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(54) Title: KIT INHIBITORS, COMPOUNDS, PHARMACEUTICAL COMPOSITIONS, AND METHODS OF USE THEREOF

(57) Abstract: Provided herein are compounds and compositions useful in inhibiting a receptor tyrosine kinase, KIT.#The compounds and compositions provided herein are useful for the prevention or treatment of one or more KIT mediated diseases or conditions (e.g., cancers, autoimmune diseases, allergic diseases, inflammatory diseases, fibrosis, metabolic disorders, and neurodegenerative diseases).

Description

Title of Invention: KIT INHIBITORS, COMPOUNDS, PHARMACEUTICAL COMPOSITIONS, AND METHODS OF USE THEREOF

Technical Field

[0001] This application is directed to inhibitors of a receptor tyrosine kinase, KIT (c-KIT), and methods for their use, such as to prevent or treat one or more KIT mediated diseases or conditions.

Background Art

[0002] Protein phosphorylation is an important cellular regulatory mechanism as many enzymes and receptors are activated/deactivated by phosphorylation and dephosphorylation events, by means of kinases and phosphatases. Receptor tyrosine kinases (RTKs) play an important role in a variety of cellular processes including growth, motility, differentiation, and metabolism. KIT (c-KIT) is a tyrosine kinase receptor that acts as a facultative onco-protein and regulates the development and function of multiple distinct cell lineages. These include hematopoietic progenitors, melanocytes, germ cells, and mast cells (MCs), which are all significantly affected by loss-of-function mutations of KIT or its cytokine ligand, stem cell factor (SCF) (Valent et al., Theranostics 2020, 10(23), 10743).

[0003] Abnormalities in the expression and function of KIT are associated with several human diseases. KIT activation has been implicated in various human cancers, including mastocytosis, germ cell tumors, small-cell lung carcinoma, gastrointestinal stromal tumors (GIST), acute myelogenous leukemia, neuroblastoma, melanoma, ovarian carcinoma, and breast carcinoma (Turner et al., Blood 1992, 80: 374-381; Heinrich et al., J Clin Oncol 2002, 20: 1692-1703). KIT activation in these tumors is generally accomplished by one or more of three mechanisms: autocrine and/or paracrine stimulation by SCF, cross-activation by other kinases, and/or the acquisition of activating mutations (Hirota et al., Science (Wash DC) 1998, 279: 577-580; Heinrich et al. 2002). Pharmacological inhibition of KIT or SCF with small molecule inhibitors or specific antibodies can also affect the function of healthy and carcinogenic cells expressing KIT receptor (Valent et al., J Allergy Clin Immunol 2022, 149:1866-74). Indeed, several kinase inhibitors are approved for the treatment of GIST and other malignancies with KIT activation in both humans and non-human mammals.

[0004] It has become evident that KIT and its ligand participate in the development and function of multiple distinct cell lineages. These include cells in parts of the central nervous system, the interstitial cells of Cajal in the gut, taste cells, as well as several

hematopoietic cell lineages in addition to MCs, including dendritic cells, eosinophils, and ILC2s (Tsai M et al., J. Allergy Clin. Immunol. 2022, 149:1845-54). While most lineages lose KIT as they differentiate, MCs are one of the few cell types that retain KIT expression even after differentiation into mature cells (Lennartsson J et al., Stem Cells 2005, 23:16-43).

[0005] KIT and its ligand SCF play a dominant role in the development and maturation of tissue MCs. In contrast to other myeloid cells, MCs are long-lived. This is because the development of fully mature MCs from stem cells through pluripotent and committed MC progenitor cells may take several months. In addition, some mature tissue MCs survive months or perhaps years when residing within local tissue microenvironments (Cerny-Reiterer S et al., Oncotarget 2015, 6:3071-84). At maturation, MCs reside in local tissue sites at which SCF and other growth factors and cytokines are expressed, supporting long-term survival as well as effector cell functions.

[0006] As multifunctional cells of the innate immune system, MCs contribute to adaptive immune responses, and they play a role in allergic and other inflammatory reactions, as well. MCs express high-affinity receptors for IgE and produce numerous biologically active substances, some of which are stored in cytoplasmic granules for rapid release (Valent et al. 2020). MCs can be activated by many different stimuli, including allergens through IgE and IgE receptors; by IgG immune complexes; by complement and cytokines; by toxins, venom, and bacterial byproducts, as well as by certain medications (Valent et al. 2020). MC activation occurs in a number of different disease states and pathologies. Clinical symptoms may be severe, resulting in challenges to everyday life. In patients with allergic (atopic) disorders and in those with mastocytosis, MC activation may be substantial and systemic, even resulting in overt anaphylaxis.

[0007] Imatinib is a small molecule TKI which blocks KIT and other kinases including ABL1, ABL2, PDGFRs, and many more. Initially developed as a targeted cancer drug, Imatinib is approved by both the US Food and Drug Administration and European Medicines Agency for the treatment of systemic mastocytosis (SM), where the numbers of MCs are excessively elevated. The rationale for the use of imatinib in SM came from several studies. In one report, patients with chronic myeloid leukemia were treated with imatinib for several years. During this therapy, the number of MCs in the bone marrow were found to have decreased after 12 months; and after 24 months, MCs were almost completely absent in bone marrow sections (Cerny-Reiterer S et al. 2015). Simultaneously, serum tryptase levels, a MC activation marker, decreased to the point where they were low to undetectable (Cerny-Reiterer S et al. 2015). In a different study, 62 patients with poorly controlled or uncontrolled severe asthma who had airway hyperresponsiveness despite receiving maximal medical therapy were treated

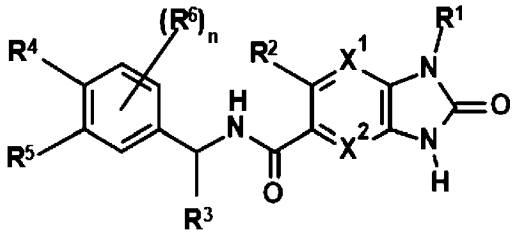
with imatinib (400 mg per day orally) for 24 weeks. Therapy with imatinib was found to reduce airway hyperresponsiveness and bronchoalveolar lavage tryptase levels more effectively in these patients than in the placebo control (Cahill KN et al., N Engl J Med 2017, 376:1911-20). Taken together, these data suggest that therapy with KIT-targeting drugs may lead to partial or even complete eradication of the MC lineage in patients with various MC diseases. In addition, some of these TKIs can also suppress IgE-dependent activation of MCs and basophils (Valent et al. 2022). Therefore, highly specific KIT inhibitors may offer a new, safer treatment option for patients with severe MC diseases.

Summary of Invention

[0008] Provided herein, inter alia, are compounds and compositions comprising such compounds that are useful for inhibiting KIT. In particular, disclosed herein are methods inhibiting the activity of KIT for the prevention or treatment of KIT mediated diseases or conditions associated with improperly regulated kinase signal transduction of MCs such as cancers, autoimmune diseases, allergic diseases, inflammatory diseases, fibrosis, metabolic disorders, and neurodegenerative diseases by administering to a subject a therapeutically effective amount of one or more compounds or compositions provided herein.

