, 2H), 7.27-7.16 (m, 7H), 2.79-2.38 (m, 2H), 1.93-1.85 (m, 4H), 1.62-1.46 (m, 4H). MS: m/z 430.4 $[M+H]^+$.

Example 45

N-(3-(1H-benzo[d]imidazol-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compoud was prepared from 3-(1H-benzo[d]imidazol-2-yl)aniline and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the synthsis of compound of Example 2. White solid (9.59 mg, 10.2%). ^{1}H NMR (DMSO-d_6): 12.95 (brs, 1H), 10.58 (s, 1H), 8.77 (s, 1H), 7.97 (d, J = 8.1 Hz, 2H), 7.89-

7.84 (m, 3H), 7.74-7.64 (m, 5H), 7.56-7.51 (m, 2H), 7.24-7.22 (m, 2H), 2.53 (s, 3H). MS: m/z 472.1 $[M+H]^+$.

Example 46

N-(3-(1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from 3-(1H-benzo[d]imidazol-2-yl)-4-methylaniline and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the synthesis of compound of Example 21b. White solid (5.15 mg, 8.3%)。^{1}H NMR (CD_3OD): 8.03 (d, J = 1.8 Hz, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.81-7.77 (m, 3H), 7.71-7.60 (m, 4H), 7.43 (d, J = 8.4 Hz, 2H), 7.33-7.31 (m, 2H), 2.59 (s, 3H), 2.54 (s, 3H). MS: m/z 486.2 $[M+H]^+$.

Example 47

N-(3-(1-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

a) 2-(2-Chloro-5-nitrophenyl)-1-methylbenzo[d]imidazole: A mixture of 2-(2-chloro-5-nitrophenyl)-1H-benzo[d]imidazole (0.80 g, 2.93 mmol) and THF (50 mL) was stirred and cooled to 5°C, then was added 60% NaH (0.23 g, 5.87 mmol) in batches. The mixture was warmed to r.t. and stirred for 2 h under N_2. Then CH_3I (1.83 g, 5.87 mmol) was added dropwise to the mixture slowly, and left stirring overnight. Water (50 mL) was added, and THF was removed under evaporation. The aqueous phase was extracted with DCM (100 mL × 2) and the organic phase was collected, washed with brine (30 mL), and dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated to give the title compound as a yellow solid (220 mg, 26.0%). MS: m/z 288.3 $[M+H]^+$.
b) 4-Chloro-3-(1-methyl-1H-benzo[d]imidazol-2-yl)aniline: The title compound was prepared from 2-(2-chloro-5-nitrophenyl)-1-methylbenzo[d]imidazole using a procedure similar to those described for the synthesis of compound of Example 24. Yellow solid (0.18 g, 92.0%). MS: m/z 258.3 $[M+H]^+$.
c) N-(3-(1-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide: The title compound was prepared from 3-(1-methyl-1H-benzo[d]imidazol-2-yl)-4-chloroaniline and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to

those described for the synthesis of compound of Example 2. White solid (10.12 mg, 9.70%). ^{1}H NMR (DMSO-d_6): 10.72 (s, 1H), 8.07 (d, J = 1.8 Hz, 1H), 7.95-7.92 (m, 3H), 7.83 (d, J = 8.4 Hz, 2H), 7.71-7.61 (m, 6H), 7.36-7.25 (m, 2H), 3.67 (s, 3H), 2.47 (s, 3H). MS: m/z 520.3 $[M+H]^+$.

Example 48

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-N,3-dimethyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

a) Tert-butyl 2-(2-chloro-5-nitrophenyl)-1H-benzo[d]imidazole-1-carboxylate: A mixture of 2-(2-chloro-5-nitrophenyl)-1H-benzo[d]imidazole (0.50 g, 1.83 mmol), di-tert-butyl dicarbonate (0.62 g, 2.38 mmol) and 4-dimethylaminopyridine (22.4 mg, 0.18 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature overnight. The mixture was washed with 1 N hydrochloric acid (30 mL × 2) and brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give the title compound as a white solid (0.58 g, 84.8%). MS: m/z 318.2 $[M+H]^+$.
b) Tert-butyl 2-(5-amino-2-chlorophenyl)-1H-benzo[d]imidazole-1-carboxylate: The title compound was prepared from tert-butyl 2-(2-chloro-5-nitrophenyl)-1H-benzo[d]imidazole-1-carboxylate using a procedure similar to those described for those described for the synthesis of compound of Example 24. Yellow solid (200 mg, 43.4%). MS: m/z 344.3 $[M+H]^+$.
c) Tert-butyl 2-(2-chloro-5-(methylamino)phenyl)-1H-benzo[d]imidazole-1-carboxylate: To a mixture of tert-butyl 2-(5-amino-2-chlorophenyl)-1H-benzo[d]imidazole-1-carboxylate (200 mg, 0.58 mmol) in DMF (1.5 mL) was added dropwise iodomethane (91.3 mg, 0.64 mmol), the mixture was stirred at room temperature for 3 days. The mixture was added water (60 mL) and ethyl acetate (40 mL), then the aqueous phase was extracted with ethyl acetate (30 mL), and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by the preparative plate of silica to give the title compound as a yellow solid (40.0 mg, 19.3%). MS: m/z 358.3 $[M+H]^+$.
d) 2-(2-Chloro-5-(N,3-dimethyl-4'-(trifluoromethyl)biphenyl-4-ylcarboxamido)phenyl)-1H-benzo[d]imidazole-1-carboxylate: The title compound was prepared from tert-butyl 2-(2-chloro-5-(methylamino)phenyl)-1H-benzo[d]imidazole-1-carboxylate and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the synthesis of compound of Example 2. Yellow solid (30 mg, 44.0%). MS: m/z 520.3 $[M+H]^+$.

e) N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-N,3-dimethyl-4'-(trifluoromethyl)biphenyl-4-carboxamide: 2-(2-Chloro-5-(N,3-dimethyl-4'-(trifluoromethyl)biphenyl-4-ylcarboxamido)phenyl)-1H-benzo[d]imidazole-1-carboxylate (30.0 mg, 0.05 mmol) in the solution of HCl in ethyl acetate (2 N, 5 mL, 10 mmol) was stirred at room temperature overnight. The mixture was concentrated, and Na_2CO_3 aqueous solution (2 N, 20 mL) and ethyl acetate (35 mL) were added, the organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by the preparative plate of silica to give the title compound as an off-white solid (7.29 mg, 28.0%). ^{1}H NMR (DMSO-d_6): 12.69 (s, 1H), 7.97-7.93 (m, 1H), 7.85 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 7.5 Hz, 1H), 7.56-7.46 (m, 4H), 7.35-7.19 (m, 4H), 3.38 (s, 3H), 2.35 (s, 3H). MS: m/z 520.3 $[M+H]^+$.

Example 49

N-(3-(1H-imidazo[4,5-c]pyridin-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from 4-chloro-3-(1H-imidazo[4,5-c]pyridin-2-yl)aniline and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the synthesis of compound of Example 21b. Off-white solid (12.88 mg, 21%). ^{1}H NMR (DMSO-d_6): 13.41 (brs, 1H), 10.70 (s, 1H), 9.02-9.01 (m, 1H), 8.43 (s, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.85-7.82 (m, 5H), 7.71-7.62 (m, 5H), 2.48 (s, 3H). MS: m/z 507.3 $[M+H]^+$.

Example 50

N-(3-(5-phenyl-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

a) 2-Chloro-5-nitro-N-(2-oxo-2-phenylethyl)benzamide: The title compound was prepared from 2-amino-1-phenylethanone hydrochloride and 2-chloro-5-nitrobenzoic acid using a procedure similar to those described for the synthesis of compound of Example 21b. Yellow solid (0.9 g, 60%). MS: m/z 319.3 $[M+H]^+$.

b) 2-(2-Chloro-5-nitrophenyl)-5-phenyl-1H-imidazole: To the solution of 2-chloro-5-nitro-N-(2-oxo-2-phenylethyl)benzamide (1.5 g, 5 mmol) in AcOH (5 mL) was added NH_4OAc (7.2 g, 100 mmol) at r.t. under N_2, then the mixture was heated to reflux overnight. Until the material was consumed by LCMS, the reaction solution was cooled to r.t. and poured into

water (50 mL), a solid was precipitated, collected and dried under vacuum to give the title compound as a yellow solid (300 mg), which was used for the next step without further purification. MS: m/z 300.2 $[M+H]^+$.

c) 4-Chloro-3-(5-phenyl-1H-imidazol-2-yl)aniline: To a solution of 2-(2-chloro-5-nitrophenyl)-5-phenyl-1H-imidazole (0.2 g, 0.67 mmol) in methanol (5 mL) was added $SnCl_2 \cdot 2H_2O$ (0.6 g, 2.88 mmol) at r.t. under N_2, then the mixture was heated to reflux and stirred overnight. After cooling, the reaction solution was concentrated under vacuum, the residue was diluted with EA (100 mL) and then saturated aqueous $NaHCO_3$ solution was added to this solution slowly until the pH of this solution is 7~8, lots of the white solid was precipitated, filtered, and the filtrate was dried over anhydrous Na_2SO_4, then concentrated to give the crude compound (150 mg), which was used for the next step without further purification. MS: m/z 270.1 $[M+H]^+$.

d) N-(3-(5-phenyl-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide: The title compound was prepared from 4-chloro-3-(5-phenyl-1H-imidazol-2-yl)aniline and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the synthesis of compound of Example 21b. Off-white solid (5 mg, 5%). ^1H NMR (CD_3OD): 8.08 (s, 1H), 7.92-7.75 (m, 7H), 7.65-7.63 (m, 3H), 7.57-7.54 (m, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.29-7.24 (m, 1H), 2.56 (s, 3H). MS: m/z 532.2 $[M+H]^+$.

Example 51

N-(3-(5-(pyridin-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from 2-amino-1-(pyridin-3-yl)ethone hydrochloride, 2-chloro-5-nitrobenzoic acid, ammonium acetate and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the synthesis of compound of Example 50. Beige solid (0.72 mg, 3%). ^1H NMR (CD_3OD): 9.01 (s, 1H), 8.43 (d, J = 3.3 Hz, 1H), 8.27 (d, J = 7.5 Hz, 1H), 8.15 (s, 1H), 7.92-7.85 (m, 3H), 7.78-7.74 (m, 3H), 7.66-7.63 (m, 3H), 7.58 (d, J = 8.7 Hz, 1H), 7.50-7.46 (m, 1H), 2.56 (s, 3H). MS: m/z 533.3 $[M+H]^+$.

Example 52

N-(3-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

a) 2-Chloro-5-nitro-N'-(pyridin-2-yl)benzohydrazide: A mixture of 2-hydrazinylpyridine (1.0 g, 9.1 mmol), 2-chloro-5-nitrobenzoic acid (1.8 g, 9.1 mmol), BOP (11.8 mmol), 4-methylmorpholine (1.8 g, 18.2 mmol) and CH_2Cl_2 (30 mL) was stirred at room temperature overnight. The reaction mixture was filtered to give the title compound (2.1g, 78%). MS: m/z 293.2 $[M+H]^+$.

b) 3-(2-Chloro-5-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyridine: A mixture of 2-chloro-5-nitro-N'-(pyridin-2-yl)benzohydrazide (1.0 g, 3.4 mmol) and $POCl_3$ (10 mL) was heated to reflux overnight under N_2. After cooled to ambient temperature, the residue was concentrated, then saturated $NaHCO_3$ solution was added under stirring to adjust pH to 7~8. The solid was filtered and washed with water and then dried to give the crude title compound (0.78 g, 84%). MS: m/z 275.1 $[M+H]^+$.

c) 3-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-4-chloroaniline: A mixture of 3-(2-chloro-5-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyridine (500 mg, 1.82 mmol), $SnCl_2 \cdot 2H_2O$ (1.6 g, 7.3 mmol) in MeOH (20 mL) was refluxed overnight. The mixture was cooled to room temperature, concentrated to remove the solvent, and then the residue was mixed with EA (25 mL), and adjusted pH to 7~8 with $NaHCO_3$ (a.q.). After dried over Na_2SO_4, the solvent was removed in vacuo to give the title compound (350 mg, 79%). MS: m/z 245.1 $[M+H]^+$.

d) N-(3-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide: The title compound was prepared from 3-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-4-chloroaniline and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the synthesis of compound of Example 21b. White solid (7.31 mg, 12%). ^1H NMR (CD_3OD): 8.25-8.17 (m, 3H), 8.00-7.97 (m, 3H), 7.90-7.75 (m, 3H), 7.72-7.67 (m, 4H), 7.24 (t, J = 6.9 Hz, 1H), 2.67 (s, 3H). MS: m/z 507.2 $[M+H]^+$.

The following compounds were prepared from 2-hydrazinylpyrimidine or 2-hydrazinylpyrazine, 2-chloro-5-nitrobenzoic acid, and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the syntheses of compounds of Examples 52a~b, 24 and 2.

Example 53

N-(3-([1,2,4]triazolo[4,3-a]pyrimidin-3-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (6 mg, 4.7%). ^{1}H NMR (DMSO-d_6): 10.69 (s, 1H), 9.50 (dd, J = 6.8 and 1.7 Hz, 1H), 8.93 (dd, J = 4.2 and 1.8 Hz, 1H), 8.59 (d, J = 2.4 Hz, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.88-7.82 (m, 3H), 7.70-7.60 (m, 4H), 7.42 (dd, J = 6.6 and 4.2 Hz, 1H), 2.47 (s, 3H). MS: m/z 508.2 $[M+H]^+$.

Example 54

N-(3-([1,2,4]triazolo[4,3-a]pyrazin-3-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (10 mg, 5.5%). ^{1}H NMR (DMSO-d_6): 10.79 (s, 1H), 9.56 (d, J = 1.5 Hz, 1H), 8.28 (dd, J = 4.8 and 1.5 Hz, 1H), 8.21 (d, J = 2.4 Hz, 1H), 8.06-8.02 (m, 2H), 7.95 (d, J = 8.1 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 9.0 Hz, 1H), 7.73-7.69 (m, 2H), 7.64 (d, J = 7.8 Hz, 1H), 2.48 (s, 3H). MS: m/z 508.4 $[M+H]^+$.

Example 55

N-(3-(imidazo[1,2-a]pyrimidin-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

a) 2-(3-Nitrophenyl)imidazo[1,2-a]pyrimidine: A flask was charged with 2-aminopyrimidine (475 mg, 5 mmol), 2-bromo-1-(3-nitrophenyl)ethanone (1.22 g, 5 mmol) and EtOH (20 mL). The reaction solution was heated to reflux under Nitrogen over 5 h. After cooed to room temperature, the resulting precipitate was collected by filtered to give the title compound as a yellow solid (1.1 g, 91.6%). MS: m/z 241.1 $[M+H]^+$.
b) N-(3-(imidazo[1,2-a]pyrimidin-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide: The title compound was prepared from 2-(3-nitrophenyl)imidazo[1,2-a]pyrimidine and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the syntheses of compounds of Examples 24 and 2. White solid (21 mg, 12.5%). ^{1}H NMR (DMSO-d_6): 10.51 (s, 1H), 8.98 (dd, J = 6.8 and 2.0 Hz, 1H), 8.55-8.52 (m, 2H), 8.35 (s, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.85 (d, J = 8.1 Hz, 2H), 7.74-7.63 (m, 5H), 7.44 (t, J = 8.1 Hz, 1H), 7.07 (dd, J = 6.6 and 4.2 Hz, 1H), 2.51 (s, 3H). MS: m/z 473.4 $[M+H]^+$.

Example 56

N-(3-(imidazo[1,2-a]pyridin-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from 2-aminopyridine, 2-bromo-1-(3-nitrophenyl)ethone and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid using a procedure similar to those described for the synthesis of compound of Example 55. White solid (45 mg, 37.7%). ^{1}H NMR (DMSO-d_6): 10.46 (s, 1H), 8.57-8.51 (m, 2H), 8.38 (s, 1 H), 7.96 (d, J = 8.1 Hz, 2H), 7.85 (d, J = 8.1 Hz, 2H), 7.72-7.57 (m, 6H), 7.41 (t, J = 8.1 Hz, 1H), 7.26 (t, J = 7.2 Hz, 1H), 6.91 (t, J = 6.6 Hz, 1H), 2.49 (s, 3H). MS: m/z 472.3 $[M+H]^+$.

The following compounds were prepared from 6-chloronicotinic acid, the corresponding 3-(imidazo[1,2-a]pyrimidin-2-yl)aniline or 3-([1,2,4]triazolo[4,3-a]pyrazin-3-yl)-4-chloroaniline (the intermediates of compounds of Examples 55 and 54, respectively), and (2S,6R)-2,6-dimethylmorpholine using a procedure similar to those described for the syntheses of compounds of Examples 2 and 35b.

Example 57

N-(3-(imidazo[1,2-a]pyrimidin-2-yl)phenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide

Beige solid (22.87 mg, 41.1%). ^{1}H NMR (DMSO-d_6): 10.15 (s, 1H), 8.98 (dd, J = 6.8 and 2.0 Hz, 1H), 8.78 (d, J = 2.4 Hz, 1H), 8.54 (dd, J = 4.1 and 2.0 Hz, 1H), 8.44 (s, 1H), 8.35 (s, 1H), 8.15 (dd, J = 9.0 and 2.4 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 8.07 (dd, J = 6.8 and 4.1 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 4.32 (d, J = 12.0 Hz, 2H), 3.66-3.56 (m, 2H), 2.58-2.51 (m, 2H), 1.18 (d, J = 6.3 Hz, 6H). MS: m/z 429.3 $[M+H]^+$.

Example 58

N-(3-([1,2,4]triazolo[4,3-a]pyrazin-3-yl)-4-chlorophenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide

White solid (15.6 mg, 16.9%). ^{1}H NMR (DMSO-d_6): 10.38 (s, 1H), 9.56 (d, J = 1.5 Hz, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.28 (dd, J = 4.8 and 1.5 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 8.12-8.07 (m, 2H), 8.02 (d, J = 4.8 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 4.32 (d, J = 12.9 Hz, 2H), 3.63-3.54 (m, 2H), 2.57-2.53 (m, 2H), 1.16 (d, J = 6.3 Hz, 6H). MS: m/z 464.2 $[M+H]^+$.

Example 59

N-(3-(pyridin-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from 4-chloro-3-(pyridin-2-yl)aniline and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the synthesis of compound of Example 21b. White solid (5 mg, 5%). ^{1}H NMR ($CDCl_3$): 8.67 (d, J = 4.5 Hz, 1H), 7.80-7.70 (m, 9H), 7.57-7.45 (m, 4H), 7.35-7.26 (m, 1H), 2.58 (s, 3H). MS: m/z 467.3 $[M+H]^+$.

Example 60

N-(5-(1H-benzo[d]imidazol-2-yl)pyridin-3-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

a) 5-(4-Bromo-2-methylbenzamido)nicotinic acid: The title compound was prepared from 4-bromo-2-methylbenzoic acid and methyl 5-aminonicotinate using a procedure similar to those described for the syntheses of compounds of Examples 21b and 30b. Off-white solid (380 mg, 87.3%). MS: m/z 335.0 $[M+H]^+$.
b) N-(2-aminophenyl)-5-(4-bromo-2-methylbenzamido)nicotinamide: The title compound was prepared from 5-(4-bromo-2-methylbenzamido)nicotinic acid and o-phenylenediamine using a procedure similar to those described for the synthesis of compound of Example 21b. Yellow solid (400 mg, 85.5%). MS: m/z 425.1 $[M+H]^+$.
c) N-(5-(1H-benzo[d]imidazol-2-yl)pyridin-3-yl)-4-bromo-2-methylbenzamide: A mixture of N-(2-aminophenyl)-5-(4-bromo-2-methylbenzamido)nicotinamide (400 mg, 0.94 mmol) in glacial acetic acid (5 mL) was heated to reflux for 2 h. Then water (30 mL) was added to the mixture and there were a lot of solids formed. Filtered, the residue was washed with water (20 mL), and dried to give the title compound as a yellow solid (250 mg, 61.4%). MS: m/z 407.1 $[M+H]^+$.
d) N-(5-(1H-benzo[d]imidazol-2-yl)pyridin-3-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide: The title compound was prepared from N-(5-(1H-benzo[d]imidazol-2-yl)pyridin-3-yl)-4-bromo-2-methylbenzamide and 4-(trifluoromethyl)phenylboronic acid using a procedure similar to those described for the synthesis of compound of Example 1. White solid (33.8mg, 28.6%). ^{1}H NMR (DMSO-d_6): 13.14 (brs, 1H), 10.78 (s, 1H), 9.09 (t, J = 2.1 Hz, 1H), 9.05 (d, J = 1.8 Hz, 1H), 8.86 (d, J = 2.1 Hz, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.74-7.63 (m, 5H), 7.25-7.22 (m, 2H), 2.52 (s, 3H). MS: m/z 473.2 $[M+H]^+$.

Example 61

N-(4-(1H-benzo[d]imidazol-2-yl)pyridin-2-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from 4-bromo-2-methylbenzoic acid, methyl 2-aminoisonicotinate, o-phenylenediamine, acetic acid and 4-(trifluoromethyl)phenylboronic acid using a procedure similar to those described for the synthesis of compound of Example 60. White solid (14.3mg, 25%). ^{1}H NMR (DMSO-d_6): 13.31 (brs, 1H), 11.03 (s, 1H), 9.02 (s, 1H), 8.54 (d, J = 5.1 Hz, 1H), 7.96 (d, J = 5.1 Hz, 2H), 7.88-7.84 (m, 3H),7.72-7.68 (m, 5H), 7.30-7.25 (m, 2H), 2.54 (s, 3H). MS: m/z 473.2 $[M+H]^+$.

The following compounds were prepared from 3-(1H-benzo[d]imidazol-2-yl)-substituted-aniline and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the synthesis of compound of Example 21b.

Example 62

N-(3-(1H-benzo[d]imidazol-2-yl)-5-(trifluoromethyl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (1.19 mg, 5.2%). ^{1}H NMR (DMSO-d_6): 13.22 (brs, 1H), 10.86 (s, 1H), 8.97 (s, 1H), 8.25-8.19 (m, 2H), 7.96 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 8.1 Hz, 2H), 7.73-7.68 (m, 4H), 7.56 (d, J = 6.9 Hz, 1H), 7.25-7.22 (m, 2H), 2.52 (s, 3H). MS: m/z 540.2 $[M+H]^+$.

