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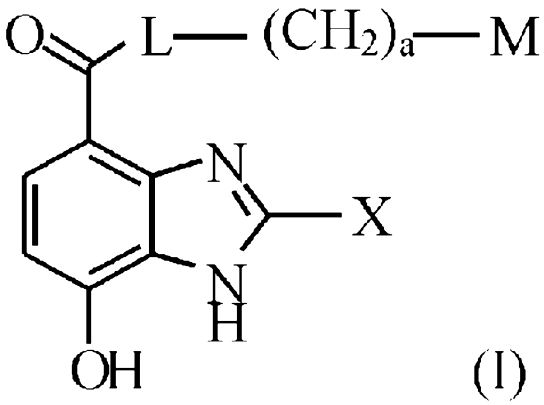
(54) **Title**: GLYCOGEN SYNTHASE KINASE-3 BETA INHIBITORS CONTAINING 7-HYDROXY-BENZOIMIDAZOLE-4-YL-METHANONE DERIVATIVES



(I)

(57) **Abstract**: GSK-3beta inhibitors comprising 7-Hydroxy-benzoimidazole-4-yl-methanone Derivatives are provided. For example, the inhibitors have following general formula (I).

WO 2010/058512 A1

Description

Title of Invention: GLYCOGEN SYNTHASE KINASE-3 BETA INHIBITORS CONTAINING 7-HYDROXY-BENZOIMIDAZOLE-4-YL-METHANONE DERIVATIVES

Technical Field

[0001] Priority

The present application claims the benefit of U.S. Provisional Application No. 61/116,543, filed on November 20, 2008, the entire contents of which are incorporated by reference herein.

Technical Field

The present invention relates to a compound for inhibiting GSK-3beta activity, a method for the preparation thereof, and a pharmaceutical composition containing the compound as an active ingredient.

Background Art

[0002] Glycogen synthase kinase-3 (GSK-3) is a proline-directed serine-threonine kinase that was initially identified as a protein which inactivates glycogen synthase through phosphorylation. Two isoforms have been identified, alpha (GSK-3alpha) and beta (GSK-3beta), which show a high degree of amino acid homology to each other. Previous studies have reported that the GSK-3beta is involved in energy metabolism, neural cell development, and body pattern formation (NPL 1).

Neurodegenerative naturopathies, including Alzheimer disease, are characterized by abnormal hyperphosphorylation of the microtubule-associated protein tau at proline-directed serine/threonine phosphorylation sites (NPL 2). GSK-3beta has been identified as a prime candidate mediating aberrant tau phosphorylation at disease-associated sites (NPLs 3-6). Hence, GSK-3beta is a promising target for therapeutic intervention in neurodegenerative tauopathies including Alzheimer disease.

[0003] Lithium carbonate, lithium citrate and lithium chloride are commonly used for the treatment of various disorders like mania, depression and migraine, and also used as an "augmenting" agent to increase the benefits of other standard drugs used for unipolar depression. Lithium is a GSK-3beta inhibitor, and therefore, GSK-3beta inhibition is a promising target for the treatment of various such disorders.

There have been reports that the activity of GSK-3 in obese diabetic mice is about twice as high as that in control (NPL 7), and the activity and expression of GSK-3 in patients with type 2 diabetes is significantly higher relativity to that in normal persons

(NPL 8). Therefore, GSK-3 inhibitors are available for treatment of type 2 diabetes by reducing the activity of glucose synthase.

Taken together, GSK-3beta inhibitors can be used for a broad spectrum of diseases such as Alzheimer disease, mania, depression, migraine and type 2 diabetes and there is a strong need to develop such inhibitors for the treatment and/or prevention of GSK-3beta dependent diseases.

The present inventors have endeavored to develop an effective inhibitor of GSK-3beta and have found that a benzoimidazole derivative can selectively inhibit the activity of GSK-3beta.

Citation List

Non Patent Literature

[0004] [NPL 1] Plyte SE, et al., Biochim. Biophys. Acta, 1114:147-162, 1992

[NPL 2] Lee VM, et al., Annu. Rev. Neurosci. 24: 1121-1159, 2001

[NPL 3] Hanger DP, et al., Neurosci. Lett. 147: 58-62, 1992

[NPL 4] Ishiguro K, et al., J. Biol. Chem. 267: 10897-10901, 1992

[NPL 5] Mandelkow EM, et al., FEBS Lett. 314: 315-321, 1992

[NPL 6] Paudel HK, et al., J. Biol. Chem. 268: 23512-23518, 1993

[NPL 7] Eldar-Finkelman H, et al., Diabetes, 48:1662-1666, 1999

[NPL 8] Nikoulina SE, et al., Diabetes, 49:263-271, 2000

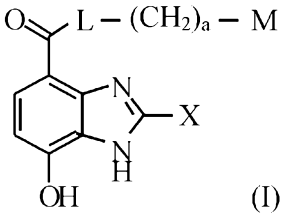
Summary of Invention

[0005] Accordingly, it is an object of the present invention to provide a GSK-3beta inhibitor having high inhibitory activity against GSK-3beta.

It is a further object of the present invention to provide a pharmaceutical composition including the compound, a pharmaceutically acceptable salt, hydrate, solvate, or isomer thereof for use in the treatment of GSK-3beta dependent diseases in a patient in need thereof.

In accordance with one aspect of the present invention, there is provided a compound of formula (I), and a pharmaceutically acceptable salt, hydrate, solvate, or isomer thereof:

[Chem.1]



(I)

wherein

X is phenyl, thiophen-2-yl, furan-2-yl, cyclopropyl, cyclopentyl, phenylC_1-C_6alkyl,

thiophen-2-ylC_1-C_6 alkyl, furan-2-ylC_1-C_6 alkyl, cyclopropylC_1-C_6 alkyl, or cyclopentylC_1-C_6 alkyl;

the said phenyl, thiophen-2-yl, furan-2-yl, cyclopropyl, cyclopentyl, phenylC_1-C_6 alkyl, thiophen-2-ylC_1-C_6 alkyl, furan-2-ylC_1-C_6 alkyl, cyclopropylC_1-C_6 alkyl, or cyclopentyl C_1-C_6 alkyl are optionally substituted by 1-3 substituent(s) each independently selected from the group A;

L is -NH- or a single bond;

M is selected from C_3-C_8 cycloalkyl or 3-8 membered saturated heterocyclic group;

the C_3-C_8 cycloalkyl, and 3-8 membered saturated heterocyclic group are optionally substituted by 1-3 substituent(s) each independently selected from group A;

wherein group A consists of hydroxyl, oxo, nitro, cyano, amino, C_1-C_6 alkylamino, C_3-C_8 cycloalkylamino, amide, halogen, sulfamoyl, trifluolomethyl, p-toluenesulfonylamino, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonylamino, C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino, C_1-C_6 alkenyl, C_1-C_6 alkynyl, phosphoryl, carbonyl, carboxyl, and 3-8 membered saturated heterocyclic group; and

a is an integer from 0-5.

Description of Embodiments

[0006] Definition

In this invention, a "GSK-3beta dependent disease" is a disease in which inhibiting GSK-3beta activity is relevant to therapeutic efficacy. Such diseases include, for example, Alzheimer disease, mania, depression, migraine and type 2 diabetes. It will be understood by one of skill that such diseases do not include cancers, such as breast cancer, bladder cancer and small cell lung cancer. Thus, in some embodiments, the claimed methods of treating or preventing a GSK-3beta dependent disease exclude patients also suffering from cancer, such as breast cancer, bladder cancer or small cell lung cancer. Thus, in some embodiments, the term " a patient in need thereof" refers to a patient suffering from a GSK-3beta dependent disease, with the proviso that the patient is not also suffering from cancer, such as breast cancer, bladder cancer or small cell lung cancer.

In this invention, "alkyl" refers to a straight chain or a branched chain hydrocarbon group which does not contain any hetero atoms or unsaturated carbon-carbon bonds. "C_1-C_6 alkyl" refers to an alkyl group which has 1-6 carbon atom(s). "C_1-C_4 alkyl" refers to an alkyl group which has 1-4 carbon atom(s).

Examples of "C_1-C_6 alkyl" include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 1-butyl, 2-butyl, 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-2-butyl, 3-methyl-2-butyl,

2,2-dimethyl-1-propyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2-methyl-3-pentyl, 3-methyl-3-pentyl, 2,3-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2,2-dimethyl-1-butyl, 2-ethyl-1-butyl, 3,3-dimethyl-2-butyl, and 2,3-dimethyl-2-butyl.

[0007] In this invention, "phenylC_1-C_6 alkyl, thiophen-2-ylC_1-C_6 alkyl, furan-2-ylC_1-C_6 alkyl, cyclopropylC_1-C_6 alkyl, or cyclopentylC_1-C_6 alkyl" refers to the C_1-C_6 alkyl bound to a phenyl, thiophen-2-yl, furan-2-yl, cyclopropyl or cyclopentyl group. In one embodiment, phenylC_1-C_6 alkyl, thiophen-2-ylC_1-C_6 alkyl, furan-2-ylC_1-C_6 alkyl, cyclopropylC_1-C_6 alkyl, or cyclopentylC_1-C_6 alkyl is optionally substituted by 1-3 substituent(s) each independently selected from group A mentioned above. Such substitution may occur at either the phenyl, thiophen-2-yl, furan-2-yl, cyclopropyl, or cyclopentyl moiety or the C_1-C_6 alkyl moiety of the group, or may occur at both moieties of the group.

Examples of "phenylC_1-C_6 alkyl, thiophen-2-ylC_1-C_6 alkyl, furan-2-ylC_1-C_6 alkyl, cyclopropylC_1-C_6 alkyl, or cyclopentylC_1-C_6 alkyl" include, but are not limited to, phenylmethyl, phenylethyl, phenyl-1-propyl, phenyl-2-propyl, phenyl-n-butyl, phenyl-s-butyl, phenyl-t-butyl, phenyl-2-ethylbutyl, thiophen-2-ylmethyl, thiophen-2-ylethyl, thiophen-2-yl-1-propyl, thiophen-2-yl-2-propyl, thiophen-2-yl-n-butyl, thiophen-2-yl-s-butyl, thiophen-2-yl-t-butyl, thiophen-2-yl-2-ethylbutyl, furan-2-ylmethyl, furan-2-ylethyl, furan-2-yl-1-propyl, furan-2-yl-2-propyl, furan-2-yl-n-butyl, furan-2-yl-s-butyl, furan-2-yl-t-butyl, furan-2-yl-2-ethylbutyl, cyclopropylmethyl, cyclopropylethyl, cyclopropyl-1-propyl, cyclopropyl-2-propyl, cyclopropyl-n-butyl, cyclopropyl-s-butyl, cyclopropyl-t-butyl, cyclopropyl-2-ethylbutyl, cyclopentylmethyl, cyclopentylethyl, cyclopentyl-1-propyl, cyclopentyl-2-propyl, cyclopentyl-n-butyl, cyclopentyl-s-butyl, cyclopentyl-t-butyl and cyclopentyl-2-ethylbutyl.

[0008] In this invention, "alkenyl" refers to a straight chain or a branched chain hydrocarbon group which contains one unsaturated carbon-carbon bonds and does not contain any hetero atoms. "C_1-C_6 alkenyl" refers to an alkenyl group which has 1-6 carbon atom(s).

Examples of "C_1-C_6 alkenyl", include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 3-propenyl, 2-methyl-prop-1-en-1-yl, 2-methyl-prop-1-en-3-yl, but-1-en-1-yl, but-1-en-2-yl, but-1-en-3-yl, but-2-en-1-yl, but-2-en-2-yl, pent-1-en-1-yl, pent-1-en-2-yl, pent-1-en-3-yl, pent-1-en-4-yl, pent-1-en-5-yl, pent-2-en-1-yl, pent-2-en-2-yl, pent-2-en-3-yl, pent-2-en-4-yl, pent-2-en-5-yl, 2-methyl-but-1-en-1-yl, 2-methyl-but-1-en-2-yl, 2-methyl-but-1-en-3-yl, 2-methyl-but-1-en-4-yl, 2-methyl-but-2-en-1-yl, 2-methyl-but-2-en-3-yl, 2-methyl-but-2-en-4-yl, 3-methyl-but-1-en-1-yl, 3-methyl-but-1-en-2-yl, 3-methyl-but-1-en-3-yl, 3-methyl-but-1-en-4-yl, 2,2-dimethyl-prop-1-en-1-yl, 2,2-dimethyl-prop-1-en-2-yl,

hex-1-en-1-yl, hex-1-en-2-yl, hex-1-en-3-yl, hex-1-en-4-yl, hex-1-en-5-yl, hex-1-en-6-yl, hex-2-en-1-yl, hex-2-en-2-yl, hex-2-en-3-yl, hex-2-en-4-yl, hex-2-en-5-yl, hex-2-en-6-yl, hex-3-en-1-yl, hex-3-en-2-yl, hex-3-en-3-yl, 2-methyl-pent-1-en-1-yl, 2-methyl-pent-1-en-3-yl, 2-methyl-pent-1-en-4-yl, 2-methyl-pent-1-en-5-yl, 2-methyl-pent-2-en-1-yl, 2-methyl-pent-2-en-3-yl, 2-methyl-pent-2-en-4-yl, 2-methyl-pent-2-en-5-yl, 3-methyl-pent-1-en-1-yl, 3-methyl-pent-1-en-2-yl, 3-methyl-pent-1-en-3-yl, 3-methyl-pent-1-en-4-yl, 3-methyl-pent-1-en-5-yl, 3-methyl-pent-2-en-1-yl, 3-methyl-pent-2-en-2-yl, 3-methyl-pent-2-en-4-yl, 3-methyl-pent-2-en-5-yl, 4-methyl-pent-1-en-1-yl, 4-methyl-pent-1-en-2-yl, 4-methyl-pent-1-en-3-yl, 4-methyl-pent-1-en-4-yl, 4-methyl-pent-1-en-5-yl, 4-methyl-pent-2-en-1-yl, 4-methyl-pent-2-en-2-yl, 4-methyl-pent-2-en-3-yl, 4-methyl-pent-2-en-4-yl, 4-methyl-pent-2-en-5-yl, 2,3-dimethyl-but-1-en-1-yl, 2,3-dimethyl-but-1-en-3-yl, 2,3-dimethyl-but-1-en-4-yl, 2,3-dimethyl-but-2-en-1-yl, 3,3-dimethyl-but-1-en-1-yl, 3,3-dimethyl-but-1-en-2-yl, 3,3-dimethyl-but-1-en-4-yl, 2-ethyl-but-1-en-1-yl, 2-ethyl-but-1-en-3-yl, 2-ethyl-but-1-en-4-yl, 3-ethyl-but-1-en-1-yl, 3-ethyl-but-1-en-2-yl, 3-ethyl-but-1-en-3-yl, 3-ethyl-but-1-en-4-yl, 2-ethyl-but-2-en-1-yl, 2-ethyl-but-2-en-3-yl and 2-ethyl-but-2-en-4-yl.

[0009] In this invention, "alkynyl" refers to a straight chain or a branched chain hydrocarbon group which contains one unsaturated carbon-carbon bonds and does not contain any hetero atoms. "C_1-C_6 alkynyl" refers to an alkynyl group which has 1-6 carbon atom(s).

Examples of "C_1-C_6 alkynyl", include, but are not limited to, ethinyl, 1-propinyl, 2-propinyl, 3-propinyl, 2-methyl-prop-1-in-1-yl, 2-methyl-prop-1-in-3-yl, but-1-in-1-yl, but-1-in-2-yl, but-1-in-3-yl, but-2-in-1-yl, but-2-in-2-yl, pent-1-in-1-yl, pent-1-in-2-yl, pent-1-in-3-yl, pent-1-in-4-yl, pent-1-in-5-yl, pent-2-in-1-yl, pent-2-in-2-yl, pent-2-in-3-yl, pent-2-in-4-yl, pent-2-in-5-yl, 2-methyl-but-1-in-1-yl, 2-methyl-but-1-in-2-yl, 2-methyl-but-1-in-3-yl, 2-methyl-but-1-in-4-yl, 2-methyl-but-2-in-1-yl, 2-methyl-but-2-in-3-yl, 2-methyl-but-2-in-4-yl, 3-methyl-but-1-in-1-yl, 3-methyl-but-1-in-2-yl, 3-methyl-but-1-in-3-yl, 3-methyl-but-1-in-4-yl, 2,2-dimethyl-prop-1-in-1-yl, 2,2-dimethyl-prop-1-in-2-yl, hex-1-in-1-yl, hex-1-in-2-yl, hex-1-in-3-yl, hex-1-in-4-yl, hex-1-in-5-yl, hex-1-in-6-yl, hex-2-in-1-yl, hex-2-in-2-yl, hex-2-in-3-yl, hex-2-in-4-yl, hex-2-in-5-yl, hex-2-in-6-yl, hex-3-in-1-yl, hex-3-in-2-yl, hex-3-in-3-yl, 2-methyl-pent-1-in-1-yl, 2-methyl-pent-1-in-3-yl, 2-methyl-pent-1-in-4-yl, 2-methyl-pent-1-in-5-yl, 2-methyl-pent-2-in-1-yl, 2-methyl-pent-2-in-3-yl, 2-methyl-pent-2-in-4-yl, 2-methyl-pent-2-in-5-yl, 3-methyl-pent-1-in-1-yl, 3-methyl-pent-1-in-2-yl, 3-methyl-pent-1-in-3-yl, 3-methyl-pent-1-in-4-yl, 3-methyl-pent-1-in-5-yl, 3-methyl-pent-2-in-1-yl, 3-methyl-pent-2-in-2-yl, 3-methyl-pent-2-in-4-yl,

3-methyl-pent-2-in-5-yl, 4-methyl-pent-1-in-1-yl, 4-methyl-pent-1-in-2-yl, 4-methyl-pent-1-in-3-yl, 4-methyl-pent-1-in-4-yl, 4-methyl-pent-1-in-5-yl, 4-methyl-pent-2-in-1-yl, 4-methyl-pent-2-in-2-yl, 4-methyl-pent-2-in-3-yl, 4-methyl-pent-2-in-4-yl, 4-methyl-pent-2-in-5-yl, 2,3-dimethyl-but-1-in-1-yl, 2,3-dimethyl-but-1-in-3-yl, 2,3-dimethyl-but-1-in-4-yl, 2,3-dimethyl-but-2-in-1-yl, 3,3-dimethyl-but-1-in-1-yl, 3,3-dimethyl-but-1-in-2-yl, 3,3-dimethyl-but-1-in-4-yl, 2-ethyl-but-1-in-1-yl, 2-ethyl-but-1-in-3-yl, 2-ethyl-but-1-in-4-yl, 3-ethyl-but-1-in-1-yl, 3-ethyl-but-1-in-2-yl, 3-ethyl-but-1-in-3-yl, 3-ethyl-but-1-in-4-yl, 2-ethyl-but-2-in-1-yl, 2-ethyl-but-2-in-3-yl and 2-ethyl-but-2-in-4-yl.