[0009] In one embodiment, provided herein is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by the following Formula (I):

[0010] [Chem.1]



(I)

[0011] or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, C_{1-3}-alkyl, or C_{1-3}-deuteroalkyl,

R^2 is hydrogen, halogen, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, nitro, amino, or mono- or di-(C_{1-4}-alkyl)amino,

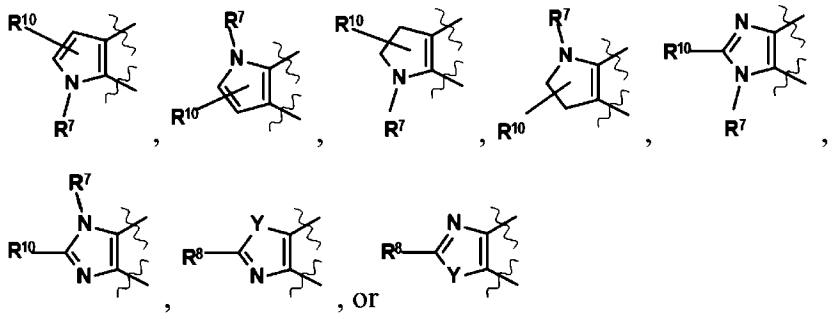
R^3 is hydrogen or C_{1-4}-alkyl,

R^4 is halogen, hydroxy, nitro, amino, mono- or di- or tri-(C_{1-4}-alkyl)silyl, R^A, -O-R^A, -N(R^A)(R^B), or -CO-N(R^A)(R^C), and

R^5 is hydrogen, halogen, hydroxy, nitro, amino, R^A, -O-R^A, -N(R^A)(R^B), or -CO-N(R^A)(R^C), or

R^4 and R^5 are taken together to form a group of the formula:

[0012] [Chem.2]



[0013] the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^7 is hydrogen or R^A,

R^8 is hydrogen or -N(R^A)(R^B),

X^1 and X^2 are each independently N or C-R^9,

R^9 is hydrogen, halogen, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, nitro, amino, or mono- or di-(C_{1-4}-alkyl)amino,

R^{10} is hydrogen, halogen, or C_{1-4}-alkyl,

Y is O or S,

n is an integer having a value of 0, 1, 2 or 3,

R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl, in which said C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with

heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino;

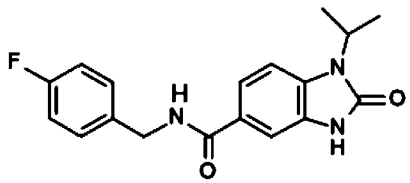
R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl, and

R^C is C_{1-4}-alkyl or C_{3-6}-cycloalkyl, or

R^A and R^B at the -N(R^A)(R^B), or R^A and R^C at the -CO-N(R^A)(R^C) are taken together with the nitrogen atom to form an N-containing heterocyclic ring optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino,

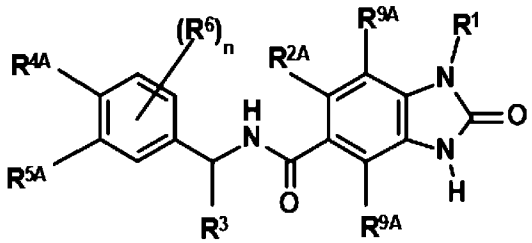
provided that the compound is not

[0014] [Chem.3]



[0015] In another embodiment, provided herein is a compound represented by the following Formula (Ia):

[0016] [Chem.4]



(Ia)

[0017] or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, C_{1-3}-alkyl, or C_{1-3}-deuteroalkyl,

R^{2A} is hydrogen or halogen,

R^3 is hydrogen or C_{1-4}-alkyl,

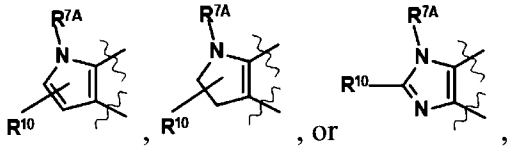
R^{4A} is mono- or di- or tri-(C_{1-4}-alkyl)silyl, R^A, -O-R^A or -N(R^A)(R^B), and

R^{5A} is hydrogen, halogen, or -O-R^A, or

R^{4A} and R^{5B} are taken together to form a group of the formula:

[0018]

[Chem.5]



[0019] the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^{7A} is R^A,

R^{9A} is hydrogen or halogen,

R^{10} is hydrogen, halogen, or C_{1-4}-alkyl,

n is an integer having a value of 0, 1, 2 or 3,

R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl, in which said C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}

-alkyl)amino; and

R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl, or

R^A and R^B are taken together with the nitrogen atom to form an N-containing heterocyclic ring optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino.

[0020] Another embodiment comprises method for preventing or treating a KIT mediated disease or condition in a subject by administering to the subject a therapeutically effective amount of one or more of the disclosed compounds, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound(s).

[0021] Also provided herein is use of one or more of the disclosed compounds, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the prevention or treatment of a KIT mediated disease or condition.

[0022] In another embodiment, provided herein is one or more of the disclosed compounds, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the disclosed compound(s) for use in preventing or treating a KIT mediated disease or condition.

Description of Embodiments

[0023] <Definitions>

The term “alkyl" used alone or as part of a larger moiety, such as “haloalkyl”, "cycloalkyl", “alkylamino”, and the like, means saturated aliphatic straight-chain or branched monovalent hydrocarbon radical. Unless otherwise specified, an alkyl group typically has 1 to 4 carbon atoms, i.e., C_{1-4}-alkyl. As used herein, a “C_{1-4}-alkyl” group means a radical having from 1 to 4 carbon atoms in a linear or branched arrangement, and includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

[0024] The term “deuteroalkyl” means an alkyl having one or more deuterium atoms. For example, the term “C_{1-3}-deuteroalkyl” means a radical having from 1 to 3 carbon atoms, and includes mono, di, and trideuteromethyl.

[0025] The term “alkylamino” means amino substituted with one or more alkyl groups. For example, “mono- or di-(C_{1-4}-alkyl)amino” includes methylamino, ethylamino, isopropylamino, dimethylamino, diethylamino, (ethyl)(methyl)amino, (isopropyl)(methyl)amino and (tert-butyl)(methyl)amino.

[0026] The term “alkylsilyl” means silyl substituted with one or more alkyl groups. For example, “mono- or di- or tri-(C_{1-4}-alkyl)silyl” includes methylsilyl, ethylsilyl, dimethylsilyl, diethylsilyl and trimethylsilyl.

[0027] The term “haloalkyl” means alkyl substituted with one or more halogen atoms.