Example 63

N-(3-(1H-benzo[d]imidazol-2-yl)-5-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (2.48 mg, 7.6%). ^{1}H NMR (DMSO-d_6): 13.02 (brs, 1H), 10.71 (s, 1H), 8.65 (s, 1H), 7.97-7.91 (m, 4H), 7.84 (d, J = 8.4 Hz, 2H), 7.73 (s, 1H), 7.68 (d, J = 5.7 Hz, 2H), 7.64-7.55 (m, 2H), 7.23-7.20 (m, 2H), 2.51 (s, 3H). MS: m/z 506.1 $[M+H]^+$.

Example 64

N-(3-(1H-benzo[d]imidazol-2-yl)-2-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (12.69 mg, 15.3%). ^{1}H NMR (DMSO-d_6): 7.85-7.80 (m, 5H), 7.62-7.59 (m, 1H), 7.52 (s, 1H), 7.44-7.40 (m, 4H), 6.89 (t, J = 7.8 Hz, 1H), 6.67 (dd, J = 7.5 and 2.0 Hz, 1H), 6.61 (dd, J = 8.1 and 2.0 Hz, 1H), 2.34 (s, 3H). MS: m/z 506.1 $[M+H]^+$.

Example 65

N-(3-(1H-benzo[d]imidazol-2-yl)-2-methylphenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide

The title compound was prepared from 6-chloronicotinic acid, 3-(1H-benzo[d]imidazol-2-yl)-2-methylaniline and (2S,6R)-2,6-dimethylmorpholine using a procedure similar to those described for the synthesis of compound of Example 35. White solid (19.52 mg, 21.3%). ^{1}H NMR (DMSO-d_6): 12.65 (brs, 1H), 9.82 (s, 1H), 8.76 (d, J = 2.1 Hz, 1H), 8.12 (dd, J = 9.0 and 2.4 Hz, 1H), 7.68-7.52 (m, 3H), 7.45 (d, J = 7.2 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.21-7.18 (m, 2H), 6.94 (d, J = 9.0 Hz, 1H), 4.31 (d, J = 12.0 Hz, 2H), 3.62-3.54 (m, 2H), 2.53-2.50 (m, 2H), 2.41 (s, 3H), 1.15 (d, J = 6.0 Hz, 6H). MS: m/z 442.3 $[M+H]^+$.

Example 66

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(6-methoxypyridin-3-yl)benzamide

The title compound was prepared from 4-bromo-2-methylbenzoic acid, 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline and 2-methoxy-5-pyridineboronic acid using a procedure similar to those described for the syntheses of compounds of Examples 2 and 1. White solid (11.7 mg, 11.4%). ^{1}H NMR (DMSO-d_6): 12.70 (s, 1H), 10.62 (s, 1H), 8.53 (s, 1H), 8.40 (s, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.70-7.59 (m, 6H), 7.24-7.22 (m, 2H), 6.92 (d, J = 8.7 Hz, 1H), 3.89 (s, 3H), 2.48 (s, 3H). MS: m/z 469.2 $[M+H]^+$.

Example 67

N-(3-(imidazo[1,2-a]pyridin-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from 2-aminopyridine, 2-bromo-1-(4-chloro-3-nitrophenyl)ethone and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid using a procedure similar to those described for the synthesis of compound of Example 55. Yellow solid (1 mg, 0.8%). ^{1}H NMR (CD_3OD): 8.93 (dd, J = 6.9 and 1.8 Hz, 1H), 8.62 (dd , J = 4.2 and

1.8 Hz, 1H), 8.49 (s, 1H), 8.23 (d, *J* = 2.4 Hz, 1H), 8.00-7.96 (m, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.58-7.55 (m, 3H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.10 (dd, *J* = 6.9 and 4.2 Hz, 1H), 2.58 (s, 3H). MS: m/z 507.2 $[M+H]^+$.

Example 68

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from 2-amino-1-(thiophen-2-yl)ethone hydrochloride, 2-chloro-5-nitrobenzoic acid, ammonium acetate and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid using a procedure similar to those described for the synthesis of compound of Example 50. White solid (1.41 mg, 2.5%). ^{1}H NMR ($CDCl_3$): 8.32-8.22 (m, 3H), 7.76-7.67 (m, 4H), 7.51-7.42 (m, 4H), 7.22-7.21 (m, 2H), 7.05-7.02 (m, 1H), 2.08 (s, 3H). MS: m/z 538.1 $[M+H]^+$.

Example 69

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from 5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-carboxamide and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid using a procedure similar to those described for the synthesis of compound of Example 2. White solid (0.94 mg, 1.03%). ^{1}H NMR (DMSO-d_6): 12.84 (s, 1H), 10.89 (s, 1H), 8.89-8.83 (s, 2H), 7.95 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.73-7.70 (m, 4H), 7.61 (d, *J* = 6.9 Hz, 1H), 7.31-7.21 (m, 2H), 2.50 (s, 3H). MS: m/z 507.1 $[M+H]^+$.

The following compounds were prepared from 5-(1H-benzo[d]imidazol-2-yl)-6-substituted-pyridin-3-amine and the corresponding 3-methyl-4'-substituted-biphenyl-4-carboxylic acid using a procedure similar to those described for the synthesis of compound of Example 2.

Example 70

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-3-methyl-4'-cyanobiphenyl-4-carboxamide

White solid (4.22 mg, 4.8%). ^{1}H NMR (DMSO-d_6): 12.86 (s, 1H), 10.91 (s, 1H), 8.87 (d, *J* = 2.1 Hz, 2H), 8.00-7.94 (m, 4H), 7.76-7.72 (m, 4H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.33-7.23 (m, 2H), 2.50 (s, 3H). MS: m/z 464.1 $[M+H]^+$.

Example 71

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

Off-white solid (14.01 mg, 16.0%). ^{1}H NMR (DMSO-d_6): 12.82 (s, 1H), 10.71 (s, 1H), 8.82 (s, 1H), 8.63 (s, 1H), 7.96 (d, *J* = 7.8 Hz, 2H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.74-7.68 (m, 4H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.31-7.19 (m, 2H), 2.76 (s, 3H), 2.52 (s, 3H). MS: m/z 487.3 $[M+H]^+$.

Example 72

N-(6-(1H-benzo[d]imidazol-2-yl)pyridin-2-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from 4-bromo-2-methylbenzoic acid, methyl 5-aminonicotinate, o-phenylenediamine, acetic acid, and 4-(trifluoromethyl)phenylboronic acid using a procedure similar to those described for the synthesis of compound of Example 60. White solid (10.6 mg, 9.0%). ^{1}H NMR (DMSO-d_6): 12.58 (s, 1H), 10.61 (s, 1H), 8.88 (dd, *J* = 6.6 and 2.4 Hz, 1H), 8.09-8.05 (m, 2H), 7.98 (d, *J* = 8.1 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 2H), 7.75-7.71 (m, 4H), 7.58 (d, *J* = 6.9 Hz, 1H), 7.28-7.19 (m, 2H), 2.55 (s, 3H). MS: m/z 473.2 $[M+H]^+$.

Example 73

N-(3-([1,2,4]triazolo[1,5-a]pyridin-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

The title compound was prepared from 3-([1,2,4]triazolo[1,5-a]pyridin-2-yl)aniline and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid using a procedure similar to those described for the synthesis of compound of Example 2. Yellow solid (6 mg, 50%). ^{1}H NMR (DMSO-d_6): 10.56 (s, 1H), 9.03 (s, 1H), 8.96-8.94 (m, 1H), 8.62 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.87-7.82 (m, 3H), 7.72-7.62 (m, 3H), 7.53-7.48 (m, 2H), 7.20 (d, *J* = 9.3 Hz, 1H), 6.81 (t, *J* = 6.6 Hz, 1H), 2.51 (s, 3H). MS: m/z 473.2 $[M+H]^+$.

The following compounds were prepared from the corresponding 3-(1H-benzo[d]imidazol-2-yl)-4-substituted-aniline and 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid (Example 21a) using a procedure similar to those described for the synthesis of compound of Example 21b.

Example 74

N-(3-(1H-benzo[d]imidazol-2-yl)-4-fluorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

Off-white solid (36.52 mg, 34%). ^{1}H NMR (DMSO-d_6): 12.54 (s, 1H), 10.58 (s, 1H), 8.75 (dd, J = 6.5 and 2.6 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.85-7.82 (m, 3H), 7.71-7.63 (m, 5H), 7.43 (t, J = 9.1 Hz, 1H), 7.23-7.21 (m, 2H), 2.49 (s, 3H). MS: m/z 490.2 $[M+H]^+$.

Example 75

N-(3-(1H-benzo[d]imidazol-2-yl)-4-bromophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (5.27 mg, 13%). ^{1}H NMR (DMSO-d_6): 12.74 (s, 1H), 10.68 (s, 1H), 8.26 (s, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.86-7.80 (m, 4H), 7.72-7.56 (m, 5H), 7.29-7.20 (m, 2H), 2.50 (s, 3H). MS: m/z 552.1 $[M+H]^+$.

Example 76

N-(3-(1H-benzo[d]imidazol-2-yl)-4-methoxyphenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

Off-white solid (5.16 mg, 11%). ^{1}H NMR (DMSO-d_6): 12.14 (s, 1H), 10.39 (s, 1H), 8.79 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.86-7.84 (m, 3H), 7.72-7.65 (m, 5H), 7.27-7.20 (m, 3H), 4.03 (s, 3H), 2.50 (s, 3H). MS: m/z 502.2 $[M+H]^+$.

The following compounds were prepared from the corresponding 2-amino-1-p-substituted-phenylethanone hydrochloride or 2-amino-1-(furan-2-yl)ethanone hydrochloride or 2-amino-1-(thiophen-2-yl)ethanone hydrochloride, 2-chloro-5-nitrobenzoic acid, ammonium acetate and the corresponding 3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxylic acid or 2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzoic acid or 2-substiuted-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid (the compounds were prepared from methyl 4-halo-2-

substituted-benzoate and (2S,6R)-1,2,6-trimethylpiperazine hydrochloride using a procedure similar to those described for the syntheses of compounds of Examples 30a-b) using a procedure similar to those described for the synthesis of compound of Example 50.

Example 77

N-(3-(5-p-tolyl-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (2.98 mg, 5.0%). ^{1}H NMR ($CDCl_3$): 8.54 (s,1H), 8.32 (s,1H), 8.25 (d, J = 8.7 Hz, 1H), 7.73-7.65 (m, 4H), 7.58-7.53 (m, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.42-7.40 (m, 3H), 7.27 (s, 1H), 7.17 (d, J = 7.8 Hz, 2H), 2.45 (s, 3H), 2.35 (s, 3H). MS: m/z 546.2 $[M+H]^+$.

Example 78

N-(3-(5-(4-fluorophenyl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (2.16 mg, 3.0%). ^{1}H NMR ($CDCl_3$): 10.30 (brs, 1H), 8.30 (d, J = 15.6 Hz, 2H), 8.20 (dd, J = 8.7 and 1.5 Hz, 1H), 7.74-7.67 (m, 5H), 7.50-7.41 (m, 4H), 7.30 (s, 1H), 7.09-7.04 (m, 2H), 2.49 (s, 3H). MS: m/z 550.1 $[M+H]^+$.

Example 79

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide

White solid (0.43 mg, 1.0%). ^{1}H NMR ($CDCl_3$): 10.30 (brs, 1H), 8.27-8.18 (m, 2H), 7.93 (s, 1H), 7.75-7.69 (m, 3H), 7.56 (d, J = 7.5 Hz, 1H), 7.50-7.47 (m, 3H), 7.42 (s, 1H), 7.36 (s, 1H), 6.68-6.64 (m, 1H), 6.47-6.44 (m, 1H), 2.57 (s, 3H). MS: m/z 522.1 $[M+H]^+$.

Example 80

N-(3-(5-p-tolyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide

White solid (4.68 mg, 17%). ^{1}H NMR (DMSO-d_6): 12.33 (s, 1H), 10.27 (s, 1H), 8.26 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 8.9 and 2.6 Hz, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.71-7.68 (m, 1H),

7.50 (d, J = 8.7 Hz, 1H), 7.45-7.42 (m, 1H), 7.18 (d, J = 8.1 Hz, 2H), 6.86-6.82 (m, 2H), 3.72-3.65 (m, 4H), 2.40 (s, 3H), 2.34-2.26 (m, 5H), 1.17 (d, J = 6.0 Hz, 6H). MS: m/z 515.4 $[M+H]^+$.

Example 81

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (12 mg, 8%). ^{1}H NMR (CD_3OD): 8.00 (s, 1H), 7.85 (dd, J = 8.7 and 2.4 Hz, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.47-7.44 (m, 2H), 7.35 (d, J = 3.3 Hz, 1H), 7.30-7.29 (m, 1H), 7.06 (t, J = 4.1 Hz, 1H), 6.86-6.82 (m, 2H), 3.70 (d, J = 11.7 Hz, 2H), 2.59 (t, J = 11.4 Hz, 2H), 2.52-2.48 (m, 2H), 2.47 (s, 3H), 2.38 (s, 3H), 1.22 (d, J = 6.0 Hz, 6H). MS: m/z 520.1 $[M+H]^+$.

Example 82

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (15.8 mg, 11.5%). ^{1}H NMR (CD_3OD): 8.03 (s, 1H), 7.89-7.85 (m, 1H), 7.55-7.48 (m, 3H), 7.35 (d, J = 3.0 Hz, 1H), 7.30-7.28 (m, 1H), 7.07-7.03 (m, 2H), 6.97 (dd, J = 8.7 and 2.4 Hz, 1H), 3.72 (d, J = 12.0 Hz, 2H), 2.62 (t, J = 11.4 Hz, 2H), 2.49-2.40 (m, 2H), 2.36 (s, 3H), 1.22 (d, J = 6.0 Hz, 6H). MS: m/z 542.0 $[M+H]^+$.

Example 83

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide

To a solution of 5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-amine (50 mg, 0.2 mmol) and 2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzoic acid (the intermediate of Example 32, 50 mg, 0.2 mmol) in pyridine (3 mL) was added EDCI (80 mg, 0.4 mmol), the resulting mixture was stirred over night at room temperature. Then the mixture concentrated under reduced pressure, water (5 mL) was added and extracted with ethyl acetate (5 mL × 3), the organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to get the crude product, which was purified through TLC (CH_2Cl_2/CH_3OH) to give the title compound as a white solid (12.47 mg, 13.1%). ^{1}H NMR (DMSO-d_6): 12.81 (brs, 1H), 10.53 (s, 1H), 8.86-8.84 (m, 2H), 7.74-7.62 (m, 2H), 7.52 (d, J = 8.7 Hz, 1H), 7.29-7.26 (m, 2H), 6.88-6.85 (m, 2H),

3.75-3.66 (m, 4H), 2.43 (s, 3H), 2.35-2.28 (m, 2H), 1.17 (d, J = 6.0 Hz, 6H). MS: m/z 476.3 $[M+H]^+$.

The following compounds were prepared from 5-(1H-benzo[d]imidazol-2-yl)-6-substituted-pyridin-3-amine and the corresponding 2- or 4-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinic acid (the compounds were prepared from ethyl 2- or 4-methyl-6-chloronicotinate and (2S,6R)-2,6-dimethylmorpholine using a procedure similar to those described for the syntheses of compounds of Examples 30a-b) or 6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinic acid (the compound was prepared from methyl 6-chloronicotinate and (2S,6R)-1,2,6-trimethylpiperazine hydrochloride using a procedure similar to those described for the syntheses of compounds of Examples 30a-b) or 2- or 3-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid (the compounds were prepared from methyl 2- or 3-methyl-4-halobenzoate and (2S,6R)-1,2,6-trimethylpiperazine hydrochloride using a procedure similar to those described for the syntheses of compounds of Examples 30a or 33a, and 30b) using a procedure similar to those described for the synthesis of compound of Example 83.

Example 84

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide

Light-yellow solid (18.35 mg, 19.2%). ^{1}H NMR (DMSO-d_6): 12.83 (brs, 1H), 10.54 (s, 1H), 8.84 (d, J = 5.7 Hz, 2H), 7.83 (d, J = 8.7 Hz, 1H), 7.76-7.58 (m, 2H), 7.33-7.20 (m, 2H), 6.77 (d, J = 9.0 Hz, 1H), 4.28 (d, J = 12.6 Hz, 2H), 3.61-3.57 (m, 2H), 2.50 (s, 3H), 2.46-2.39 (m, 2H), 1.17 (d, J = 6.0 Hz, 6H). MS: m/z 477.1 $[M+H]^+$.

Example 85

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-4-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide

Light-yellow solid (20.64 mg, 21.6%). ^{1}H NMR (DMSO-d_6): 12.81 (brs, 1H), 10.63 (s, 1H), 8.82 (dd, J = 5.3 and 2.6 Hz, 2H), 8.39 (s, 1H), 7.73-7.61 (m, 2H), 7.27-7.24 (m, 2H), 6.78 (s, 1H), 4.26 (d, J = 12.0 Hz, 2H), 3.62-3.52 (m, 2H), 2.46-2.42 (m, 2H), 2.40 (s, 3H), 1.15 (d, J = 6.3 Hz, 6H). MS: m/z 477.1 $[M+H]^+$.

Example 86

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide

Brown solid (9.66 mg, 5.1%). ^{1}H NMR (DMSO-d_6): 12.82 (s, 1H), 10.50 (s, 1H), 8.96 (d, J = 2.7 Hz, 1H), 8.85 (d, J = 2.7 Hz, 1H), 8.77 (d, J = 2.1 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 6.9 Hz, 1H), 7.30-7.21 (m, 2H), 7.01-6.95 (m, 1H), 4.47-4.29 (m, 2H), 2.85-2.62 (m, 2H), 2.41-1.98 (m, 5H), 1.32-1.01 (m, 6H). MS: m/z 476.0 $[M+H]^+$.

Example 87

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Yellow solid (17.08 mg, 9.5%). ^{1}H NMR (DMSO-d_6): 12.85 (s, 1H), 10.55 (s, 1H), 8.86-8.83 (m, 2H), 7.72 (d, J = 6.9 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.29-7.21 (m, 2H), 6.86-6.84 (m, 2H), 3.76 (d, J = 11.4 Hz, 2H), 2.59-2.53 (m, 4H), 2.48 (s, 3H), 2.29 (s, 3H), 1.13 (d, J = 5.7 Hz, 6H). MS: m/z 489.1 $[M+H]^+$.

Example 88

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (9.3 mg, 18.0%). ^{1}H NMR (DMSO-d_6): 12.81 (s, 1H), 10.36 (s, 1H), 8.81 (d, J = 2.1 Hz, 1H), 8.58 (d, J = 2.1 Hz, 1H), 7.71 (d, J = 6.9 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.28-7.20 (m, 2H), 6.90-6.87 (m, 2H), 3.82-3.80 (m, 2H), 2.74 (s, 3H), 2.69-2.57 (m, 4H), 2.46-2.35 (m, 6H), 1.28-1.14 (m, 6H). MS: m/z 469.3 $[M+H]^+$.

Example 89

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-3-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Light-yellow solid (15.6 mg, 8.8%). ^{1}H NMR (CD_3OD): 8.92 (d, J = 2.4 Hz, 1H), 8.52 (d, J = 2.4 Hz, 1H), 7.85-7.82 (m, 2H), 7.72-7.63 (m, 2H), 7.36-7.31 (m, 2H), 7.15 (d, J = 8.1 Hz, 1H), 3.23 (d, J = 12.0 Hz, 2H), 3.01-2.86 (m, 2H), 2.81-2.74 (m, 2H), 2.72 (s, 3H), 2.62 (s, 3H), 2.41 (s, 3H), 1.30 (d, J = 6.3 Hz, 6H). MS: m/z 469.3 $[M+H]^+$.

Example 90

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide

White solid (8.74 mg, 9%). ^{1}H NMR (DMSO-d_6): 12.81 (s, 1H), 10.39 (s, 1H), 8.89 (d, J = 2.4 Hz, 1H), 8.81 (d, J = 2.1 Hz, 1H), 8.60 (d, J = 2.1 Hz, 1H), 8.18 (dd, J = 8.7 and 1.8 Hz, 1H), 7.73-7.56 (m, 2H), 7.25-7.24 (m, 2H), 7.04 (d, J = 8.7 Hz, 1H), 4.44 (d, J = 12.0 Hz, 2H), 3.22-3.14 (m, 2H), 2.97-2.82 (m, 2H), 2.76 (s, 3H), 2.45-2.41 (m, 3H), 1.30-1.17 (m, 6H). MS: m/z 456.2 $[M+H]^+$.

The following compounds were prepared from 3-(6-(un)substituted-1H-benzo[d]imidazol-2-yl)-4-substituted-aniline and the corresponding 4-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinic acid (the intermediate of Example 85) or 2-methyl-4-(4-methylpiperazin-1-yl)benzoic acid hydrochloride (the compound was prepared from methyl 4-fluoro-2-methylbenzoate and 1-methylpiperazine using a procedure similar to those described for the syntheses of compounds of Examples 30a-b) or 2-substituted-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid (the compounds were prepared from methyl 4-halo-2-substituted-benzoate and (2S,6R)-1,2,6-trimethylpiperazine hydrochloride using a procedure similar to those described for the syntheses of compounds of Examples 30a-b) or 2-methyl-4-((3S,5R)-4-alkyl-3,5-dimethylpiperazin-1-yl)benzoic acid (the compounds were prepared from methyl 4-fluoro-2-methylbenzoate and (2S,6R)-1-alkyl-2,6-dimethylpiperazine hydrochloride using a procedure similar to those described for the syntheses of compounds of Examples 30a-b) using a procedure similar to those described for the synthesis of compound of Example 83.

Example 91

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide

Off-white solid (10 mg, 6.4%). ^{1}H NMR (DMSO-d_6): 12.72 (brs, 1H), 10.41 (s, 1H), 8.37-8.34 (m, 2H), 7.83 (dd, J = 8.7 and 2.7 Hz, 1H), 7.58-7.55 (m, 3H), 7.22-7.13 (m, 2H), 6.78 (s, 1H), 4.28 (d, J = 11.7 Hz, 2H), 3.61-3.56 (m, 2H), 2.48-2.42 (m, 2 H), 2.39 (s, 3H), 1.17 (d, J = 6.3 Hz, 6H). MS: m/z 476.2 $[M+H]^+$.

Example 92

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(4-methylpiperazin-1-yl)benzamide

White solid (6.0 mg, 13.0%). ^{1}H NMR (DMSO-d_6): 12.67 (s, 1H), 10.31 (s, 1H), 8.37 (d, *J* = 2.7 Hz, 1H), 7.87-7.83 (m, 1H), 7.68 (d, *J* = 6.0 Hz, 1H), 7.58-7.55 (m, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.23-7.22 (m, 2H), 6.85-6.82 (m, 2H), 3.46-3.41 (m, 4H), 2.68-2.62 (m, 4H), 2.41-2.36 (m, 6H). MS: m/z 460.2 $[M+H]^+$.