[0010] In the present invention, "alkoxy" refers to a group represented by -OR, wherein R is alkyl.

"C_1-C_6 alkoxy" refers to an alkoxy group which has 1-6 carbon atom(s). "C_1-C_4 alkoxy" refers to an alkoxy group which has 1-4 carbon atom(s).

Examples of "C_1-C_6 alkoxy" include, but are not limited to, methoxy, ethoxy, 1-propyloxy, 2-propyloxy, 2-methyl-1-propyloxy, 2-methyl-2-propyloxy, and 1-butyloxy, and 2- butyloxy.

In this invention, "C_1-C_6 alkylcarbonyl" refers to a carbonyl group bound to the C_1-C_6 alkyl. "C_1-C_4 alkylcarbonyl" refers to a carbonyl group bound to the C_1-C_4 alkyl.

Examples of "C_1-C_6 alkylcarbonyl" include, but are not limited to, methylcarbonyl, ethylcarbonyl, 1-propylcarbonyl, 2-propylcarbonyl, n-butylcarbonyl, s-butylcarbonyl, t-butylcarbonyl, and 2-ethylbutylcarbonyl.

In the present invention, "cycloalkyl" refers to a saturated carbohydrate ring system. "C_3-C_8 cycloalkyl" refers to 3-8 membered cycloalkyl.

Examples of "C_3-C_8 cycloalkyl" include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, and cyclooctanyl.

[0011] In this invention, "amino" refers to a group represented by -NH_2 whose hydrogens are optionally substituted by a substituent.

In the present invention, "C_1-C_6 alkylamino" refers to an amino group bound to the C_1-C_6 alkyl.

Examples of "C_1-C_6 alkylamino" include, but are not limited to, methylamino, ethylamino, 1-propylcarbonylamino, 2-propylamino, n-butylamino, s-butylamino, t-butylamino, and 2-ethylbutylamino.

In the present invention, "C_1-C_6 alkylcarbonylamino" refers to an amino group bound to the C_1-C_6 alkylcarbonyl. "C_1-C_4 alkylcarbonylamino" refers to an amino group bound to the C_1-C_4 alkylcarbonyl.

Examples of "C_1-C_6 alkylcarbonylamino" include, but are not limited to, methylcarbonylamino, ethylcarbonylamino, 1-propylcarbonylamino, 2-propylcarbonylamino, n-

butylcarbonylamino, s-butylcarbonylamino, t-butylcarbonylamino, and 2-ethylbutylcarbonylamino.

In the present invention, "C_3-C_8 cycloalkylamino" refers to an amino group bound to the C_3-C_8 cycloalkyl.

Examples of "C_3-C_8 cycloalkyl amino" include, but are not limited to, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cycloheptanylamino, and cyclooctanyl amino.

[0012] In this invention, "sulfonyl" is a group represented by -SO_2-.

In this invention, "C_1-C_6 alkylsulfonyl" refers to a sulfonyl group bound to the C_1-C_6 alkyl. "C_1-C_4 alkylsulfonyl" refers to a sulfonyl group bound to the C_1-C_4 alkyl.

Examples of "C_1-C_6 alkylsulfonyl" include, but are not limited to, methylsulfonyl, ethylsulfonyl, 1-propylsulfonyl, 2-propylsulfonyl, n-butylsulfonyl, s-butylsulfonyl, t-butylsulfonyl, and 2-ethylbutylsulfonyl.

In the present invention, "C_1-C_6 alkylsulfonylamino" refers to an amino group bound to the "C_1-C_6 alkylsulfonyl". "C_1-C_4 alkylsulfonylamino" refers to an amino group bound to the "C_1-C_4 alkylsulfonyl".

Examples of "C_1-C_6 alkylsulfonylamino" include, but are not limited to, methylsulfonylamino, ethylsulfonylamino, 1-propylsulfonylamino, 2-propylsulfonylamino, n-butylsulfonylamino, s-butylsulfonylamino, t-butylsulfonylamino, and 2-ethylbutylsulfonylamino.

[0013] In the present invention, "a saturated heterocyclic group" refers to a saturated heterocyclic group having one or more than one hetero atom in the ring system. "3-8 membered saturated heterocyclic group" refers to a saturated heterocyclic group whose ring consists of 3-8 atoms.

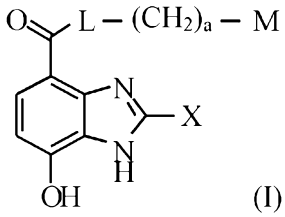
Examples of "3-8 membered saturated heterocyclic group" include, but are not limited to, aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, piperidinyl, azepanyl, and morpholinyl.

A salt is defined as the product formed from the neutralization reaction of acids and bases. Salts are ionic compounds composed of cations (positively charged ions) and anions (negative ions) so that the product is electrically neutral. These component ions can be inorganic as well as organic.

Hydrate is a term used in inorganic chemistry and organic chemistry to indicate that a substance contains water. Solvate refers to a molecule in a solution complexed by solvent molecules. Isomers are compounds with the same molecular formula but different structural formulae. More specifically, isomer includes geometric isomer, optical isomer, stereoisomer, tautomer of the compound, and mixtures thereof.

[0014] The present invention provides a compound represented by formula (I):

[Chem.2]



(I)

wherein

X is phenyl, thiophen-2-yl, furan-2-yl, cyclopropyl, cyclopentyl, phenylC_1-C_6 alkyl, thiophen-2-ylC_1-C_6 alkyl, furan-2-ylC_1-C_6 alkyl, cyclopropylC_1-C_6 alkyl, or cyclopentylC_1-C_6 alkyl;

the phenyl, thiophen-2-yl, furan-2-yl, cyclopropyl, cyclopentyl, phenylC_1-C_6 alkyl, thiophen-2-ylC_1-C_6 alkyl, furan-2-ylC_1-C_6 alkyl, cyclopropylC_1-C_6 alkyl, or cyclopentylC_1-C_6 alkyl are optionally substituted by 1-3 substituent(s) each independently selected from group A;

L is -NH- or single bond;

M is selected C_3-C_8 cycloalkyl or 3-8 membered saturated heterocyclic group;

the C_3-C_8 cycloalkyl, and 3-8 membered saturated heterocyclic group are optionally substituted by 1-3 substituent(s) each independently selected from group A;

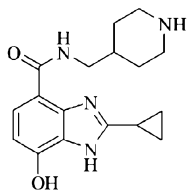
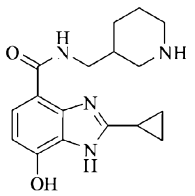
wherein group A consists of hydroxyl, oxo, nitro, cyano, amino, C_1-C_6 alkylamino, C_3-C_8 cycloalkylamino, amide, halogen, sulfamoyl, trifluolomethyl, p-toluenesulfonylamino, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonylamino, C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino, C_1-C_6 alkenyl, C_1-C_6 alkynyl, phosphoryl, carbonyl, carboxyl, and 3-8 membered saturated heterocyclic group;

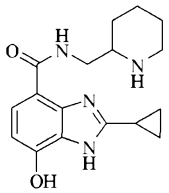
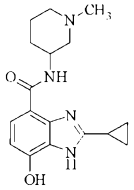
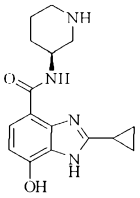
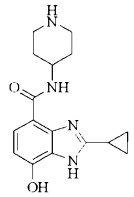
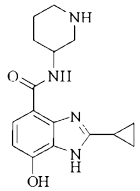
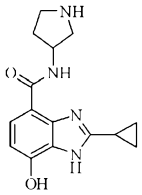
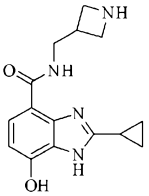
and a is an integer from 0-5.

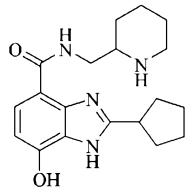
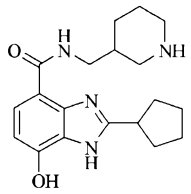
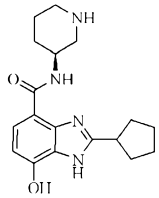
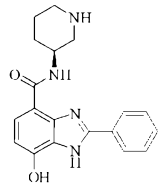
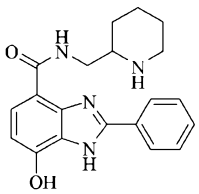
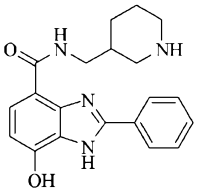
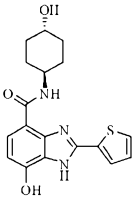
[0015] Preferred compounds include those selected from the group consisting of: Example Nos. 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, and 72 listed in Table 1 below; and the pharmaceutically acceptable salts, prodrugs, hydrates and solvates of the forgoing compounds.

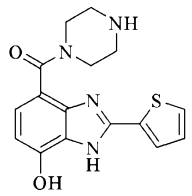
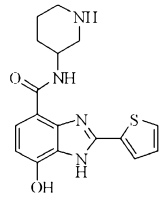
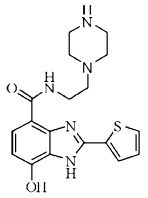
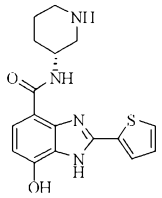
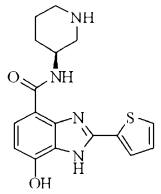
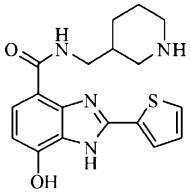
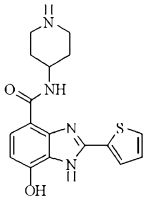
[0016]

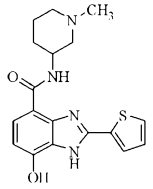
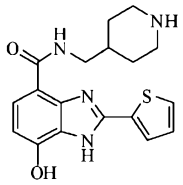
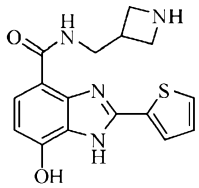
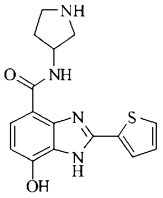
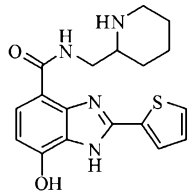
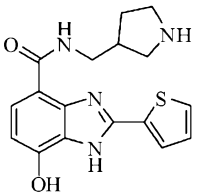
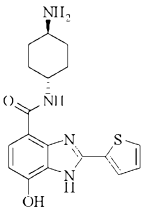
[Table 1]

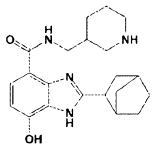
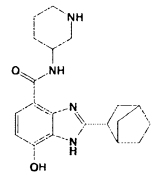
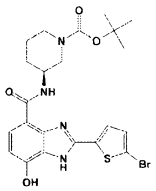
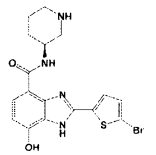
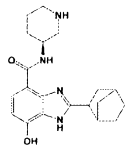
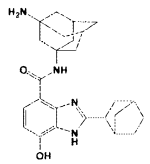
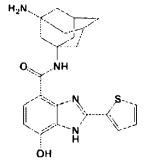
Example No.	structure	compound
5		2-Cyclopropyl-4-hydroxy-N-(piperidin-4-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide
6		2-Cyclopropyl-4-hydroxy-N-(piperidin-3-yl-methyl)-1H-benzo[d]imidazole-7-carboxamide

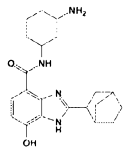
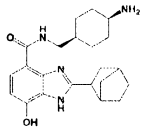
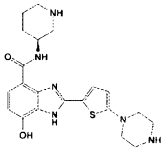
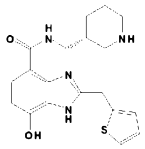
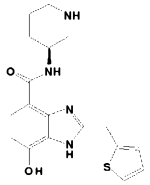
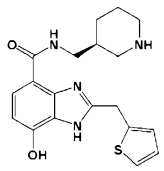
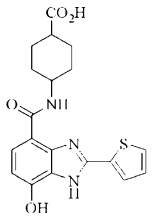
7		2-Cyclopropyl-4-hydroxy-N-(piperidin-2-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide
8		2-cyclopropyl-4-hydroxy-N-(1-methylpiperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide
9		(S)-2-cyclopropyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide
10		2-cyclopropyl-4-hydroxy-N-(piperidin-4-yl)-1H-benzo[d]imidazole-7-carboxamide
11		2-cyclopropyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide
12		2-cyclopropyl-4-hydroxy-N-(pyrrolidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide
13		N-(azetidin-3-ylmethyl)-2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxamide

14		2-cyclopentyl-4-hydroxy-N-(piperidin-2-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide
15		2-Cyclopentyl-4-hydroxy-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide
16		(S)-2-Cyclopentyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide
17		(S)-4-Hydroxy-2-phenyl-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide
18		4-Hydroxy-2-phenyl-N-(piperidin-2-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide
19		4-hydroxy-2-phenyl-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide
20		7-Hydroxy-N-(4-hydroxycyclohexyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

21		(7-hydroxy-2-[thiophen-2-yl]-1H-benzo[d]imidazol-4-yl)(piperazin-1-yl)methanone
35		7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide
36		7-Hydroxy-N-[2-(piperazin-1-yl)ethyl]-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide
37		(R)-7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide
38		(S)-7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide
39		7-Hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide
40		7-Hydroxy-N-(piperidin-4-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

41		7-Hydroxy-N-(1-methylpiperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide
42		7-Hydroxy-N-(piperidin-4-ylmethyl)-2-(thiophen-2-yl)-1 H-benzo[d]imidazole-4-carboxamide
43		N-(Azetidin-3-ylmethyl)-7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide
44		7-Hydroxy-N-(pyrrolidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide
45		7-Hydroxy-N-(piperidin-2-ylmethyl)-2-(thiophen-2-yl)-1 H-benzo[d]imidazole-4-carboxamide
46		7-Hydroxy-N-(pyrrolidin-3-ylmethyl)-2-(thiophen-2-yl)-1 H-benzo[d]imidazole-4-carboxamide
47		N-(4-Aminocyclohexyl)-7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

48		2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide
49		2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide
50		(S)-tert-Butyl 3-(2-(5-bromothiophen-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamido)piperidine-1-carboxylate
51		(S)-2-(5-bromothiophen-2-yl)-7-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide
52		2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-((S)-piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide
53		2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(adamantane-3-ylamino)-1H-benzo[d]imidazole-4-carboxamide
54		2-(Thiophene-2-yl)-7-hydroxy-N-(adamantane-3-ylamino)-1H-benzo[d]imidazole-4-carboxamide

55		N-(3-Aminocyclohexyl)-2-(bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamide
56		N-{[(cis)-4-Aminocyclohexyl]methyl}-2-(bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamide
57		(S)-7-hydroxy-2-(5-(piperazin-1-yl)thiophen-2-yl)-N-(piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide
58		(R)-7-hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide
59		(S)-7-hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide
60		(S)-7-hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide
72		4-[7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]cyclohexanecarboxylic Acid

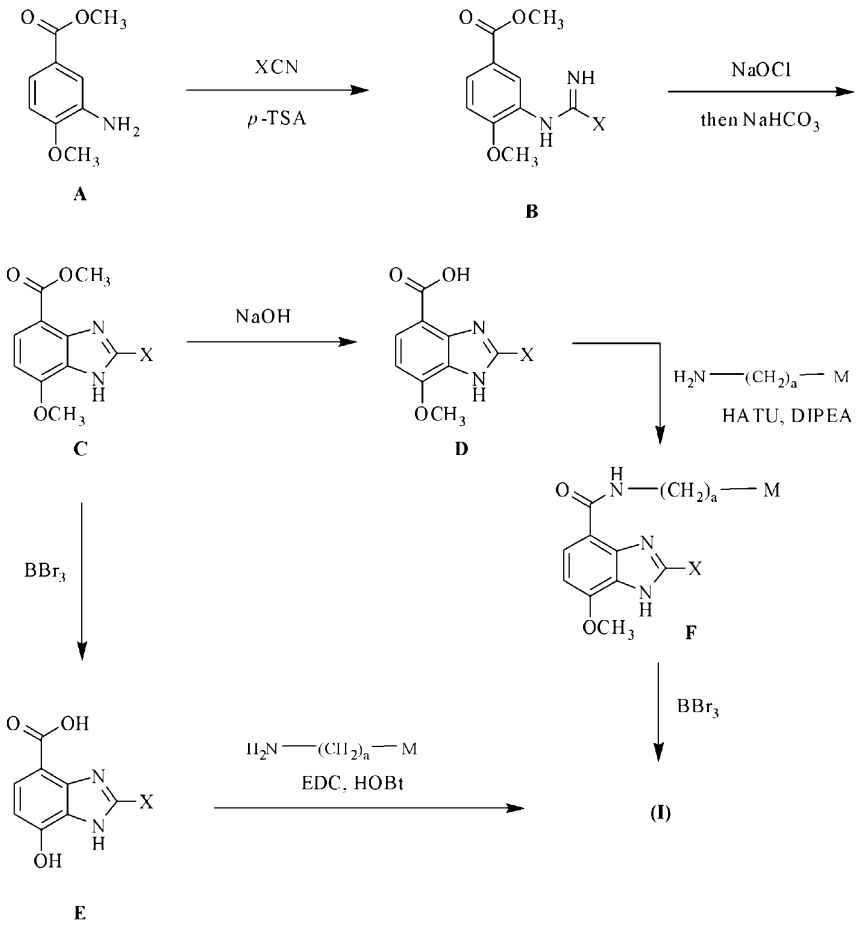
[0017] The compound of formula (I) of the present invention may be in the form of a pharmaceutically acceptable salt derived from an inorganic or organic acid, and repre-

sentative examples of the pharmaceutically acceptable salt derived from an inorganic or organic acid include salts obtained by adding an inorganic acid such as hydrochloric acid, hydrobromic acid, phosphoric acid or sulfonic acid, or organic carboxylic acids such as acetic acid, trifluoroacetic acid, citric acid, formic acid, maleic acid, oxalic acid, succinic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, ascorbic acid or malic acid, methanesulfonic acid, or para toluenesulfonic acid, which do not limit its scope, to the compound of formula (I). Such acids may be prepared by the conventional processes, and other acids, which themselves are not pharmaceutically acceptable, including oxalic acid may be employed in the preparation of the bases. Alternatively, the compound of formula (I) of the present invention may also be in the form of a pharmaceutically acceptable salt derived from an inorganic or organic base include salts obtained by adding an inorganic or organic base. For example, alkalis including sodium hydroxide or potassium hydroxide, or alkaline earth metal hydroxides including calcium hydroxide, magnesium hydroxide, aluminum hydroxide or ammonium hydroxide may be used for the preparation of inorganic salt of the compound. Further, organic bases including triethylamine or diisopropylethylamine may also be used for the preparation of organic salt of the compound.