For example, "C_{1-4}-haloalkyl" includes fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, bromomethyl, fluoroethyl, difluoroethyl, dichloroethyl and chloropropyl. In one aspect, an example of C_{1-4}-haloalkyl includes difluoromethyl or trifluoromethyl, and in another aspect, an example of C_{1-4}-haloalkyl includes trifluoromethyl.

[0028] The term "halogen" or "halo" means fluorine or fluoro (F), chlorine or chloro (Cl), bromine or bromo (Br), or iodine or iodo (I).

[0029] The term "aryl" means a monocyclic or bicyclic aromatic hydrocarbon radical such as phenyl, naphthyl, anthracenyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indanyl and indenyl. In one aspect, an example of aryl includes phenyl or naphthyl, and in another aspect, an example of aryl includes phenyl.

[0030] The term "cycloalkyl" means a 3-12 membered saturated aliphatic cyclic hydrocarbon radical. It can be monocyclic, bicyclic (e.g., a bridged, spirofused, or fused bicyclic ring), or tricyclic. For example, monocyclic C_{3-6}-cycloalkyl means a radical having from 3 to 6 carbon atoms arranged in a monocyclic ring. For example, "C_{3-6}-cycloalkyl" includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentyl, bicyclo[3.1.0]hexyl, and spiro[2.3]hexyl.

[0031] The term "heteroaryl" refers to monocyclic or bicyclic aromatic ring radical having at least one (typically 1 to 4, more typically 1 or 2) heteroatoms (e.g., oxygen, nitrogen, or sulfur). Examples of such heteroaryl groups include pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, oxazolyl, isoxazolyl, oxadiazolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalyl, pyrolopyridyl, and imidazolopyridyl.

[0032] The term "heterocyclyl" refers to a monocyclic or bicyclic non-aromatic ring radical having at least one (typically 1 to 4, more typically 1 or 2) heteroatoms (e.g., oxygen, nitrogen, or sulfur). Each heteroatom is independently selected from nitrogen, quaternary nitrogen, oxidized nitrogen (e.g., NO); oxygen; and sulfur, including sulfoxide and sulfone. Some of bonds that constitute the heterocyclyl may be unsaturated bonds. A part of the bicyclic heterocyclyl may have aromaticity. Examples thereof include aspects in a state where the monocyclic heterocyclyl having a 5- and 6-membered ring is fused with a benzene ring, a pyrrole ring, a furan ring, a thiophene ring, a pyrazole ring, an imidazole ring, an oxazole ring, a thiazole ring, or a pyridine ring, and a state where at least a partially unsaturated hydrocarbon ring radical having a 5- and 6-membered ring is fused with a pyrrole ring, a furan ring, a thiophene ring, a pyrazole ring, an imidazole ring, an oxazole ring, a thiazole ring, or a pyridine ring.

Examples of such heterocyclyl groups include aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, dihydropyridyl, tetrahydropyridyl, dihydropyridazinyl, tetrahydropyridazinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, dihydropyrazinyl, tetrahydropyrazinyl, oxetanyl, tetrahydrofuryl, dihydrofuryl, tetrahydropyranyl, dihydropyranyl, tetrahydrothienyl, tetrahydrothiopyranyl, dihydrothiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, dihydroindolyl, dihydroisoindolyl, dihydrobenzofuryl, dihydroisobenzofuryl, tetrahydrobenzoxazolyl, dihydrofuropyridyl, dihydropyrazolomorpholinyl, pyridinodioxanyl, dihydroazabenzofuryl, dihydroazaisobenzofuryl, dihydroazaindolyl, 2-oxaspiro[3.5]nonyl, and 2-oxaspiro[3.3]heptyl.

[0033] Examples of "N-containing heterocyclic ring" formed by taken together R^A and R^B at the -N(R^A)(R^B), or R^A and R^C at the -CO-N(R^A)(R^C) with the nitrogen atom include azetidine, pyrrolidine, pyrazole, imidazole, triazole, tetrazole, piperidine, dihydropyridine, tetrahydropyridine, piperazine, morpholine, and thiomorpholine.

[0034] If a group is described as being "substituted", a non-hydrogen substituent is in the place of a hydrogen substituent on a carbon, sulfur or nitrogen of the substituent. Thus, for example, a substituted alkyl is an alkyl wherein at least one non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro substituent, and difluoroalkyl is alkyl substituted with two fluoro substituents. It should be recognized that if there is more than one substitution on a substituent, each non-hydrogen substituent can be identical or different (unless otherwise stated).

[0035] Compounds having one or more chiral centers can exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Stereoisomers include all diastereomeric, enantiomeric, and epimeric forms as well as racemates and mixtures thereof. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. The term "geometric isomer" refers to compounds having at least one double bond, wherein the double bond(s) may exist in cis (also referred to as syn or entgegen (E)) or trans (also referred to as anti or zusammen (Z)) forms as well as mixtures thereof. When a disclosed compound is named or depicted by structure without indicating stereochemistry, it is understood that the name or the structure encompasses one or more of the possible stereoisomers, or geometric isomers, or a mixture of the encompassed stereoisomers or geometric isomers.

[0036] When a geometric isomer is depicted by name or structure, it is to be understood that the named or depicted isomer exists to a greater degree than another isomer, that is that the geometric isomeric purity of the named or depicted geometric isomer is greater than 50%, such as at least 60%, 70%, 80%, 90%, 99% or 99.9% pure by weight. Geometric isomeric purity is determined by dividing the weight of the named or

depicted geometric isomer in the mixture by the total weight of all of the geometric isomers in the mixture.

[0037] Racemic mixture means 50% of one enantiomer and 50% of is corresponding enantiomer. When a compound with one chiral center is named or depicted without indicating the stereochemistry of the chiral center, it is understood that the name or structure encompasses both possible enantiomeric forms (e.g., both enantiomerically-pure, enantiomerically-enriched or racemic) of the compound. When a compound with two or more chiral centers is named or depicted without indicating the stereochemistry of the chiral centers, it is understood that the name or structure encompasses all possible diastereomeric forms (e.g., diastereomerically pure, diastereomerically enriched and equimolar mixtures of one or more diastereomers (e.g., racemic mixtures) of the compound.

[0038] Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and diastereomers also can be obtained from diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[0039] When a compound is designated by a name or structure that indicates a single enantiomer, unless indicated othe1wise, the compound is at least 60%, 70%, 80%, 90%, 99% or 99.9% optically pure (also referred to as "enantiomerically pure"). Optical purity is the weight in the mixture of the named or depicted enantiomer divided by the total weight in the mixture of both enantiomers.

[0040] When the stereochemistry of a disclosed compound is named or depicted by structure, and the named or depicted structure encompasses more than one stereoisomer (e.g., as in a diastereomeric pair), it is to be understood that one of the encompassed stereoisomers or any mixture of the encompassed stereoisomers is included. It is to be further understood that the stereoisomeric purity of the named or depicted stereoisomers at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight. The stereoisomeric purity in this case is determined by dividing the total weight in the mixture of the stereoisomers encompassed by the name or structure by the total weight in the mixture of all of the stereoisomers.