Example 93

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (3.85 mg, 5.80%). ^{1}H NMR (DMSO-d_6): 12.69 (brs, 1H), 10.35 (s, 1H), 8.36 (d, *J* = 2.7 Hz, 1H), 7.86 (dd, *J* = 8.9 and 2.6 Hz, 1H), 7.70-7.56 (m, 3H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.23-7.22 (m, 2H), 6.93-6.91 (m, 2H), 4.01 (d, *J* = 13.2 Hz, 2H), 2.93 (t, *J* = 12.0 Hz, 2H), 2.82-2.74 (m, 2H), 2.48-2.45 (m, 3H), 2.40 (s, 3H), 1.37 (d, *J* = 5.1 Hz, 6H). MS: m/z 488.2 $[M+H]^+$.

Example 94

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (37.27 mg, 15.3%). ^{1}H NMR (DMSO-d_6): 12.73 (s, 1H), 10.55 (s, 1H), 8.34 (d, *J* = 2.1 Hz, 1H), 7.85 (dd, *J* = 8.9 and 2.3 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.62-7.57 (m, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.27-7.24 (m, 2H), 7.04 (s, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 3.73 (d, *J* = 11.7 Hz, 2H), 2.47-2.44 (m, 2H), 2.26-2.13 (m, 5H), 1.08 (d, *J* = 6.0 Hz, 6H). MS: m/z 508.1 $[M+H]^+$.

Example 95

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Light-yellow solid (60.51 mg, 16.4%). ^{1}H NMR (DMSO-d_6): 12.70 (s, 1H), 10.22 (s, 1H), 8.32 (d, *J* = 2.7 Hz, 1H), 7.89 (dd, *J* = 9.0 and 2.7 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.61-7.54

(m, 3H), 7.28-7.19 (m, 2H), 6.86-6.84 (m, 2H), 3.86-3.78 (m, 2H), 2.61-2.53 (m, 2H), 2.33-2.13 (m, 5H), 1.22-1.01 (m, 6H). MS: m/z 246.6 $[M/2+H]^+$.

Example 96

N-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (65 mg, 26.7%). ^{1}H NMR (DMSO-d_6): 12.91 (d, J = 2.1 Hz, 1H), 10.56 (s, 1H), 8.36 (s, 1H), 7.85 (d, J = 8.7 Hz 1H), 7.77-7.71 (m, 1H), 7.63-7.61 (m, 2H), 7.56 (d, J = 8.7 Hz, 1H), 7.27 (t, J = 9.2 Hz, 1H), 7.06 (s, 1H), 6.98 (d, J = 8.1 Hz, 1H), 3.76 (d, J = 10.5 Hz, 2H), 2.44-2.38 (m, 2H), 2.31-2.15 (m, 5H), 1.18-1.03 (m, 6H). MS: m/z 542.0 $[M+H]^+$.

Example 97

N-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (37.52 mg, 14.9%). ^{1}H NMR (DMSO-d_6): 12.91 (d, J = 13.5 Hz, 1H), 10.35 (s, 1H), 8.40 (s, 1H), 7.87 (d, J = 11.7 Hz 1H), 7.77-7.71 (m, 1H), 7.61-7.58 (m, 2H), 7.44 (d, J = 8.1 Hz, 1H), 7.31-7.24 (m, 1H), 6.87-6.85 (m, 2H), 3.82-3.70 (m, 2H), 2.65-2.54 (m, 2H), 2.40-2.19 (m, 8H), 1.21-1.08 (m, 6H). MS: m/z 522.1 $[M+H]^+$.

Example 98

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (46.01 mg, 18.7%). ^{1}H NMR (DMSO-d_6): 12.82 (brs, 1H), 10.32 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 8.9 and 2.6 Hz, 1H), 7.70-7.54 (m, 2H), 7.50-7.35 (m, 2H), 7.11 (t, J = 9.0 Hz, 1H), 6.84-6.82 (m, 2H), 3.69 (d, J = 11.1 Hz, 2H), 2.48-2.44 (m, 2H), 2.39 (s, 3H), 2.24-2.21 (m, 2H), 2.18 (s, 3H), 1.08 (d, J = 6.0 Hz, 6H). MS: m/z 506.1 $[M+H]^+$.

Example 99

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (58.06 mg, 21.0%). ^{1}H NMR (DMSO-d_6): 12.85 (s, 1H), 10.55 (s, 1H), 8.36 (s, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.71-7.35 (m, 4H), 7.13-6.97 (m, 3H), 3.74 (d, J = 12.0 Hz, 2H), 2.46-2.41 (m, 2H), 2.28-2.13 (m, 5H), 1.08 (d, J = 5.7 Hz, 6H). MS: m/z 526.0 $[M+H]^+$.

Example 100

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide

White solid (36.0 mg, 15.3%). ^{1}H NMR (DMSO-d_6): 12.69 (s, 1H), 10.32 (s, 1H), 8.36 (d, J = 2.7 Hz, 1H), 7.84 (dd, J = 8.9 and 2.6 Hz, 1H), 7.68 (d, J = 6.9 Hz, 1H), 7.59-7.55 (m, 2H), 7.42 (d, J = 8.7 Hz, 1H), 7.27-7.18 (m, 2H), 6.88-6.81 (m, 2H), 3.79-3.63 (m, 2H), 3.12-2.55 (m, 6H), 2.38 (s, 3H), 1.33-0.80 (m, 9H). MS: m/z 502.1 $[M+H]^+$.

Example 101

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-4-isopropyl-3,5-dimethylpiperazin-1-yl)benzamide

Off-white solid (7.5 mg, 12.1%). ^{1}H NMR (DMSO-d_6): 12.70 (s, 1H), 10.29 (brs, 1H), 8.37 (d, J = 2.7 Hz, 1H), 7.85 (dd, J = 8.9 and 2.3 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 8.7 Hz, 2H), 7.45-7.43 (m, 1H), 7.27-7.18 (m, 2H), 6.76-6.58 (m, 2H), 3.84-3.64 (m, 2H), 3.24-2.98 (m, 4H), 2.58-2.48 (m, 2H), 2.39 (s, 3H), 1.47-1.25 (m, 6H), 1.13-0.88 (m, 6H). MS: m/z 516.1 $[M+H]^+$.

Example 102

N-(3-(1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Yellow solid (45.97 mg, 12.1%). ^{1}H NMR (CD_3OD): 7.96 (d, J = 1.8 Hz, 1H), 7.71 (dd, J = 8.4 and 2.1 Hz, 1H), 7.64-7.61 (m, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.30-7.27 (m, 2H), 7.03 (d, J = 2.1 Hz, 1H), 6.97 (dd, J = 8.7 and 2.1 Hz, 1H), 3.73 (d, J = 12.0 Hz, 2H), 2.64 (t, J = 11.6 Hz, 2H), 2.56-2.53 (m, 2H), 2.49 (s, 3H), 2.41 (s, 3H), 1.24 (d, J = 6.3 Hz, 6H). MS: m/z 488.1 $[M+H]^+$.

The following compounds were prepared from N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-chloronicotinamide (Example 35a) and the corresponding 1-methylpiperazine or (2S,6R)-1,2,6-trimethylpiperazine trifluoroacetate or (2S,6R)-1-ethyl-2,6-dimethylpiperazine trifluoroacetate using a procedure similar to those described for the synthesis of compound of Example 35b.

Example 103

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-(4-methylpiperazin-1-yl)nicotinamide

Off-white solid (9.1 mg, 15.6%). ^{1}H NMR (DMSO-d_6): 12.66 (s, 1H), 10.25 (s, 1H), 8.74 (d, J = 2.1 Hz, 1H), 8.38 (d, J = 2.4 Hz, 1H), 8.09 (dd, J = 9.0 and 2.4 Hz, 1H), 7.96 (dd, J = 8.9 and 2.6 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.60-7.57 (m, 2H), 7.27-7.18 (m, 2H), 6.90 (d, J = 9.0 Hz, 1H), 3.62 (t, J = 4.8 Hz, 4H), 2.38 (t, J = 4.8 Hz, 4H), 2.21 (s, 3H). MS: m/z 447.2 $[M+H]^+$.

Example 104

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide

Light-yellow solid (5.86 mg, 9.5%). ^{1}H NMR (DMSO-d_6): 12.78 (s, 1H), 10.35 (s, 1H), 8.84 (d, J = 2.4 Hz, 1H), 8.49 (d, J = 2.7 Hz, 1H), 8.19 (dd, J = 9.2 and 2.3 Hz, 1H), 8.08 (dd, J = 8.9 and 2.6 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.72-7.69 (m, 2H), 7.39-7.30 (m, 2H), 7.05 (d, J = 9.0 Hz, 1H), 4.39 (d, J = 12.9 Hz, 2H), 2.74 (t, J = 11.9 Hz, 2H), 2.28 (s, 3H), 2.24-2.19 (m, 2H), 1.19 (d, J = 6.3 Hz, 6H). MS: m/z 475.2 $[M+H]^+$.

Example 105

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)nicotinamide

Brown solid (18.0 mg, 18.4%). ^{1}H NMR (DMSO-d_6): 12.71 (s, 1H), 10.37 (s, 1H), 8.79 (d, J = 2.1 Hz, 1H), 8.41 (d, J = 2.7 Hz, 1H), 8.17 (dd, J = 9.0 and 2.1 Hz, 1H), 8.00 (dd, J = 8.9 and 2.6 Hz, 1H), 7.76-7.65 (m, 1H), 7.61 (d, J = 9.0 Hz, 2H), 7.26-7.24 (m, 2H), 7.02 (d, J = 9.0 Hz, 1H), 4.46 (d, J = 11.7 Hz, 2H), 3.17-2.89 (m, 6H), 1.26 (d, J = 5.1 Hz, 6H), 1.02 (t, J = 6.3 Hz, 3H). MS: m/z 489.2 $[M+H]^+$.

Example 106

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide

The title compound was prepared from 6-chloronicotinic acid, 5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-carboxamide and (2S,6R)-2,6-dimethylmorpholine using a procedure similar to those described for the synthesis of compound of Example 35. White solid (16 mg, 18.2%). ^{1}H NMR (DMSO-d_6): 12.73 (brs, 1H), 10.49 (brs, 1H), 8.93 (d, J = 2.7 Hz, 1H), 8.82 (d, J = 2.7 Hz, 1H), 8.76 (d, J = 2.1 Hz, 1H), 8.12 (dd, J = 9.0 and 2.4 Hz, 1H), 7.67-7.65 (m, 2H), 7.27-7.24 (m, 2H), 6.94 (d, J = 9.0 Hz, 1H), 4.30 (d, J = 12.3 Hz, 2H), 3.80-3.71 (m, 2H), 2.60-2.55 (m, 2H), 1.15 (d, J = 6.3 Hz, 6H). MS: m/z 463.2 $[M+H]^+$.

Example 107

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-methyl-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide

a) N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-chloro-4-methylnicotinamide: A solution of 6-hydroxy-4-methylnicotinic acid (85 mg, 0.53 mmol) in phosphorus oxychloride (2 mL) was heated to reflux over 5 hours. After cooled to room temperature, the mixture was concentrated to give 6-chloro-4-methylnicotinoyl chloride, which used in the next step without purification. To a solution of 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline (130 mg, 0.53 mmol), Et_3N (210 mg, 2.1 mmol) in DCM (10 mL) was added dropwise the solution of 6-chloro-4-methylnicotinoyl chloride in DCM (3 mL) at ice-bath. The mixture was stirred at r.t. overnight, then concentrated to give the crude product as a yellow solid (130 mg, 61.9%). MS: m/z 397.1 $[M+H]^+$.

b) N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-methyl-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide: The title compound was prepared from N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-chloro-4-methylnicotinamide and (2S,6R)-1,2,6-trimethylpiperazine hydrochloride using a procedure similar to those described for the synthesis of compound of Example 35b. White solid (15 mg, 9.6%). ^{1}H NMR (DMSO-d_6): 12.70 (s, 1H), 10.43 (s, 1H), 8.35 (d, J = 12.0 Hz, 2 H), 7.86 (d, J = 8.7 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.61-7.57 (m, 2H), 7.29-7.20 (m, 2H), 6.81 (s, 1H), 4.29-4.23 (m, 2H), 2.64-2.57 (m, 2H), 2.39 (s, 3H), 2.29-2.00 (m, 5H), 1.23-1.01 (m, 6H). MS: m/z 489.1 $[M+H]^+$.

Example 108

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(piperazin-1-yl)benzamide

a) Methyl 2-methyl-4-(piperazin-1-yl)benzoate: A mixture of methyl 4-fluoro-2-methylbenzoate (150 mg, 0.89 mmol) and piperazine (230 mg, 2.67 mmol) in dimethyl sulfoxide (2 mL) was stirred at 80°C overnight. The reaction mixture was cooled to room temperature, added water (50 mL) and stirred. The aqueous phase was extracted with ethyl acetate (50 mL × 3), the combined organic phases were dried over Na_2SO_4, filtered and concentrated to give the title compound as a yellow oil (122 mg, 58.3%). MS: m/z 235.2 $[M+H]^+$.

b) 2-Methyl-4-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzoic acid: A mixture of methyl 2-methyl-4-(piperazin-1-yl)benzoate (122 mg, 0.52 mmol), 2 N NaOH aqueous solution (0.78 mL, 1.56 mmol) in methanol (10 mL) was stirred at 60°C overnight. The reaction mixture was concentrated to move methanol, added water (1.5 mL) and dioxane (5 mL), stirred and added di-tert-butyl dicarbonate (170 mg, 0.78 mmol). The mixture was stirred at room temperature overnight, concentrated and added water (40 mL). The aqueous phase was acidified to pH = 1 with 1 N hydrochloric aicd and extracted with ethyl acetate (50 mL × 2), the combined organic phases were dried over Na_2SO_4, filtered and concentrated to give the title compound as a yellow solid (103 mg, 62.1%). MS: m/z 321.2 $[M+H]^+$.

c) N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzamide: The title compound was prepared from 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline and 2-methyl-4-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzoic acid using a procedure similar to those described for the synthesis of compound of Example 83. White solid (70 mg, 61.1%). MS: m/z 546.3 $[M+H]^+$.

d) N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(piperazin-1-yl)benzamide: A mixture of N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzamide (70 mg, 0.13 mmol) in 2,2,2-trifluoroacetic acid (1 mL) and CH_2Cl_2 (3 mL) was stirred at room temperature overnight. The mixture was concentrated, to the residue was added ethyl acetate (50 mL) and saturated aqueous $NaHCO_3$ solution, stirred and separated. The organic phase was dried over Na_2SO_4, filtered and concentrated, and the residue was purified by the preparative plate of silica to give the title compound as an off-white solid (4.8 mg, 8.3 %). ^1H NMR (DMSO-d_6): 12.67 (brs, 1H), 10.32 (s, 1H), 8.37 (d, J = 1.5 Hz, 1H), 7.87-7.84 (m, 1H), 7.66-7.63 (m, 3H), 7.57 (d, J = 8.7 Hz, 1H), 7.46-7.43 (m, 2H), 6.86-6.84 (m, 2H), 3.50-3.44 (m, 4H), 3.07-3.03 (m, 4H), 2.39 (s, 3H). MS: m/z 446.2 $[M+H]^+$.

Example 109

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,5-dimethylpiperazin-1-yl)benzamide

The title compound was prepared from methyl 4-fluoro-2-methylbenzoate, (2S,6R)-2,6-dimethylpiperazine, di-tert-butyl dicarbonate and 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline using a procedure similar to those described for the synthesis of compound of Example 108. White solid (3.8 mg, 3.8%). ^{1}H NMR (DMSO-d_6): 12.69 (s, 1H), 10.32 (s, 1H), 8.38 (d, J = 2.7 Hz, 1H), 7.87 (dd, J = 8.9 and 2.6 Hz, 1H), 7.71-7.69 (m, 1H), 7.60-7.57 (m, 2H), 7.45 (d, J = 8.7 Hz, 1H), 7.29-7.20 (m, 2H), 6.86-6.84 (m, 2H), 3.80 (d, J = 11.1 Hz, 2H), 3.16-2.96 (m, 4H), 2.40 (s, 3H), 1.14 (d, J = 6.3 Hz, 6H). MS: m/z 474.2 $[M+H]^+$.

Example 110

N-(3-(1-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

The title compound was prepared from 3-(1-methyl-1H-benzo[d]imidazol-2-yl)-4-chloroaniline (Example 47b) and 2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the synthesis of compound of Example 83. Light-yellow solid (22.0 mg, 23.4%). ^{1}H NMR (DMSO-d_6): 10.57 (s, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.89 (dd, J = 8.9 and 2.6 Hz, 2H), 7.70-7.61 (m, 3H), 7.43 (d, J = 8.4 Hz, 1H), 7.35-7.24 (m, 2H), 7.03 (s, 1H), 6.97 (d, J = 8.7 Hz, 1H), 3.76-3.72 (m, 2H), 3.65 (s, 3H), 2.58-2.52 (m, 2H), 2.30-2.10 (m, 5H), 1.09-1.07 (m, 6H). MS: m/z 522.1 $[M+H]^+$.

The following compounds were prepared from 3-(6-substituted-1H-benzo[d]imidazol-2-yl)-4-substituted-aniline and the corresponding 2-substituted-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid or 2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzoic acid (the compound was prepared from methyl 2-chloro-4-fluorobenzoate and (2S,6R)-1-ethyl-2,6-dimethylpiperazine dihydrochloride using a procedure similar to those described for the syntheses of compounds of Examples 30a and 30b) using a procedure similar to those described for the synthesis of compound of Exmaple 83.

Example 111

N-(3-(6-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (16.46 mg, 9.0%). ^{1}H NMR (CD_3OD): 8.12 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 9.0 and 2.4 Hz, 1H), 7.62-7.51 (m, 3H), 7.47 (s, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 1.8 Hz, 1H), 7.04 (dd, J = 8.4 and 2.4 Hz, 1H), 3.89 (d, J = 11.4 Hz, 2H), 2.97-2.73 (m, 4H), 2.66 (s, 3H), 2.52 (s, 3H), 1.36 (d, J = 5.7 Hz, 6H). MS: m/z 522.0 $[M+H]^+$.

Example 112

N-(3-(6-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (14.16 mg, 6.7%). ^{1}H NMR (CD_3OD): 8.09 (d, J = 2.7 Hz, 1H), 7.92 (dd, J = 9.0 and 2.7 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.55-7.48 (m, 2H), 7.45 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.95-6.92 (m, 2H), 3.96 (d, J = 13.5 Hz, 2H), 3.28-3.25 (m, 2H), 2.92-2.76 (m, 5H), 2.50 (s, 3H), 2.48 (s, 3H), 1.44 (d, J = 6.6 Hz, 6H). MS: m/z 251.6 $[M/2+H]^+$.

Example 113

N-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (36 mg, 15.3%). ^{1}H NMR (CD_3OD): 7.99 (d, J = 2.1 Hz, 1H), 7.71 (dd, J = 8.3 and 1.7 Hz, 1H), 7.68-7.62 (m, 1H), 7.61-7.55 (m, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.04 (d, J = 1.8 Hz, 1H), 6.98 (dd, J = 8.7 and 2.1 Hz, 1H), 3.73 (d, J = 11.7 Hz, 2H), 2.67-2.59 (m,2H), 2.58-2.45 (m, 5H), 1.24 (d, J = 6.0 Hz, 6H). MS: m/z 522.0 $[M+H]^+$.

Example 114

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide

Off-white solid (30.15 mg, 24.30%). ^{1}H NMR (CD_3OD): 8.14 (d, J = 2.4 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.61-7.58 (m, 2H), 7.51 (d, J = 8.7 Hz, 1H), 7.37-7.34 (m, 1H), 7.14-7.06 (m, 2H), 6.99 (dd, J = 8.9 and 2.3 Hz, 1H), 3.83 (d, J = 12.3 Hz, 2H), 3.22-3.15 (m, 4H), 2.71 (t, J = 11.9 Hz, 2H), 1.29 (d, J = 6.3 Hz, 6H), 1.11 (t, J = 7.2 Hz, 3H). MS: m/z 540.0 $[M+H]^+$.

Example 115

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (16.36 mg, 10.40%). ^{1}H NMR (CD_3OD): 7.98 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.62-7.58 (m, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.40-7.31 (m, 2H), 7.12-7.04 (m, 2H), 6.97 (d, J = 8.7 Hz, 1H), 3.74 (d, J = 11.7 Hz, 2H), 2.64 (t, J = 11.6 Hz, 2H), 2.56-2.52 (m, 2H), 2.49 (s, 3H), 2.42 (s, 3H), 1.24 (d, J = 6.0 Hz, 6H). MS: m/z 506.0 $[M+H]^+$.

The following compounds were prepared from 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline and the corresponding substituted 6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinic acid (the compounds were prepared from ethyl substituted 6-chloronicotinate and (2S,6R)-1,2,6-trimethylpiperazine dihydrochloride using a procedrue similar to those described for the syntheses of compounds of Examples 30a-b) or (un)substituted-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid (the compounds were prepared from methyl (un)substituted-4-halobenzoate and (2S,6R)-1,2,6-trimethylpiperazine dihydrochloride using a procedure similar to those described for the syntheses of compounds of Examples 30a or 33a and 30b) or 2-chloro-4-((3S,5R)-4-alkyl-3,5-dimethylpiperazin-1-yl)benzoic acid (the compounds were prepared from methyl 2-chloro-4-fluorobenzoate and (2S,6R)-1-alkyl-2,6-dimethylpiperazine dihydrochloride using a procedure similar to those described for the syntheses of compounds of Examples 30a-b) or (S)-2-chloro-4-(3,4-dimethylpiperazin-1-yl)benzoic acid (the compound was prepared from methy 2-chloro-4-fluorobenzoate and (S)-1,2-dimethylpiperazine dihydrochloride using a procedure similar to those described for the syntheses of compounds of Examples 30a-b) using a procedure similar to those described for the synthesis of compound of Example 83.