[0018] The preferred inventive compound of formula (I-II) and (I-III) may be prepared as in Scheme (I).

Scheme (I)

[Chem.3]

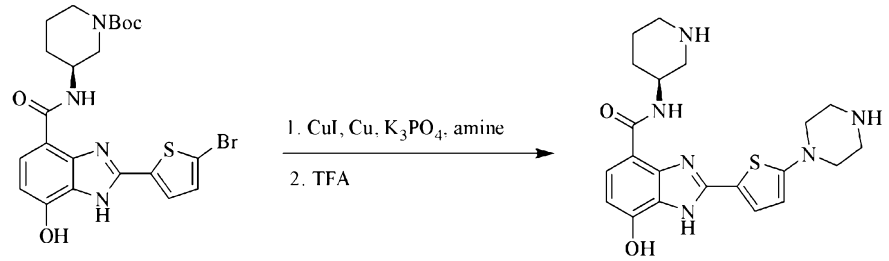


Wherein, p-TSA is p-toluenesulfonic acid, HATU is 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium, DIPEA is N,N-diisopropylethylamine, EDC is 1-[3-(dimethylaminopropyl)-3-ethylcarbodiimide, HOBt is 1-hydroxybenzotriazole and X, a, and M have the same meaning as defined previously.

Aniline A is reacted with the requisite nitrile in the presence of p-toluenesulfonic acid to afford amidine B. Amidine B is chlorinated with sodium hypochlorite and cyclized using sodium bicarbonate to form benzimidazole C. Intermediate C is saponified with sodium hydroxide to afford methoxy acid D which is reacted with various amines in the presence of HATU to afford amides F. Amides F are treated with boron tribromide to afford compounds of formula (I). Intermediate C is treated with boron tribromide to afford hydroxy acid E which is reacted with various amines using EDC and HOBt to afford compounds of formula (I).

Scheme (II)

[Chem.4]



T U

Compound T was reacted with the requisite amine in the presence of copper and copper (I) iodide followed by deprotection to afford compound U (Scheme II).

[0019] A salt, hydrate, solvate and isomer of the inventive compound of formula (I) may be prepared by employing any of the known methods. The inventive compound of formula (I), a salt, hydrate, solvate or isomer thereof may be used for the treatment of GSK-3beta dependent diseases such as Alzheimer disease, mania, depression, migraine and type 2 diabetes,, by way of inhibiting GSK-3beta activity, the inventive compound having an IC_{50} value (micro M), generally in the range of 0.0001 to 100, for example 0.001 to 50, preferably 0.001 to 10, more preferably 0.001 to 5.

Accordingly, the present invention includes a pharmaceutical composition which contains a therapeutically effective amount of the compound of formula (I), a salt, hydrate, solvate or isomer thereof as an active ingredient and a pharmaceutically acceptable carrier; therefore, the pharmaceutical composition of the present invention exerts superior preventive and treating effects on GSK-3beta dependent diseases.

A pharmaceutical formulation may be prepared in accordance with any of the conventional procedures. In preparing the formulation, the active ingredient is preferably admixed or diluted with a carrier, or enclosed within a carrier, sachet or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material acting as a vehicle, excipient or medium for the active ingredient. Thus, the formulations may be in the form of a tablet, pill, powder, sachet, elixir, suspension, emulsion, solution, syrup, aerosol, soft and hard gelatin capsule, sterile injectable solution, sterile packaged powder and the like.

[0020] Examples of suitable carriers, excipients, and diluents are lactose, dextrose, sucrose, sorbitol, mannitol, calcium silicate, cellulose, methyl cellulose, microcrystalline cellulose, polyvinylpyrrolidone, water, and mineral oil. The formulations may additionally include fillers, antiemulsifiers, preservatives and the like. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after their administration to a mammal by employing any of the procedures well known in the art.

The pharmaceutical composition of the present invention can be administered via various routes including oral, transdermal, subcutaneous, intravenous and intramuscular introduction.

In addition to the above, the present composition may contain other pharmaceutical active ingredients so long as they do not inhibit the in vivo function of the compound of the present invention. For example, the composition may further contain chemotherapeutic agents conventionally used for treating Alzheimer disease, mania, depression, migraine or type 2 diabetes .

The compounds disclosed here can be used to treat or prevent GSK-3beta dependent diseases including Alzheimer disease, mania, depression, migraine and type 2 diabetes. For example, the present invention provides methods for treating or preventing GSK-3beta dependent diseases including Alzheimer disease, mania, depression, migraine and type 2 diabetes in a subject by administering to the subject the compounds disclosed here. In a preferred embodiment, such compound can be administered to the subject in the form of pharmaceutical composition including the compound of the present invention and pharmaceutically or physiologically acceptable carrier. The pharmaceutical composition of the present invention can be administered via various routes including oral, transdermal, subcutaneous, intravenous and intramuscular introduction for treating GSK-3beta dependent diseases including Alzheimer disease, mania, depression, migraine and type 2 diabetes in a subject.

[0021] In another embodiment, the present invention also provides the use of the compound of the present invention in manufacturing a pharmaceutical composition for treating GSK-3beta dependent diseases including Alzheimer disease, mania, depression, migraine and type 2 diabetes . For example, the present invention relates to a use of the compound of the present invention for manufacturing a pharmaceutical composition for treating GSK-3beta dependent diseases including Alzheimer disease, mania, depression, migraine and type 2 diabetes.

Alternatively, the present invention further provides the compound of the present invention for use in the treatment of GSK-3beta dependent diseases including Alzheimer disease, mania, depression, migraine and type 2 diabetes.

Alternatively, the present invention further provides a method or process for manufacturing a pharmaceutical composition for treating GSK-3beta dependent diseases including Alzheimer disease, mania, depression, migraine and type 2 diabetes , wherein the method or process includes the step for formulating a pharmaceutically or physiologically acceptable carrier with the compound of the present invention as active ingredients.

In another embodiment, the present invention also provides a method or process for manufacturing a pharmaceutical composition for treating GSK-3beta dependent

diseases including Alzheimer disease, mania, depression, migraine and type 2 diabetes, wherein the method or process includes the step for admixing an active ingredient with a pharmaceutically or physiologically acceptable carrier, wherein the active ingredient is the compound of the present invention.

[0022] The dosage and method of administration vary according to the body-weight, age, and symptoms of the patient; however, one skilled in the art can suitably select them.

For example, although the dose of a compound of the present invention that regulates its activity depends on the symptoms, the dose is generally about 0.1 mg to about 100 mg per day, preferably about 1.0 mg to about 50 mg per day and more preferably about 1.0 mg to about 20 mg per day, when administered orally to a normal adult human (weight 60 kg).

When administering the compound parenterally, in the form of an injection to a normal adult human (weight 60 kg), although there are some differences according to the patient, target organ, symptoms and method of administration, it is convenient to intravenously inject a dose of about 0.01 mg to about 30 mg per day, preferably about 0.1 to about 20 mg per day and more preferably about 0.1 to about 10 mg per day. In the case of other animals, the appropriate dosage amount may be routinely calculated by converting to 60 kg of body-weight.

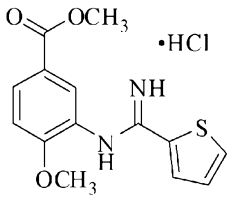
Examples

[0023] The following examples are intended to further illustrate the present invention without limiting its scope.

Example 1

STEP 1: Synthesis of Methyl 4-Methoxy-3-(thiophene-2-carboximidamido)benzoate

[Chem.5]

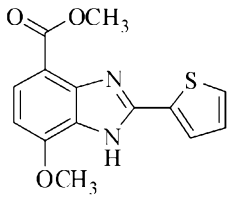


p-Toluenesulfonic acid monohydrate (42 g, 110 mmol) was heated at 120 degrees C and once the solid completely melted, it was placed under high vacuum for 1 h to remove the water. The vacuum was released, aniline (20 g, 55 mmol) and 2-thiophenecarbonitrile (24 g, 110 mmol) were added, and the reaction mixture was heated at 160 degrees C for 4 h. The reaction mixture was cooled to room temperature followed by addition of satd. aq $NaHCO_3$ (250 mL) and ethyl acetate (250 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (100 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography to obtain 16 g of the crude

amidine intermediate. The crude intermediate was dissolved in ethyl acetate (350 mL) and HCl (2.0 M in diethyl ether, 55 mL, 110 mmol) was added. The resulting precipitate was filtered to obtain the desired product (16 g, 42% yield) as an off-white solid: ESI MS m/z 291 $[C_{14}H_{14}N_3O_2S + H]^+$.

STEP 2: Synthesis of Methyl 7-Methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxylate

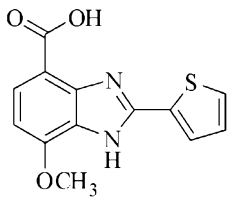
[Chem.6]



To a solution of the product from step 1 (16 g, 49 mmol) in methanol (100 mL) was added 5% aq NaOCl (75 mL, 55 mmol) and the reaction mixture was stirred at room temperature for 2 h. Next, satd. aq $NaHCO_3$ (150 mL) and methanol (150 mL) were added and the resulting reaction mixture was heated at 60 degrees C for 2 d. The reaction mixture was cooled to room temperature and concentrated to remove methanol. The reaction mixture was acidified to pH 4 using 6 N HCl and the resulting precipitate was filtered and dried to obtain the desired product (8 g, 57% yield) as a brown solid: ^{1}H NMR (500 MHz, $CDCl_3$) delta 7.86 (d, J = 8.5 Hz, 1H), 7.71-7.68 (m, 1H), 7.48-7.45 (m, 1H), 7.17-7.14 (m, 1H), 7.73 (d, J = 8.5 Hz, 1H), 4.16 (m, 3H), 3.98 (m, 3H); ESI MS m/z 289 $[C_{14}H_{12}N_2O_3S + H]^+$.

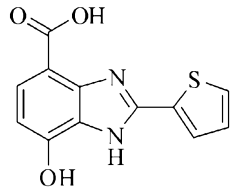
[0024] STEP 3: Synthesis of 7-Methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxylic Acid

[Chem.7]



To a solution of the product from step 2 (4.2 g, 14 mmol) in ethanol (30 mL) and water (15 mL) was added 6 N NaOH (55 mL) and the reaction mixture was heated at 90 degrees C for 2 h. The reaction mixture was cooled and concentrated to dryness. The crude residue was dissolved in water (30 ml) and acidified to pH 4 using 6 N HCl. The resulting precipitate was filtered and dried to obtain the desired product (2.2 g, 58% yield) as a brown solid: ^{1}H NMR (500 MHz, DMSO-d_6) delta 8.25 (d, J = 3.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.73-7.68 (m, 1H), 7.22-7.18 (m, 1H), 6.82 (d, J = 8.5 Hz, 1H), 3.97 (m, 3H); ESI MS m/z 275 $[C_{13}H_{10}N_2O_3S + H]^+$.

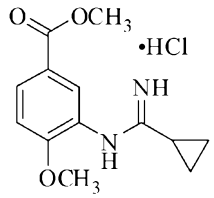
STEP 4: Synthesis of
7-Methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxylic Acid
[Chem.8]



To a solution of the product from step 3 (2.5 g, 9.1 mmol) in dichloroethane (100 mL) was added BBr_3 (23g, 91 mmol) and the reaction mixture was heated at 90 degrees C for 2 d. The reaction mixture was cooled and poured onto ice. The resulting solids were filtered to obtain the desired product (0.45 g, 19% yield) as a brown solid. The filtrate was acidified to pH 4 using 6 N HCl and the resulting precipitate was filtered to obtain a second batch of the desired product (ALB 128328, 1.6 g, 88% yield) as a brown solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.93-7.90 (m, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.62-7.58 (m, 1H), 7.19-7.14 (m, 1H), 6.65 (d, J = 8.1 Hz, 1H); ESI MS m/z 261 $[C_{12}H_8N_2O_3S + H]^+$.

[0025] Example 2

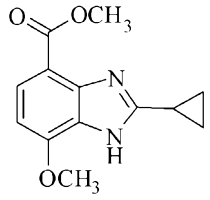
STEP 1: Synthesis of Methyl
3-(Cyclopropanecarboximidamido)-4-methoxybenzoate Hydrochloride
[Chem.9]



Following the procedure outlined for step 1 in Example 1, methyl 3-amino-4-methoxybenzoate (10 g, 55 mmol) was reacted with cyclopropanecarbonitrile (7.4 g, 110 mmol) to afford the desired product (16 g crude) as a black solid: ESI MS m/z 249 $[C_{13}H_{16}N_2O_3 + H]^+$.

STEP 2: Synthesis of Methyl
2-Cyclopropyl-7-methoxy-1H-benzo[d]imidazole-4-carboxylate

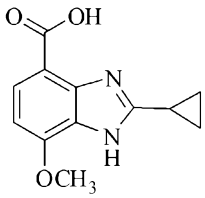
[Chem.10]



Following the procedure outlined for step 2 in Example 1, methyl 3-(cyclopropanecarboximidamido)-4-methoxybenzoate hydrochloride (15 g, 50 mmol) was reacted with aq NaOCl followed by satd. aq $NaHCO_3$ to afford the desired product (12 g crude) as a brown solid: ESI MS m/z 247 $[C_{13}H_{14}N_2O_3 + H]^+$.

[0026] STEP 3: Synthesis of 2-Cyclopropyl-7-methoxy-1H-benzo[d]imidazole-4-carboxylic Acid

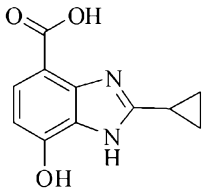
[Chem.11]



Following the procedure outlined for step 3 in Example 1, methyl 2-cyclopropyl-7-methoxy-1H-benzo[d]imidazole-4-carboxylate (2.0 g, 8.0 mmol) was reacted with sodium hydroxide to afford the desired product (1.7 g crude) as a black solid: ESI MS m/z 233 $[C_{12}H_{12}N_2O_3 + H]^+$.

STEP 4: Synthesis of 2-Cyclopropyl-7-hydroxy-1H-benzo[d]imidazole-4-carboxylic Acid

[Chem.12]

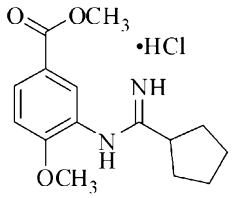


Following the procedure outlined for step 4 in Example 1, 2-cyclopropyl-7-methoxy-1H-benzo[d]imidazole-4-carboxylic acid (1.5 g, 6.1 mmol) was reacted with boron tribromide to afford the desired product (1.2 g crude) as a black solid: ESI MS m/z 219 $[C_{11}H_{10}N_2O_3 + H]^+$.

[0027] Example 3

STEP 1: Synthesis of Methyl 3-(Cyclopentanecarboximidamido)-4-methoxybenzoate Hydrochloride

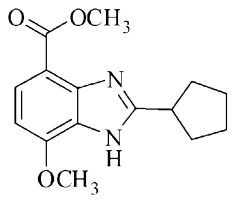
[Chem.13]



Following the procedure outlined for step 1 in Example 1, methyl 3-amino-4-methoxybenzoate (5.0 g, 27 mmol) was reacted with cyclopentanecarbonitrile (5.2 g, 55 mmol) to afford the desired product (7.7 g crude) as a brown solid: ESI MS m/z 277 $[C_{15}H_{20}N_2O_3+ H]^+$.

STEP 2: Synthesis of Methyl 2-Cyclopentyl-7-methoxy-1H-benzo[d]imidazole-4-carboxylate

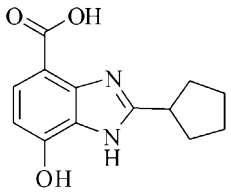
[Chem.14]



Following the procedure outlined for step 2 in Example 1, methyl 3-(cyclopentanecarboximidamido)-4-methoxybenzoate hydrochloride (5.6 g, 18 mmol) was reacted with aq NaOCl followed by satd. aq $NaHCO_3$ to afford the desired product (4.9 g crude) as a black solid: ESI MS m/z 275 $[C_{15}H_{18}N_2O_3 + H]^+$.

[0028] STEP 3: Synthesis of 2-Cyclopentyl-7-hydroxy-1H-benzo[d]imidazole-4-carboxylic Acid

[Chem.15]

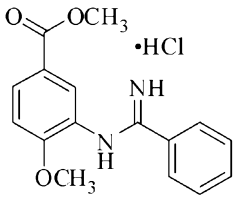


Following the procedure outlined for step 4 in Example 1, methyl 2-cyclopentyl-7-methoxy-1H-benzo[d]imidazole-4-carboxylate (1.1 g, 4.0 mmol) was reacted with boron tribromide to afford the desired product (0.92 g crude) as a black solid: ESI MS m/z 247 $[C_{13}H_{14}N_2O_3 + H]^+$.

[0029] Example 4

STEP 1: Synthesis of Methyl 3-Benzimidamido-4-methoxybenzoate Hydrochloride

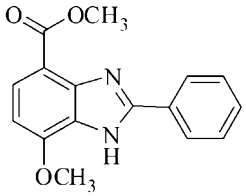
[Chem.16]



Following the procedure outlined for step 1 in Example 1, methyl 3-amino-4-methoxybenzoate (5.0 g, 27 mmol) was reacted with benzonitrile (5.7 g, 55 mmol) to afford the desired product (7.8 g crude) as a black solid: ESI MS m/z 285 [$C_{16}H_{16}N_2O_3$+ H]$^+$.