[0041] It is to be understood that when a compound herein is represented by a structural formula or designated by a chemical name herein, all other tautomeric forms which may exist for the compound are encompassed by the structural formula.

[0042] As used herein, the term "pharmaceutically acceptable salt" refers to pharmaceutical salts that are, within the scope of sound medical judgment, suitable for use in

contact with the tissues of humans and lower animals without undue toxicity, irritation, and allergic response, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmacologically acceptable salts in J. Pharm. Sci., 1977, 66:1-19.

[0043] Included in the present teachings are pharmaceutically acceptable salts of the compounds disclosed herein. Compounds having basic amine groups can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically acceptable acid addition salts of the compounds described herein include salts of inorganic acids (such as hydrochloric, hydrobromic, phosphoric, nitric, and sulfuric acids) and of organic acids (such as, e.g., acetic, trifluoroacetic, benzenesulfonic, benzoic, methanesulfonic, and p-toluenesulfonic acids). Compounds with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

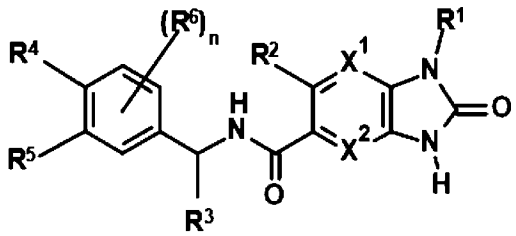
[0044] Furthermore, the present invention also includes various hydrates or solvates, and any of crystalline polymorphs of the compound of Formula (I) and a pharmaceutically acceptable salt thereof. In addition, the present invention also includes compounds labeled with various radioactive or non-radioactive isotopes.

[0045] It is to be noted that the compound of Formula (Ia) is included within the scope of the compound of Formula (I), and accordingly suitable examples or embodiments of the compound of Formula (Ia) are to be referred to those as exemplified for the compound of Formula (I).

[0046] <Compositions and Compounds of the Invention>

In a first embodiment, the invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by the following Formula (I).

[0047] [Chem.6]



(I)

[0048] or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, C_{1-3}-alkyl, or C_{1-3}-deuteroalkyl,

R^2 is hydrogen, halogen, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, nitro, amino, or mono- or di-(C_{1-4}-alkyl)amino,

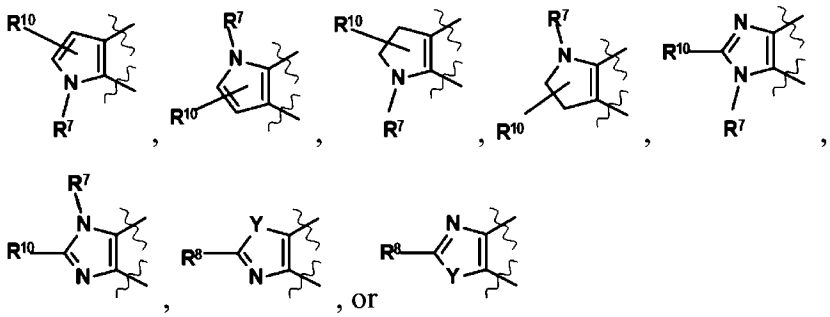
R^3 is hydrogen or C_{1-4}-alkyl,

R^4 is halogen, hydroxy, nitro, amino, mono- or di- or tri-(C_{1-4}-alkyl)silyl, R^A, -O-R^A, -N(R^A)(R^B), or -CO-N(R^A)(R^C), and

R^5 is hydrogen, halogen, hydroxy, nitro, amino, R^A, -O-R^A, -N(R^A)(R^B), or -CO-N(R^A)(R^C), or

R^4 and R^5 are taken together to form a group of the formula:

[0049] [Chem.7]



[0050] the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^7 is hydrogen or R^A,

R^8 is hydrogen or -N(R^A)(R^B),

X^1 and X^2 are each independently N or C-R^9,

R^9 is hydrogen, halogen, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, nitro, amino, or mono- or di-(C_{1-4}-alkyl)amino,

R^{10} is hydrogen, halogen, or C_{1-4}-alkyl,

Y is O or S,

n is an integer having a value of 0, 1, 2 or 3,

R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl, in which said C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in

which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino;

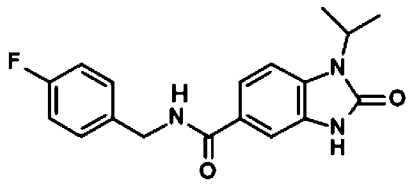
R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl, and

R^C is C_{1-4}-alkyl or C_{3-6}-cycloalkyl, or

R^A and R^B at the -N(R^A)(R^B), or R^A and R^C at the -CO-N(R^A)(R^C) are taken together with the nitrogen atom to form an N-containing heterocyclic ring optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino,

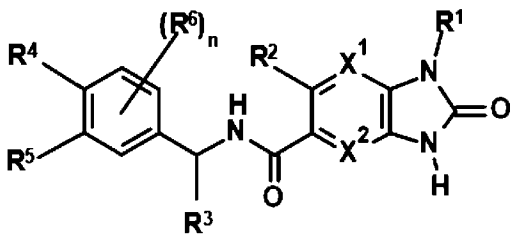
provided that the compound is not

[0051] [Chem.8]



[0052] In a 2nd embodiment, the invention provides a pharmaceutical composition according to the 1st embodiment, which is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by the following Formula (I):

[0053] [Chem.9]



(I)

[0054] or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-3}-alkyl,

R^2 is hydrogen, halogen, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, nitro, amino, or mono- or di-(C_{1-4}-alkyl)amino,

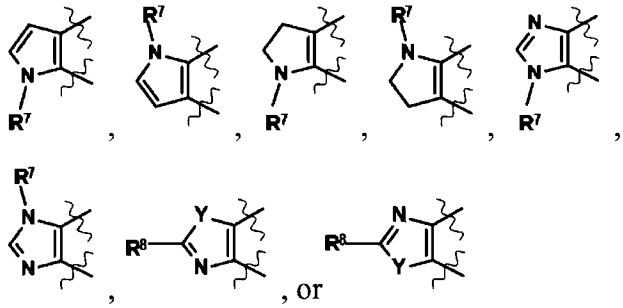
R^3 is hydrogen or C_{1-4}-alkyl,

R^4 is halogen, hydroxy, nitro, amino, R^A, -O-R^A, -N(R^A)(R^B), or -CO-N(R^A)(R^C), and

R^5 is hydrogen, halogen, hydroxy, nitro, amino, R^A, -O-R^A, -N(R^A)(R^B), or -CO-N(R^A)(R^C), or

R^4 and R^5 are taken together to form a group of the formula:

[0055] [Chem.10]



[0056] the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^7 is hydrogen or R^A,