Example 116

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide

Brown solid (50.32 mg, 25.1%). ^{1}H NMR (CD_3OD): 8.12 (d, J = 2.7 Hz, 1H), 7.92 (dd, J = 8.7 and 2.7 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.67-7.65 (m, 2H), 7.60 (d, J = 8.7 Hz, 1H), 7.35-7.29 (m, 2H), 6.80 (d, J = 8.7 Hz, 1H), 4.56 (d, J = 12.0 Hz, 2H), 3.18-3.03 (m, 2H), 2.97-2.89 (m, 2H), 2.78 (s, 3H), 2.57 (s, 3H), 1.42 (d, J = 6.3 Hz, 6H). MS: m/z 489.0 $[M+H]^+$.

Example 117

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide

Off-white solid (45.12 mg, 24%). ^{1}H NMR (CD_3OD): 8.12 (d, J = 2.7 Hz, 1H), 7.90 (dd, J = 9.0 and 2.7 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.72-7.62 (m, 2H), 7.59 (d, J = 9.0 Hz, 1H), 7.34-7.28 (m, 2H), 6.82 (d, J = 8.7 Hz, 1H), 4.28 (d, J = 12.9 Hz, 2H), 2.80-2.72 (m, 2H), 2.48-2.32 (m, 5H), 1.23 (d, J = 6.0 Hz, 6H). MS: m/z 509.2 $[M+H]^+$.

Example 118

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (28.08 mg, 17.9%). ^{1}H NMR (CD_3OD): 8.13 (d, J = 2.4 Hz, 1H), 7.93 (dd, J = 8.9 and 2.6 Hz, 3H), 7.89 (d, J = 9.0 Hz, 2H), 7.71-7.62 (m, 2H), 7.57 (d, J = 8.7 Hz, 1H), 7.32-7-29 (m, 2H), 7.03 (d, J = 9.0 Hz, 2H), 3.80 (d, J = 12.0 Hz, 2H), 2.71-2.63 (m, 2H), 2.59-2.48 (m, 2H), 2.42 (s, 3H), 1.25 (d, J = 6.0 Hz, 6H). MS: m/z 474.2 $[M+H]^+$.

Example 119

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (27.12 mg, 20.0%). ^{1}H NMR (CD_3OD): 8.09 (d, J = 1.8 Hz, 1H), 7.89 (dd, J = 9.3 and 1.5 Hz, 1H), 7.72-7.54 (m, 4H), 7.32-7.22 (m, 4H), 3.75 (d, J = 11.1 Hz, 2H), 2.68-2.60 (m, 2H), 2.46-2.43 (m, 2H), 2.36 (s, 3H), 1.23 (d, J = 6.3 Hz, 6H). MS: m/z 542.2 $[M+H]^+$.

Example 120

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (120 mg, 57.6%). ^{1}H NMR (CD_3OD): 8.17 (d, J = 2.7 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.97 (dd, J = 8.9 and 2.6 Hz, 2H), 7.69-7.66 (m, 2H), 7.61 (d, J = 8.7 Hz, 1H), 7.36-7.30 (m, 3H), 3.74-3.62 (m, 2H), 3.60-3.46 (m, 2H), 3.06-2.88 (m, 5H), 1.46 (d, J = 6.6 Hz, 6H). MS: m/z 508.0 $[M+H]^+$.

Example 121

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (19.07 mg, 18.6%). ^{1}H NMR (DMSO-d_6): 12.74 (s, 1H), 10.41 (s, 1H), 8.42 (d, J = 2.1 Hz, 1H), 8.02 (dd, J = 8.9 and 2.3 Hz, 1H), 7.86-7.83 (m, 2H), 7.71 (d, J = 7.2 Hz, 1H), 7.64-7.58 (m, 2H), 7.29-7.21 (m, 2H), 7.11 (d, J = 8.1 Hz, 1H), 3.17-3.16 (m, 2H), 2.70-2.60 (m, 4H), 2.50 (s, 3H), 2.34 (s, 3H), 1.32-1.12 (m, 6H). MS: m/z 488.0 $[M+H]^+$.

Example 122

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (56.21 mg, 27.8%). ^{1}H NMR (DMSO-d_6): 12.74 (s, 1H), 10.60 (s, 1H), 8.38 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 9.0 and 2.1 Hz, 1H), 7.70 (d, J = 6.9 Hz, 1H), 7.64-7.57 (m, 2H), 7.36-7.20 (m, 3H), 7.09-7.01 (m,1H), 3.70-3.40 (m, 4H), 3.04-2.91 (m, 2H), 2.87 (s, 3H), 2.31 (s, 3H), 1.48-0.98 (m, 6H). MS: m/z 506.2 $[M+H]^+$.

Example 123

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (10.68 mg, 5.1%). ^{1}H NMR (DMSO-d_6): 12.72 (s, 1H), 10.71 (s, 1H), 8.35 (d, J = 2.7 Hz, 1H), 7.83 (dd, J = 9.0 and 2.7 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.60-7.52 (m, 2H), 7.29-7.16 (m, 3H), 3.52-3.40 (m, 2H), 2.81-2.62 (m, 4H), 2.47-2.27 (m, 3H), 1.25-1.09 (m, 6H). MS: m/z 526.1 $[M+H]^+$.

Example 124

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide

White solid (45.2 mg, 21.1%). ^{1}H NMR (CD_3OD): 8.13 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 8.7 and 2.4 Hz, 1H), 7.68-7.65 (m, 2H), 7.60 (d, J = 8.7 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.34-7.30 (m, 2H), 7.15 (d, J = 2.1 Hz, 1H), 7.05 (dd, J = 8.7 and 2.4 Hz, 1H), 3.99 (d, J = 12.9 Hz, 2H), 3.46-3.40 (m, 4H), 2.92-2.84 (m, 2H), 1.41 (d, J = 6.3 Hz, 6H), 1.25 (t, J = 7.4 Hz, 3H). MS: m/z 522.0 $[M+H]^+$.

Example 125

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-isopropyl-3,5-dimethylpiperazin-1-yl)benzamide

Off-white solid (23.50 mg, 15.10%). ^{1}H NMR (CD_3OD): 8.14 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 8.9 and 2.3 Hz, 1H), 7.73-7.64 (m, 2H), 7.61 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.35-7.32 (m, 2H), 6.91 (d, J = 1.8 Hz, 1H), 6.84 (dd, J = 8.7 and 2.1 Hz, 1H), 3.62-3.58 (m, 5H), 3.38-3.34 (m, 2H), 1.31-1.27 (m, 12H). MS: m/z 536.2 $[M+H]^+$.

Example 126

(S)-N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-(3,4-dimethylpiperazin-1-yl)benzamide

Light-yellow solid (23.31 mg, 29.6%). ^{1}H NMR (CD_3OD): 8.13 (d, J = 2.4 Hz, 1H), 7.92 (dd, J = 8.9 and 2.3 Hz, 1H), 7.67-7.64 (m, 2H), 7.59 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.33-7.30 (m, 2H), 7.03 (d, J = 2.1 Hz, 1H), 6.97 (dd, J = 8.7 and 2.4 Hz, 1H), 3.75-3.67 (m, 2H), 3.00-2.93 (m, 2H), 2.64-2.57 (m, 1H), 2.50-39 (m, 5H), 1.19 (d, J = 6.3 Hz, 3H). MS: m/z 494.1 $[M+H]^+$.

The following compounds were prepared from 5-(6-(un)substituted-1H-benzo[d]imidazol-2-yl)-6-chloropyridine-3-amine and the corresponding 2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid or 2-chloro-4-((2S,6R)-2,6-dimethylmorpholino)benzoic aicd (the compound was prepared from methyl 4-bromo-2-chlorobenzoate and (2S,6R)-2,6-dimethylmorpholine using a procedure similar to those described for the syntheses of compounds of Examples 33a and 30b) using a procedure similar to those described for the synthesis of compound of Example 83.

Example 127

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white (18.11 mg, 8.7%). ^{1}H NMR (CD_3OD): 8.88 (d, J = 2.4 Hz, 1H), 8.66 (d, J = 2.7 Hz, 1H), 7.70-7.67 (m, 2H), 7.53 (d, J = 8.7 Hz, 1H), 7.37-7.31 (m, 2H), 7.07 (d, J = 2.4 Hz,

1H), 6.98 (dd, *J* = 8.7 and 2.4 Hz, 1H), 3.83 (d, *J* = 10.8 Hz, 2H), 2.81-2.70 (m, 4H), 2.56 (s, 3H), 1.31 (d, *J* = 5.7 Hz, 6H). MS: m/z 509.0 $[M+H]^+$.

Example 128

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((2S,6R)-2,6-dimethylmorpholino)benzamide

Off-white solid (41.72 mg, 20.5%). ^{1}H NMR (DMSO-d_6): 12.85 (s, 1H), 10.79 (s, 1H), 8.80 (d, *J* = 1.8 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.29-7.20 (m, 2H), 7.05 (d, *J* = 2.1 Hz, 1H), 6.99 (dd, *J* = 9.0 and 2.4 Hz, 1H), 3.75 (d, *J* = 12.9 Hz, 2H), 3.67-3.60 (m, 2H), 2.32 (t, *J* = 11.3 Hz, 2H), 1.14 (d, *J* = 6.0 Hz, 6H). MS: m/z 495.9 $[M+H]^+$.

Example 129

N-(5-(6-fluoro-1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Light-yellow solid (17.50 mg, 14.0%). ^{1}H NMR (CD_3OD): 8.84 (d, *J* = 2.7 Hz, 1H), 8.68 (d, *J* = 2.4 Hz, 1H), 7.67-7.62 (m, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.36 (dd, *J* = 9.0 and 1.8 Hz, 1H), 7.15-7.08 (m, 1H), 7.00 (d, *J* = 2.1 Hz, 1H), 6.92 (dd, *J* = 8.7 and 2.4 Hz, 1H), 3.72 (d, *J* = 11.7 Hz, 2H), 2.68-2.60 (m, 2H), 2.55-2.53 (m, 2H), 2.41 (s, 3H), 1.23 (d, *J* = 6.3 Hz, 6H). MS: m/z 527.0 $[M+H]^+$.

Example 130

N-(5-(6-chloro-1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Beige solid (19.01 mg, 9.7%). ^{1}H NMR (CD_3OD): 8.87 (d, *J* = 2.4 Hz, 1H), 8.69 (d, *J* = 2.4 Hz, 1H), 7.73-7.60 (m, 2H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.05 (s, 1H), 6.98 (dd, *J* = 9.0 and 1.8 Hz, 1H), 3.76 (d, *J* = 12.0 Hz, 2H), 2.66 (t, *J* = 11.7 Hz, 2H), 2.60-2.48 (m, 2H), 2.42 (s, 3H), 1.25 (d, *J* = 6.0 Hz, 6H). MS: m/z 543.0 $[M+H]^+$.

Example 131

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

A mixture of N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide (Example 99, 23.0 mg, 0.044 mmol) in HCl/EA solution (7 M, 5 mL) was stirred at room temperature overnight. The mixture was filtered, the solids were washed with diethyl ether (5 mL) and dried in vacuo to give the title compound as a white solid (12.0 mg, 45.4%). ^{1}H NMR (DMSO-d_6): 10.73 (s, 1H), 10.61 (brs, 1H), 8.42 (d, J = 2.1 Hz, 1H), 7.87 (dd, J = 8.7 and 2.4 Hz, 1H), 7.76-7.72 (m, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.56-7.51 (m, 2H), 7.28-7.22 (m, 2H), 7.10 (d, J = 8.7 Hz, 1H), 4.10 (d, J = 13.2 Hz, 2H), 3.31-3.23 (m, 2H), 3.07-2.98 (m, 2H), 2.81 (s, 3H), 1.40 (d, J = 6.0 Hz, 6H). MS: m/z 526.1 $[M+H]^+$.

The following compounds were prepared from the corresponding N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide (Example 94) or N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide (Example 120) using a procedure similar to those described for the synthesis of compound of Example 131.

Example 132

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

White solid (518 mg, 72%). ^{1}H NMR (DMSO-d_6): 10.99 (brs, 1H), 10.84 (s, 1H), 8.49 (d, J = 2.4 Hz, 1H), 7.93 (dd, J = 8.9 and 2.6 Hz, 1H), 7.88-7.85 (m, 2H), 7.77 (d, J = 8.7 Hz, 1H), 7.59-7.51 (m, 3H), 7.22 (d, J = 2.4 Hz, 1H), 7.10 (dd, J = 8.7 and 2.4 Hz, 1H), 4.08 (d, J = 12.9 Hz, 2H), 3.42-3.30 (m, 2H), 3.13-3.04 (m, 2H), 2.51-2.49 (m, 3H), 1.42 (d, J = 6.3 Hz, 6H). MS: m/z 508.2 $[M+H]^+$.

Example 133

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

Light-yellow solid (31.1 mg, 53.5%). ^{1}H NMR (CD_3OD): 8.58 (d, J = 2.4 Hz, 1H), 8.13 (d, J = 2.1 Hz, 1H), 8.04-7.90 (m, 4H), 7.81 (d, J = 8.7 Hz, 1H), 7.76-7.70 (m, 2H), 7.36 (d, J = 8.4 Hz, 1H), 3.74 (d, J = 13.5 Hz, 2H), 3.69-3.61 (m, 2H), 3.11-3.03 (m, 5H), 1.53 (d, J = 6.3 Hz, 6H). MS: m/z 508.3 $[M+H]^+$.

Example 134

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-cyano-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

The compound was prepared from 3-(1H-benzo[d]imidazol-2-yl)-4-chloroaniline and 2-cyano-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic aicd (the compound was prepared from methyl 2-cyano-4-fluorobenzoate and (2S,6R)-1,2,6-trimethylpiperazine dihydrochloride using a procedre similar to those described for the syntheses of compounds of Examples 30a-b) using a procedure similar to those described for the syntheses of compounds of Examples 83 and 131. Yellow solid (2.64 mg, 46.2%). ^{1}H NMR (DMSO-d_6): 12.80 (s, 1H), 8.00 (d, J = 2.4 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 7.76-7.70 (m, 2H), 7.64-7.58 (m, 2H), 7.45 (s, 1H), 7.34-7.23 (m, 3H), 3.99 (d, J = 13.8 Hz, 2H), 2.71-2.63 (m, 2H), 2.38-2.12 (m, 5H), 1.11 (d, J = 5.7 Hz, 6H). MS: m/z 500.2 $[M+H]^+$.

Example 135

N-(3-(5-(4-methylthiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

a) 2-(2-Chloro-5-nitrophenyl)-5-(4-methylthiophen-2-yl)-1H-imidazole: A solution of 2-chloro-5-nitrobenzimidamide hydrochloride (0.05 g, 0.212 mmol) and potassium carbonate (0.088 g, 0.635 mmol) in tetrahydrofuran/water (6 mL/1.5 mL) was stirred at 75°C, then 2-bromo-1-(4-methylthiophen-2-yl)ethanone (0.046 g, 0.212 mol) in tetrahydrofuran (2 mL) was added dropwise. The reaction mixture was stirred at the same temperature for additional 2 h, and then it was quenched with water and extracted with dichloromethane (15 mL × 3). The combined organic layers were washed with water (5 mL × 2) and brine (5 mL), dried over anhydrous sodium sulfate and concectrated. Then the crude product was purified by flash column chromatograph to give the title compound as a yellow solid (0.06 g, 74%). MS: m/z 319.9 $[M+H]^+$.

b) 4-Chloro-3-(5-(4-methylthiophen-2-yl)-1H-imidazol-2-yl)aniline: The title compound was prepared from 2-(2-chloro-5-nitrophenyl)-5-(4-methylthiophen-2-yl)-1H-imidazole using a procedure similar to those described for the synthesis of compound of Example 24. Yellow solid (0.05 g, 92%). MS: m/z 289.9 $[M+H]^+$.

c) N-(3-(5-(4-methylthiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide: The title compound was prepared from 4-chloro-3-(5-

(4-methylthiophen-2-yl)-1H-imidazol-2-yl)aniline and 2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the synthesis of compound of Example 83. Yellow solid (9.27 mg, 10%). ^{1}H NMR (CD_3OD): 7.99 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 8.7 and 2.4 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.46 (d, J = 9.0 Hz, 1H), 7.39 (s, 1H), 7.17 (s, 1H), 6.88-6.85 (m, 3H), 3.76 (d, J = 9.3 Hz, 2H), 2.67-2.60 (m, 4H), 2.49 (s, 3H), 2.47 (s, 3H), 2.27 (s, 3H), 1.28 (d, J = 5.7 Hz, 6H). MS: m/z 534.1 $[M+H]^+$.

Example 136

N-(3-(5-(4-methylthiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

The compound was prepared from 4-chloro-3-(5-(4-methylthiophen-2-yl)-1H-imidazol-2-yl)aniline (Example 135b) and 2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the synthesis of compound of Example 83. Off-white solid (58.05 mg, 20.1%). ^{1}H NMR (CD_3OD): 8.02 (d, J = 2.4 Hz, 1H), 7.88 (dd, J = 8.7 and 2.4 Hz, 1H), 7.56-7.50 (m, 2H), 7.41 (s, 1H), 7.19 (d, J = 0.9 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 7.01 (dd, J = 8.7 and 2.4 Hz, 1H), 6.89 (s, 1H), 3.79 (d, J = 10.5 Hz, 2H), 2.74-2.62 (m, 4H), 2.49 (s, 3H), 2.29 (s, 3H), 1.29 (d, J = 6.0 Hz, 6H). MS: m/z 554.2 $[M+H]^+$.

The following compounds were prepared from 2-chloro-5-nitrobenzimidamide hydrochloride, the corresponding 2-bromo-1-(5-chlorothiophen-2-yl)ethanone or 2-bromo-1-(thiophen-3-yl)ethanone or 2-bromo-1-(thiophen-2-yl)propan-1-one, and the corresponding 3-chloro-4-((2S,6R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid (the intermediate of Example 120) or subsituted-4-((3S,5R)-4-alkyl-3,5-dimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the synthesis of compound of Example 135.

Example 137

N-(3-(5-(5-chlorothiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Yellow solid (22.36 mg, 8.1%). ^{1}H NMR (CD_3OD): 8.07-8.05 (m, 2H), 7.95-7.88 (m, 2H), 7.53 (d, J = 8.7 Hz, 1H), 7.48 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 3.9 Hz, 1H), 6.93 (d, J = 3.9 Hz, 1H), 3.59 (d, J = 12.6 Hz, 2H), 3.27-3.19 (m, 2H), 2.89 (t, J = 11.7 Hz, 2H), 2.80 (s, 3H), 1.39 (d, J = 6.3 Hz, 6H). MS: m/z 573.9 $[M+H]^+$.

Example 138

N-(3-(5-(5-chlorothiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Brown solid (47.08 mg, 16.4%). ^{1}H NMR (CD_3OD): 8.02 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 8.7 and 2.4 Hz, 1H), 7.53-7.46 (m, 3H), 7.14 (d, J = 3.9 Hz, 1H), 7.05 (d, J = 2.1 Hz, 1H), 6.98 (dd, J = 8.7 and 2.4 Hz, 1H), 6.92 (d, J = 3.9 Hz, 1H), 3.82-3.73 (m, 2H), 2.74-2.62 (m, 4H), 2.49 (s, 3H), 1.27 (d, J = 5.7 Hz, 6H). MS: m/z 574.1 $[M+H]^+$.

Example 139

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (5.92 mg, 3.2%). ^{1}H NMR (CD_3OD): 7.99 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 8.9 and 2.6 Hz, 1H), 7.65-7.64 (m, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.49-7.44 (m, 4H), 6.90-6.87 (m, 2H), 3.82 (d, J = 9.0 Hz, 2H), 2.91-2.78 (m, 2H), 2.70 (t, J = 12.0 Hz, 2H), 2.59 (s, 3H), 2.47 (s, 3H), 1.32 (d, J = 6.3 Hz, 6H). MS: m/z 520.2 $[M+H]^+$.

Example 140

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (14.39 mg, 6.1%). ^{1}H NMR (CD_3OD): 8.00 (d, J = 2.1 Hz, 1H), 7.85 (dd, J = 8.6 and 2.0 Hz, 1H), 7.64-7.63 (m, 1H), 7.54-7.47 (m, 5H), 7.03 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 8.7 and 2.4 Hz, 1H), 3.72 (d, J = 6.0 Hz, 2H), 2.63 (t, J = 11.7 Hz, 2H), 2.53-2.45 (m, 2H), 2.38 (s, 3H), 1.23 (d, J = 6.0 Hz, 6H). MS: m/z 540.2 $[M+H]^+$.

Example 141

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Gray solid (1.73 mg, 1.8%). ^{1}H NMR (CD_3OD): 8.10 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 8.7 and 2.1 Hz, 1H), 7.65-7.64 (m, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.46-7.45 (m, 3H), 7.31 (d, J = 8.1 Hz, 1H), 6.98-6.93 (m, 1H), 3.45 (d, J = 9.6 Hz, 2H), 2.70-2.63 (m, 4H), 2.48 (s, 3H), 2.37 (d, J = 2.7 Hz, 3H), 1.25 (d, J = 5.7 Hz, 6H). MS: m/z 538.2 $[M+H]^+$.

Example 142

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Pale-yellow solid (4.58mg, 4.6%). ^{1}H NMR (CD_3OD): 7.19 (d, J = 2.1 Hz, 1H), 7.03 (dd, J = 8.9 and 2.6 Hz, 1H), 6.83-6.81 (m, 1H), 6.72 (d, J = 8.7 Hz, 1H), 6.64-6.62 (m, 3H), 6.53 (d, J = 12.6 Hz, 1H), 6.27 (d, J = 7.5 Hz, 1H), 2.64 (d, J = 10.8 Hz, 2H), 1.89-1.75 (m, 4H), 1.60 (s, 3H), 0.39 (d, J = 5.7 Hz, 6H). MS: m/z 558.2 $[M+H]^+$.

Example 143

N-(3-(4-methyl-5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (6.77 mg, 7.5%). ^{1}H NMR (CD_3OD): 7.98 (d, J = 2.4 Hz, 1H), 7.88 (dd, J = 8.7 and 2.4 Hz, 1H), 7.56-7.49 (m, 2H), 7.39 (d, J = 5.4 Hz, 1H), 7.32-7.31 (m, 1H), 7.14 (dd, J = 5.1 and 3.6 Hz, 1H), 6.94-6.91 (m, 2H), 3.89-3.84 (m, 2H), 2.98-2.84 (m, 2H), 2.79-2.70 (m, 2H), 2.65 (s, 3H), 2.53 (s, 3H), 2.51 (s, 3H), 1.37 (d, J = 6.0 Hz, 6H). MS: m/z 534.3 $[M+H]^+$.