STEP 2: Synthesis of Methyl 7-Methoxy-2-phenyl-1H-benzo[d]imidazole-4-carboxylate

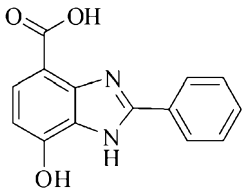
[Chem.17]



Following the procedure outlined for step 1 in Example 1, methyl 3-benzimidamido-4-methoxybenzoate hydrochloride (2.0 g, 8.0 mmol) was reacted with aq NaOCl followed by satd. aq $NaHCO_3$ to afford the desired product (1.7 g crude) as an off-white solid: ESI MS m/z 283 [$C_{16}H_{14}N_2O_3$ + H]$^+$.

[0030] STEP 3: Synthesis of 7-Hydroxy-2-phenyl-1H-benzo[d]imidazole-4-carboxylic Acid

[Chem.18]



Following the procedure outlined for step 4 in Example 1, methyl 7-methoxy-2-phenyl-1H-benzo[d]imidazole-4-carboxylate (4.0 g, 12 mmol) was reacted with boron tribromide to afford the desired product (2.1 g crude) as a black solid: ESI MS m/z 255 [$C_{14}H_{10}N_2O_3$ + H]$^+$.

General Procedure A - synthesis of compounds of formula I-II as described in Scheme (1):

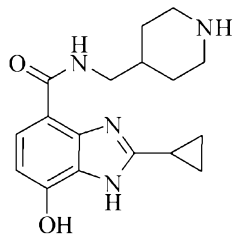
To a solution of hydroxy acids E (1.0 equiv) in THF (5-10 mL) was added EDC (1.2 equiv), HOBt (1.1 equiv), and the amine (1.2 equiv) and the reaction mixture was

either stirred at room temperature for 16 h or heated at 50-70 degrees C for 16 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (25 ml). The layers were separated and the organic layer was dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18 silica, 10-90% acetonitrile/water with 0.05% TFA). In some instances the desired product was dissolved in trifluoroacetic acid (2 mL) and stirred for 1 h at room temperature. The reaction mixture was concentrated and eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to obtain the desired products.

[0031] Example 5

2-Cyclopropyl-4-hydroxy-N-(piperidin-4-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide

[Chem.19]

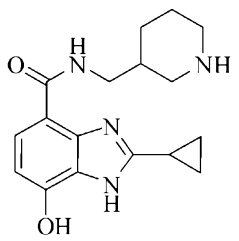


Following general procedure A, 2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (55 mg, 0.25 mmol) was reacted with racemic tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (81 mg, 0.38 mmol) to afford the desired product (21 mg, 27% yield) as a light brown-yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) delta 9.67 (bs, 1H), 7.57 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 3.25-3.22 (m, 2H), 2.98-2.96 (m, 2H), 2.48-2.46 (m, 2H), 2.16 (bs, 1H), 1.68-1.58 (m, 3H), 1.18-1.06 (m, 6H); ESI MS m/z 315 $[C_{17}H_{22}N_4O_2 + H]^+$; HPLC 98.6% (AUC), t_R = 6.38 min.

[0032] Example 6

2-Cyclopropyl-4-hydroxy-N-(piperidin-3-yl-methyl)-1H-benzo[d]imidazole-7-carboxamide

[Chem.20]



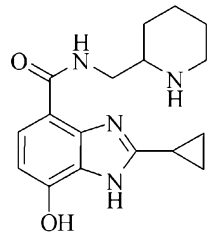
Following general procedure A,

2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (55 mg, 0.25 mmol) was reacted with racemic tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (81 mg, 0.38 mmol) to afford the desired product (12 mg, 15% yield) as a light gray solid: ^{1}H NMR (500 MHz, CD_3OD) delta 7.66 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 3.51-3.49 (m, 2H), 3.14 (d, J = 12.5 Hz, 1H), 2.94 (bs, 1H), 2.75-2.73 (m, 1H), 2.19-2.17 (m, 1H), 1.90-1.88 (m, 2H), 1.71-1.68 (m, 2H), 1.54-1.49 (m, 1H), 1.35 (bs, 1H), 1.15-1.13 (m, 4H); ESI MS m/z 315 $[C_{17}H_{22}N_4O_2 + H]^+$; HPLC 99.7% (AUC), t_R = 5.98 min.

[0033] Example 7

2-Cyclopropyl-4-hydroxy-N-(piperidin-2-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide

[Chem.21]

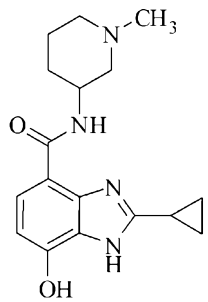


Following general procedure A, 2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (55 mg, 0.25 mmol) was reacted with racemic tert-butyl 2-(aminomethyl)piperidine-1-carboxylate (81 mg, 0.38 mmol) to afford the desired product (13 mg, 17% yield) as a light gray solid: ^{1}H NMR (500 MHz, CD_3OD) delta 7.66 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 3.39-3.38 (m, 2H), 3.22 (d, J = 12 Hz, 1H), 3.08 (d, J = 12 Hz, 1H), 2.69-2.68 (m, 1H), 2.66-2.63 (m, 1H), 2.55-2.50 (m, 1H), 2.18-2.15 (m, 1H), 1.99-1.97 (m, 2H), 1.92-1.89 (m, 1H), 1.82-1.80 (m, 1H), 1.62-1.59 (m, 1H), 1.32-1.34 (m, 1H), 1.13 (bs, 4H); ESI MS m/z 315 $[C_{17}H_{22}N_4O_2 + H]^+$; HPLC 96.8% (AUC), t_R = 6.78 min.

[0034] Example 8

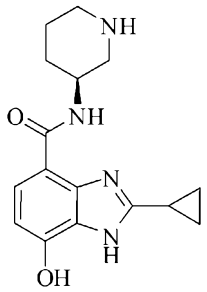
2-cyclopropyl-4-hydroxy-N-(1-methylpiperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide

[Chem.22]



Following general procedure A,
2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (55 mg, 0.25 mmol) was reacted with racemic 1-methylpiperidin-3-amine (43 mg, 0.38 mmol) to afford the desired product (21 mg, 32% yield) as a brown-yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) delta 12.7 (bs, 1H), 10.5 (bs, 1H), 9.97 (bs, 1H), 7.58 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 4.06 (bs, 1H), 3.32 (bs, 2H), 2.40-2.34 (m, 1H), 2.22-2.11 (m, 2H), 1.75 (bs, 1H), 1.65 (bs, 1H), 1.55 (bs, 1H), 1.44 (bs, 1H), 1.14-1.1 0 (m, 4H); ESI MS m/z 315 [$C_{17}H_{22}N_4O_2$ + H]$^+$; HPLC 96.8% (AUC), t_R = 7.12 min.

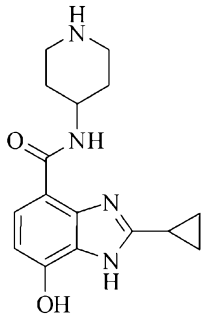
[0035] Example 9
(S)-2-cyclopropyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide
[Chem.23]



Following general procedure A,
2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (55 mg, 0.25 mmol) was reacted with (S)-tert-butyl 3-aminopiperidine-1-carboxylate (75 mg, 0.38 mmol) to afford the desired product (28 mg, 37% yield) as a brown-yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) delta 12.7 (bs, 1H), 9.82 (bs, 1H), 7.58 (d, J = 8.5 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 3.93-3.91 (m, 1H), 3.17 (bs, 1H), 3.03-3.00(m, 1H), 2.77 (m, 1H), 2.64 (bs, 1H), 2.16 (bs, 1H), 1.87 (bs, 1H), 1.73-1.70 (m, 1H), 1.50-1.45 (m, 2H), 1.11-1.10 (m, 4H); ESI MS m/z 301 [$C_{16}H_{20}N_4O_2$ + H]$^+$; HPLC 96.8% (AUC), t_R = 6.63 min.

[0036] Example 10
2-cyclopropyl-4-hydroxy-N-(piperidin-4-yl)-1H-benzo[d]imidazole-7-carboxamide

[Chem.24]

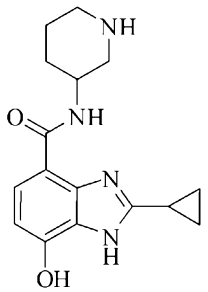


Following general procedure A, 2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (55 mg, 0.25 mmol) was reacted with racemic tert-butyl 4-aminopiperidine-1-carboxylate (75 mg, 0.38 mmol) to afford the desired product (27 mg, 36% yield over two steps as a brown-yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) delta 9.75 (d, J = 6 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 3.96 (bs, 1H), 2.99-2.97 (m, 2H), 2.70-2.66 (m, 2H), 2.16 (bs, 1H), 1.88-1.86 (m, 2H), 1.42-1.40 (m, 2H), 1.13-1.04 (m, 4H); ESI MS m/z 301 $[C_{16}H_{20}N_4O_2 + H]^+$; HPLC 95.8% (AUC), t_R = 6.21 min

[0037] Example 11

2-cyclopropyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide

[Chem.25]

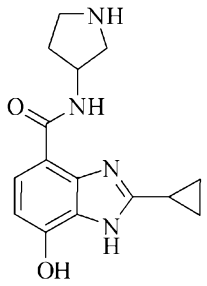


Following general procedure A, 2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (55 mg, 0.25 mmol) was reacted with racemic tert-butyl 3-aminopiperidine-1-carboxylate (75 mg, 0.38 mmol) to afford the desired product (16 mg, 21% yield) as a brown-yellow solid: ^{1}H NMR (500 MHz, CD_3OD) delta 7.67 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 4.12-4.08 (m, 1H), 3.31-3.28 (m, 1H), 3.04-3.00(m, 1H), 2.79-2.73 (m, 1H), 2.20-2.10 (m, 2H), 1.94-1.91 (m, 1H), 1.76-1.65 (m, 1H), 1.17-1.14 (m, 4H); ESI MS m/z 301 $[C_{16}H_{20}N_4O_2 + H]^+$; HPLC 96.8% (AUC), t_R = 6.63 min.

[0038] Example 12

2-cyclopropyl-4-hydroxy-N-(pyrrolidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide

[Chem.26]

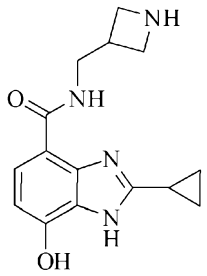


Following general procedure A, 2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (55 mg, 0.25 mmol) was reacted with racemic tert-butyl 3-aminopyrrolidine-1-carboxylate (70 mg, 0.38 mmol) to afford the desired product (19 mg, 27% yield) as a brown-yellow solid: ^{1}H NMR (500 MHz, CD_3OD) delta 7.66 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 4.56-4.51 (m, 1H), 3.36-3.32 (m, 1H), 3.26-3.20(m, 1H), 3.14-3.09 (m, 1H), 3.03-3.00 (m, 1H), 2.32-2.25 (m, 1H), 2.19-2.14 (m, 1H), 1.97-1.93 (m, 1H), 1.14-1.10 (m, 4H); ESI MS m/z 287 $[C_{15}H_{18}N_4O_2 + H]^+$; HPLC 96.8% (AUC), t_R = 6.40 min.

[0039] Example 13

N-(azetidin-3-ylmethyl)-2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxamide

[Chem.27]



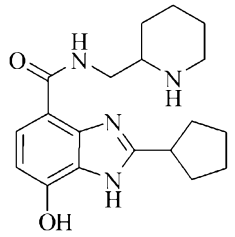
Following general procedure A, 2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (55 mg, 0.25 mmol) was reacted with tert-butyl 3-(aminomethyl)azetidine-1-carboxylate (70 mg, 0.38 mmol) to afford the desired product (22 mg, 31% yield) as a brown-yellow solid: ^{1}H NMR (500 MHz, CD_3OD) delta 7.66 (d, J = 8.5 Hz, 1H), 6.56 (d, J = 8.5 Hz, 1H), 4.00-3.85 (m, 4H), 3.69-3.67 (m, 2H), 3.17-3.14(m, 1H), 2.18-2.14 (m, 1H), 1.13-1.08 (m, 4H); ESI MS m/z 287 $[C_{15}H_{18}N_4O_2 + H]^+$; HPLC 96.8% (AUC), t_R = 6.15 min.

[0040] Example 14

Synthesis of 2-cyclopentyl-4-hydroxy-N-(piperidin-2-ylmethyl)-1H-

benzo[d]imidazole-7-carboxamide

[Chem.28]

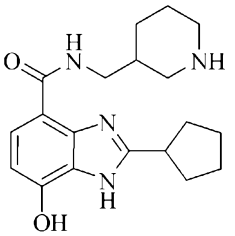


Following general procedure A, 2-cyclopentyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (62 mg, 0.25 mmol) was reacted with racemic tert-butyl 2-(aminomethyl)piperidine-1-carboxylate (81 mg, 0.38 mmol) to afford the desired product (33 mg, 39% yield) as a brown solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.69 (d, J = 9.0 Hz, 1H), 6.59 (d, J = 9.0 Hz, 1H), 3.54-3.52 (m, 2H), 3.39-3.34 (m, 1H), 3.16-3.11 (m, 1H), 2.99-2.93 (m, 1H), 2.74 (bs, 1H), 2.19-2.15 (m, 2H), 2.09-1.81 (m, 6H), 1.78-1.69 (m, 3H), 1.52-1.32 (m, 3H); ESI MS m/z 343 $[C_{19}H_{26}N_4O_2 + H]^+$; HPLC 98.6% (AUC), t_R = 1.51 min.

[0041] Example 15

2-Cyclopentyl-4-hydroxy-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide

[Chem.29]

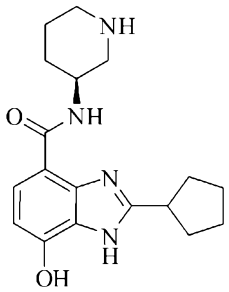


Following general procedure A, 2-cyclopentyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (62 mg, 0.25 mmol) was reacted with racemic tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (81 mg, 0.38 mmol) to afford the desired product (35 mg, 41% yield) as a off-white solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.69 (d, J = 9.0 Hz, 1H), 6.59 (d, J = 9.0 Hz, 1H), 3.43-3.41 (m, 2H), 3.30-3.25 (m, 1H), 3.16-3.12 (m, 1H), 2.72-2.59 (m, 2H), 2.18-2.15 (m, 2H), 2.03-1.75 (m, 11H), 1.39-1.34 (m, 1H); ESI MS m/z 343 $[C_{19}H_{26}N_4O_2 + H]^+$; HPLC 99.2% (AUC), t_R = 1.49 min.

[0042] Example 16

(S)-2-Cyclopentyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide

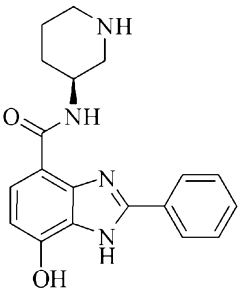
[Chem.30]



Following general procedure A,
2-cyclopentyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxylic acid (55 mg, 0.25 mmol) was reacted with (S)-tert-butyl 3-aminopiperidine-1-carboxylate (75 mg, 0.38 mmol) to afford the desired product (22 mg, 27% yield) as a brown solid: ^{1}H NMR (500 MHz, CD_3OD) delta 7.69 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 4.09 (bs, 1H), 3.39-3.30 (m, 2H), 2.99 (bs, 1H), 2.72-2.76 (m, 2H), 2.19-2.14 (m, 3H), 2.03-1.99 (m, 2H), 1.91-1.88 (m, 3H), 1.78-1.67 (m, 4H); ESI MS m/z 329 $[C_{18}H_{24}N_4O_2 + H]^+$; HPLC >99% (AUC), t_R = 1.48 min.

[0043] Example 17
(S)-4-Hydroxy-2-phenyl-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide

[Chem.31]

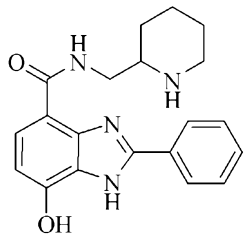


Following general procedure A,
4-hydroxy-2-phenyl-1H-benzo[d]imidazole-7-carboxylic acid (55 mg, 0.25 mmol) was reacted with (S)-tert-butyl 3-aminopiperidine-1-carboxylate (75 mg, 0.38 mmol) to afford the desired product (10 mg, 12% yield) as a green-yellow solid: ^{1}H NMR (500 MHz, CD_3OD) delta 8.20-8.18 (m, 2H), 7.78 (d, J = 8.5 Hz, 1H), 7.56-7.51 (m, 3H), 6.68 (d, J = 8.5 Hz, 1H), 4.16 (bs, 1H), 3.39-3.35(m, 1H), 3.05 (bs, 1H), 2.87-2.82 (m, 2H), 2.20-2.19 (m, 1H), 2.00 (bs, 1H), 1.80-1.76 (m, 2H); ESI MS m/z 337 $[C_{19}H_{20}N_4O_2 + H]^+$; HPLC 95.7% (AUC), t_R = 8.78 min.

[0044] Example 18
4-Hydroxy-2-phenyl-N-(piperidin-2-ylmethyl)-1H-

benzo[d]imidazole-7-carboxamide

[Chem.32]



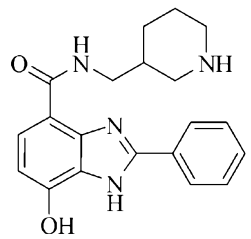
Following general procedure A,

4-hydroxy-2-phenyl-1H-benzo[d]imidazole-7-carboxylic acid (62 mg, 0.25 mmol) was reacted with racemic tert-butyl 2-(aminomethyl)piperidine-1-carboxylate (81 mg, 0.38 mmol) to afford the desired product (20 mg, 23% yield) as a brown solid: ^{1}H NMR (500 MHz, DMSO-d_6) delta 9.77 (bs, 1H), 8.32-8.30 (m, 2H), 7.70 (d, J = 8.5 Hz, 1H), 7.58-7.51 (m, 3H), 6.71 (d, J = 8.5 Hz, 1H), 3.17-3.10 (m, 2H), 2.96-2.94(m, 1H), 2.56-2.42 (m, 3H), 1.90-1.87 (m, 1H), 1.81-1.77 (m, 1H), 1.69-1.65 (m, 1H), 1.46-1.44 (m, 1H), 1.27-1.24 (m, 1H); ESI MS m/z 351 $[C_{20}H_{22}N_4O_2 + H]^+$; HPLC 99.0% (AUC), t_R = 7.74 min.