R^8 is hydrogen or -N(R^A)(R^B),

X^1 and X^2 are each independently N or C-R^9,

R^9 is hydrogen, halogen, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, nitro, amino, or mono- or di-(C_{1-4}-alkyl)amino,

Y is O or S,

n is an integer having a value of 0, 1, 2 or 3,

R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl, in which said C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C

$_{1-4}$-alkyl), C_{1-4}-haloalkyl, amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino;

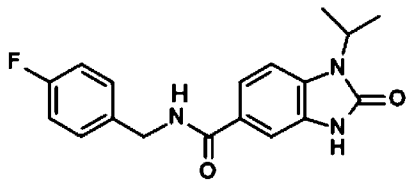
R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl, and

R^C is C_{1-4}-alkyl or C_{3-6}-cycloalkyl, or

R^A and R^B at the -N(R^A)(R^B), or R^A and R^C at the -CO-N(R^A)(R^C) are taken together with the nitrogen atom to form an N-containing heterocyclic ring optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino,

provided that the compound is not

[0057] [Chem.11]



[0058] In a 3rd embodiment, the invention provides a pharmaceutical composition according to the 2nd embodiment, wherein R^1 is hydrogen, methyl, ethyl, or isopropyl, and R^3 is hydrogen or methyl.

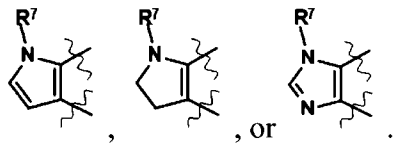
[0059] In a 4th embodiment, the invention provides a pharmaceutical composition according to the 3rd embodiment, wherein

R^4 is R^A, -O-R^A, or -N(R^A)(R^B), and

R^5 is hydrogen, halogen, or -O-R^A, or

R^4 and R^5 are taken together to form a group of the formula:

[0060] [Chem.12]



[0061] In a 5th embodiment, the invention provides a pharmaceutical composition according to the 2nd to 4th embodiments, wherein R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, phenyl, tetrahydropyranyl, piperidyl, piperazinyl, pyridyl, pyrimidyl, pyrazolyl, and indazolyl, in which said C_{3-6}-cycloalkyl, phenyl, tetrahydropyranyl, piperidyl, piperazinyl, pyridyl, pyrimidyl, pyrazolyl, and

indazolyl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; phenyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with tetrahydropyranyl, piperidyl, or piperazinyl, each of which may be further substituted with halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, or mono- or di-(C_{1-4}-alkyl)amino; tetrahydropyranyl, piperidyl, or piperazinyl, each of which may be substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; or pyridyl, pyrimidyl, pyrazolyl, or indazolyl, each of which may be substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; and R^B is methyl.

[0062] In a 6th embodiment, the invention provides a pharmaceutical composition according to the 5th embodiment, wherein R^A is isopropyl; C_{3-6}-cycloalkyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl; phenyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl; or pyridyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl.

[0063] In a 7th embodiment, the invention provides a pharmaceutical composition according to the 1st embodiment, wherein

R^4 is R^A, -O-R^A, or -N(R^A)(R^B),

R^5 is hydrogen or halogen,

R^A is C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -

O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; and

R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl.

[0064] In an 8th embodiment, the invention provides a pharmaceutical composition according to the 1st embodiment, wherein the compound is selected from the group consisting of

N-((1-(2,6-Difluorophenyl)indolin-5-yl)methyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 13),

N-(4-(Isopropyl(methyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 52),

N-(2,6-Difluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 21),

N-(4-((3,3-Difluorocyclobutyl)(methyl)amino)-2-fluorobenzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 22),

N-(2,6-Difluoro-4-((4,4-difluorocyclohexyl)(methyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 56),

N-(4-((4,4-Difluorocyclohexyl)(methyl)amino)-2-fluorobenzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 57),

N-(2-Fluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 59),

N-(2-Fluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 63),

4-Fluoro-N-(4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 64), and

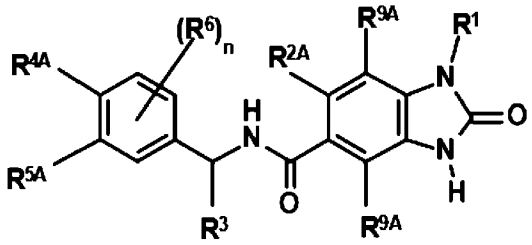
N-(4-((4,4-Difluorocyclohexyl)(methyl)amino)benzyl)-4-fluoro-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 66),

or a pharmaceutically acceptable salt thereof.

[0065] In a 9th embodiment, the invention provides a compound represented by the

following Formula (Ia):

[0066] [Chem.13]



(Ia)

[0067] or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, C_{1-3}-alkyl, or C_{1-3}-deuteroalkyl,

R^{2A} is hydrogen or halogen,

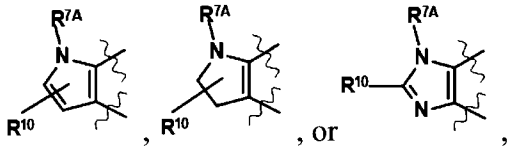
R^3 is hydrogen or C_{1-4}-alkyl,

R^{4A} is mono- or di- or tri-(C_{1-4}-alkyl)silyl, R^A, -O-R^A or -N(R^A)(R^B), and

R^{5A} is hydrogen, halogen, or -O-R^A, or

R^{4A} and R^{5B} are taken together to form a group of the formula:

[0068] [Chem.14]



[0069] the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^{7A} is R^A,

R^{9A} is hydrogen or halogen,

R^{10} is hydrogen, halogen, or C_{1-4}-alkyl,

n is an integer having a value of 0, 1, 2 or 3,

R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl, in which said C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl,

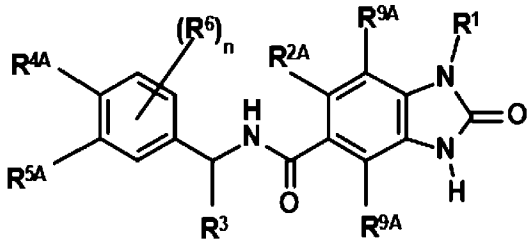
-O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; and

R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl, or

R^A and R^B are taken together with the nitrogen atom to form an N-containing heterocyclic ring optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino.

[0070] In a 10th embodiment, the invention provides a compound according to the 9th embodiment, which is a compound represented by the following Formula (Ia):

[0071] [Chem.15]



(Ia)

[0072] or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-3}-alkyl,

R^{2A} is hydrogen or halogen,

R^3 is hydrogen or C_{1-4}-alkyl,

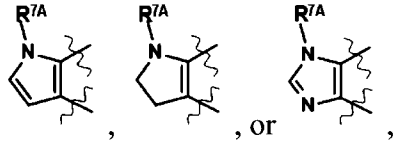
R^{4A} is R^A, -O-R^A or -N(R^A)(R^B), and

R^{5A} is hydrogen, halogen, or -O-R^A, or

R^{4A} and R^{5B} are taken together to form a group of the formula:

[0073]

[Chem.16]



[0074] the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^{7A} is R^A,

R^{9A} is hydrogen or halogen,

n is an integer having a value of 0, 1, 2 or 3,

R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl, in which said C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; and

R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl, or

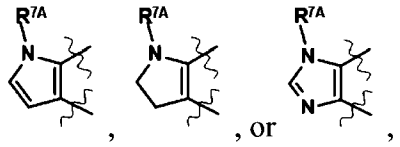
R^A and R^B are taken together with the nitrogen atom to form an N-containing heterocyclic ring optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino.