The following compounds were prepared from 2-chloro-5-nitrobenzimidamide hydrochloride, the corresponding 2-bromo-1-(furan-2-yl)ethanone or 2-bromo-1-(5-methylfuran-2-yl)ethanone or 2-bromo-1-(thiazol-2-yl)ethanone or 2-bromo-1-(thiophen-2-yl)ethanone or 2-bromo-1-(1-methyl-1H-pyrrol-2-yl)ethanone and the corresponding substituted-4-((3S,5R)-4-alkyl-3,5-dimethylpiperazin-1-yl)benzoic acid or 2-chloro-4-(methylsulfonyl)benzoic acid using a procedure similar to those described for the syntheses of compounds of Examples 135a, 50c and 83.

Example 144

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (11.68 mg, 11.7%). ^{1}H NMR (CD_3OD): 8.00 (d, J = 1.8 Hz, 1H), 7.87 (dd, J = 8.9 and 2.3 Hz, 1H), 7.55-7.43 (m, 4H), 7.06 (d, J = 2.1 Hz, 1H), 6.99 (dd, J = 8.7 and 2.1 Hz, 1H), 6.67 (d, J = 3.3 Hz, 1H), 6.50-6.49 (m, 1H), 3.79 (d, J = 9.0 Hz, 2H), 2.75-2.60 (m, 4H), 2.49 (s, 3H), 1.27 (d, J = 6.0 Hz, 6H). MS: m/z 524.1 $[M+H]^+$.

Example 145

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Light-yellow solid (35.03 mg, 18%). ^{1}H NMR (CD_3OD): 8.00 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 8.7 and 2.4 Hz, 1H), 7.53-7.38 (m, 4H), 7.16 (s, 1H), 7.04 (d, J = 2.1 Hz, 1H), 6.97 (dd, J = 8.7 and 2.4 Hz, 1H), 6.86 (s, 1H), 3.76 (d, J = 10.5 Hz, 2H), 2.71-2.64 (m, 4H), 2.46 (s, 3H), 2.26 (s, 3H), 1.26 (d, J = 5.7 Hz, 6H). MS: m/z 504.3 $[M+H]^+$.

Example 146

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (3.5 mg, 3.5%). ^{1}H NMR (CD_3OD): 7.96 (d, J = 2.4 Hz, 1H), 7.84 (dd, J = 8.7 and 2.4 Hz, 1H), 7.58-7.48 (m, 3H), 7.43 (s, 1H), 7.31-7.22 (m, 2H), 6.67 (d, J = 3.3 Hz, 1H), 6.51-6.47 (m, 1H), 3.88-3.78 (m, 2H), 2.77-2.67 (m, 4H), 2.52 (s, 3H), 1.30 (d, J = 5.4 Hz, 6H). MS: m/z 558.2 $[M+H]^+$.

Example 147

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-cyano-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Yellow solid (3.27 mg, 5.3%). ^{1}H NMR (CD_3OD): 7.87 (d, J = 2.4 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.56 (dd, J = 8.4 and 2.4 Hz, 1H), 7.50-7.45 (m, 3H), 7.31 (dd, J = 8.6 and 2.0 Hz, 1H), 6.68 (d, J = 3.3 Hz, 1H), 6.50-6.48 (m, 1H), 3.96 (d, J = 12.9 Hz, 2H), 2.87-2.79 (m, 2H), 2.71-2.59 (m, 2H), 2.48 (s, 3H), 1.28 (d, J = 6.3 Hz, 6H). MS: m/z 516.3 $[M+H]^+$.

Example 148

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (3.5 mg, 3.5%). ^{1}H NMR (CD_3OD): 8.00 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.50-7.45 (m, 2H), 7.31 (d, J = 8.4 Hz, 1H), 6.97 (t, J = 8.4 Hz, 1H),

6.67 (d, J = 3.3 Hz, 1H), 6.50 (s, 1H), 3.47 (d, J = 10.5 Hz, 2H), 2.80-2.65 (m, 4H), 2.53 (s, 3H), 2.36 (d, J = 3.0 Hz, 3H), 1.26 (d, J = 5.4 Hz, 6H). MS: m/z 522.2 $[M+H]^+$.

Example 149

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (4.53 mg, 12.7%). ^{1}H NMR (CD_3OD): 8.00 (d, J = 1.8 Hz, 1H), 7.86 (dd, J = 8.7 and 2.4 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.50-7.44 (m, 2H), 7.38 (d, J = 12.9 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.67 (d, J = 3.3 Hz, 1H), 6.51-6.49 (m, 1H), 3.55-3.50 (m, 2H), 2.80-2.68 (m, 4H), 2.54 (s, 3H), 1.27 (d, J = 5.1 Hz, 6H). MS: m/z 542.2 $[M+H]^+$.

Example 150

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide

Pale-yellow solid (22.41 mg, 24%). ^{1}H NMR (CD_3OD): 8.00 (d, J = 2.1 Hz, 1H), 7.87 (dd, J = 8.9 and 2.3 Hz, 1H), 7.55-7.50 (m, 3H), 7.43 (s, 1H), 7.11 (d, J = 2.1 Hz, 1H), 7.03 (dd, J = 8.7 and 2.1 Hz, 1H), 6.67 (d, J = 3.3 Hz, 1H), 6.51-6.49 (m, 1H), 3.93 (d, J = 12.3 Hz, 2H), 3.41-3.29 (m, 4H), 2.88-2.80 (m, 2H), 1.38 (d, J = 6.6 Hz, 6H), 1.21 (t, J = 7.4 Hz, 3H). MS: m/z 538.1 $[M+H]^+$.

Example 151

N-(3-(5-(5-methylfuran-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (12.6 mg, 6.4%). ^{1}H NMR (CD_3OD): 7.98 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 8.7 and 2.1 Hz, 1H), 7.54-7.45 (m, 2H), 7.36 (s, 1H), 7.04 (d, J = 2.1 Hz, 1H), 6.98 (dd, J = 8.7 and 2.4 Hz, 1H), 6.53 (d, J = 3.0 Hz, 1H), 6.07 (d, J = 2.4 Hz, 1H), 3.74 (d, J = 12 Hz, 1H), 2.70-2.60 (m, 2H), 2.58-2.48 (m, 2H), 2.41 (s, 3H), 2.35 (s, 3H), 1.23 (d, J = 6.3 Hz, 6H)。MS: m/z 538.2 $[M+H]^+$。

Example 152

N-(3-(5-(5-methylfuran-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Yellow solid (22.6 mg, 11.9%). ^{1}H NMR (CD_3OD): 7.99 (d, J = 2.4 Hz, 1H), 7.87 (dd, J = 8.7 and 2.7 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.38 (s, 1H), 6.92-6.88 (m, 2H), 6.56 (d, J = 3.0 Hz, 1H), 6.10 (d, J = 2.1 Hz, 1H), 3.83 (d, J = 12.0 Hz, 1H), 2.93-2.79 (m, 2H), 2.75-2.64 (m, 2H), 2.60 (s, 3H), 2.49 (s, 3H), 2.37 (s, 3H), 1.33 (d, J = 6.0 Hz, 6H). MS: m/z 518.3 $[M+H]^+$.

Example 153

N-(3-(5-(thiazol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Light-yellow solid (28.03 mg, 14.3%). ^{1}H NMR (CD_3OD): 8.14 (s, 1H), 7.91-7.84 (m, 3H), 7.58-7.52 (m, 3H), 7.12 (d, J = 2.1 Hz, 1H), 7.03 (dd, J = 8.7 and 2.4 Hz, 1H), 3.89 (d, J = 12.9 Hz, 2H), 3.05-2.91 (m, 2H), 2.80 (t, J = 12.0 Hz, 2H), 2.67 (s, 3H), 1.37 (d, J = 6.3 Hz, 6H). MS: m/z 541.2 $[M+H]^+$.

Example 154

N-(3-(5-(thiazol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (17.6 mg, 9.4%). ^{1}H NMR (CD_3OD): 8.11 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 8.9 and 2.6 Hz, 1H), 7.81-7.80 (m, 2H), 7.54-7.51 (m, 2H), 7.46 (d, J = 9.0 Hz, 1H), 6.88-6.86 (m, 2H), 3.78 (d, J = 10.8 Hz, 2H), 2.85-2.60 (m, 4H), 2.53 (s, 3H), 2.46 (s, 3H), 1.29 (d, J = 6 Hz, 6H). MS: m/z 521.2 $[M+H]^+$.

Example 155

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Yellow solid (26 mg, 12.5%). ^{1}H NMR (CD_3OD): 8.01 (d, J = 2.1 Hz, 1H), 7.85 (dd, J = 8.7 and 2.4 Hz, 1H), 7.60-7.54 (m, 2H), 7.49-7.43 (m, 1H), 7.37 (d, J = 3.6 Hz, 1H), 7.33-7.27 (m, 3H), 7.10-7.07 (m, 1H), 3.88-3.85 (m, 2H), 2.86-2.67 (m, 4H), 2.55 (s, 3H), 1.32(d, J = 4.5 Hz, 6H). MS: m/z 574.2 $[M+H]^+$.

Example 156

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (17.01 mg, 17.3%). ^{1}H NMR (CD_3OD): 8.02 (d, J = 1.8 Hz, 1H), 7.70 (dd, J = 9.0 and 2.4 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.44 (s, 1H), 7.36-7.30 (m, 3H), 7.06 (dd, J = 5.1 and 3.6 Hz, 1H), 6.97 (t, J = 8.4 Hz, 1H), 3.51 (d, J = 11.7 Hz, 2H), 3.04-2.85 (m, 2H), 2.78-2.70 (m, 2H), 2.61 (s, 3H), 2.36 (d, J = 2.7 Hz, 3H), 1.30 (d, J = 6.3 Hz, 6H). MS: m/z 538.2 $[M+H]^+$.

Example 157

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (8.16 mg, 22.2%). ^{1}H NMR (CD_3OD): 8.02 (d, J = 2.1 Hz, 1H), 7.87 (dd, J = 9.0 and 2.4 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.44 (s, 1H), 7.42-7.30 (m, 3H), 7.14 (d, J = 7.5 Hz, 1H), 7.06 (dd, J = 5.1 and 3.6 Hz, 1H), 3.55 (d, J = 11.4 Hz, 2H), 3.00-2.83 (m, 2H), 2.81-2.73 (m, 2H), 2.60 (s, 3H), 1.30 (d, J = 6.0 Hz, 6H). MS: m/z 558.1 $[M+H]^+$.

Example 158

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide

White solid (6.16 mg, 15%). ^{1}H NMR (CD_3OD): 8.01 (s, 1H), 7.85 (dd, J = 8.9 and 1.4 Hz, 1H), 7.54-7.43 (m, 3H), 7.35 (dd, J = 3.6 and 0.9 Hz, 1H), 7.30 (d, J = 4.8 Hz, 1H), 7.07-7.03 (m, 2H), 6.97 (dd, J = 8.7 and 2.4 Hz, 1H), 3.75 (d, J = 11.7 Hz, 2H), 3.12-3.04 (m, 2H), 3.00-2.89 (m, 2H), 2.63 (t, J = 11.6 Hz, 2H), 1.23 (d, J = 6.0 Hz, 6H), 1.03 (t, J = 7.1Hz, 3H). MS: m/z 554.2 $[M+H]^+$.

Example 159

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-isopropyl-3,5-dimethylpiperazin-1-yl)benzamide

White solid (2.46 mg, 5.8%). ^{1}H NMR (CD_3OD): 8.01 (s, 1H), 7.86 (dd, J = 9.0 and 1.8 Hz, 1H), 7.54-7.48 (m, 3H), 7.35 (d, J = 3.0 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.07-7.04 (m,

1H), 6.86 (s, 1H), 6.81 (dd, J = 8.6 and 2.0 Hz, 1H), 3.62-3.42 (m, 5H), 3.30-3.15 (m, 2H), 1.29-1.15 (m, 12H). MS: m/z 568.2 $[M+H]^+$.

Example 160

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-(methylsulfonyl)benzamide

White solid (9.4 mg, 26%). ^{1}H NMR (CD_3OD): 8.12 (d, J = 1.8 Hz, 1H), 8.05-8.00 (m, 2H), 7.88 (dd, J = 8.7 and 2.4 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.48-7.42 (m, 1H), 7.35 (d, J = 3.3 Hz, 1H), 7.30 (d, J = 4.5 Hz, 1H), 7.07-7.04 (m, 1H), 3.20 (s, 3H). MS: m/z 492.1 $[M+H]^+$.

Example 161

N-(3-(5-(1-methyl-1H-pyrrol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Gray solid (12.96 mg, 12.6%). ^{1}H NMR (CD_3OD): 7.96 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 8.7 and 2.4 Hz, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.23 (s, 1H), 6.90-6.87 (m, 2H), 6.75-6.73 (m, 1H), 6.33-6.63 (m, 1H), 6.09 (t, J = 3.2 Hz, 1H), 3.83 (d, J = 12.0 Hz, 1H), 3.77 (s, 3H), 2.96-2.83 (m, 2H), 2.76-2.68 (m, 2H), 2.62 (s, 3H), 2.47 (s, 3H), 1.33 (d, J = 6.3 Hz, 6H). MS: m/z 517.3 $[M+H]^+$.

Example 162

N-(3-(5-(1-methyl-1H-pyrrol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Gray solid (18.7 mg, 19.1%). ^{1}H NMR (CD_3OD): 8.00 (d, J = 2.4 Hz, 1H), 7.88 (dd, J = 8.9 and 2.0 Hz, 1H), 7.56-7.50 (m, 2H), 7.25 (s, 1H), 7.06 (d, J = 2.1 Hz, 1H), 7.00 (dd, J = 8.7 and 2.4 Hz, 1H), 6.76 (t, J = 2.0 Hz, 1H), 6.35-6.33 (m, 1H), 6.12-6.09 (m, 1H), 3.79-3.73 (m, 5H), 2.72-2.64 (m, 2H), 2.62-2.54 (m, 2H), 2.45 (s, 3H), 1.32 (s, 3H), 1.27 (d, J = 6.0 Hz, 6H). MS: m/z 537.1 $[M+H]^+$.

Example 163

N-(3-(5-(1-methyl-1H-pyrrol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Pale-yellow solid (19.66 mg, 19.23%). ^{1}H NMR (CD_3OD): 7.95 (d, J = 2.7 Hz, 1H), 7.84 (dd, J = 8.9 and 2.6 Hz, 1H), 7.58-7.52 (m, 2H), 7.32-7.23 (m, 3H), 6.74 (t, J = 2.1 Hz, 1H), 6.33-6.32 (m, 1H), 6.10-6.08 (m, 1H), 3.87 (d, J = 12.0 Hz, 2H), 3.76 (s, 3H), 2.90-2.81 (m, 2H), 2.80-2.72 (m, 2H), 2.58 (s, 3H), 1.33 (d, J = 6.0 Hz, 6H). MS: m/z 571.1 $[M+H]^+$.

The following compounds were prepared from 3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chloroaniline and 2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid or 2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the syntheses of compounds of Examples 83 and 131.

Example 164

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

Yellow solid (9.06 mg, 4.2%). ^{1}H NMR (CD_3OD): 7.99 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 8.7 and 2.4 Hz, 1H), 7.67-7.65 (m, 1H), 7.60-7.54 (m, 2H), 7.48-7.46 (m, 3H), 7.32-7.26 (m, 2H), 3.91-3.81 (m, 2H), 2.81-2.71 (m, 4H), 2.55 (s, 3H), 1.32 (d, J = 5.7 Hz, 6H). MS: m/z 574.3 $[M+H]^+$.

Example 165

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide dihydrochloride

Gray solid (4 mg, 4.0%). ^{1}H NMR (CD_3OD): 8.04 (d, J = 1.8 Hz, 1H), 7.86 (dd, J = 8.7 and 1.8 Hz, 1H), 7.66 (s, 1H), 7.55-7.46 (m, 5H), 7.08 (d, J = 1.8 Hz, 1H), 6.99 (dd, J = 8.7 and 1.8 Hz, 1H), 3.84 (d, J = 12.3 Hz, 2H), 3.24-3.14 (m, 4H), 2.79-2.71 (m, 2H), 1.31 (d, J = 6.3 Hz, 6H), 1.12 (t, J = 7.2 Hz, 3H). MS: m/z 554.2 $[M+H]^+$.

The following compounds were prepared from 2-chloro-5-nitrobenzimidamide hydrochloride, the corresponding 2-bromoacetaldehyde or 2-bromobutanal or 2-bromo-3-methylbutanal or 2-bromopentanal or 1-bromo-3,3-dimethylbutan-2-one or 2-bromo-1-cycloalkylethanone and the corresponding substituted 4-((3S,5R)-4-alkyl-3,5-dimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the synthesis of compound of Example 135.

Example 166

N-(3-(1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (16.76 mg, 7.36%). ^{1}H NMR (CD_3OD): 7.95 (s, 1H), 7.88 (d, J = 9.3 Hz, 1H), 7.54-7.47 (m,2H), 7.23 (s, 2H), 6.97-6.87 (m, 2H), 3.84 (d, J = 12.3 Hz, 2H), 2.99-2.81 (m, 2H), 2.76-2.69 (m, 2H), 2.62 (s,3H), 2.48 (s, 3H), 1.35 (d, J = 6.3 Hz, 6H). MS: m/z 438.2 $[M+H]^+$.

Example 167

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (1.04 mg, 1.42%). ^{1}H NMR (DMSO-d_6): 10.60 (s, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.68 (dd, J = 8.9 and 2.3 Hz, 1H), 7.56-7.49 (m, 1H), 7.41 (d, J = 8.7 Hz, 1H), 7.30-7.24 (m, 2H), 7.19-7.12 (m, 1H), 3.88-3.77 (m, 2H), 2.69-2.47 (m, 6H), 2.22-2.21 (m, 3H), 1.23-1.09 (m, 9H). MS: m/z 520.1 $[M+H]^+$.

Example 168

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Pale-yellow solid (2.48 mg, 3.79%). ^{1}H NMR (CD_3OD): 7.94 (d, J = 2.7 Hz, 1H), 7.84 (dd, J = 9.0 and 2.4 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.01-6.93 (m, 2H), 3.50 (d, J = 12.0 Hz, 2H), 2.90-2.81 (m, 2H), 2.78-2.67 (m, 4H), 2.58 (s, 3H), 2.38 (d, J = 3.0 Hz, 3H), 1.34-1.29 (m, 9H). MS: m/z 484.1 $[M+H]^+$.

Example 169

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide

Pale-yellow solid (1.72 mg, 2.54%). ^{1}H NMR (CD_3OD): 7.94 (d, J = 2.7 Hz, 1H), 7.84 (dd, J = 8.6 and 2.3 Hz, 1H), 7.52-7.50 (m, 2H), 7.07 (d, J = 2.1 Hz, 1H), 7.00 (dd, J = 8.7 and 2.1

Hz, 1H), 6.92 (s, 1H), 3.82 (d, *J* = 12.3 Hz, 2H), 3.18 (q, *J* = 7.2 Hz, 2H), 3.12-3.06 (m, 2H), 2.76-2.67 (m, 4H), 1.34-1.29 (m, 9H), 1.11 (t, *J* = 7.2 Hz, 3H). MS: m/z 500.1 $[M+H]^+$.

Example 170

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Yellow solid (9.12 mg, 3.5%). ^1H NMR (CD_3OD): 7.88 (d, *J* = 2.4 Hz, 1H), 7.81 (dd, *J* = 8.6 and 2.6 Hz, 1H), 7.49-7.43 (m, 2H), 6.88-6.84 (m, 3H), 3.73 (d, *J* = 9.9 Hz, 2H), 3.03-2.94 (m, 1H), 2.66-2.55 (m, 4H), 2.45 (s, 3H), 2.44 (s, 3H), 1.31 (d, *J* = 6.9 Hz, 6H), 1.25 (d, *J* = 5.7 Hz, 6H). MS: m/z 480.3 $[M+H]^+$.

Example 171

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Gray solid (19.99 mg, 9.9%). ^1H NMR (CD_3OD): 7.90 (d, *J* = 2.7 Hz, 1H), 7.81 (dd, *J* = 8.7 and 2.7 Hz, 1H), 7.59-7.51 (m, 2H), 7.32-7.26 (m, 2H), 6.92 (s, 1H), 3.90-3.80 (m, 2H), 3.05-3.29 (m, 1H), 2.80-2.70 (m, 4H), 2.54 (s, 3H), 1.35-1.31 (m, 12H). MS: m/z 534.4 $[M+H]^+$.

Example 172

N-(3-(5-propyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (4.43 mg, 3.1%). ^1H NMR (CD_3OD): 7.94 (d, *J* = 2.7 Hz, 1H), 7.84 (dd, *J* = 8.7 and 2.4 Hz, 1H), 7.54-7.48 (m, 2H), 6.96-6.94 (m, 2H), 6.92-6.85 (m, 1H), 3.93 (d, *J* = 12.6 Hz, 2H), 3.25-3.08 (m, 2H), 2.89-2.82 (m, 2H), 2.78 (s, 3H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.49 (s, 3H), 1.81-1.68 (m, 2H), 1.42 (d, *J* = 6.3 Hz, 6H), 1.03 (t, *J* = 7.5 Hz, 3H). MS: m/z 480.2 $[M+H]^+$.

Example 173

N-(3-(5-propyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (18.05 mg, 12.0%). ^{1}H NMR (CD_3OD): 7.94 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 9.0 and 2.4 Hz, 1H), 7.54-7.51 (m, 2H), 7.10 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.7 and 2.4 Hz, 1H), 6.95 (s, 1H), 3.87 (d, J = 12.3 Hz, 2H), 2.96-2.87 (m, 2H), 2.81-2.73 (m, 2H), 2.66 (t, J = 7.8 Hz, 2H), 2.62 (s, 3H), 1.80-1.68 (m, 2H), 1.35 (d, J = 6.3 Hz, 6H), 1.03 (t, J = 7.5 Hz, 3H). MS: m/z 500.2 $[M+H]^+$.

Example 174

N-(3-(5-tert-butyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (16.97 mg, 12.3%). ^{1}H NMR (CD_3OD): 7.91 (d, J = 2.7 Hz, 1H), 7.83 (dd, J = 9.0 and 2.7 Hz, 1H), 7.53-7.46 (m, 2H), 6.91-6.88 (m, 3H), 3.81 (d, J = 11.7 Hz, 2H), 2.85-2.76 (m, 2H), 2.74-2.64 (m, 2H), 2.57 (s, 3H), 2.48 (s, 3H), 1.38 (s, 9H), 1.32 (d, J = 6.0 Hz, 6H). MS: m/z 494.3 $[M+H]^+$.