[0045] Example 19

4-hydroxy-2-phenyl-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide

[Chem.33]



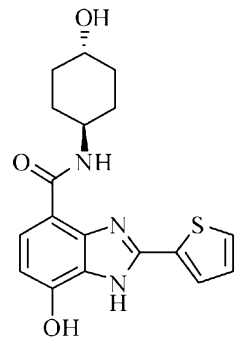
Following general procedure A,

4-hydroxy-2-phenyl-1H-benzo[d]imidazole-7-carboxylic acid (62 mg, 0.25 mmol) was reacted with tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (81 mg, 0.38 mmol) to afford the desired product (20 mg, 23% yield) as a brown solid: ^{1}H NMR (500 MHz, DMSO-d_6) delta 9.99 (bs, 1H), 8.40-8.38 (m, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.57-7.52 (m, 3H), 6.72 (d, J = 8.5 Hz, 1H), 3.43-3.41 (m, 2H), 3.11-3.08(m, 1H), 2.64 (bs, 1H), 1.78-1.71 (m, 2H), 1.57 (bs, 1H), 1.69-1.65 (m, 1H), 1.46-1.44 (m, 1H), 1.27-1.24 (m, 1H); ESI MS m/z 351 $[C_{20}H_{22}N_4O_2 + H]^+$; HPLC 99.1 (AUC), t_R = 8.99 min.

[0046] Example 20

7-Hydroxy-N-(4-hydroxycyclohexyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.34]

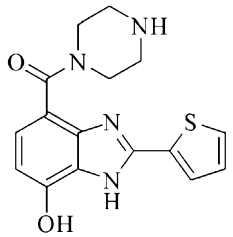


To a solution of 4-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.15 g, 0.57 mmol) in DMF (10 mL) was added HATU (0.26 g, 0.68 mmol), DIPEA (0.30 mL, 1.7 mmol) and trans-4-aminocyclohexanol (0.13 g, 1.1 mmol). The reaction mixture was heated at 50 degrees C for 16 h. The reaction mixture was diluted with satd. aq $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18 silica, 10-90% acetonitrile/water with 0.05% TFA). The desired product was obtained as the trifluoroacetic acid salt which was eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to afford the desired product (13 mg, 32%) as an off-white solid: ^1H NMR (300 MHz, CD_3OD) delta 10.19-10.17 (m, 1H), 7.87-7.85 (m, 1H), 7.79-7.75 (m, 1H), 7.64-7.61 (m, 1H), 7.22-7.19 (m, 1H), 6.71-6.67 (m, 1H), 4.02-3.97 (m, 1H), 3.77-3.71 (m, 1H), 2.19-2.08 (m, 4H), 1.55-1.50 (m, 4H); ESI MS m/z 358 $[C_{18}H_{19}N_3O_3S + H]^+$; HPLC 98.8% (AUC), t_R = 11.84 min.

[0047] Example 21

(7-hydroxy-2-[thiophen-2-yl]-1H-benzo[d]imidazol-4-yl) (piperazin-1-yl)methanone

[Chem.35]



To a solution of 4-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.20 g, 0.76 mmol) in DMF (10 mL) was added HATU (0.34 g, 0.92 mmol), DIPEA (0.39 mL, 2.3 mmol) and tert-butyl piperazine-1-carboxylate (0.17 g, 0.92 mmol). The reaction mixture was heated at 50 degrees C for 16 h. The reaction mixture was diluted with satd. aq $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over Na_2SO_4, concentrated, and purified

by preparative HPLC (C18 silica, 10-90% acetonitrile/water with 0.05% TFA). The intermediate was dissolved in methylene dichloride and treated with 2 N HCl in ether and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated and the residue was eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to afford the desired product (13 mg, 32%) as an off-white solid: ^{1}H NMR (500 MHz, DMSO-d_6) delta 8.01 (bs, 1H), 7.70 (d, J = 5.0, Hz, 1H), 7.20 (dd, J = 5.0, 4.0 Hz, 1H), 7.00 (d, J = 8.0, Hz, 1H), 6.56-6.57 (m, 1H), 3.70-3.05 (m, 8H); ESI MS m/z 329 $[C_{16}H_{16}N_4O_2S + H]^+$; HPLC 95.5% (AUC), t_R = 8.79 min.

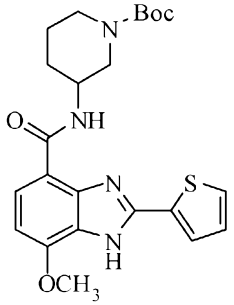
[0048] General Procedure B - synthesis of amides F as described in Scheme (1):

To a suspension of 7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxylic acid (1.0 equiv) in toluene (5-15 mL) was added thionyl chloride (4.0 equiv). After stirring at room temperature for 16 h, the reaction mixture was heated at 70 degrees C for 2 h. The reaction mixture was cooled, and concentrated, and the residue was suspended in THF (10 -20 mL) followed by the addition of pyridine (2.0 equiv) and the corresponding amine (2.0 equiv) and the reaction mixture was heated at 70 degrees C for 16 h. The reaction mixture was concentrated and the residue was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with satd. aq $NaHCO_3$ (20 mL), concentrated, and purified by flash chromatography (silica, 0-15% methanol/dichloromethane) to afford amides F. In most cases these intermediates were isolated as crude products and were carried forward without extensive characterization or further purification.

[0049] Example 22

tert-Butyl 3-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]piperidine-1-carboxylate

[Chem.36]



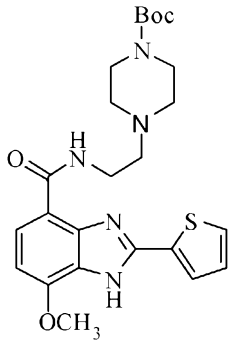
Following general procedure B, 4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.15 g, 0.44 mmol) was reacted with racemic 3-amino-1-boc-piperidine (0.18 g, 0.88 mmol) to

afford the desired product (0.13 g) as a brown solid: ESI MS m/z 443 [$C_{23}H_{28}N_4O_4S$ + H]$^+$.

[0050] Example 23

tert-Butyl 4-{2-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]ethyl}piperazine-1-carboxylate

[Chem.37]

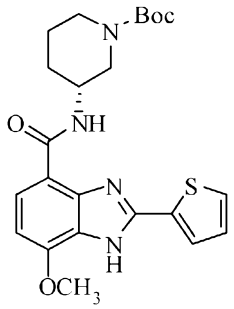


Following general procedure B, 4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.16 g, 0.58 mmol) was reacted with tert-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (0.27 g, 1.2 mmol) to afford the desired product (0.24 g) as a foam: ESI MS m/z 486 [$C_{24}H_{31}N_5O_4S$ + H]$^+$.

[0051] Example 24

(R)-tert-Butyl 3-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]piperidine-1-carboxylate

[Chem.38]

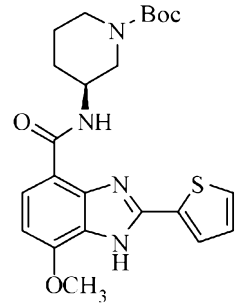


Following general procedure B, 4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.13 g, 0.46 mmol) was reacted with (R)-3-amino-1-boc-piperidine (0.18 g, 0.92 mmol) to afford the desired product (0.12 g) as a brown solid: ESI MS m/z 457 [$C_{23}H_{28}N_4O_4S$ + H]$^+$.

[0052] Example 25

(S)-tert-Butyl
3-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]piperidine-1-carboxylate

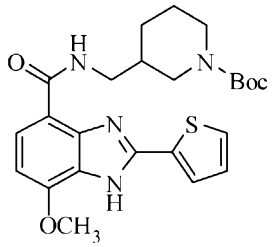
[Chem.39]



Following general procedure B,
4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.13 g, 0.46 mmol) was reacted with (S)-3-amino-1-boc-piperidine (0.18 g, 0.92 mmol) to afford the desired product (0.13 g) as a brown oil: ESI MS m/z 457 $[C_{23}H_{28}N_4O_4S + H]^+$.

[0053] Example 26
tert-Butyl
3-{[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]methyl}piperidine-1-carboxylate

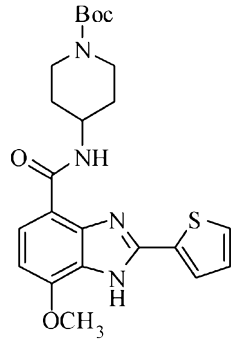
[Chem.40]



Following general procedure B,
4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.17 g, 0.62 mmol) was reacted with racemic 3-aminomethyl-1-boc-piperidine (0.26 g, 1.2 mmol) to afford the desired product (0.23 g) as a brown oil: ESI MS m/z 471 $[C_{24}H_{30}N_4O_4S + H]^+$.

[0054] Example 27
tert-Butyl
4-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]piperidine-1-carboxylate

[Chem.41]

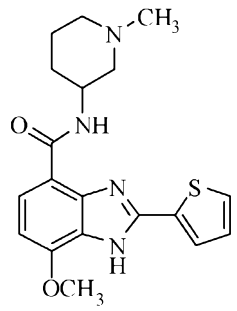


Following general procedure B, 4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.16 g, 0.58 mmol) was reacted with 4-amino-1-boc-piperidine (0.23 g, 1.2 mmol) to afford the desired product (0.20 g) as a brown oil: ESI MS m/z 457 $[C_{23}H_{28}N_4O_4S + H]^+$.

[0055] Example 28

7-Methoxy-N-(1-methylpiperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.42]

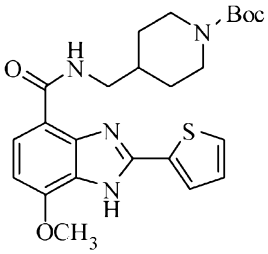


Following general procedure B, 4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.16 g, 0.59 mmol) was reacted with racemic 1-methyl-piperidin-3-amine (0.14 g, 1.2 mmol) to afford the desired product (0.15 g) as a brown glass: ESI MS m/z 371 $[C_{19}H_{22}N_4O_2S + H]^+$.

[0056] Example 29

tert-Butyl 4-{[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]methyl}piperidine-1-carboxylate

[Chem.43]

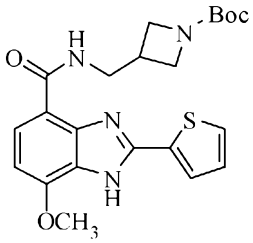


Following general procedure B, 4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.15 g, 0.56 mmol) was reacted with 4-aminomethyl-1-boc-piperidine (0.24 g, 1.1 mmol) to afford the desired product (0.16 g) as a brown foam: ESI MS m/z 471 $[C_{24}H_{30}N_4O_4S + H]^+$.

[0057] Example 30

tert-Butyl 3-{[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]methyl}azetidine-1-carboxylate

[Chem.44]

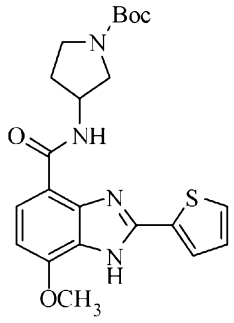


Following general procedure B, 4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.15 g, 0.56 mmol) was reacted with 1-boc-3(aminomethyl)azetidine (0.20 g, 1.1 mmol) to afford the desired product (0.17 g) as a brown foam: ESI MS m/z 443 $[C_{22}H_{26}N_4O_4S + H]^+$.

[0058] Example 31

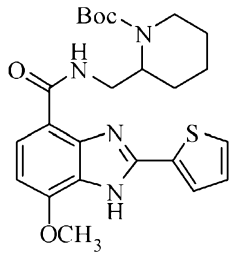
tert-Butyl 3-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]pyrrolidine-1-carboxylate

[Chem.45]



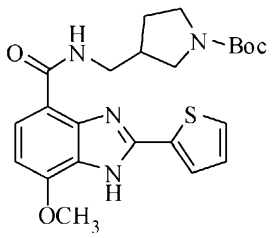
Following general procedure B,
4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.15 g, 0.56 mmol) was reacted with 3-amino-1-Boc-pyrrolidine (0.21 g, 1.1 mmol) to afford the desired product (0.20 g) as a brown oil: ESI MS m/z 443 $[C_{22}H_{26}N_4O_4S + H]^+$.

[0059] Example 32
tert-Butyl 2-{[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]methyl}piperidine-1-carboxylate
[Chem.46]



Following general procedure B,
4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.16 g, 0.58 mmol) was reacted with racemic 2-(aminomethyl)-1-N-boc-piperidine (0.25 g, 1.2 mmol) to afford the desired product (0.23 g) as a brown foam: ESI MS m/z 471 $[C_{24}H_{30}N_4O_4S + H]^+$.

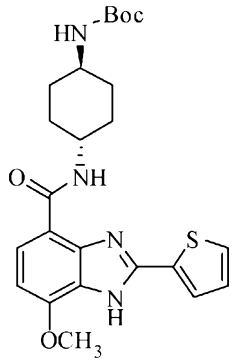
[0060] Example 33
tert-Butyl 3-{[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]methyl}pyrrolidine-1-carboxylate
[Chem.47]



Following general procedure B,
4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.16 g, 0.58 mmol) was reacted with 3-(aminomethyl)-1-N-Boc-pyrrolidine (0.24 g, 1.2 mmol) to afford the desired product (0.19 g) as a brown oil: ESI MS m/z 457 $[C_{23}H_{28}N_4O_4S + H]^+$.

[0061] Example 34
tert-Butyl-4-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]cyclohexylcarbamate

[Chem.48]



Following general procedure B, 4-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid (0.15 g, 0.55 mmol) was reacted with 1-Boc-amino-1,4-cyclohexyldiamine (0.23 g, 1.1 mmol) to afford the desired product (92 mg) as a brown oil: ESI MS m/z 471 $[C_{24}H_{30}N_4O_4S + H]^+$.

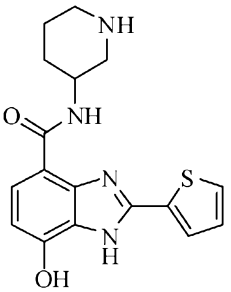
[0062] General Procedure C - synthesis of compounds as described in Scheme (1):

To a suspension of amides F (1.0 equiv) in dichloroethane (10-25 mL) was added boron tribromide (6.0-10 equiv) and the reaction mixture was heated at 80 degrees C for 16 h. The reaction mixture was poured over ice and the resulting mixture was concentrated. The crude residue was eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) as a crude purification. The crude product was further purified by preparative HPLC (C18 silica, 10-90% acetonitrile/water with 0.05% TFA). The desired product was obtained as the trifluoroacetic acid salt which was eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to obtain the desired products.

[0063] Example 35

7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.49]



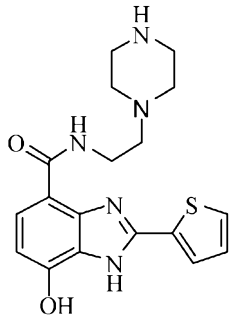
Following general procedure C, tert-Butyl

3-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]piperidine-1-carboxylate (0.13 g) was reacted with boron tribromide to afford the desired product (34 mg, 23% yield) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.86-7.85 (m, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.63-7.61 (m, 1H), 7.22-7.19 (m, 1H), 6.66 (d, J = 8.4 Hz, 1H), 4.14-4.10 (m, 1H), 3.04-3.00 (m, 1H), 2.86-2.77 (m, 2H), 2.18-1.99 (m, 2H), 1.79-1.72 (m, 2H); ESI MS m/z 343 $[C_{17}H_{18}N_4O_2S + H]^+$; HPLC 99.2% (AUC), t_R = 9.73 min.

[0064] Example 36

7-Hydroxy-N-[2-(piperazin-1-yl)ethyl]-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.50]

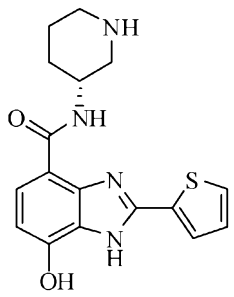


Following general procedure C, tert-Butyl 4-{2-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]ethyl}piperazine-1-carboxylate (0.24 g) was reacted with boron tribromide to afford the desired product (70 mg, 32% yield) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) delta 9.50 (s, 1H), 8.08 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 5.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.25-7.24 (m, 1H), 6.71 (d, J = 8.0 Hz, 1H), 3.55-3.51 (m, 3H), 2.90-2.84 (m, 5H), 2.56-2.50 (m, 3H); ESI MS m/z 372 $[C_{18}H_{21}N_5O_2S + H]^+$; HPLC >99% (AUC), t_R = 8.74 min.

[0065] Example 37

(R)-7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.51]

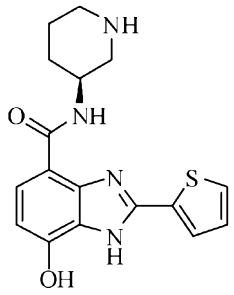


Following general procedure C, (R)-tert-Butyl 3-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]piperidine-1-carboxylate (0.12 g) was reacted with boron tribromide to afford the desired product (25 mg, 16% yield) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.88-7.87 (m, 1H), 7.79-7.75 (m, 1H), 7.65-7.63 (m, 1H), 7.24-7.21 (m, 1H), 6.70-6.67 (m, 1H), 4.17-4.14 (m, 1H), 3.08-3.00 (m, 1H), 2.89-2.78 (m, 2H), 2.24-1.98 (m, 2H), 1.82-1.76 (m, 2H); ESI MS m/z 343 $[C_{17}H_{18}N_4O_2S + H]^+$; HPLC 96.1% (AUC), t_R = 10.50 min.

[0066] Example 38

(S)-7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.52]

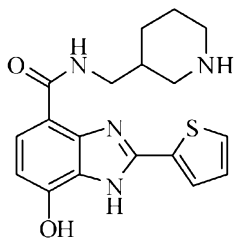


Following general procedure C, (S)-tert-Butyl 3-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]piperidine-1-carboxylate (0.13 g) was reacted with boron tribromide to afford the desired product (45 mg, 29% yield) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.88-7.87 (m, 1H), 7.79-7.75 (m, 1H), 7.65-7.63 (m, 1H), 7.24-7.21 (m, 1H), 6.70-6.66 (m, 1H), 4.17-4.14 (m, 1H), 3.08-3.00 (m, 1H), 2.89-2.78 (m, 2H), 2.24-1.98 (m, 2H), 1.82-1.76 (m, 2H); ESI MS m/z 343 $[C_{17}H_{18}N_4O_2S + H]^+$; HPLC >99% (AUC), t_R = 9.80 min.