[0075] In an 11th embodiment, the invention provides a compound according to the 10th embodiment, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen or methyl, and R^3 is hydrogen or methyl.

[0076] In a 12th embodiment, the invention provides a compound according to the 11th embodiment, or a pharmaceutically acceptable salt thereof, wherein R^{4A} is -N(R^A)(R^B),

and R^{5A} is hydrogen or halogen, or R^{4A} and R^{5B} are taken together to form a group of the formula:

[0077] [Chem.17]



[0078] In a 13th embodiment, the invention provides a compound according to the 12th embodiment, or a pharmaceutically acceptable salt thereof, wherein R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, phenyl, tetrahydropyranyl, piperidyl, piperazinyl, pyridyl, pyrimidyl, pyrazolyl, and indazolyl, in which said C_{3-6}-cycloalkyl, phenyl, tetrahydropyranyl, piperidyl, piperazinyl, pyridyl, pyrimidyl, pyrazolyl, and indazolyl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; phenyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with tetrahydropyranyl, piperidyl, or piperazinyl, each of which may be further substituted with halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, or mono- or di-(C_{1-4}-alkyl)amino; tetrahydropyranyl, piperidyl, or piperazinyl, each of which may be substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; or pyridyl, pyrimidyl, pyrazolyl, or indazolyl, each of which may be substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; and R^B is methyl.

[0079] In a 14th embodiment, the invention provides a compound according to the 13th embodiment, or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen or methyl,

R^{2A} is hydrogen or halogen,

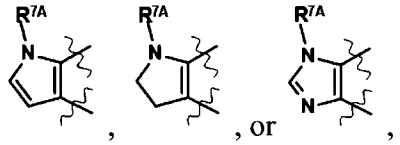
R^3 is hydrogen or methyl,

R^{4A} is -N(R^A)(R^B), and

R^{5A} is hydrogen, or halogen, or

R^{4A} and R^{5B} are taken together to form a group of the formula:

[0080] [Chem.18]



[0081] the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^{7A} is R^A,

R^{9A} is hydrogen or halogen,

n is an integer having a value of 0, 1, 2 or 3,

R^A is isopropyl; C_{3-6}-cycloalkyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl; phenyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl; or pyridyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl; and

R^B is methyl.

[0082] In a 15th embodiment, the invention provides a compound according to the 9th embodiment, or a pharmaceutically acceptable salt thereof, wherein

R^{4A} is -O-R^A or -N(R^A)(R^B),

R^{5A} is hydrogen or halogen,

R^A is C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected

from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; and

R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl.

[0083] In a 16th embodiment, the invention provides a compound according to the 9th embodiment, or a pharmaceutically acceptable salt thereof, wherein

R^{4A} is -N(R^A)(R^B),

R^{5A} is hydrogen or halogen,

R^A is C_{3-6}-cycloalkyl substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino, and

R^B is hydrogen or C_{1-4}-alkyl.

[0084] In a 17th embodiment, the invention provides a compound according to the 9th embodiment, or a pharmaceutically acceptable salt thereof, wherein

R^{4A} is R^A,

R^{5A} is hydrogen or halogen, and

R^A is C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino.

[0085] In an 18th embodiment, the invention provides a compound according to the 9th

embodiment, or a pharmaceutically acceptable salt thereof, wherein

R^{4A} is R^{A},

R^{5A} is hydrogen or halogen, and

R^{A} is C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl, such as thiazolyl or pyrazolyl, substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino.

[0086] In a 19th embodiment, the invention provides a compound according to the 9th embodiment, or a pharmaceutically acceptable salt thereof, wherein R^{4A} is R^{A} or -N(R^{A})(R^{B}), and R^{5A} is -O-R^{A}.

[0087] In a 20th embodiment, the invention provides a compound according to the 9th embodiment, or a pharmaceutically acceptable salt thereof, wherein

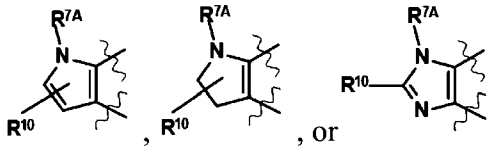
R^{4A} is C_{1-4}-alkyl substituted with halogen,

R^{5A} is -O-R^{A}, and

R^{A} is C_{1-4}-alkyl substituted with one or more groups selected from the group consisting of C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl, in which said C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino.

[0088] In a 21st embodiment, the invention provides a compound according to the 9th embodiment, or a pharmaceutically acceptable salt thereof, wherein R^{4A} and R^{5B} are taken together to form a group of the formula:

[0089] [Chem.19]



, , or .

[0090] In a 22nd embodiment, the invention provides a compound according to the 21st embodiment, or a pharmaceutically acceptable salt thereof, wherein

R^{7A} is R^{A},

R^{10} is hydrogen, halogen, or C_{1-4}-alkyl, and

R^A is C_{1-4}-alkyl substituted with C_{3-6}-cycloalkyl; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino.

[0091] In a 23rd embodiment, the invention provides a compound according to the 9th embodiment, or a pharmaceutically acceptable salt thereof, wherein

R^{4A} is -N(R^A)(R^B),

R^{5A} is hydrogen or halogen,

R^A is isopropyl, and

R^B is methyl.

[0092] In a 24th embodiment, the invention provides a compound according to the 9th embodiment, wherein the compound is selected from the group consisting of

N-((1-(2,6-Difluorophenyl)indolin-5-yl)methyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 13),

N-(4-(Isopropyl(methyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 52),

N-(2,6-Difluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 21),

N-(4-((3,3-Difluorocyclobutyl)(methyl)amino)-2-fluorobenzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 22),

N-(2,6-Difluoro-4-((4,4-difluorocyclohexyl)(methyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 56),

N-(4-((4,4-Difluorocyclohexyl)(methyl)amino)-2-fluorobenzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 57),

N-(2-Fluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 59),

N-(2-Fluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 63),

4-Fluoro-N-(4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 64), and

N-(4-((4,4-Difluorocyclohexyl)(methyl)amino)benzyl)-4-fluoro-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 66),

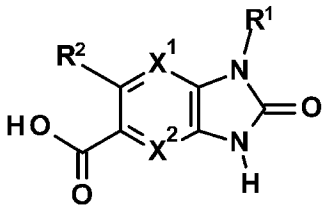
or a pharmaceutically acceptable salt thereof.