Example 175

N-(3-(5-tert-butyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (18.02 mg, 12.5%). ^{1}H NMR (CD_3OD): 7.91 (d, J = 2.4 Hz, 1H), 7.84 (dd, J = 8.7 and 2.1 Hz, 1H), 7.53-7.49 (m, 2H), 7.05 (d, J = 2.1 Hz, 1H), 6.99 (dd, J = 8.7 and 2.4 Hz, 1H), 6.89 (s, 1H), 3.76 (d, J = 12.0 Hz, 2H), 2.71-2.63 (m, 2H), 2.60-2.50 (m, 2H), 2.44 (s, 3H), 1.38 (s, 9H), 1.27 (d, J = 6.0 Hz, 6H). MS: m/z 514.2 $[M+H]^+$.

Example 176

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Gray solid (9.74 mg, 3.9%). ^{1}H NMR (CD_3OD): 7.90 (s, 1H), 7.82 (dd, J = 8.4 and 1.5 Hz, 1H), 7.51-7.48 (m, 2H), 7.08 (d, J = 1.8 Hz, 1H), 7.01 (dd, J = 8.7 and 1.8 Hz, 1H), 6.86 (s, 1H), 3.85 (d, J = 12.9 Hz, 2H), 2.96-2.84 (m, 2H), 2.75 (t, J = 12.0 Hz, 2H), 2.61 (s, 3H), 1.96-1.85 (m, 1H), 1.33 (d, J = 6.0 Hz, 6H), 0.94-0.87 (m, 2H), 0.74-0.69 (m, 2H). MS: m/z 498.2 $[M+H]^+$.

Example 177

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (8.35 mg, 7.0%). ^{1}H NMR (CD_3OD): 7.91 (d, J = 2.7 Hz, 1H), 7.84 (dd, J = 8.7 and 2.7 Hz, 1H), 7.52-7.47 (m, 2H), 6.92-6.88 (m, 3H), 3.86 (d, J = 13.2 Hz, 2H), 3.02-2.91 (m, 2H), 2.80-2.72 (m, 2H), 2.66 (s, 3H), 2.48 (s, 3H), 1.97-1.87 (m, 1H), 1.37 (d, J = 6.3 Hz, 6H), 0.94-0.91 (m, 2H), 0.74-0.73 (m, 2H). MS: m/z 478.2 $[M+H]^+$.

Example 178

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (16.23 mg, 8.0%). ^{1}H NMR (CD_3OD): 7.87 (d, J = 2.4 Hz, 1H), 7.79 (dd, J = 9.0 and 2.7 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.32-7.25 (m, 2H), 6.86 (s, 1H), 3.86 (d, J = 11.4 Hz, 2H), 2.86-2.72 (m, 4H), 2.57 (s, 3H), 1.95-1.86 (m, 1H), 1.33 (d, J = 6.0 Hz, 6H), 0.94-0.88 (m, 2H), 0.74-0.69 (m, 2H). MS: m/z 532.2 $[M+H]^+$.

Example 179

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (17.05 mg, 9.0%). ^{1}H NMR (CD_3OD): 7.89 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 8.7 and 2.4 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 6.98-6.93 (m, 1H), 6.85 (s, 1H), 3.47 (d, J = 11.7 Hz, 2H), 2.88-2.77 (m, 2H), 2.73-2.66 (m, 2H), 2.54 (s, 3H), 2.35 (d, J = 6.3 Hz, 3H), 1.95-1.86 (m, 1H), 1.26 (d, J = 6.0 z, 6H), 0.93-0.87 (m, 1H), 0.73-0.68 (m, 2H). MS: m/z 496.2 $[M+H]^+$.

Example 180

N-(3-(5-cyclobutyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (35.02 mg, 13.7%). ^{1}H NMR (CD_3OD): 7.91 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 8.7 and 2.4 Hz, 1H), 7.51-7.48 (m, 2H), 7.07 (d, J = 2.1 Hz, 1H), 6.99 (dd, J = 8.7 and 2.4 Hz, 1H), 6.96 (s, 1H), 3.82 (d, J = 11.4 Hz, 2H), 3.63-3.52 (m, 1H), 2.85-2.69 (m, 4H), 2.56 (s,

3H), 2.42-2.32 (m, 2H), 2.30-2.17 (m, 2H), 2.12-1.87 (m, 2H), 1.31 (d, *J* = 5.7 Hz, 6H). MS: m/z 512.2 $[M+H]^+$.

Example 181

N-(3-(5-cyclobutyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (3.11 mg, 1.26%). ^{1}H NMR (CD_3OD): 7.89 (d, *J* = 2.7 Hz, 1H), 7.81 (dd, *J* = 8.7 and 2.4 Hz, 1H), 7.49-7.43 (m, 2H), 6.94 (s,1H), 6.86-6.81 (m, 2H), 3.78-3.69 (m, 2H), 3.63-3.51 (m, 1H), 2.66-2.56 (m, 4H), 2.45 (s, 6H), 2.40-2.29 (m, 2H), 2.26-2.17 (m, 2H), 2.12-1.86 (m, 2H), 1.25 (d, *J* = 5.4 Hz, 6H). MS: m/z 492.3 $[M+H]^+$.

Example 182

N-(3-(5-cyclopentyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (13.03 mg, 8.2%). ^{1}H NMR (CD_3OD): 7.91 (d, *J* =2.4 Hz, 1H), 7.82 (dd, *J* = 9.0 and 2.4 Hz, 1H), 7.51-7.48 (m, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.99 (dd, *J* = 8.7 and 2.4 Hz, 1H), 6.91 (s, 1H), 3.84-3.75 (m, 2H), 3.18-3.05 (m, 1H), 2.75-2.66 (m, 4H), 2.51 (s, 3H), 2.12-2.06 (m, 2H), 1.85-1.69 (m, 6H), 1.29 (d, *J* = 5.7 Hz, 6H). MS: m/z 526.2 $[M+H]^+$.

Example 183

N-(3-(5-cyclopentyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Pink solid (6.40 mg, 3.7%). ^{1}H NMR (CD_3OD): 7.90 (d, *J* = 2.7 Hz, 1H), 7.81 (dd, *J* = 9.0 and 2.4 Hz, 1H), 7.50-7.44 (m, 2H), 6.91-6.86 (m,3H), 3.83 (d, *J* = 12.3 Hz, 2H), 3.16-3.06 (m, 1H), 2.99-2.85 (m, 2H), 2.77-2.69 (m, 2H), 2.63 (s, 3H), 2.45 (s, 3H), 2.13-2.05 (m, 2H), 1.84-1.79 (m, 2H), 1.76-1.63 (m,4H), 1.34 (d, *J* = 6.3 Hz, 6H). MS: m/z 506.3 $[M+H]^+$.

Example 184

N-(3-(5-cyclohexyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Brown solid (60.96 mg, 25.6%). ^{1}H NMR (CD_3OD): 7.95 (d, J = 2.7 Hz, 1H), 7.84 (dd, J = 8.7 and 2.1 Hz, 1H), 7.54-7.51 (m, 2H), 7.12 (d, J = 1.8 Hz, 1H), 7.04 (dd, J = 8.7 and 2.1 Hz, 1H), 6.94 (s, 1H), 3.91 (d, J = 12.6 Hz, 2H), 3.10-3.01 (m, 2H), 2.90-2.75 (m, 2H), 2.69 (s, 3H), 2.65-2.61 (m, 1H), 2.16-2.00 (m, 2H), 1.93-1.76 (m, 3H), 1.55-1.44 (m, 5H), 1.38 (d, J = 6.0 Hz, 6H). MS: m/z 540.3 $[M+H]^+$.

Example 185

N-(3-(5-cyclohexyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Pink solid (4.32 mg, 1.9%). ^{1}H NMR (CD_3OD): 7.88 (d, J = 2.7 Hz, 1H), 7.81 (dd, J = 8.7 and 2.4 Hz, 1H), 7.49-7.43 (m, 2H), 6.88-6.85 (m, 3H), 3.78 (d, J = 11.7 Hz, 2H), 2.78-2.62 (m, 5H), 2.53 (s, 3H), 2.45 (s, 3H), 2.08-1.99 (m, 2H), 1.89-1.80 (m, 2H), 1.78-1.73 (m, 1H), 1.55-1.35 (m, 5H), 1.29 (d, J = 6.0 Hz, 6H). MS: m/z 520.3 $[M+H]^+$.

The following compounds were prepared from 2-chloro-5-nitrobenzimidamide hydrochloride, the corresponding 2-bromopropanal or 2-bromobutanal or 2-bromo-3-methylbutanal or 2-bromo-1-cyclopropylthanone and substituted 4-((3S,5R)-4-alkyl-3,5-dimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the syntheses of compounds of Examples 135 and 131.

Example 186

N-(3-(5-methyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

Whtie solid (1.66 mg, 0.7%). ^{1}H NMR (CD_3OD): 7.89 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 8.9 and 2.6 Hz, 1H), 7.49-7.43 (m, 2H), 6.88-6.84 (m, 3H), 3.73 (d, J = 9.6 Hz, 2H), 2.66-2.53 (m, 4H), 2.45-2.44 (m, 6H), 2.29 (s, 3H), 1.25 (d, J = 5.7 Hz, 6H). MS: m/z 452.2 $[M+H]^+$.

Example 187

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

Off-white solid (0.9 mg, 0.4%). ^{1}H NMR (CD_3OD): 7.90 (d, J = 2.7 Hz, 1H), 7.82 (dd, J = 8.7 and 2.7 Hz, 1H), 7.50-7.44 (m, 2H), 6.93-6.86 (m, 3H), 3.80 (d, J = 12.0 Hz, 2H), 2.84-2.75

(m, 2H), 2.72-2.64 (m, 4H), 2.56 (s, 3H), 2.46 (s, 3H), 1.32-1.27 (m, 9H). MS: m/z 466.2 $[M+H]^+$.

Example 188

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

Off-white solid (9.98 mg, 4.4%). ^1H NMR (CD_3OD): 7.93 (s, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.53-7.50 (m, 2H), 7.08 (s, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.93 (s, 1H), 3.86-3.76 (m, 2H), 2.76-2.67 (m, 6H), 2.52 (s, 3H), 1.34-1.24 (m, 9H). MS: m/z 486.3 $[M+H]^+$.

Example 189

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

Gray solid (14.63 mg, 6.7%). ^1H NMR (CD_3OD): 8.29 (s, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.54 (d, J = 6.9 Hz, 1H), 7.47 (s, 1H), 7.18 (s, 1H), 7.09 (d, J = 6.3 Hz, 1H), 4.07 (d, J = 13.2 Hz, 2H), 3.57-3.42 (m, 2H), 3.20-3.06 (m, 3H), 2.99 (s, 3H), 1.52 (s, 6H), 1.40 (d, J = 6.9 Hz, 6H). MS: m/z 500.3 $[M+H]^+$.

Example 190

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

Orange red solid (23.03 mg, 10.6%). ^1H NMR (CD_3OD): 7.94 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 8.7 and 2.7 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.00 (t, J = 8.4 Hz, 1H), 6.94 (s, 1H), 3.60 (d, J = 12.9 Hz, 2H), 3.29-3.23 (m, 2H), 3.05-2.96 (m, 1H), 2.92-2.84 (m, 2H), 2.81 (s, 3H), 2.37 (d, J = 2.7 Hz, 3H), 1.40 (d, J = 6.6 Hz, 6H), 1.32 (d, J = 6.9 Hz, 6H). MS: m/z 498.3 $[M+H]^+$.

Example 191

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

Off-white solid (7.79 mg, 7.8%). ^{1}H NMR (CD_3OD): 7.92 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 9.0 and 2.4 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.37 (d, J = 12.3 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.91 (s, 1H), 3.56 (d, J = 12.3 Hz, 2H), 3.04-2.89 (m, 3H), 2.83-2.75 (m, 2H), 2.62 (s, 3H), 1.33-1.30 (m,12H). MS: m/z 518.2 $[M+H]^+$.

Example 192

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide dihydrochloride

White solid (12.07 mg, 7.1%). ^{1}H NMR (CD_3OD): 7.94 (d, J = 2.4 Hz, 1H), 7.84 (dd, J = 8.7 and 2.4 Hz, 1H), 7.53-7.50 (m, 2H), 7.11 (d, J = 2.1 Hz, 1H), 7.03 (dd, J = 8.7 and 2.1 Hz, 1H), 6.92 (s, 1H), 3.91 (d, J = 12.0 Hz, 2H), 3.34-3.25 (m, 4H), 3.03-2.96 (m, 1H), 2.86-2.78 (m, 2H), 1.38-1.33 (m, 12H), 1.19 (t, J = 7.2 Hz, 3H). MS: m/z 514.2 $[M+H]^+$.

Example 193

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride

White solid (0.86 mg, 0.3%). ^{1}H NMR (CD_3OD): 7.92 (d, J = 2.7 Hz, 1H), 7.83 (dd, J = 8.7 and 2.7 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.37 (d, J =12.9 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 6.87 (s, 1H), 3.55-3.45 (m, 2H), 2.77-2.71 (m, 4H), 2.50 (s, 3H), 1.95-1.88 (m, 1H), 1.26 (d, J = 5.4 Hz, 6H), 0.95-0.89 (m, 2H), 0.76-0.71 (m, 2H). MS: m/z 516.1 $[M+H]^+$.

Example 194

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide dihydrochloride

Off-white solid (2.63 mg, 3.3%). ^{1}H NMR (CD_3OD): 7.92 (s, 1H), 7.84 (d, J = 6.6 Hz, 1H), 7.53-7.51 (m, 2H), 7.12 (s, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.88 (s, 1H), 3.92 (d, J = 12.6 Hz, 2H), 3.29-3.20 (m, 4H), 2.83 (t, J = 11.7 Hz, 2H), 2.01-1.87 (m, 1H), 1.37 (d, J = 5.7 Hz, 6H), 1.20 (t, J = 6.9 Hz, 3H), 0.98-0.86 (m, 2H), 0.79-0.67 (m, 2H). MS: m/z 512.1 $[M+H]^+$.

Example 195

N-(3-(3H-imidazo[4,5-b]pyridin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

a) N-(3-aminopyridin-2-yl)-2-chloro-5-nitrobenzamide. To a stirred solution of pyridine-2,3-diamine (0.90 g, 8.28 mmol), 2-chloro-5-nitrobenzoic acid (1.67 g, 8.28 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU, 3.14 g, 8.28 mmol) in CH_3CN (30 mL) was added dropwise triethylamine (3.44 mL, 24.84 mmol) at 0°C, then was stirred at room temperature overnight. The mixture was concentrated. The residue was used for the next step without further purification. MS: m/z 293.1 $[M+H]^+$.

b) 3-(3H-imidazo[4,5-b]pyridin-2-yl)-4-chloroaniline. The title compound was prepared from N-(3-aminopyridin-2-yl)-2-chloro-5-nitrobenzamide using a procedure similar to those described for the syntheses of compounds of Examples 50b and 24. Yellow solid. MS: m/z 245.1 $[M+H]^+$.

c) N-(3-(3H-imidazo[4,5-b]pyridin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide. The title compound was prepared from 3-(3H-imidazo[4,5-b]pyridin-2-yl)-4-chloroaniline and 2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the synthesis of compound of Example 83. Light-yellow solid (11.82 mg, 4.10%). ^1H NMR (CD_3OD): 8.44 (d, J = 4.8 Hz, 1H), 8.20 (s, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 8.1 and 4.8 Hz, 1H), 7.11 (d, J = 2.1 Hz, 1H), 7.02 (dd, J = 8.7 and 2.1 Hz, 1H), 3.93 (d, J = 12.9 Hz, 2H), 3.28-3.15 (m, 2H), 2.93-2.85 (m, 2H), 2.79 (s, 3H), 1.41 (d, J = 6.3 Hz, 3H). MS: m/z 509.2 $[M+H]^+$.

The following compounds were prepared from pyridine-1,4-diamine, 2-chloro-5-nitrobenzoic acid, and the corresponding 2-substituted-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the synthesis of compound of Example 195.

Example 196

N-(3-(3H-imidazo[4,5-c]pyridin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (35 mg, 15.3%). ^1H NMR (CD_3OD): 8.99 (s, 1H), 8.40 (d, J = 6.0 Hz, 1H), 8.52 (d, J = 2.4 Hz, 1H), 7.95 (dd, J = 8.9 and 2.6 Hz, 1H), 7.74 (d, J = 5.4 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 5.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.9 and 2.3 Hz,

1H), 3.86 (d, J = 11.7 Hz, 2H), 2.90-2.73 (m, 4H), 2.60 (s, 3H), 1.34 (d, J = 6.0 Hz, 6H). MS: m/z 509.2 $[M+H]^+$.

Example 197

N-(3-(3H-imidazo[4,5-c]pyridin-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (35 mg, 15.3%). ^1H NMR (CD_3OD): 8.99 (s, 1H), 8.40 (d, J =5.7 Hz, 1H), 8.25 (d, J = 2.4 Hz, 1H), 7.95 (dd, J = 8.7 and 2.7 Hz, 1H), 7.74 (d, J = 5.7 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 6.95-6.92 (m, 2H), 3.92 (d, J = 13.5 Hz, 2H), 3.18-3.11 (m, 2H), 2.88-2.79 (m, 2H), 2.77 (s, 3H), 2.50 (s, 3H), 1.42 (d, J = 6.0 Hz, 6H). MS: m/z 489.3 $[M+H]^+$.

Example 198

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

a) N-(4-aminothiophen-3-yl)-2-chloro-5-nitrobenzamide. A mixture of thiophene-3,4-diamine (0.90 g, 7.89 mmol), 2-chloro-5-nitrobenzoic acid (1.32 g, 6.57 mmol) and BOP (3.49 g, 7.89 mmol) in triethylamine (1.8 mL, 13.1 mmol) and MeCN (40 mL) was stirred at room temperature overnight under N_2. The mixture was concentrated. The residue was purified by the flash column chromatography (EA/PE) to give the title compound as a yellow solid (1.16 g, 49.5%). MS: m/z 298.0 $[M+H]^+$.

b) 2-(2-Chloro-5-nitrophenyl)-1H-thieno[3,4-d]imidazole. The title compound was prepared from N-(4-aminothiophen-3-yl)-2-chloro-5-nitrobenzamide using a procedure similar to those described for the synthesis of compound of Example 52b. Black solid (1.0 g, 91.7%). MS: m/z 280.0 $[M+H]^+$.

c) 3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chloroaniline. The title compound was prepared from 2-(2-chloro-5-nitrophenyl)-1H-thieno[3,4-d]imidazole using a procedure similar to those described for the synthesis of compound of Example 24. Claybank solid (0.40 g, 44.7%). MS: m/z 250.0 $[M+H]^+$.

d) N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide. The title compound was prepared from 3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chloroaniline and 2-methyl-4-((3S,5R)-3,4,5-

trimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the synthesis of compound of Example 83. Pale-yellow solid (2.0 mg, 2.5%). ^{1}H NMR (CD_3OD): 8.08 (d, J = 2.4 Hz, 1H), 7.92 (dd, J = 8.7 and 1.8 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.07-6.94 (m, 2H), 6.91-6.89 (m, 2H), 3.86 (d, J = 12.9 Hz, 2H), 3.04-2.92 (m, 2H), 2.79-2.75 (m, 2H), 2.67 (s, 3H), 2.47 (s, 3H), 1.36 (d, J = 6.3 Hz, 3H). MS: m/z 494.2 $[M+H]^+$.

The following compounds were prepared from 3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chloroaniline (Example 198c) and the corresponding substituted 4-((3S,5R)-4-alkyl-3,5-dimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the synthesis of compound of Example 83.

Example 199

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Pale-yellow solid (1.88 mg, 3.5%). ^{1}H NMR (CD_3OD): 8.20 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.14-7.06 (m, 4H), 3.84 (d, J = 11.7 Hz, 2H), 2.80-2.73 (m, 2H), 2.67-2.59 (m, 2H), 2.53 (s, 3H), 1.35 (d, J = 6.0 Hz, 6H). MS: m/z 514.2 $[M+H]^+$.

Example 200

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Pale-yellow solid (5.99 mg, 6.8%). ^{1}H NMR (CD_3OD): 8.05 (d, J = 2.7 Hz, 1H), 7.89 (dd, J = 9.0 and 2.7 Hz, 1H), 7.60-7.55 (m, 2H), 7.30-7.24 (m, 2H), 7.08-6.92 (m, 2H), 3.85-3.77 (m, 2H), 2.75-2.61 (m, 4H), 2.48 (s, 3H), 1.28 (d, J = 5.7 Hz, 6H). MS: m/z 548.2 $[M+H]^+$.

Example 201

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Brown solid (2.55 mg, 3.13%). ^{1}H NMR (CD_3OD): 8.10 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 8.6 and 2.6 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.33 (d, J = 8.7 Hz, 1H), 7.01-6.95 (m, 3H), 3.47

(d, J = 9.9 Hz, 2H), 2.72-2.65 (m, 4H), 2.51 (s, 3H), 2.39 (d, J = 2.7 Hz, 3H), 1.26 (d, J = 5.4 Hz, 6H). MS: m/z 512.1 $[M+H]^+$.

Example 202

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Pale-yellow solid (1.5 mg, 2.3%). ^{1}H NMR (CD_3OD): 8.09 (d, J = 2.4 Hz, 1H), 7.91 (dd, J = 8.7 and 2.7 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.36 (d, J = 12.6 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.05-6.93 (m, 2H), 3.46 (d, J = 10.5 Hz, 2H), 2.72-2.58 (m, 4H), 2.43 (s, 3H), 1.22 (d, J = 5.7 Hz, 6H). MS: m/z 532.0 $[M+H]^+$.

Example 203

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide

Pale-yellow solid (17.92 mg, 17.0 %). ^{1}H NMR (CD_3OD): 8.11 (d, J = 2.4 Hz, 1H), 7.92 (dd, J = 8.9 and 2.3 Hz, 1H), 7.58 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.03-7.00 (m, 3H), 3.89 (d, J = 12.3 Hz, 2H), 3.38-3.26 (m, 4H), 2.91-2.77 (m, 2H), 1.35 (d, J = 6.3 Hz, 6H), 1.18 (t, J = 7.4 Hz, 3H). MS: m/z 528.0 $[M+H]^+$.

The following compounds were prepared from the corresponding 3-substituted-4-chloroanline and 2-substituted-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzoic acid using a procedure similar to those described for the synthesis of compound of Example 83.