[0067] Example 39

7-Hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.53]



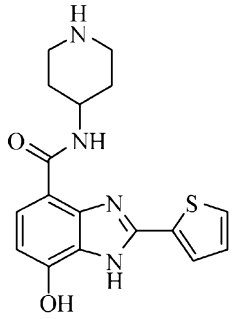
Following general procedure C, tert-Butyl 3-{[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]methyl}piperi

dine-1-carboxylate (0.23 g) was reacted with boron tribromide to afford the desired product (90 mg, 41% yield) as a light brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) delta 9.62 (s, 1H), 8.06-8.04 (m, 1H), 7.74 (d, J = 4.8 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.24-7.21 (m, 1H), 6.66 (d, J = 8.4 Hz, 1H), 3.29 (t, J = 6.0 Hz, 2H), 3.17-3.10 (m, 1H), 2.93-2.89 (m, 1H), 2.47-2.37 (m, 2H), 1.95-1.90 (m, 1H), 1.76-1.63 (m, 2H), 1.49-1.20 (m, 2H); ESI MS m/z 357 $[C_{18}H_{20}N_4O_2S + H]^+$; HPLC >99% (AUC), t_R = 9.41 min.

[0068] Example 40

7-Hydroxy-N-(piperidin-4-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.54]

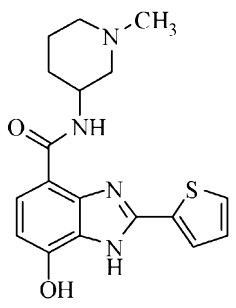


Following general procedure C, tert-Butyl 4-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]piperidine-1-carboxylate (0.2 g) was reacted with boron tribromide to afford the desired product (85 mg, 42% yield) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.85-7.84 (m, 1H), 7.76 (d, J = 5.1 Hz, 1H), 7.62-7.60 (m, 1H), 7.21-7.19 (m, 1H), 6.66 (d, J = 5.1 Hz, 1H), 4.21-4.20 (m, 1H), 3.29-3.24 (m, 2H), 2.99-2.93 (m, 2H), 2.17-2.14 (m, 2H), 1.80-1.74 (m, 2H); ESI MS m/z 343 $[C_{17}H_{18}N_4O_2S + H]^+$; HPLC >99% (AUC), t_R = 9.07 min.

[0069] Example 41

7-Hydroxy-N-(1-methylpiperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.55]

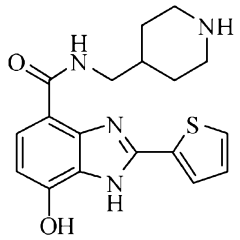


Following general procedure C, 7-methoxy-N-(1-methylpiperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide (0.15 g) was reacted with boron tribromide to afford the desired product (75 mg, 36% yield) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.89-7.88 (m, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.65-7.64 (m, 1H), 7.23-7.20 (m, 1H), 6.71 (d, J = 8.4 Hz, 1H), 4.26-4.24 (m, 1H), 3.01-2.98 (m, 1H), 2.67-2.65 (m, 1H), 2.38 (s, 5H), 2.05-1.92 (m, 2H), 1.80-1.59 (m, 2H); ESI MS m/z 357 $[C_{18}H_{20}N_4O_2S + H]^+$; HPLC 96.2% (AUC), t_R = 9.55 min.

[0070] Example 42

7-Hydroxy-N-(piperidin-4-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.56]

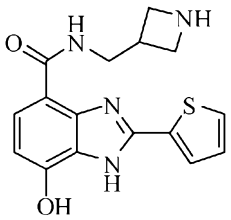


Following general procedure C, tert-Butyl 4-{[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]methyl}piperidine-1-carboxylate (0.16 g) was reacted with boron tribromide to afford the desired product (700 mg, 35% yield) as a yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.85-7.84 (m, 1H), 7.78-7.74 (m, 1H), 7.63-7.61 (m, 1H), 7.23-7.19 (m, 1H), 6.64-6.61 (m, 1H), 3.49 (d, J = 6.6 Hz, 2H), 2.88-2.79 (m, 2H), 2.07-2.03 (m, 2H), 1.94-1.93 (m, 1H), 1.56-1.44 (m, 2H); ESI MS m/z 357 $[C_{18}H_{20}N_4O_2S + H]^+$; HPLC >99% (AUC), t_R = 9.15 min.

[0071] Example 43

N-(Azetidin-3-ylmethyl)-7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.57]



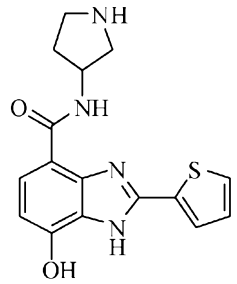
Following general procedure C, tert-Butyl 3-{[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]methyl}azetid

ine-1-carboxylate (0.17 g) was reacted with boron tribromide to afford the desired product (43 mg, 24% yield) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.84-7.83 (m, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.62-7.59 (m, 1H), 7.22-7.19 (m, 1H), 6.61 (d, J = 8.4 Hz, 1H), 4.02-3.96 (m, 2H), 3.90-2.84 (m, 2H), 3.74 (d, J = 6.3 Hz, 2H); ESI MS m/z 329 $[C_{16}H_{16}N_4O_2S + H]^+$; HPLC >99% (AUC), t_R = 8.70 min.

[0072] Example 44

7-Hydroxy-N-(pyrrolidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.58]

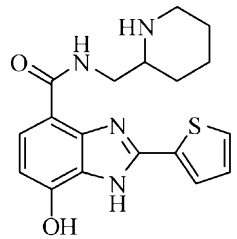


Following general procedure C, tert-Butyl 3-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]pyrrolidine-1-carboxylate (0.20 g) was reacted with boron tribromide to afford the desired product (0.12 g, 63% yield) as a light brown solid: ^{1}H NMR (300 MHz, CD_3OD) delta 8.09 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.36-7.33 (m, 1H), 6.87 (d, J = 8.4 Hz, 1H), 4.75-4.71 (m, 1H), 3.69-3.64 (m, 2H), 3.54-3.48 (m, 2H), 2.54-2.50 (m, 1H), 2.35-2.30 (m, 1H); ESI MS m/z 329 $[C_{16}H_{16}N_4O_2S + H]^+$; HPLC >99% (AUC), t_R = 8.80 min.

[0073] Example 45

7-Hydroxy-N-(piperidin-2-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.59]



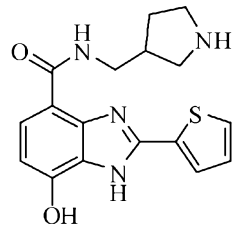
Following general procedure C, tert-Butyl 2-{[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]methyl}piperidine-1-carboxylate (0.23 g) was reacted with boron tribromide to afford the desired product (90 mg, 44% yield) as a yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 8.03-8.02 (m, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.82-7.81 (m, 1H), 7.32-7.29 (m, 1H),

6.83 (d, J = 8.4 Hz, 1H), 3.78-3.75 (m, 2H), 3.44-3.36 (m, 2H), 3.06-3.02 (m, 1H), 2.14-2.10 (m, 1H), 2.00-1.90 (m, 2H), 1.75-1.66 (m, 3H); ESI MS m/z 357 [$C_{18}H_{20}N_4O_2S$ + H]$^+$; HPLC >99% (AUC), t_R = 9.49 min.

[0074] Example 46

7-Hydroxy-N-(pyrrolidin-3-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.60]

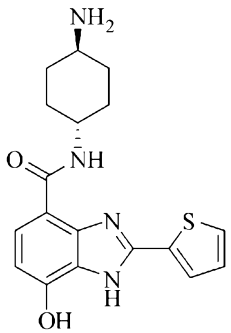


Following general procedure C, tert-Butyl 3-{[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]methyl}pyrrolidine-1-carboxylate (0.19 g) was reacted with boron tribromide to afford the desired product (79 mg, 39% yield) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.84-7.82 (m, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.61-7.59 (m, 1H), 7.21-7.18 (m, 1H), 6.61 (d, J = 8.4 Hz, 1H), 3.63-3.54 (m, 2H), 3.37-3.33 (m, 1H), 3.27-3.06 (m, 2H), 2.98-2.91 (m, 1H), 2.66-2.61 (m, 1H), 2.24-2.18 (m, 1H), 1.86-1.79 (m, 1H); ESI MS m/z 343 [$C_{17}H_{18}N_4O_2S$ + H]$^+$; HPLC >99% (AUC), t_R = 8.91 min.

[0075] Example 47

N-(4-Aminocyclohexyl)-7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.61]



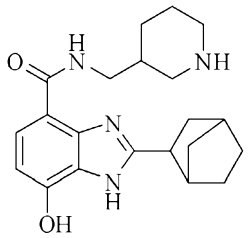
Following general procedure C, tert-Butyl-4-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]cyclohexylcarbamate (92 mg) was reacted with boron tribromide to afford the desired product (21 mg, 10% yield over two steps) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.85-7.84 (m, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.61-7.59 (m, 1H), 7.22-7.17

(m, 1H), 6.63 (d, J = 8.4 Hz, 1H), 4.24-4.23 (m, 1H), 3.01-2.97 (m, 1H), 2.15-2.10 (m, 2H), 2.03-1.78 (m, 6H); ESI MS m/z 357 $[C_{18}H_{20}N_4O_2S + H]^+$; HPLC 95.6% (AUC), t_R = 9.22 min.

[0076] Example 48

2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.62]

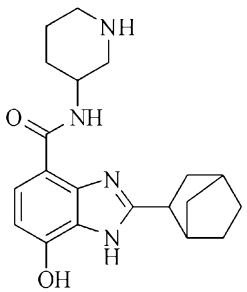


Following General Procedure C, tert-Butyl 3-((2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido)methyl)piperidine-1-carboxylate (330 mg crude) was reacted with boron tribromide to afford the desired product (71 mg, 45% yield) as a light yellow solid: ^{1}H NMR (500 MHz, CD_3OD) delta 7.75-7.68 (m, 1H), 6.58 (dd, 1H, J = 4.0, 8.2 Hz), 3.47-3.36 (m, 2H), 3.27-3.20 (m, 1H), 3.11-3.05 (m, 1H), 3.01-2.96 (m, 1H, minor diastereomer), 2.69-2.62 (m, 1H), 2.57-2.51 (m 1H), 2.43-2.37 (m, 1H), 2.25-2.19 (m, 1H, minor diastereomer), 2.09-2.01 (m, 2H), 1.96-1.88 (m, 1H), 1.84-1.74 (m, 2H), 1.71-1.55 (m, 3H), 1.53-1.16 (m, 5H); ESI MS m/z 369 $[C_{21}H_{28}N_4O_2 + H]^+$; HPLC >99% (AUC), t_R = 9.75 min.

[0077] Example 49

2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.63]



Following General Procedure C, tert-Butyl 3-(2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido)piperidine-1-carboxylate (210 mg crude) was reacted with boron tribromide to afford the desired product (72 mg, 43% yield) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3

OD) delta 7.69 (dd, J = 3.6, 8.1 Hz, 1H), 6.61 (dd, J = 2.7, 8.1 Hz, 1H), 4.12-4.01 (m, 1H), 3.45-3.36 (m, 1H), 3.03-2.93 (m, 1H), 2.78-2.52 (m, 3H), 2.44-2.36 (m, 1H), 2.25-1.16 (m 13H); ESI MS m/z 355 $[C_{20}H_{26}N_4O_2 + H]^+$; HPLC >99% (AUC), t_R = 9.55 min (minor diastereomer), 9.74 min (major diastereomer).

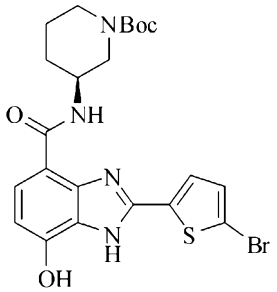
[0078] General Procedure D - synthesis of compounds of formula I-II as described in Scheme (1):

To a solution of acid (1.0 equiv) in DMF (5-10 mL) was added HATU (1.2-1.5 equiv), DIPEA (3.0-5.0 equiv), and the amine (1.5-2.0 equiv) and the reaction mixture was either stirred at room temperature for 16 h or heated at 50-70 degrees C for 16 h. The reaction mixture was diluted with satd. aq $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18 silica, 10-90% acetonitrile/water with 0.05% TFA). The desired product was obtained as the trifluoroacetic acid salt which was eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to obtain the desired products. In some instances the desired product was treated with TFA (1-2 mL) for 1 h, concentrated and purified by preparative HPLC (C18 silica, 10-90% acetonitrile/water with 0.05% TFA). The desired product was obtained as the trifluoroacetic acid salt which was eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to obtain the desired products

[0079] Example 50

(S)-tert-Butyl 3-(2-(5-bromothiophen-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamido)piperidine-1-carboxylate

[Chem.64]



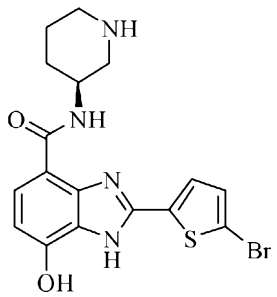
Following General Procedure D, 2-(5-bromothiophen-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxylic acid (90 mg, 0.27 mmol) was reacted with (S)-tert-butyl 3-aminopiperidine-1- carboxylate (106 mg, 0.53 mmol) to afford the desired product (48 mg, 35% yield) as yellow-brown solid: ^1H NMR (500 MHz, CD_3OD) delta 7.84 (d, J = 8.5 Hz, 1H), 7.71 (s, 1H), 7.28 (s, 1H), 6.78 (d, J = 8.5 Hz, 1H), 4.21 (bs, 1H), 3.86 (bs, 1H), 3.58-3.18 m, 2H), 2.14-2.03 (m, 2H), 1.89 (bs, 1H), 1.59 (bs, 1H), 1.17 (bs, 1H); ESI MS m/z 521 $[C_{22}H_{25}BrN_4O_4S]^+$;

HPLC >99% (AUC), t_R = 15.30 min.

[0080] Example 51

(S)-2-(5-bromothiophen-2-yl)-7-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.65]

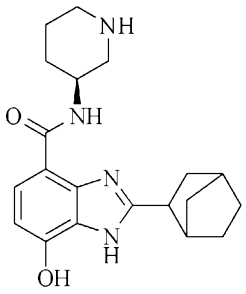


A solution of (S)-tert-butyl 3-(2-(5-bromothiophen-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamido)piperidine-1-carboxylate (35 mg, 0.067 mmol) in CH_2Cl_2 (1 mL) and TFA (1 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated and purified by purified by preparative HPLC (C18 silica, 10-90% acetonitrile/water with 0.05% TFA). The desired product was obtained as the trifluoroacetic acid salt which was eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to obtain the desired (20 mg, 72%) as yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) delta 13.61 (s, 1H), 11.00 (s, 1H), 9.57 (d, J = 6.5 Hz, 1H), 8.75 (bs, 1H), 7.89 (d, J = 4.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 3.5 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 3.46 (d, J = 8.5 Hz, 1H), 3.21 (d, J = 12.5 Hz, 1H), 3.04- 2.96 (m, 2H), 2.10 (bs, 1H), 2.03-2.00 (m, 2H), 1.85-1.70 (m, 4H), 0.68 (bs, 1H); ESI MS m/z 421 $[C_{17}H_{17}BrN_4O_2S]^+$; HPLC 98.34% (AUC), t_R = 8.17 min.

[0081] Example 52

2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-((S)-piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.66]



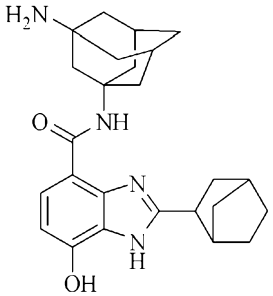
Following General Procedure C, (3S)-tert-Butyl 3-(2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido)pip

eridine-1-carboxylate (230 mg crude) was reacted with boron tribromide to afford the desired product (103 mg, 52% over two steps) as a light brown solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.69 (dd, J = 3.6, 8.4 Hz, 1H), 6.60 (dd, J = 2.7, 8.4 Hz, 1H), 4.12-4.02 (m, 1H), 3.46-3.35 (m, 1H), 3.03-2.93 (m, 1H), 2.78-2.60 (m, 3H), 2.56-2.36 (m, 1H), 2.25-1.17 (m, 13H); ESI MS m/z 355 $[C_{20}H_{26}N_4O_2 + H]^+$; HPLC 99.0% (AUC), t_R = 9.35 min (minor diastereomer), 9.49 min (major diastereomer).

[0082] Example 53

2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(adamantane-3-ylamino)-1H-benzo[d]imidazole-4-carboxamide

[Chem.67]

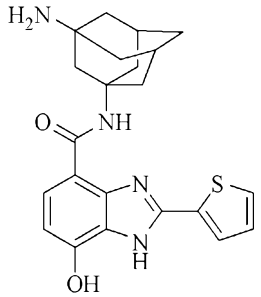


Following General Procedure C, tert-Butyl 3-{[2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido]methyl}adamantane-1-carboxylate (140 mg crude) was reacted with boron tribromide to afford the desired product (57 mg, 31% over two steps) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.66-7.62 (m, 1H), 6.57-6.53 (m, 1H), 3.45-3.35 (m, 1H), 3.00-2.90 (m, 1H, minor diastereomer), 2.68-2.62 (m, 1H, major diastereomer), 2.56-2.52 (m, 1H, minor diastereomer), 2.43-2.18 (m, 7H), 2.13-1.99 (m 3H), 1.84-1.21 (m, 12H); ESI MS m/z 421 $[C_{25}H_{32}N_4O_2 + H]^+$; HPLC 96.6% (AUC), t_R = 10.45 min.

[0083] Example 54

2-(Thiophene-2-yl)-7-hydroxy-N-(adamantate-3-ylamino)-1H-benzo[d]imidazole-4-carboxamide

[Chem.68]

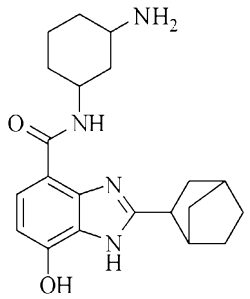


Following General Procedure C, tert-Butyl 3-((2-thiophene-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido)methyl)adamantane-1-carboxylate (110 mg) was reacted with boron tribromide to afford the desired product (62 mg, 28% over two steps) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3 OD) delta 7.80 (d, J = 3.9 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.58 (d, 4.8 Hz), 7.20-7.17 (m, 1H), 6.59 (d, 1H, J = 8.4 Hz), 2.38-2.11 (m, 8H), 1.86-1.63 (m, 6H); ESI MS m/z 409 $[C_{22}H_{24}N_4O_2S + H]^+$; HPLC >99% (AUC), t_R = 11.27 min.