[0093] In certain embodiments, the invention is any one of the compounds depicted in the exemplification section of the instant application; and pharmaceutically acceptable salts as well as the neutral forms of these compounds also are included in the invention. Specifically, the invention is any one of the compounds depicted in Examples 1-96; and pharmaceutically acceptable salts as well as the neutral forms of these compounds also are included in the invention. In preferred embodiments, the invention is any one of Compounds 1-96; and pharmaceutically acceptable salts as well as the neutral forms of these compounds also are included in the invention.

[0094] <Methods of Preparing Compounds of the Invention>

Methods of preparing compounds of Formula (I) are disclosed. In general, a compound of Formula (I) or a pharmaceutically acceptable salt thereof may be prepared by reacting a compound of Formula (II)

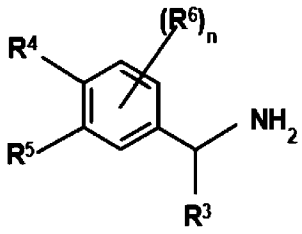
[0095] [Chem.20]



(II)

[0096] or its salt with a compound of Formula (III)

[0097] [Chem.21]



(III)

[0098] or its salt.

[0099] Suitable salts of the compounds (II) and (III) can be referred to the salts as exemplified for the compound (I).

[0100] The reaction is usually carried out in a presence of a conventional condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) or its hydrochloride, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), or propanephosphonic acid anhydride (T3P), in a conventional solvent, such as methylene chloride, chloroform, pyridine, dioxane, tetrahydrofuran, or N,N-dimethylformamide.

[0101] The reaction temperature is not critical and the reaction can be carried out under cooling, at room temperature, or under heating.

[0102] This reaction is preferably carried out in the presence of a conventional inorganic base or in the presence of a conventional organic base.

[0103] The compounds obtained by the above process can be isolated and purified by a conventional method such as pulverization, recrystallization, chromatography, and reprecipitation.

[0104] Detailed synthetic protocols for preparing exemplary compounds of Formula (I) and their intermediate compounds can be referred to Examples and Preparations below or similar manners thereto or conventional manners.

[0105] <Pharmaceutical Compositions>

The compounds of Formula (I) disclosed therein are KIT inhibitors. The pharmaceutical composition of the present invention comprises one or more KIT inhibitors, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

[0106] "Pharmaceutically acceptable carrier" and "pharmaceutically acceptable diluent" refer to a substance that aids the formulation and/or administration of an active agent to and/or absorption by a subject and can be included in the compositions of the present disclosure without causing a significant adverse toxicological effect on the subject. Non-limiting examples of pharmaceutically acceptable carriers and/or diluents include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with or interfere with the activity of the compounds provided herein. One of ordinary skill in the art will recognize that other pharmaceutical excipients are suitable for use with disclosed compounds.

[0107] The pharmaceutical compositions of the present teachings optionally include one or more pharmaceutically acceptable carriers and/or diluents therefor, such as lactose, starch, cellulose and dextrose. Other excipients, such as flavoring agents; sweeteners; and preservatives, such as methyl, ethyl, propyl and butyl parabens, can also be included. More complete listings of suitable excipients can be found in the Handbook of Pharmaceutical Excipients (5th Ed., Pharmaceutical Press (2005)). A person skilled in the art would know how to prepare formulations suitable for various types of administration routes. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003 -20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999. The carriers, diluents and/or excipients are "acceptable" in the sense of being compatible with the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

[0108] <Methods of Treatment>

Methods of preventing or treating a KIT mediated disease or condition, especially, the KIT mediated disease or condition associated with improperly regulated kinase signal transduction of mast cells, in a subject are disclosed. The methods can include administering to the subject a therapeutically effective amount of one or more compounds of Formula (I) or compositions provided herein.

[0109] A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

[0110] In one embodiment, the KIT mediated disease or condition is a cancer. Examples of cancers include, but are not limited to, mastocytosis, mastocytoma, solid tumor, gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinoma, gastric carcinoma, testicular cancer, glioblastoma, astrocytoma, melanoma, mast cell tumor, neuroblastoma, sarcoma, and seminoma.

[0111] In other embodiments, the KIT mediated disease or condition is an autoimmune disease. Examples of autoimmune diseases include, but are not limited to, multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy, and proliferative glomerulonephritis.

[0112] In some embodiments, the KIT mediated disease or condition is an allergic

disease. Examples of allergic diseases include, but are not limited to, asthma, severe asthma, allergic rhinitis, chronic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, food allergy, seasonal allergy, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, and blood sucking parasitic infestation.

[0113] In other embodiments, the KIT mediated disease or condition is an inflammatory disease. Examples of inflammatory diseases include, but are not limited to, rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS), and eosinophilic esophagitis.

[0114] In yet other embodiments, the KIT mediated disease or condition is fibrosis. Examples of fibrosis includes, but are not limited to, pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, and myelofibrosis.

[0115] In still other embodiments, the KIT mediated disease or condition is a metabolic disorder. Examples of metabolic disorders include, but are not limited to, diabetes mellitus and its chronic complications; obesity; type I diabetes or type II diabetes; hyperlipidemias and dyslipidemias; atherosclerosis; hypertension; and cardiovascular disease.

[0116] In other embodiments, the KIT mediated disease or condition is a neurodegenerative disease. Examples of neurodegenerative diseases include, but are not limited to, Alzheimer's disease, Parkinson's disease, Huntington's disease, the prion diseases, motor neuron disease (MND), and amyotrophic lateral sclerosis (ALS).

[0117] In yet other embodiments, the KIT mediated disease or condition includes bone loss, tumor angiogenesis, interstitial cystitis, pulmonary arterial hypertension (PAH), and primary pulmonary hypertension (PPH).

[0118] <Methods of Administration and Dosage Forms>

The precise amount of compound administered to provide an "effective amount" to the subject will depend on the mode of administration, the type, and severity of the disease or condition, and on the characteristics of the subject, such as general health, age, sex, body weight, and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. When administered in combination with other therapeutic agents, e.g., when administered in combination with an anti-cancer agent, an "effective amount" of any additional therapeutic agent(s) will depend on the type of drug used. Suitable dosages are known for approved therapeutic agents and can be adjusted by the skilled artisan according to the condition of the subject, the type of condition(s) being treated and the amount of a compound of the invention being used by following, for example, dosages reported in the literature and recommended in the Physician 's Desk Reference (57th ed., 2003).

[0119] The term "effective amount" means an amount when administered to the subject which results in beneficial or desired results, including clinical results, e.g., inhibits, suppresses, or reduces the symptoms of the condition being treated in the subject as compared to a control. For example, a therapeutically effective amount can be given in unit dosage form (e.g., 0.1 mg to about 50 g per day, alternatively from 1 mg to about 5 grams per day; and in another alternatively from 10 mg to 1 gram per day).