Example 204

N-(3-(quinoxalin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Pale-yellow solid (26.2 mg, 18.6%). ^{1}H NMR (CD_3OD): 9.22 (s, 1H), 8.22-8.13 (m, 3H), 7.97-7.89 (m, 3H), 7.63 (d, J = 8.7 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 2.1 Hz, 1H), 7.00 (dd, J = 8.7 and 2.4 Hz, 1H), 3.80 (d, J = 9.9 Hz, 2H), 2.75-2.62 (m, 4H), 2.50 (s, 3H), 1.29 (d, J = 5.7 Hz, 6H). MS: m/z 520.2 $[M+H]^+$.

Example 205

N-(3-(imidazo[2,1-b]thiazol-6-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (19.3 mg, 18.8%). ^{1}H NMR (CD_3OD): 8.32 (s, 1H), 8.14 (d, J = 2.4 Hz, 1H), 7.84-7.79 (m, 2H), 7.54-7.48 (m, 2H), 7.20 (d, J = 4.5 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 7.01 (dd, J = 8.7 and 2.7 Hz, 1H), 3.86-3.77 (m,2H), 2.80-2.68 (m, 4H), 2.54 (s, 3H), 1.31 (d, J = 5.4 Hz, 6H). MS: m/z 514.1 $[M+H]^+$.

Example 206

N-(3-(benzo[d]oxazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (25.90 mg, 26.5%). ^{1}H NMR (CD_3OD): 8.54 (d, J = 2.7 Hz, 1H), 7.92 (dd, J = 8.7 and 2.7 Hz, 1H), 7.86-7.83 (m, 1H), 7.77-7.74 (m,1H), 7.64 (d, J = 8.7 Hz, 1H), 7.53-7.48 (m, 3H), 6.94-6.91 (m, 2H), 3.87 (d, J = 13.2 Hz, 2H), 2.95-2.94 (m, 2H), 2.79-2.71 (m, 2H), 2.66 (s, 3H), 2.51 (s, 3H), 1.37 (d, J = 6.3 Hz, 3H). MS: m/z 489.2 $[M+H]^+$.

Example 207

N-(3-(benzo[d]thiazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

White solid (23.31 mg, 29.6%). ^{1}H NMR (CD_3OD): 8.49 (d, J = 2.1 Hz, 1H), 8.11-8.07 (m, 2H), 7.89 (dd, J = 8.7 and 2.4 Hz, 1H), 7.62-7.49 (m, 4H), 7.07 (d, J = 2.4 Hz, 1H), 7.00 (dd, J = 8.7 and 2.4 Hz, 1H), 3.82 (d, J = 10.5 Hz, 2H), 2.75-2.68 (m, 4H), 2.55 (s, 3H), 1.30 (d, J = 5.7 Hz, 6H). MS: m/z 525.1 $[M+H]^+$.

Example 208

N-(3-(pyridin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Off-white solid (75.13 mg, 29%). ^{1}H NMR (CD_3OD): 8.64 (d, J = 4.8 Hz, 1H), 7.99-7.93 (m, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.79 (dd, J = 8.7 and 2.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.54-7.45 (m, 3H), 7.16 (d, J = 2.1 Hz, 1H), 7.06 (dd, J = 8.6 and 2.2 Hz, 1H), 4.03 (d, J = 13.2 Hz, 2H), 3.56-3.40 (m, 2H), 3.01-2.97 (m, 2H), 2.94 (s, 3H), 1.47 (d, J = 6.6 Hz, 6H). MS: m/z 469.1 $[M+H]^+$.

Example 209

N-(3-(pyrimidin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide

Pale-yellow solid (54.07 mg, 20.9%). ^{1}H NMR (CD_3OD): 8.95 (d, J = 5.1 Hz, 2H), 8.06 (d, J = 2.4 Hz, 1H), 7.84 (dd, J = 8.7 and 2.4 Hz, 1H), 7.57-7.49 (m, 3H), 7.05 (d, J = 2.4 Hz, 1H), 6.98 (dd, J = 8.7 and 2.4 Hz, 1H), 3.74 (d, J = 12.0 Hz, 2H), 2.70-2.62 (m, 2H), 2.56-2.45 (m, 2H), 2.41 (s, 3H), 1.25 (d, J = 6.0 Hz, 6H). MS: m/z 470.1 $[M+H]^+$.

Example 210

The application of SAG to induce pluripotent mesenchymal mouse embryonic cell C3H/10T1/2 to differentiatate into osteoblastic cells for the determination of the inhibitory acitivity of N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide and analogs on hedgehog signaling pathway

The pluripotent mesenchymal mouse embryonic cellline C3H10T1/2 (C3H/10T1/2, Clone 8 from Chinese Cellbank, Shanghai) can be induced to differentiate into osteoblastic cells with stimulation of the hedgehog pathway. The intracellular alkaline phosphatase activity is a reliable indication of the differentiation process. Therefore this enzymatic activity can be used to monitor the activity of hedgehog pathway inhibitors.

The C3H10T1/2 cells were grown in DMEM medium supplemented with 10% fetal bovine serum (FBS, Hyclone) at 37°C with 5% CO_2. 10000 cells were sown to each well of a 96-well microplate a day before the experiment and grown overnight. At the day of experiment, the inducing medium and inhibitor solutions were prepared as follows: the reference compound and testing compounds were serially diluted 1 to 3 and 1 to 10 in DMSO to seven concentrations with the eighth concentration being DMSO. A 10-fold dilution was prepared by mixing 10 μL of the DMSO dilution with 90 μL of fresh growing medium. The inducing medium was prepared by diluting 1 mM DMSO stock solution of hedgehog pathway activator SAG (Yang, H. et al. J. Biol. Chem. **2009**, 284, 20876-84) 1000-fold into fresh growth medium (DMEM with 10% FBS) with the final SAG concentration being 1 μM and DMSO 0.1%. Pre-sown cells were taken out from incubator and the medium was removed. To each well, 180 μL inducing medium was added and followed immediately with 20 μL of testing or reference compound dilutions. The testing compound concentrations are between 10 μM and 1 nM. The cells were then return to CO_2 incubator to grow additional 5 days at 37°C.

After incubating for 5 days, the cells were taken out and intracellular alkaline phosphatase activity was tested. The alkaline phosphatase activity was measured as follows:

1) Preparation of substrate solution:

Solution A: A 0.5 mM $MgCl_2$ (Sigma Prod. No. M-0250) solution was prepared.

Solution B: A 1 M diethanol amine solution was prepared as follows: weigh out 10.51 g diethanol amine (Sigma Prod. No. D-8885) and dissolved in 80 mL double distilled water. After the pH value was adjusted to 9.8 with 5 M HCl at 37°C, the total volume was adjusted to 100 mL.

Solution C: Weigh out 3.71 mg p-NPP (molecular weight 371.14) and dissolved in double distilled water. After it is completely dissolved the total volume was adjusted to 10 mL with the final concentration being 1 mM.

Substrate reaction medium: To 10 mL of solution B, 250 μL of solution A and 200 μL of solution C were added, and mixed well.

2) The measurement of intracellular alkaline phosphatase activity:

After taking out the cells from the incubator, the cell culture medium was removed and cells were washed twice with PBS. 20 μL of lysis solution (0.2% Triton solution) was added to each well. After being shaken for 30 min at room temperature, each well of cells received 80 μL of substrate reaction medium. The microplate was placed immediately into a VariSkan Flashplate reader and absorbance at OD_{405} was read as background reading. The plate was replaced back to cell culture incubator at 37°C for additional 30 min and the absorbance was read again using VariSkan Flash plate reader at OD_{405}.

Data analysis:

The data were analyzed by subtracting the background reading from the reading at 30 min, and the obtained numbers were plotted and analyzed with Prism 5 software (GraphPad). The phosphatase activity (calculated OD_{405}) was plotted against the log concentration of testing compound, and the obtained plot was fitted with non-linear curve fitting equation to calculate IC_{50} values. The curve fitting equation is Y = Bottom + (Top-Bottom)/(1+10^((X-LogIC_{50}))). X is the logarithm of concentration. Y is the measure of alkaline phosphatase activity (OD_{405}).

The calculated IC_{50} value is a measurement of the inhibitory activity of compound to Hh pathway. The data are listed in Table 1.

Table 1 IC_{50} values of compounds that inhibit Hh pathway

Example	2	3	4	5	6	7	8
IC_{50} (nM)	74	111	86	26	19	25	86
Example	9	10	11	12	13	14	15

IC_{50} (nM)	156	74	31	153	86	80	>10000
Example	16	17	18	19	20	21	22
IC_{50} (nM)	>10000	81	60	161	>10000	30	124
Example	23	24	25	26	27	28	29
IC_{50} (nM)	163	255	191	>10000	151	228	>10000
Example	30	31	32	33	34	35	36
IC_{50} (nM)	88	229	53	83	263	56	362
Example	37	38	39	40	41	42	43
IC_{50} (nM)	167	28	40	27	99	230	16
Example	44	45	46	47	48	49	50
IC_{50} (nM)	139	284	89	102	>10000	261	125
Example	51	52	53	54	55	56	57
IC_{50} (nM)	>10000	740	>10000	>10000	>10000	2369	>10000
Example	58	59	60	61	62	63	64
IC_{50} (nM)	>10000	232	141	>10000	>10000	1345	636
Example	65	66	67	68	69	70	71
IC_{50} (nM)	522	24	>10000	69	33	34	181
Example	72	73	74	75	76	77	78
IC_{50} (nM)	>10000	163	191	17	>10000	139	166
Example	79	80	81	82	83	84	85
IC_{50} (nM)	100	28	6.4	12	43	44	49
Example	86	87	88	89	90	91	92
IC_{50} (nM)	40	21	119	381	461	52	312
Example	93	94	95	96	97	98	99
IC_{50} (nM)	32	16	111	106	32	24	81
Example	100	101	102	103	104	105	106
IC_{50} (nM)	33	46	47	449	58	58	58
Example	107	108	109	110	111	112	113
IC_{50} (nM)	47	698	96	28	68	83	1042
Example	114	115	116	117	118	119	120
IC_{50} (nM)	77	145	68	27	260	39	57
Example	121	122	123	124	125	126	127
IC_{50} (nM)	29	29	53	38	23	81	34
Example	128	129	130	131	132	133	134

IC_{50} (nM)	60	82	178	81	28	54	>10000
Example	135	136	137	138	139	140	141
IC_{50} (nM)	67	9.2	51	39	44	4.8	9.4
Example	143	144	145	146	147	148	149
IC_{50} (nM)	108	17	3.3	25	>10000	15	15
Example	153	154	155	156	157	158	159
IC_{50} (nM)	280	178	13	7.0	10	8.2	10
Example	160	166	170	172	173	174	175
IC_{50} (nM)	66	347	30	127	165	91	176
Example	176	177	178	179	180	181	182
IC_{50} (nM)	7.2	23	26	21	47	70	100
Example	183	184	185	189	195	196	197
IC_{50} (nM)	90	184	169	30	258	157	306
Example	198	199	204	205	206	207	208
IC_{50} (nM)	26	11	201	250	244	158	52
Example	209	GDC-0449					
IC_{50} (nM)	1800	108					

Therefore, compounds of the present invention, including N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide (Example 32) and analogs, show strong inhibitory effects on hedgehog pathway.

Example 211

The application of SHH to induce pluripotent mesenchymal mouse embryonic cell C3H10T1/2 to differentiatate into osteoblastic cells for the determination of the inhibitory acitivity of N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide and analogs on hedgehog signaling pathway

The C3H10T1/2 cells were grown in DMEM medium supplemented with 10% fetal bovine serum (FBS, Hyclone) at 37°C with 5% CO_2. 10000 cells were sown to each well of a 96-well microplate a day before the experiment and grown overnight. At the day of experiment, the inducing medium and inhibitor solutions were prepared as follows: the conditioned medium containing recombinant mouse SHH-N (N-terminal 1-198 aa) was taken out of −80°C freezer, thawed and diluted to the concentration of 10 nM in complete growth medium. The reference

compound and testing compounds were serially diluted 1 to 3 and 1 to 10 in DMSO to seven concentrations with the eighth concentration being DMSO. A 10-fold dilution was prepared by mixing 10 μL of the DMSO dilutions with 90 μL of fresh growing medium. Pre-sown cells were taken out from incubator and the medium was removed. To each well, 180 μL of inducing medium containing 10 nM of SHH-N was added and followed immediately with 20 μL of 10 x testing or reference compound dilutions. The testing compound concentrations are between 10 μM and 10 nM. The cells were then returned to CO_2 incubator to grow additional 5 days at 37°C.

After incubating for 5 days, the cells were taken out and intracellular alkaline phosphatase activity was tested. The alkaline phosphatase activity was measured as follows:

3) Preparation of substrate solution:

Solution A: A 0.5 mM $MgCl_2$ (Sigma Prod. No. M-0250) solution was prepared.

Solution B: A 1 M diethanol amine solution was prepared as follows: weigh out 10.51 g diethanol amine (Sigma Prod. No. D-8885) and dissolved in 80 mL double distilled water. After the pH value was adjusted to 9.8 with 5 M HCl at 37°C, the total volume was adjusted to 100 mL.

Solution C: weigh out 3.71 mg p-NPP (molecular weight 371.14) and dissolved in double distilled water. After it is completely dissolved the total volume was adjusted to 10 mL with the final concentration being 1 mM.

Substrate reaction medium: to 10 mL of solution B, 250 μL of solution A and 200 μL of solution C were added, and mixed well.

4) The measurement of intracellular alkaline phosphatase activity:

After taking out the cells from the incubator, the cell culture medium was removed and cells were washed twice with PBS. 20 μL of lysis solution (0.2% Triton solution) was added to each well. After being shaken for 30 min at room temperature, each well of cells received 80 μL of substrate reaction medium. The microplate was placed immediately into a VariSkan Flashplate reader and absorbance at OD_{405} was read as background reading. The plate was replaced back to cell culture incubator at 37°C for additional 30 min and the absorbance was read again using VariSkan Flash plate reader at OD_{405}.

Data analysis:

The data were analyzed by subtracting the background reading from the reading at 30 min, and the obtained numbers were plotted and analyzed with Prism 5 software (GraphPad). The phosphatase activity (calculated OD_{405}) was plotted against the log concentration of testing compound, and the obtained plot was fitted with non-linear curve fitting equation to calculate IC_{50} values. The curve fitting equation is Y = Bottom + (Top − Bottom)/(1 + 10^(X −

$LogIC_{50}$)). X is the logarithm of concentration. Y is the measure of alkaline phosphatase activity (OD_{405}).

The calculated IC_{50} value is a measurement of the inhibitory activity of compound to Hh pathway. These data are listed in Table 2.

Table 2 IC_{50} values of compounds that inhibit Hh pathway

Example	2	3	4	5	6	7	8
IC_{50} (nM)	14	39	7.8	5.9	2.6	3.5	3.6
Example	9	10	11	12	13	14	15
IC_{50} (nM)	43	6.3	1.7	18	14.6	5.5	40
Example	16	17	18	19	20	21	22
IC_{50} (nM)	>10000	15	3.7	23	59	2.3	15
Example	23	24	25	26	27	28	29
IC_{50} (nM)	24	62	5.5	>10000	57	59	72
Example	30	31	32	33	34	35	36
IC_{50} (nM)	31	44	7.9	22	162	10	95
Example	37	38	39	40	41	42	43
IC_{50} (nM)	52	4.9	15	13	32	337	8.5
Example	44	45	46	47	48	49	50
IC_{50} (nM)	18	20	5.1	3.3	>10000	2.4	7.9
Example	51	52	53	54	55	56	57
IC_{50} (nM)	77	465	>10000	>10000	>10000	189	>10000
Example	58	59	60	61	62	63	64
IC_{50} (nM)	>10000	7.5	18	>10000	409	39	1131
Example	65	66	67	68	69	70	71
IC_{50} (nM)	501	7.1	68	4.0	0.55	2.8	3.6
Example	72	73	74	75	76	77	78
IC_{50} (nM)	467	134	4.5	2.9	>10000	1.9	4.8
Example	79	80	81	82	83	84	85
IC_{50} (nM)	2.7	2.7	0.16	0.21	9.2	7.1	5.6
Example	86	87	88	89	90	91	92
IC_{50} (nM)	1.7	1.7	11	55	35	6.8	45
Example	93	94	95	96	97	98	99
IC_{50} (nM)	0.69	0.81	13	5.0	0.59	1.4	2.6

Example	100	101	102	103	104	105	106
IC_{50} (nM)	2.3	0.64	3.9	40	0.61	2.2	19
Example	107	108	109	110	111	112	113
IC_{50} (nM)	2.3	76	6.4	0.66	0.94	8.6	>10000
Example	114	115	116	117	118	119	120
IC_{50} (nM)	9.0	31	2.1	4.6	13	0.76	7.4
Example	121	122	123	124	125	126	127
IC_{50} (nM)	23	0.52	0.97	0.49	1.2	25	1.1
Example	128	129	130	131	132	133	134
IC_{50} (nM)	5.3	7.5	18	7.2	0.53	6.3	>10000
Example	135	136	137	138	139	140	141
IC_{50} (nM)	1.5	4.0	15	1.6	1.8	0.20	0.24
Example	143	144	145	146	147	148	149
IC_{50} (nM)	15	0.82	0.93	0.49	>10000	0.33	0.27
Example	153	154	155	156	157	158	159
IC_{50} (nM)	34	22	0.11	0.20	0.15	0.42	0.36
Example	160	166	170	172	173	174	175
IC_{50} (nM)	>10000	47	0.22	45	60	11	6.1
Example	176	177	178	179	180	181	182
IC_{50} (nM)	3.9	1.0	0.30	0.39	9.9	19	9.0
Example	183	184	185	189	195	196	197
IC_{50} (nM)	22	28	6.1	5.2	8.1	54	115
Example	198	199	204	205	206	207	208
IC_{50} (nM)	0.30	0.19	49	94	46	31	1.3
Example	209	GDC-0449					
IC_{50} (nM)	>10000	38					

Therefore, compounds of the present invention, including N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide (Example 32) and analogs, show strong inhibitory effects on hedgehog pathway.

Example 212

The application of reporter gene cell assay for the determination of the inhibitory acitivity of N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide and analogs on hedgehog signaling pathway

The binding of Sonic hedgehog (Shh) to its receptor Patched 1 initiates numerous intracellular signal transmission, and leads to the nuclear translocation of Gli and the elevated transcription of Gli target genes. When C3H10T1/2 cells are stably transfected with the Gli-Luc plasmids containing the luciferase gene under the control of Gli response element and stimulated with Shh, the expression of luciferase is elevated. Luciferase activity is indicative of the hedgehog signaling pathway activity. Therefore, the inhibitory activity of compounds on hedgehog signaling pathway can be measured using the luciferase activity when the transfected cells are stimulated with Shh.

The day before experiment, C3H10T1/2 /Gli-Luc cells in log phase of growth were seeded into 96 well plate at a density of 20000 cells per well. The cells were maintained in DMEM (Hyclone) supplemented with 10% FBS (Hyclone) and incubated at 37°C with 5% CO_2 overnight. The compounds to be examined were diluted into 7 different concentrations by series of dilutions (1/3 and 1/10), and the eighth point of concentration is the DMSO control. Those solutions were diluted 100-fold in the fresh growth medium. The cells were taken out of the incubator and the medium of cultured cells were removed. Then, each well was added in an orderly manner with 80 μL of fresh growth medium, 20 μL of medium pre-dilution of positive compound and compounds to be tested, as well as 100 μL of growth medium containing 30 nM of Shh. The cells are returned to the incubator, and incubated for 24 hours.

Measurement of luciferase activity: After taking the 96 well plate out of the incubator, the supernatants were discarded and the cells were washed twice with PBS. Thereafter, each well was dispensed with 20 μL of lysis buffer (Promega E1531), and the plate was shaken for 30 min at room temperature. Following transferring 5 μL of cell lysate into 384 well plate (Greiner 781074), adding 25 μL of luciferase reaction buffer (Promega E1501) into each well and mixing the plate, the relative light unit (RLU) was immediately captured by VarioSkan Flash.

The data were analyzed with Prism 5 software (GraphPad). The relative light unit (RLU) was plotted against the log concentration of testing compound, and the obtained plot was fitted with non-linear curve fitting equation to calculate IC_{50} values. The curve fitting equation is Y (RLU) = Bottom + (Top − Bottom)/(1 + 10^((X − $LogIC_{50}$))). X is the logarithm of concentration. Y is the measure of relative light unit (RLU).

The calculated IC_{50} value is a measurement of the inhibitory activity of compound to Hh pathway. These data are listed in Table 3.

Table 3 IC_{50} values of compounds that inhibit Hh pathway

Example	6	7	8	14	18	21	22
IC_{50} (nM)	3.3	4.6	4.6	9.5	8.2	5.8	16
Example	25	32	35	38	39	43	46
IC_{50} (nM)	4.0	7.2	7.8	8.4	8.2	12	5.5
Example	47	49	50	59	60	66	68
IC_{50} (nM)	8.7	7.2	10	9.1	23	6.1	9.9
Example	69	70	71	77	78	79	80
IC_{50} (nM)	4.2	1.7	7.1	7.1	15	6.6	1.8
Example	81	82	83	84	85	86	87
IC_{50} (nM)	0.15	0.16	6.3	10	7.1	0.94	0.53
Example	88	89	90	91	93	94	95
IC_{50} (nM)	6.7	21	25	7.8	0.50	0.63	3.3
Example	96	97	98	99	100	101	103
IC_{50} (nM)	3.3	1.7	0.96	1.6	0.58	0.67	9.4
Example	104	105	107	109	110	111	112
IC_{50} (nM)	0.94	1.1	0.75	3.8	0.57	2.2	5.5
Example	113	114	115	116	117	118	119
IC_{50} (nM)	27	0.85	3.4	1.4	1.2	5.1	0.45
Example	120	121	122	123	124	125	126
IC_{50} (nM)	1.7	1.6	0.39	0.39	0.80	0.57	2.3
Example	127	128	129	130	131	132	133
IC_{50} (nM)	1.1	5.2	4.0	8.5	1.2	0.74	1.6
Example	134	135	136	137	138	139	140
IC_{50} (nM)	>10000	1.2	0.97	2.3	0.58	1.1	0.21
Example	141	142	143	144	145	146	147
IC_{50} (nM)	0.35	0.28	2.3	0.15	0.38	0.39	>10000
Example	148	149	150	151	152	153	154
IC_{50} (nM)	0.26	0.28	0.50	2.0	1.2	8.7	6.7
Example	155	156	157	158	159	160	161
IC_{50} (nM)	0.22	0.21	0.23	0.30	0.31	6.5	0.38

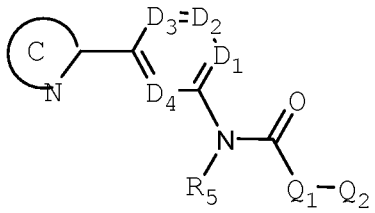
Example	162	164	165	166	167	168	169
IC_{50} (nM)	0.30	0.24	0.19	11	28	0.38	0.67
Example	170	171	172	173	174	175	176
IC_{50} (nM)	0.22	0.46	17	15	5.7	7.6	0.97
Example	177	178	179	180	181	182	183
IC_{50} (nM)	0.67	1.0	0.43	2.4	3.2	4.5	6.6
Example	184	185	186	187	188	189	190
IC_{50} (nM)	10	17	3.4	0.45	1.0	0.82	0.20
Example	191	192	193	194	195	196	197
IC_{50} (nM)	0.34	0.52	0.56	0.63	8.9	5.7	9.5
Example	198	199	200	203	204	205	206
IC_{50} (nM)	0.29	0.27	0.28	0.29	9.6	29	27
Example	207	208	209	GDC-0449			
IC_{50} (nM)	8.5	3.7	>10000	43			

Therefore, compounds of the present invention, including N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide (Example 32) and analogs, show strong inhibitory effects on hedgehog pathway.

Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

WHAT IS CLAIMED IS:

1. A compound having the Formula I:



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

C cyclic group is an optionally substituted N-containing heteroaryl;

D_1 is N or CR_6; D_2 is N or CR_7; D_3 is N or CR_8; D_4 is N or CR_9;

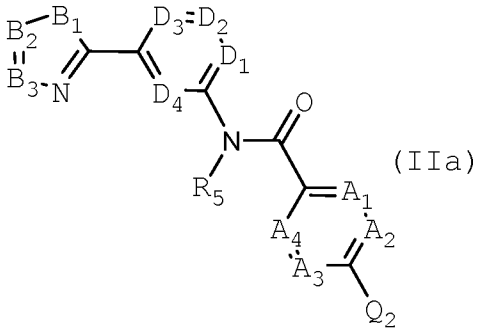
Q_1 and Q_2 independently are optionally substituted aryl, heteroaryl, a carbocyclic group or heterocyclic group;

R_6-R_9 independently are hydrogen, halo, optionally substituted amino, alkoxy, C_{1-10} alkyl, C_{3-8} cycloalkyl, haloalkyl, aryl, a carbocyclic group, a heterocyclic group, heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, carboxyalkoxy, nitro, cyano, acylamino, aminocarbonyl, hydroxy, thiol, acyloxy, azido, carboxy, hydroxyacylamino, alkylsulfonyl, aminosulfonyl, dialkylaminosulfonyl, alkylsulfinyl, or alkylthiol;

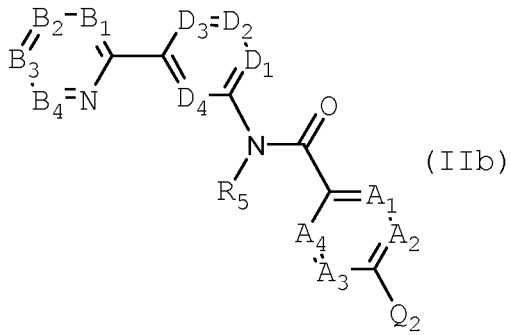
R_5 is hydrogen or C_{1-10} alkyl, or R_5 is taken together with N atom to which it is attached, and other groups, and an atom of Q_1 to form a heterocyclic group.

2. The compound of claim 1, wherein the C cyclic group is an optionally substituted pyridyl, pyrimidinyl, imidazolyl, benzimidazolyl, or thienoimidazolyl.

3. The compound of Formulae IIa and IIb:



(IIa)



(IIb)

or pharmaceutically acceptable salts or prodrugs thereof, wherein:

D_1-D_4 and Q_2 are defined as in claim 1;

A_1 is N or CR_1; A_2 is N or CR_2; A_3 is N or CR_3; A_4 is N or CR_4;

B_1 is O, S, CR_{10} or NR_{14}; B_2 is O, S, CR_{11} or NR_{15}; B_3 is O, S, CR_{12} or NR_{16} for Formula IIa;

B_1 is N or CR_{10}; B_2 is N or CR_{11}; B_3 is N or CR_{12}, B_4 is N or CR_{13} for Formula IIb;

R_1-R_4 and R_{10}-R_{13} independently are hydrogen, halo, optionally substituted amino, alkoxy, C_{1-10} alkyl, C_{3-8} cycloalkyl, haloalkyl, optionally substituted aryl, a carbocyclic group, a heterocyclic group, optionally substituted heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, carboxyalkoxy, nitro, cyano, acylamino, aminocarbonyl, hydroxy, thiol, acyloxy, azido, carboxy, hydroxyacylamino, alkylsulfonyl, aminosulfonyl, acyl, dialkylaminosulfonyl, alkylsulfinyl, or alkylthiol;

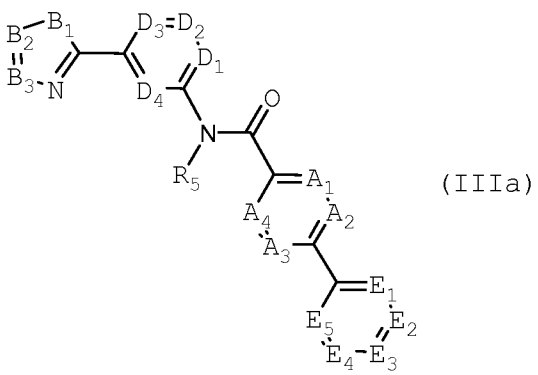
R_5 is hydrogen, C_{1-10} alkyl, or R_5 and R_1 or R_4 are taken together with N atom to which they are attached to form a heterocyclic group;

R_{14}-R_{16} independently are hydrogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, haloalkyl, optionally substituted aryl, a carbocyclic group, a heterocyclic group, optionally substituted heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl; or

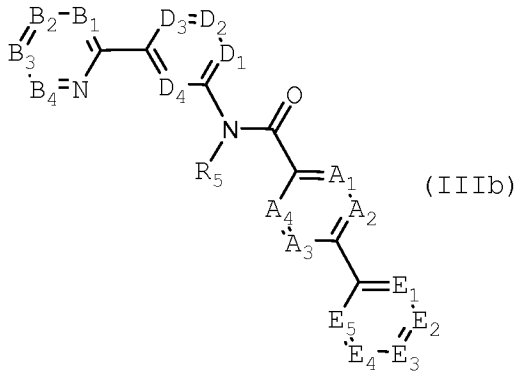
R_{10} or R_{14} and R_{11} or R_{15}, R_{11} or R_{15} and R_{12} or R_{16}, or R_{12} and R_{13}, are taken together with C or N atom to which they are attached to form a five- or six-member aryl or heteroaryl.

4. The compound of claim 3, wherein Q_2 is an optionally substituted phenyl, pyridyl, morpholinyl, piperazinyl or piperidyl.

5. The compound of Formulae IIIa and IIIb:



(IIIa)



(IIIb)

or pharmaceutically acceptable salts or prodrugs thereof, wherein:

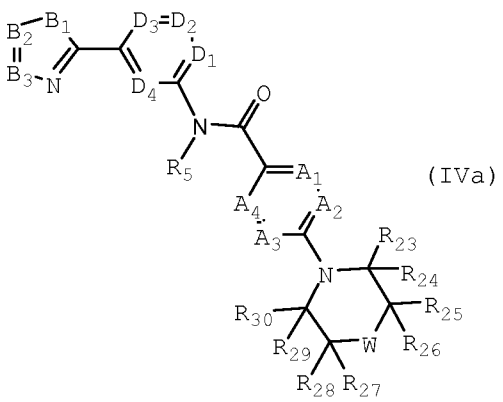
A_1-A_4, D_1-D_4, B_1-B_4 and R_5 are defined as in claims 1 and 3;

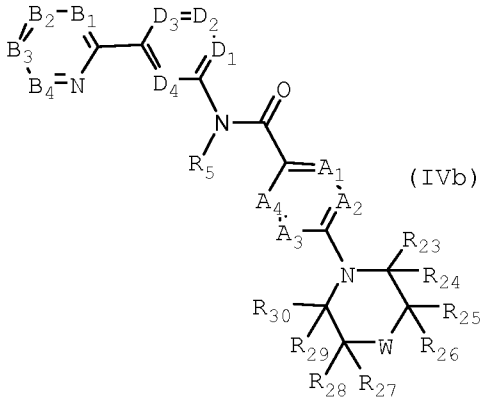
E_1 is N or CR_{18}; $E_2$is N or CR_{19}; E_3 is N or CR_{20}; E_4 is N or CR_{21}; E_5 is N or CR_{22};

R_{18}-R_{22} independently are hydrogen, halo, optionally substituted amino, alkoxy, C_{1-10} alkyl, C_{3-8} cycloalkyl, haloalkyl, aryl, a carbocyclic group, a heterocyclic group, heteroaryl,

alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, carboxyalkoxyl, nitro, cyano, acylamino, aminocarbonyl, hydroxy, thiol, acyloxy, azido, carboxy, hydroxyacylamino, alkylsulfonyl, aminosulfonyl, dialkylaminosulfonyl, acyl, alkylsulfinyl, or alkylthiol.

6. The compound of Formulae IVa and IVb:


(IVa)


(IVb)

or pharmaceutically acceptable salts or prodrugs thereof, wherein:

A_1-A_4, D_1-D_4, B_1-B_4 and R_5 are defined as in claims 1 and 3;

W is O, S, $CR_{31}R_{32}$ or NR_{33};

R_{23}-R_{32} independently are hydrogen, halo, optionally substituted amino, alkoxy, C_{1-10} alkyl, C_{3-8} cycloalkyl, haloalkyl, aryl, a carbocyclic group, a heterocyclic group, heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, carboxyalkoxyl, nitro, cyano, acylamino, aminocarbonyl, hydroxy, thiol, acyloxy, azido, carboxy, hydroxyacylamino, alkylsulfonyl, aminosulfonyl, acyl, dialkylaminosulfonyl, alkylsulfinyl, or alkylthiol;

R_{33} is optionally substituted C_{1-10} alkyl, haloalkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, a carbocyclic group, a heterocyclic group, alkenyl, alkynyl, acyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl, aminocarbonyl, alkylsulfonyl, cycloalkylsulfonyl, or aminosulfonyl.

7. The compound of claim 6, wherein the W-containing heterocyclic group is an optionally substituted morpholino, piperazinyl or piperidyl.

8. The compound of claim 1, 3, 5 or 6, wherein said compound is selected from the group consisting of:

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methylbiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-methoxybiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-fluorobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(methylsulfonyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-cyanobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-nitrobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-chlorobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-acetylbiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-3'-fluorobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-3'-cyanobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4'-fluorobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3'-fluorobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methoxy-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-hydroxy-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-fluoro-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-chloro-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-nitro-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3,5-dimethyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-aminobiphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-amino-4'-(trifluoromethyl)biphenyl-4-carboxamide;

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)quinazoline-2,4(1H,3H)-dione;

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)quinazolin-4(3H)-one;

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-(4-(trifluoromethyl)phenyl)-2H-benzo[e][1,3]oxazin-4(3H)-one;

2-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-phenyl-3,4-dihydroisoquinolin-1(2H)-one;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-morpholinobenzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(piperidin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-amino-4-((2S,6R)-2,6-dimethylmorpholino)benzamide;

3-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-7-((2S,6R)-2,6-dimethylmorpholino)quinazolin-4(3H)-one;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-chloro-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-5-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(2-methoxypyrimidin-5-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(pyridin-3-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(furan-3-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(thiophen-3-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(pyrimidin-5-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-phenylcyclohexanecarboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-N,3-dimethyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-imidazo[4,5-c]pyridin-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-phenyl-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-(pyridin-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-([1,2,4]triazolo[4,3-a]pyrimidin-3-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-([1,2,4]triazolo[4,3-a]pyrazin-3-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(imidazo[1,2-a]pyrimidin-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(imidazo[1,2-a]pyridin-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(imidazo[1,2-a]pyrimidin-2-yl)phenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-([1,2,4]triazolo[4,3-a]pyrazin-3-yl)-4-chlorophenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(pyridin-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(5-(1H-benzo[d]imidazol-2-yl)pyridin-3-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(4-(1H-benzo[d]imidazol-2-yl)pyridin-2-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-5-(trifluoromethyl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-5-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-2-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-2-methylphenyl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(6-methoxypyridin-3-yl)benzamide;

N-(3-(imidazo[1,2-a]pyridin-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-3-methyl-4'-cyanobiphenyl-4-carboxamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(6-(1H-benzo[d]imidazol-2-yl)pyridin-2-yl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-([1,2,4]triazolo[1,5-a]pyridin-2-yl)phenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-fluorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-bromophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-methoxyphenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-p-tolyl-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-(4-fluorophenyl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide;

N-(3-(5-p-tolyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-methyl-4-((2S,6R)-2,6-dimethylmorpholino)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-4-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-3-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-methylpyridin-3-yl)-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-methyl-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(4-methylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-4-isopropyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-(4-methylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-6-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)nicotinamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-6-((2S,6R)-2,6-dimethylmorpholino)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-methyl-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-(piperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(1-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-methyl-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-methylphenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-6-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)nicotinamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-isopropyl-3,5-dimethylpiperazin-1-yl)benzamide;

(S)-N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-(3,4-dimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((2S,6R)-2,6-dimethylmorpholino)benzamide;

N-(5-(6-fluoro-1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(5-(6-chloro-1H-benzo[d]imidazol-2-yl)-6-chloropyridin-3-yl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(6-fluoro-1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-2-cyano-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-(4-methylthiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(4-methylthiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(5-chlorothiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-3-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(5-chlorothiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(4-methyl-5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-cyano-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(furan-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(5-(5-methylfuran-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(5-methylfuran-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiazol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiazol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-isopropyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-(methylsulfonyl)benzamide;

N-(3-(5-(1-methyl-1H-pyrrol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(1-methyl-1H-pyrrol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(1-methyl-1H-pyrrol-2-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-(thiophen-3-yl)-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-propyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-propyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-tert-butyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-tert-butyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclobutyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclobutyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopentyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclopentyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclohexyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-cyclohexyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(5-methyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-ethyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-isopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(5-cyclopropyl-1H-imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide dihydrochloride;

N-(3-(3H-imidazo[4,5-b]pyridin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(3H-imidazo[4,5-c]pyridin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(3H-imidazo[4,5-c]pyridin-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-(trifluoromethyl)-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-methyl-3-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(1H-thieno[3,4-d]imidazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-4-ethyl-3,5-dimethylpiperazin-1-yl)benzamide;

N-(3-(quinoxalin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(imidazo[2,1-b]thiazol-6-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(benzo[d]oxazol-2-yl)-4-chlorophenyl)-2-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(benzo[d]thiazol-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(pyridin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

N-(3-(pyrimidin-2-yl)-4-chlorophenyl)-2-chloro-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)benzamide;

or a pharmaceutically acceptable salt or prodrug thereof.

9. A method of treating a disease responsive to the inhibition of hedgehog activity in a mammal suffering thereof with a compound of any of claims 1 to 8.

10. The method according to claim 9, wherein said disease is basal cell carcinoma, myelogenous cancer, basal cell nevus syndrome (BCNS), liver cancer, melanoma, Hodgkin's disease, non-Hodgkin's lymphomas, acute or chronic lymphocytic leukemia, multiple myeloma, neuroblastoma, breast carcinoma, ovarian carcinoma, lung carcinoma, Wilms' tumor, cervical carcinoma, testicular carcinoma, soft-tissue sarcoma, primary macroglobulinemia, bladder carcinoma, chronic granulocytic leukemia, primary brain carcinoma, malignant melanoma, small-cell lung carcinoma, stomach carcinoma, colon carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, choriocarcinoma, mycosis fungoide, head or neck carcinoma, osteogenic sarcoma, pancreatic carcinoma, acute granulocytic leukemia, hairy cell leukemia, rhabdomyosarcoma, Kaposi's sarcoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, malignant hypercalcemia, cervical hyperplasia, renal cell carcinoma, endometrial carcinoma, polycythemia vera, essential thrombocytosis, adrenal cortex carcinoma, skin cancer, or prostatic carcinoma.

11. The method of claim 10, further comprising administering at least one known anticancer agent, or a pharmaceutically acceptable salt of said agent.

12. The method according to claim 11, wherein said compound is administered together with at least one compound selected from the group consisting of busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide, temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin, carboplatin, camptothecin, irinotecan, topotecan, doxorubicin, epirubicin, aclarubicin, mitoxantrone, elliptinium, etoposide, 5-azacytidine, gemcitabine, 5-fluorouracil, methotrexate, 5-fluoro-2'-deoxyuridine, fludarabine, nelarabine, ara-C, alanosine, pralatrexate, pemetrexed, hydroxyurea, thioguanine, colchicine, vinblastine, vincristine, vinorelbine, paclitaxel, ixabepilone, cabazitaxel, docetaxel, campath, Panitumumab, Ofatumumab, Avastin, Herceptin®, Rituxan®, imatinib, gefitinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, temsirolimus, everolimus, vorinostat, romidepsin, tamoxifen, letrozole, fulvestrant, mitoguazone, octreotide, retinoic acid, arsenic trioxide, zoledronic acid, bortezomib, thalidomide or lenalidomide.

13. The method of claim 12, further comprising treating said mammal with radiation-therapy.

14. A pharmaceutical composition comprising the compound of any of claims 1 to 8 and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition of claim 14, further comprising at least one known anticancer agent, or a pharmaceutically acceptable salt of said agent.

16. The method according to claim 15, further comprising at least one compound selected from the group consisting of busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide,

temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin, carboplatin, camptothecin, irinotecan, topotecan, doxorubicin, epirubicin, aclarubicin, mitoxantrone, elliptinium, etoposide, 5-azacytidine, gemcitabine, 5-fluorouracil, methotrexate, 5-fluoro-2'-deoxyuridine, fludarabine, nelarabine, ara-C, alanosine, pralatrexate, pemetrexed, hydroxyurea, thioguanine, colchicine, vinblastine, vincristine, vinorelbine, paclitaxel, ixabepilone, cabazitaxel, docetaxel, campath, Panitumumab, Ofatumumab, Avastin, Herceptin®, Rituxan®, imatinib, gefitinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, temsirolimus, everolimus, vorinostat, romidepsin, tamoxifen, letrozole, fulvestrant, mitoguazone, octreotide, retinoic acid, arsenic trioxide, zoledronic acid, bortezomib, thalidomide or lenalidomide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/079651

A. CLASSIFICATION OF SUBJECT MATTER

See the extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D 235/-; C07D 403/-; C07D 413/-; C07D 401/-; C07D 405/-; C07D 409/-; C07D 471/-; C07D 487/-; C07D 213/-; A61K 31/-; A61P 35/-; A61P 7/-

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CNABS, CPRSABS, CNTXT, CNKI, DWPI, SIPOABS, CA, STN: IMPACT THERAPEUTICS, arylcarboxamides, Hedgehog pathway, inhibit+, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 102573487 A (CALIFORNIA CAPITAL EQUITY, LLC), 11 July 2012 (11.07.2012), claim 5, compounds 5, 11, 16, 40-46, 49, 52, 62-65, 68-70, 72, 78, 101, 120-125, 162-163, 165-168, 170, 180-182, 184-187, 195-198, 200, 205-206, 244-248, 250-251, 256-257, 278-279, 316-317, and paragraphs [0196]-[0204]	1-7, 9-16
Y	CN 102573487 A (CALIFORNIA CAPITAL EQUITY, LLC), 11 July 2012 (11.07.2012), compound 16	8
X	CN 102573832 A (ABRAXIS BIOSCIENCE, LLC), 11 July 2012 (11.07.2012), claims 1-19, table 5 and compounds 5, 11, 16, 65, 72, 78	1-7, 9-16

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

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08. October 2013 (08.10.2013)	**24 Oct. 2013 (24.10.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer ZHANG, Hengjun Telephone No. (86-10)82246670

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/079651

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 101501004 A (IRM LLC), 5 August 2009 (05.08.2009), pages 25-26, Table 1 and compounds 3, 4, 8-10, 16-17, 22-27,29-31, 33-36, 39-44, 181	1-4, 6-7, 9-16
Y	CN 101501004 A (IRM LLC), 5 August 2009 (05.08.2009), compounds 3	8
X	TW 200916458 A (ASTRAZENECA AB), 16 April 2009 (16.04.2009), pages 44-46, 63-68 and examples 19, 21, 34-38, 42	1-4, 6-7, 9-16
X	CN 101072755 A (GENENTECH. INC, et al.), 14 November 2007 (14.11.2007), pages 26-60, 68-69 and compounds 11, 13, 37, 58, 62, 71, 77, 106-108, 168, 173, 186-187, 261, 295-296, 298-299, 302, 304-309, 313-320, 323-327, 331-333	1-4, 6-7, 9-16
X	WO 2011014888 A1 (SELEXAGEN THERAPEUTICS, et al.), 03 February 2011 (03.02.2011), claims 53-55	1-2
X	WO 2009077956 A2 (ALLA CHEM, LLC, et al.), 25 June 2009 (25.06.2009), pages 63, 65, compounds III-1017 and III-1030	1-2
A	CN 101932313 A (NOVARTIS AG), 29 December 2010 (29.12.2010), whole document	1-16

INTERNATIONAL SEARCH REPORT

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

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

1. ☒ Claims Nos.: 9-13
because they relate to subject matter not required to be searched by this Authority, namely:
These claims relate to methods for treating diseases (PCT R39.1(iv)), but the search has been carried out and based on the use of the compound in manufacture of medicaments for treating corresponding diseases.

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

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/079651

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
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INTERNATIONAL SEARCH REPORT
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International application No.
PCT/CN2013/079651

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/079651

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/079651

A (Continuation). CLASSIFICATION OF SUBJECT MATTER

C07D 235/18 (2006.01) i

C07D 403/10 (2006.01) i

C07D 403/12 (2006.01) i

C07D 413/12 (2006.01) i

C07D 401/12 (2006.01) i

C07D 405/12 (2006.01) i

C07D 409/12 (2006.01) i

C07D 471/04 (2006.01) i

C07D 401/04 (2006.01) i

C07D 487/04 (2006.01) i

C07D 213/40 (2006.01) i

C07D 409/04 (2006.01) i

A61K 31/4184 (2006.01) i

A61K 31/517 (2006.01) i

A61K 31/506 (2006.01) i

A61K 31/5377 (2006.01) i

A61K 31/4725 (2006.01) i

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A61K 31/4985 (2006.01) i

A61K 31/4402 (2006.01) i

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