[0084] Example 55

N-(3-Aminocyclohexyl)-2-(bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamide

[Chem.69]

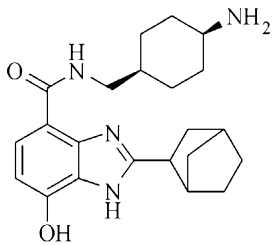


Following General Procedure C, tert-Butyl 3-(2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido)cyclohexylcarbamate (120 mg crude) was reacted with boron tribromide to afford the desired product (66 mg, 40% yield) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3 OD) delta 7.72-7.67 (m, 1H), 6.58-6.55 (m, 1H), 4.57-4.48 (m, 1H, minor diastereomer), 4.03-3.90 (m, 1H, major diastereomer), 3.45-3.35 (m, 1H), 3.03-2.90 (m, 1H), 2.66-2.52 (m, 1H), 2.44-2.32 (m 2H, major diastereomer), 2.22-1.14 (m, 15H); ESI MS m/z 369 $[C_{21}H_{28}N_4O_2 + H]^+$; HPLC >99% (AUC), t_R = 9.40, 9.53, 9.58, 9.81 min (mixture of diastereomers).

[0085] Example 56

N-{[(cis)-4-Aminocyclohexyl]methyl}-2-(bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamide

[Chem.70]

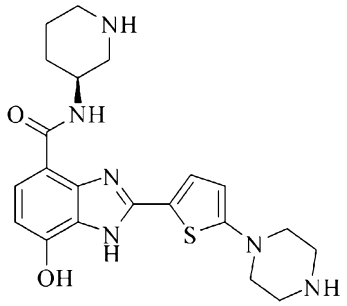


Following General Procedure C, tert-Butyl (cis)-4-{[2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido]methyl}cyclohexylcarbamate (220 mg crude) was reacted with boron tribromide to afford the desired product (64 mg, 53% over two steps) as a light yellow solid: ^{1}H NMR (300 MHz, CD_3OD) delta 7.69 (dd, J = 3.9, 8.4 Hz, 1H), 6.59-6.54 (m, 1H), 3.56-3.37 (m, 2H), 3.15-3.07 (m, 1H), 3.00-2.90 (m, 1H, minor diastereomer), 2.74-2.66 (m, 1H, minor diastereomer), 2.55-2.51 (m, 1H, minor diastereomer), 2.42-2.34 (m, 1H), 2.25-2.16 (m, 1H, minor diastereomer), 2.06-1.98 (m, 1H), 1.80-1.20 (m, 14H); ESI MS m/z 383 [$C_{22}H_{30}N_4O_2$ + H]$^+$; HPLC 99.0% (AUC), t_R = 9.53, 9.88, 9.96 min (mixture of diastereomers).

[0086] Example 57

(S)-7-hydroxy-2-(5-(piperazin-1-yl)thiophen-2-yl)-N-(piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.71]



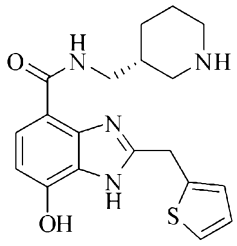
A mixture of (S)-tert-Butyl 3-(2-(5-bromothiophen-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamido)piperidine-1-carboxylate (0.12 g, 0.24 mmol), tert-butyl piperazine-1-carboxylate (110 mg, 0.60 mmol), CuI (5.7 mg, 0.030 mmol), Cu (2.0 mg, 0.030 mmol), K_3PO_4 H_2O (160 mg, 0.72 mmol) in 2-(dimethylamino)ethanol (2 mL) was stirred at 75 degrees C for 18 h. The reaction mixture was cooled, concentrated, dissolved in CH_3OH (3 mL) and filtered. The filtrate was purified by preparative HPLC (C18 silica, 10-90% acetonitrile/water with 0.05% TFA). The desired fractions were combined, concentrated and the residue was dissolved in CH_2Cl_2 (2 mL) and TFA (1 mL) and stirred at rt for 30 min. The reaction mixture was concentrated and the residue was eluted through an ion-exchange column (SCX-2) (using methanol and 7 N methanol in ammonia) to obtain the desired product (7 mg, 14 % yield) as a yellow solid: ^{1}H NMR (500 MHz, CD_3OD) delta 8.20 (d, J = 4.5 Hz, 1H), 7.50 (d, J = 4.5 Hz, 1H), 7.14 (d, J = 4.0 Hz, 1H), 6.54 (d, J = 3.5 Hz, 1H), 4.20-4.16 (m, 1H), 3.43 (dd, J = 12.5, 3.5 Hz, 1H), 3.19-3.15 (m, 2H), 3.10-2.97 (m, 3H), 2.05-1.96 (m, 2H), 1.84-1.72 (m, 3H), 1.19-1.16 (m, 1H), 1.13-1.08 (m, 1H); ESI MS m/z 427 [$C_{21}H_{26}N_6O_2S$+ H]$^+$

HPLC 97.13% (AUC), t_R = 8.29 min.

[0087] Example 58

(R)-7-hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.72]

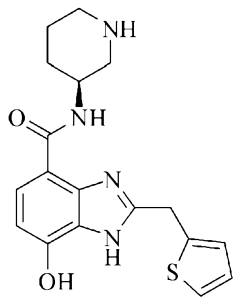


Following General Procedure D, 2-(5-bromothiophen-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxylic acid (0.13 mg, 0.47 mmol) was reacted with (S)-tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (200 mg, 0.93 mmol) and the intermediate was treated with TFA to afford the desired product (15 mg, 31% yield) as yellow solid: ^{1}H NMR (500 MHz, CD_3OD) delta 7.75 (d, J = 8.5 Hz, 1H), 7.30 (dd, J = 5.5, 1.5 Hz, 1H), 7.02-7.01 (m, 1H), 6.98 (dd, J = 5.0, 3.5 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 4.52 (s, 2H), 3.53-3.45 (m, 2H), 3.37 (dd, J = 9.0, 6.0 Hz, 1H), 2.95-2.89 (m, 2H), 2.82 (t, J = 12.0 Hz, 1H), 2.15-2.11 (m, 1H), 2.00-1.94 (m, 3H), 1.78-1.74 (m, 1H), 1.44-1.36 (m, 2H); ESI MS m/z 371 $[C_{19}H_{22}N_4O_2S+ H]^+$ HPLC 95.5% (AUC), t_R = 7.17 min.

[0088] Example 59

(S)-7-hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.73]



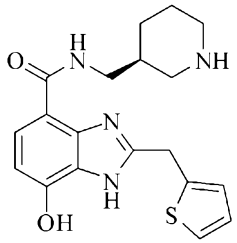
Following General Procedure D, 2-(5-bromothiophen-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxylic acid (0.17 mg, 0.62 mmol) was reacted with (S)-tert-butyl 3-aminopiperidine-1- carboxylate (250 mg, 1.3 mmol) and the intermediate was treated with TFA to afford the desired product (25 mg, 68% yield) as yellow solid: ^{1}H NMR

(500 MHz, CD_3OD) delta 7.63 (d, J = 8.5 Hz, 1H), 7.20 (dd, J = 5.0, 1.0 Hz, 1H), 6.91 (dd, J = 5.0, 3.5 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 4.37 (s, 2H), 4.15-4.11 (m, 1H), 3.37 (dd, J = 10.5, 3.5 Hz, 1H), 3.14-3.11 (m, 1H), 2.93-2.86 (m, 2H), 2.04-2.01 (m, 1H), 1.94-1.91 (m, 1H), 1.74-1.65 (m, 2H).; ESI MS m/z 357 $[C_{18}H_{20}N_4O_2S+ H]^+$ HPLC 96.59% (AUC), t_R = 7.07 min.

[0089] Example 60

(S)-7-hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide

[Chem.74]



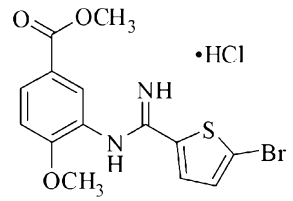
Following General Procedure D,

2-(5-bromothiophen-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxylic acid (0.13 mg, 0.47 mmol) was reacted with (R)-tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (200 mg, 0.93 mmol) and the intermediate was treated with TFA to afford the desired product (12 mg, 28% yield) as yellow solid: ^1H NMR (500 MHz, CD_3OD) delta 7.75 (d, J = 8.5 Hz, 1H), 7.30 (dd, J = 5.5, 1.5 Hz, 1H), 7.02-7.01 (m, 1H), 6.98 (dd, J = 5.0, 3.5 Hz, 1H), 6.70 (d, J = 5.0 Hz, 1H), 4.50 (s, 2H), 3.51-3.48 (m, 2H), 3.37 (dd, J = 13.0, 7.0 Hz, 1H), 2.92-2.89 (m, 2H), 2.80 (t, J = 12.0 Hz, 1H), 2.16-2.10 (m, 1H), 2.00-1.95 (m, 3H), 1.80-1.72 (m,1H), 1.44-1.39 (m, 2H); ESI MS m/z 371 $[C_{19}H_{22}N_4O_2S+ H]^+$ HPLC 96.8% (AUC), t_R = 6.93 min.

[0090] Example 61

Step 1: Synthesis of Methyl 3-(5-bromothiophene-2-carboximidamido)-4-methoxybenzoate Hydrochloride

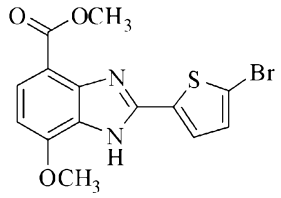
[Chem.75]



Following the procedure outlined for step 1 in Example 1, methyl 3-amino-4-methoxybenzoate (1.5 g, 7.9 mmol) was reacted with 5-bromothiophene-2-carbonitrile (3.0 g, 16 mmol) to afford the desired product (1.6 g, 54% yield) as a dark brown solid: ESI MS m/z 368 $[C_{14}H_{13}BrN_2O_3S + H]^+$.

[0091] Step 2: Synthesis of Methyl 2-(5-bromothiophen-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxylate

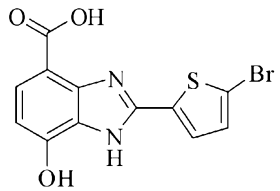
[Chem.76]



Following the procedure outlined for step 2 in Example 1, methyl 3-(5-bromothiophene-2-carboximidamido)-4-methoxybenzoate hydrochloride (1.7 g, 4.2 mmol) was reacted with 5% aq NaOCl and satd. aq $NaHCO_3$ to afford the desired product (0.45 g, 30% yield) as a brown solid: ESI MS m/z 369 $[C_{14}H_{11}BrN_2O_3S + H]^+$.

Step 3: Synthesis of 2-(5-Bromothiophen-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxylic acid

[Chem.77]

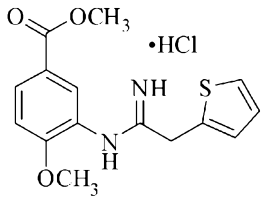


Following the procedure outlined for step 4 in Example 1, methyl 2-(5-bromothiophen-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxylate (0.40 g, 1.1 mmol) was reacted with boron tribromide (1.5 g, 6.6 mmol) to afford the desired product (0.34 g, 92% yield) as a light brown solid: ESI MS m/z 340 $[C_{12}H_7BrN_2O_3S + H]^+$.

[0092] Example 62

Step 1: Synthesis of Methyl 4-methoxy-3-(2-(thiophen-2-yl)acetimidamido)benzoate Hydrochloride

[Chem.78]

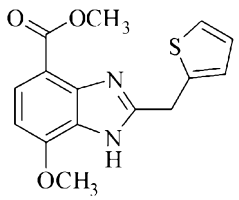


Following the procedure outlined for step 1 in Example 1, methyl 3-amino-4-methoxybenzoate (2.2 g, 12 mmol) was reacted with 2-(thiophen-2-yl)acetonitrile (3.0 g, 24 mmol) to afford the desired product (3.2 g, 78%

yield) as a yellow brown solid: ESI MS m/z 305 $[C_{15}H_{16}N_2O_3S + H]^+$.

Step 2: Synthesis of Methyl 7-methoxy-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxylate

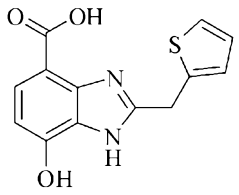
[Chem.79]



Following the procedure outlined for step 2 in Example 1, methyl 4-methoxy-3-(2-(thiophen-2-yl)acetimidamido)benzoate hydrochloride (3.1 g, 10 mmol) was reacted with 5% aq NaOCl and satd. aq $NaHCO_3$ to afford the desired product (1.1 g, 30% yield) as a brown solid: ESI MS m/z 303 $[C_{15}H_{14}N_2O_3S + H]^+$.

[0093] Step 3: Synthesis of 7-hydroxy-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxylic acid

[Chem.80]

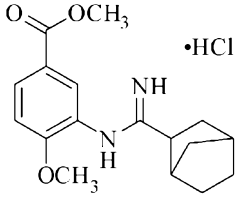


Following the procedure outlined for step 4 in Example 1, methyl 7-methoxy-2-(thiophene-2- ylmethyl)-1H-benzo[d]imidazole-4-carboxylate (0.91 g, 3.0 mmol) was reacted with boron tribromide (4.5 g, 18 mmol) to afford the desired product (0.63 g, 73% yield) as a light brown solid: ESI MS m/z 275 $[C_{13}H_{10}N_2O_3S + H]^+$.

[0094] Example 63

Step 1: Synthesis of Methyl 3-(bicyclo[2.2.1]heptane-2-carboximidamido)-4-methoxybenzoate

[Chem.81]

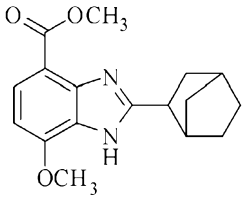


Following the procedure outlined for step 1 in Example 1, methyl-

3-amino-4-methoxy benzoate (7.5 g, 41 mmol) was reacted with 2-norbornane carbonitrile (10 g, 82 mmol) to afford product (11 g, 90%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) delta 8.29-8.20 (m, 1H), 7.99-7.96 (m, 1H), 7.33-7.28 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.70-2.62 (m, 1H), 1.87-1.17 (m, 8H); ESI MS m/z 303 [$C_{17}H_{22}N_2O_3$ + H]$^+$.

Step 2: Synthesis of Methyl 2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxylate

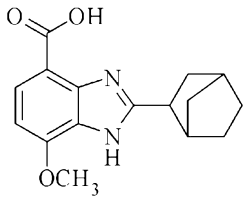
[Chem.82]



Following the procedure outlined for step 2 in Example 1, methyl 3-(bicyclo[2.2.1]heptane-2-carboximidamido)-4-methoxybenzoate (11 g, 37 mmol) was reacted with NaOCl (33 mL, 10-13%, 44 mmol) and chromatographed (hexanes/ethyl acetate) to afford product (3.9 g, 36%) as a foam: ^{1}H NMR (300 MHz, DMSO-d_6) delta 12.05 (s, 1H, tautomer 1), 11.97 (s, 1H, tautomer 2), 7.73 (dd, 1H, J = 1.2, 8.7 Hz), 6.78 (dd, 1H, J = 2.4, 8.7 Hz), 4.00 (s, 3H, tautomer 1), 3.98 (s, 3H, tautomer 2), 3.90 (s, 3H, tautomer 1), 3.89 (s, 3H, tautomer 2), 3.47-3.41 (m, 1H, tautomer 1), 3.11-3.06 (m, 1H, tautomer 2), 2.70-2.66 (m, 1H, tautomer 1), 2.38-2.18 (m, 2H), 2.08-2.00 (m, 1H, tautomer 1), 1.91-1.80 (m, 1H, tautomer 2), 1.68-1.24 (m, 5H), 1.11-0.98 (m, 1H); ESI MS m/z 301 [$C_{17}H_{20}N_2O_3$ + H]$^+$.

[0095] Step 3: Synthesis of 2-(Bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxylic Acid

[Chem.83]



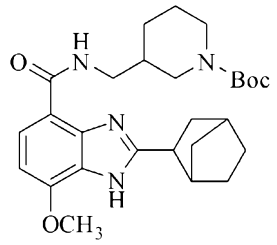
Following the procedure outlined for step 3 in Example 1, methyl 2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxylate (3.9 g, 13 mmol) was reacted with sodium hydroxide (30 mL, 3 M) to afford crude product (3.6 g) as a white solid: ESI

MS m/z 287 $[C_{16}H_{18}N_2O_3 + H]^+$.

[0096] Example 64

tert-Butyl 3-{[2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido]methyl}piperidine-1-carboxylate

[Chem.84]



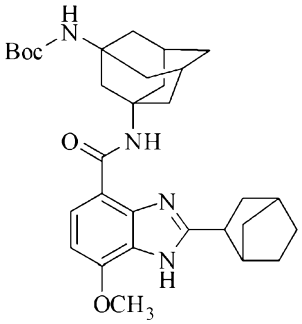
Following General Procedure D

2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxylic acid (125 mg, 0.43 mmol) was reacted with tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (138 mg, 0.65 mmol) to afford the desire product (338 mg crude) as an oil: ESI MS m/z 483 $[C_{27}H_{38}N_4O_4 + H]^+$.

[0097] Example 65

tert-Butyl 3-((2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido)methyl)adamantane-1-carboxylate

[Chem.85]



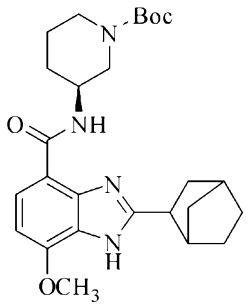
Following General Procedure D

2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxylic acid (125 mg, 0.43 mmol) was reacted with tert-butyl 3-aminoadamantanecarboxylate (176 mg, 0.65 mmol) to afford the desire product (145 mg crude) as an oil: ESI MS m/z 535 $[C_{31}H_{42}N_4O_4 + H]^+$.

[0098] Example 66

(3S)-tert-Butyl 3-(2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido)piperidine-1-carboxylate

[Chem.86]



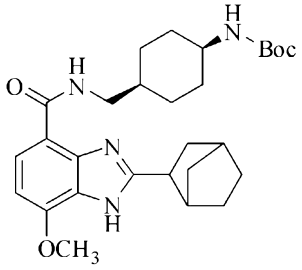
Following General Procedure D

2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxylic acid (150 mg, 0.54 mmol) was reacted with (S)-tert-butyl 3-aminopiperidine-1-carboxylate (160 mg, 0.81 mmol) to afford the desire product (237 mg crude) as an oil: ESI MS m/z 467 $[C_{26}H_{36}N_4O_4 + H]^+$.

[0099] Example 67

tert-Butyl (cis)-4-((2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido)methyl)cyclohexylcarbamate

[Chem.87]



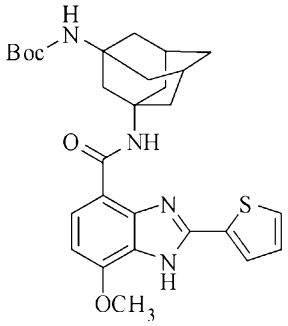
Following General Procedure D

2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxylic acid (90 mg, 0.31 mmol) was reacted with tert-butyl (1s,4s)-4-(aminomethyl)cyclohexylcarbamate (71 mg, 0.31 mmol) to afford the desire product (237 mg crude) as an oil: ESI MS m/z 497 $[C_{28}H_{40}N_4O_4 + H]^+$.

[0100] Example 68

tert-Butyl 3-((2-thiophene-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido)methyl)adamantane-1-carboxylate

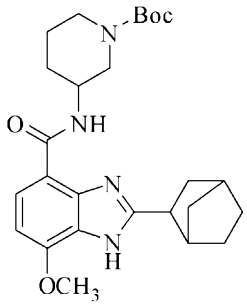
[Chem.88]



Following General Procedure B,
7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxylic acid (0.15 g, 0.55 mmol) was reacted with tert-butyl 3-aminoadamantanecarboxylate (0.22 g, 0.82 mmol) to afford the desired product (118 mg crude) as a white solid: ESI MS m/z 523 [$C_{28}H_{34}N_4O_4S$ + H]$^+$.

[0101] Example 69
tert-Butyl 3-(2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido)piperidine-1-carboxylate

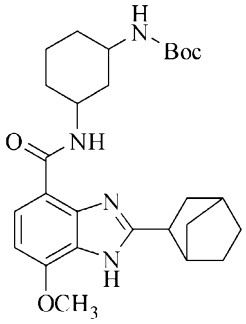
[Chem.89]



Following General Procedure B,
2-(Bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxylic acid (150 mg, 0.55 mmol) was reacted with tert-butyl 3-aminopiperidine-1-carboxylate (0.22 g, 1.1 mmol) to afford the desired product (219 mg crude) as a foam: ESI MS m/z 469 [$C_{26}H_{36}N_4O_4$ + H]$^+$.

[0102] Example 70
tert-Butyl 3-(2-(bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxamido)cyclohexylcarbamate

[Chem.90]

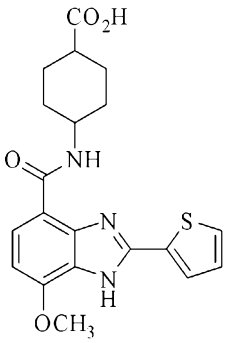


Following General Procedure B, 2-(Bicyclo[2.2.1]heptan-2-yl)-7-methoxy-1H-benzo[d]imidazole-4-carboxylic acid (150 mg, 0.55 mmol) was reacted with tert-butyl 3-aminocyclohexylcarbamate (0.24 g, 1.1 mmol) to afford the desired product (126 mg crude) as a glass: ESI MS m/z 483 [$C_{27}H_{38}N_4O_4$ + H]$^+$.

[0103] Example 71

4-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]cyclohexane carboxylic Acid

[Chem.91]

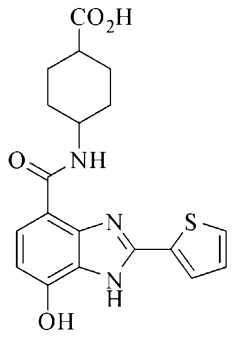


Following General Procedure B, 7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxylic acid (140 mg, 0.52 mmol) was reacted with 4-aminocyclohexanecarboxylic acid (150 mg, 1.0 mmol) to afford the desired product (53 mg) as a yellow solid: ESI MS m/z 400 [$C_{20}H_{21}N_3O_4S$ + H]$^+$.

[0104] Example 72

4-[7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]cyclohexanec arboxylic Acid

[Chem.92]



Following General Procedure C, 4-[7-methoxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]cyclohexanecarboxylic acid (53 mg) was reacted with boron tribromide to afford the desired product (18 mg, 35% yield) as a light green solid: ^{1}H NMR (300 MHz, CD_3OD) delta 8.04 (d, J = 3.6 Hz, 1H, minor diastereomer), 7.97 (d, J = 3.6 Hz, major diastereomer), 7.81 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 4.8 Hz, 1H), 7.33-7.30 (m, 1H, minor diastereomer), 7.25 (dd, J = 4.8, 3.6 Hz, 1H, major diastereomer), 6.82 (d, J = 8.4 Hz, 1H, minor diastereomer), 6.77 (d, J = 8.4 Hz, 1H, major diastereomer), 4.32-4.26 (m, 1H), 2.58-2.49 (m, 1H), 2.20-1.82 (m, 8H); ESI MS m/z 386 $[C_{19}H_{19}N_3O_4S + H]^+$; HPLC 97.3% (AUC), t_R = 12.07 min (minor diastereomer), 12.37 min (major diastereomer).

[0105] Examples 73

Kinase assay

GSK-3beta activity was measured in the presence or absence of compounds using Z'-LYTE kinase assay (Rodems SM, et al., Assay Drug Dev Technol. 1: 9-19, 2002.) kit with SER/THR 9 peptide (Invitrogen) following the manufacturer's instruction. The Z'-LYTE kinase assay kit employs a fluorescence resonance energy transfer (FRET) between two fluorophores, coumarin and fluorescein, attached to each end of a substrate peptide.

Test compounds were dissolved in DMSO at 12.5 mM and then serially diluted as the DMSO concentration in the assays to be 1%. The serially diluted compounds, 0.04 ng/micro-l GSK-3beta (Invitrogen) and 2 micro-M SER/THR 9 peptide were reacted in a reaction buffer (50 mM HEPES pH 7.5, 0.01% Brij-35, 10 mM $MgCl_2$, 1 mM EGTA, 15 micro-M ATP). For 0% phosphorylation control, ATP was omitted from the reaction mixture. For 100% phosphorylation control, SER/THR 9 phosphopeptide was used in place of the SER/THR 9 peptide. Following 1 hour incubation at room temperature, the reaction was stopped by the addition of half assay volume of development solution and further incubated for 1 hour at room temperature. After adding the half assay volume of stop reagent, emission signals of coumarin and fluorescein were measured by Wallac EnVision 2103 multilabel reader (PerkinElmer). The extent of

phosphorylation was determined according to the 0% and 100% phosphorylation control samples using the following equation:

[Math.1]

$$\%\ \text{phosphorylation} = 1 - \frac{(\text{emission ratio} \times F_{100\%}) - C_{100\%}}{(C_{0\%} - C_{100\%}) + [\text{emission ratio} \times (F_{100\%} - F_{0\%})]}$$

where:

$$\text{emission ratio} = \frac{\text{coumarin emission signal (445nm)}}{\text{fluorescein emission signal (520nm)}}$$

$C_{100\%}$ = coumarin emission signal of the 100% phosphorylation control

$C_{0\%}$ = coumarin emission signal of the 0% phosphorylation control

$F_{100\%}$ = fluorescein emission signal of the 100% phosphorylation control

$F_{0\%}$ = fluorescein emission signal of the 0% phosphorylation control

IC_{50} values were calculated by nonlinear four parameter fit using SigmaPlot, version 10.0 (Systat Software, Inc.).

IC_{50} values of the compounds in the present invention are shown in following table 2:

[0106] [Table 2]

Example No.	compound	IC_{50} (micro-M)
39	7-Hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.0086
38	(S)-7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.01
35	7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.017
40	7-Hydroxy-N-(piperidin-4-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.018
46	7-Hydroxy-N-(pyrrolidin-3-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.025
20	7-Hydroxy-N-(4-hydroxycyclohexyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.026
10	2-cyclopropyl-4-hydroxy-N-(piperidin-4-yl)-1H-benzo[d]imidazole-7-carboxamide	0.03

43	N-(Azetidin-3-ylmethyl)-7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.043
47	N-(4-Aminocyclohexyl)-7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.051
7	2-Cyclopropyl-4-hydroxy-N-(piperidin-2-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide	0.1
9	(S)-2-cyclopropyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide	0.1
42	7-Hydroxy-N-(piperidin-4-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.1
44	7-Hydroxy-N-(pyrrolidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.11
16	(S)-2-Cyclopentyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide	0.12
17	(S)-4-Hydroxy-2-phenyl-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide	0.12
15	2-Cyclopentyl-4-hydroxy-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide	0.13
19	4-hydroxy-2-phenyl-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide	0.13
13	N-(azetidin-3-ylmethyl)-2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxamide	0.14
37	(R)-7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.18
41	7-Hydroxy-N-(1-methylpiperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.18
11	2-cyclopropyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide	0.19
12	2-cyclopropyl-4-hydroxy-N-(pyrrolidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide	0.21
36	7-Hydroxy-N-[2-(piperazin-1-yl)ethyl]-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.21
45	7-Hydroxy-N-(piperidin-2-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide	0.24
5	2-Cyclopropyl-4-hydroxy-N-(piperidin-4-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide	0.32
8	2-cyclopropyl-4-hydroxy-N-(1-methylpiperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide	1.3
14	2-cyclopentyl-4-hydroxy-N-(piperidin-2-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide	1.3
18	4-Hydroxy-2-phenyl-N-(piperidin-2-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide	1.5
6	2-Cyclopropyl-4-hydroxy-N-(piperidin-3-yl-methyl)-1H-benzo[d]imidazole-7-carboxamide	1.6
21	(7-hydroxy-2-[thiophen-2-yl]-1H-benzo[d]imidazol-4-yl)(piperazin-1-yl)methanone	22
48	2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide	0.068
49	2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide	0.23

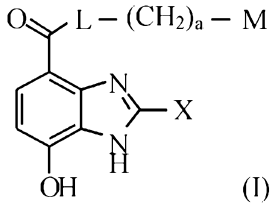
50	(S)-tert-Butyl 3-(2-(5-bromothiophen-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamido)piperidine-1-carboxylate	3.4
51	(S)-2-(5-bromothiophen-2-yl)-7-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide	0.016
52	2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-((S)-piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide	0.15
53	2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(adamantane-3-ylamino)-1H-benzo[d]imidazole-4-carboxamide	1.9
54	2-(Thiophene-2-yl)-7-hydroxy-N-(adamantane-3-ylamino)-1H-benzo[d]imidazole-4-carboxamide	0.33
55	N-(3-Aminocyclohexyl)-2-(bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamide	0.25
56	N-{[(cis)-4-Aminocyclohexyl]methyl}-2-(bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamide	0.24
57	(S)-7-hydroxy-2-(5-(piperazin-1-yl)thiophen-2-yl)-N-(piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide	0.038
58	(R)-7-hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide	0.1
59	(S)-7-hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide	0.17
60	(S)-7-hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide	0.16
72	4-[7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]cyclohexanecarboxylic Acid	0.012

Industrial Applicability

[0107] The present invention provides a novel 7-Hydroxy-benzoimidazole-4-yl-methanone derivative compound having GSK-3beta inhibitory effect. The compounds of the present invention may be used for pharmaceutical composition for inhibiting GSK-3beta activity in a patient suffering from a GSK-3beta dependent disease. Such pharmaceutical compositions are suitable for treating or preventing Alzheimer disease, mania, depression, migraine and type 2 diabetes.

Claims

[Claim 1] A GSK-3beta inhibitor comprising at least one compound, which is represented by formula (I), or a salt, hydrate, solvate, or isomer thereof:
[Chem.1]



(I)

wherein
X is phenyl, thiophen-2-yl, furan-2-yl, cyclopropyl, cyclopentyl, phenyl-C_1-C_6 alkyl, thiophen-2-yl-C_1-C_6 alkyl, furan-2-yl-C_1-C_6 alkyl, cyclopropyl-C_1-C_6 alkyl cyclopentyl-C_1-C_6 alkyl, or bicyclo[2.2.1]heptan-2-yl, wherein each group is optionally substituted by 1-3 substituent(s) each independently selected from group A;
L is -NH-, or a single bond;
M is C_3-C_8 cycloalkyl, or 3-8 membered saturated heterocyclic group, each optionally substituted by 1-3 substituent(s) each independently selected from group A;
wherein the group A is selected from a group consisting of hydroxyl, oxo, nitro, cyano, amino, C_1-C_6 alkylamino, C_3-C_{10} cycloalkylamino, amide, halogen, sulfamoyl, trifluoromethyl, p-toluenesulfonylamino, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkylcarbonylamino, C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino, C_1-C_6 alkenyl, C_1-C_6 alkynyl, phosphoryl, carbonyl, carboxyl, and a 3-8 membered saturated heterocyclic group; and
a is an integer from 0 to 5.

[Claim 2] The GSK-3beta inhibitor of claim 1, wherein M is piperidin-4-yl, piperidin-3-yl, piperidin-2-yl, piperazin-1-yl, pyrrolidin-3-yl, azetidin-3-yl, cyclohexyl, or adamantan-3-yl, which are each optionally substituted by 1 or 2 substituent(s) each independently selected from the group A..

[Claim 3] The GSK-3beta inhibitor of claim 1 or 2,
wherein X is thiophen-2-yl.

[Claim 4] The GSK-3beta inhibitor of claim 1 or 2,
wherein X is phenyl.

[Claim 5] The GSK-3beta inhibitor claim 1 or 2,

wherein X is cyclopropyl.

[Claim 6] The GSK-3beta inhibitor claim 1 or 2,
wherein X is cyclopentyl.

[Claim 7] The compound of claim 1 or 2,
wherein X is bicycle[2.2.1]heptan-2-yl.

[Claim 8] The compound of claim 1 or 2,
wherein X is 5-bromothiophen-2-yl.

[Claim 9] The compound of claim 1 or 2,
wherein X is 5-(piperazin-1-yl)thiophen-2-yl.

[Claim 10] The compound of claim 1 or 2,
wherein X is thiophen-2-ylmethyl.

[Claim 11] The GSK-3beta inhibitor of claim 1, which is selected from a group consisting of:
2-Cyclopropyl-4-hydroxy-N-(piperidin-4-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide,
2-Cyclopropyl-4-hydroxy-N-(piperidin-3-yl-methyl)-1H-benzo[d]imidazole-7-carboxamide,
2-Cyclopropyl-4-hydroxy-N-(piperidin-2-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide,
2-cyclopropyl-4-hydroxy-N-(1-methylpiperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide,
(S)-2-cyclopropyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide,
2-cyclopropyl-4-hydroxy-N-(piperidin-4-yl)-1H-benzo[d]imidazole-7-carboxamide,
2-cyclopropyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide,
2-cyclopropyl-4-hydroxy-N-(pyrrolidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide, N-(azetidin-3-ylmethyl)-2-cyclopropyl-4-hydroxy-1H-benzo[d]imidazole-7-carboxamide,
2-cyclopentyl-4-hydroxy-N-(piperidin-2-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide,
2-Cyclopentyl-4-hydroxy-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide,
(S)-2-Cyclopentyl-4-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-carboxamide,
(S)-4-Hydroxy-2-phenyl-N-(piperidin-3-yl)-1H-benzo[d]imidazole-7-c

arboxamide,
4-Hydroxy-2-phenyl-N-(piperidin-2-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide,
4-Hydroxy-2-phenyl-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-7-carboxamide,
7-Hydroxy-N-(4-hydroxycyclohexyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
(7-hydroxy-2-[thiophen-2-yl]-1H-benzo[d]imidazol-4-yl)(piperazin-1-yl)methanone,
7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
7-Hydroxy-N-[2-(piperazin-1-yl)ethyl]-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
(R)-7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
(S)-7-Hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
7-Hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
7-Hydroxy-N-(piperidin-4-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
7-Hydroxy-N-(1-methylpiperidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
7-Hydroxy-N-(piperidin-4-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide, N-(Azetidin-3-ylmethyl)-7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
7-Hydroxy-N-(pyrrolidin-3-yl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
7-Hydroxy-N-(piperidin-2-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
7-Hydroxy-N-(pyrrolidin-3-ylmethyl)-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide, N-(4-Aminocyclohexyl)-7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamide,
2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide,
2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(piperidin-3-yl)-1H-benzo[

d]imidazole-4-carboxamide, (S)-tert-Butyl 3-(2-(5-bromothiophen-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamido)piperidine-1-carboxylate, (S)-2-(5-bromothiophen-2-yl)-7-hydroxy-N-(piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide, 2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-((S)-piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide, 2-(Bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-N-(adamantane-3-ylamino)-1H-benzo[d]imidazole-4-carboxamide, 2-(Thiophene-2-yl)-7-hydroxy-N-(adamantate-3-ylamino)-1H-benzo[d]imidazole-4-carboxamide), N-(3-Aminocyclohexyl)-2-(bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamide, N-{[(cis)-4-Aminocyclohexyl]methyl}-2-(bicyclo[2.2.1]heptan-2-yl)-7-hydroxy-1H-benzo[d]imidazole-4-carboxamide, (S)-7-hydroxy-2-(5-(piperazin-1-yl)thiophen-2-yl)-N-(piperidin-3-yl)-1H-benzo[d]imidazole-4-carboxamide, (R)-7-hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide, (S)-7-hydroxy-N-(piperidin-3-yl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide, (S)-7-hydroxy-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-1H-benzo[d]imidazole-4-carboxamide, and 4-[7-hydroxy-2-(thiophen-2-yl)-1H-benzo[d]imidazole-4-carboxamido]cyclohexanecarboxylic acid.

[Claim 12] A pharmaceutical composition comprising at least one compound and pharmaceutically acceptable carrier, which is available for preventing or treating GSK-3beta dependent diseases, wherein the compound is the GSK-3beta inhibitor of any one of claims 1 to 11.

[Claim 13] The pharmaceutical composition of claim 13, wherein the GSK-3beta dependent disease is selected from a group consisting of Alzheimer disease, mania, depression, migraine and type 2 diabetes.

[Claim 14] A method for treating or preventing GSK-3beta dependent diseases in a subject, comprising administering to a subject an effective amount of one compound selected from the GSK-3beta inhibitor of any one of claims 1 to 11.

[Claim 15] Use of the GSK-3beta inhibitor of any one of claims 1 to 11 in manufacturing a pharmaceutical composition for treating or preventing a

GSK-3beta dependent disease.