[0120] The terms "administer", "administering", "administration", and the like, as used herein, refer to methods that may be used to enable delivery of compositions to the desired site of biological action. These methods include, but are not limited to, intraarticular (in the joints), intravenous, intramuscular, intratumoral, intradermal, intraperitoneal, subcutaneous, orally, topically, intrathecally, inhalationally, transdermally, rectally, and the like. Administration techniques that can be employed with the agents and methods described herein are found in e.g., Goodman and Gilman, The Pharmacological Basis of Therapeutics, current ed., Pergamon; and Remington's Pharmaceutical Sciences (current edition), Mack Publishing Co., Easton, Pa.

[0121] In addition, the compounds of Formula (I) can be co-administered with other therapeutic agents. As used herein, the terms "co-administration", "administered in combination with", and their grammatical equivalents, are meant to encompass administration of two or more therapeutic agents to a single subject, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different times. In some embodiments the one or more compounds described herein will be co-administered with other agents. These terms encompass administration of two or more agents to the subject so that both agents and/or their metabolites are present in the subject at the same time. They include simultaneous administration in separate compositions, administration at different times in separate compositions, and/or administration in a composition in which both agents are present. Thus, in some embodiments, the compounds described herein and the other agent(s) are administered in a single composition. In some embodiments, the compounds described herein and the other agent(s) are admixed in the composition. In some embodiments, the compounds of Formula (I) can be used in combination with other agents known to have beneficial activity with the compounds of Formula (I) for treating or preventing the KIT mediated diseases or conditions. For example, the compounds of Formula (I) can be administered alone or in combination with one or more other anticancer agents, immunomodulatory agents, antiallergic agents, anti-inflammatory agents, antifibrotic agents, antimetabolites, and anti-neurodegenerative disease agents for treating or preventing the KIT mediated diseases or conditions.

[0122] The particular mode of administration and the dosage regimen will be selected by

the attending clinician, taking into account the particulars of the case (e.g., the subject, the disease, the disease state involved, the particular treatment). Treatment can involve daily or multi-daily or less than daily (such as weekly or monthly etc.) doses over a period of a few days to months, or even years. However, a person of ordinary skill in the art would immediately recognize appropriate and/or equivalent doses looking at dosages of approved compositions for preventing or treating a KIT mediated diseases or conditions using the compounds of Formula (I) for guidance.

[0123] The compounds or the corresponding pharmaceutical compositions taught herein can be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the present teachings may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal and topical modes of administration. Parenteral administration can be by continuous infusion over a selected period of time.

[0124] The pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. In an embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal, or topical administration to human beings. In preferred embodiments, the pharmaceutical composition is formulated for oral or intravenous administration.

[0125] Typically, for oral therapeutic administration, a compound of the present teachings may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

[0126] Typically for parenteral administration, solutions of a compound of the present teachings can generally be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0127] Typically, for injectable use, sterile aqueous solutions, or dispersion of, and sterile powders of, a compound described herein for the extemporaneous preparation of sterile injectable solutions or dispersions are appropriate.

Examples

[0128] <Synthetic Preparation of Compound Embodiments>

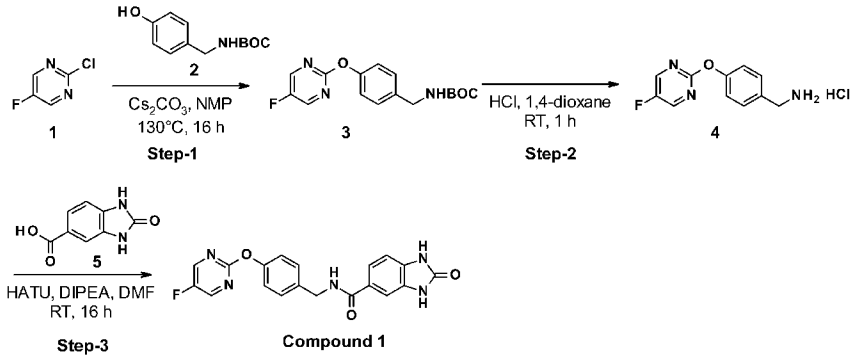
Abbreviations

[0129] [Table 1]

AIBN	2,2'-azobis(isobutyronitrile)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butyloxycarbonyl
bs	broad singlet
CDI	1,1'-carbonyldiimidazole
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	double doublet
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
LAH	lithium aluminum hydride
LC-MS	liquid chromatography-mass spectrometry
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
M	molar
MeOH	methanol
min	minutes
MHz	megahertz
N	normal acid or base
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resolution
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(OAc)_2$	palladium(II) acetate
PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
RT	room temperature
s	singlet
t	triplet
t-BuOH	*tert*-butyl alcohol
TBTU	1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium 3-oxide tetrafluoroborate
t-BuXPhos	2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TPP	triphenylphosphine
Ts	tosyl

[0130] Example-1

[Chem.22]



[0131] Step-1: tert-Butyl (4-((5-fluoropyrimidin-2-yl)oxy)benzyl)carbamate

To a stirred solution of tert-butyl (4-hydroxybenzyl)carbamate (0.50 g, 2.23 mmol) in NMP (10 mL) was added Cs_2CO_3 (2.20 g, 6.7 mmol) followed by 2-chloro-5-fluoropyrimidine (0.25 g, 1.88 mmol) and stirred at 130°C for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. This was purified by combi flash column chromatography using 30% EtOAc in hexane as an eluent to afford the title compound (0.25 g, 41%). ^{1}H-NMR (400 MHz, DMSO-D_6) δ 8.41-8.39 (s, 2H), 7.36-7.34 (d, 2H), 7.15-7.13 (d, 2H), 4.88 (bs, 1H), 4.35-4.33 (d, 2H), 1.47 (s, 9H).

[0132] Step-2: (4-((5-Fluoropyrimidin-2-yl)oxy)phenyl)methanamine hydrochloride

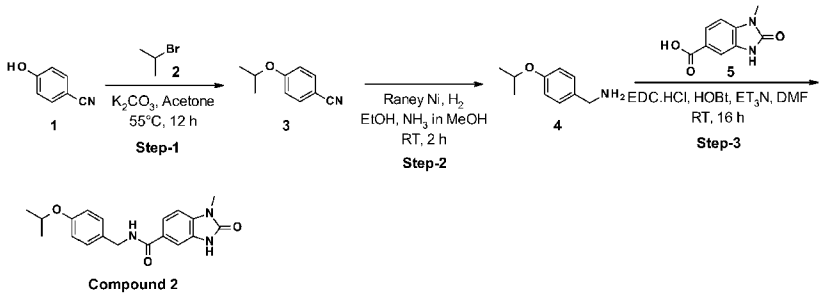
To a solution of tert-butyl (4-((5-fluoropyrimidin-2-yl)oxy)benzyl)carbamate (0.25 g, 0.78 mmol) in 1,4-dioxane (5 mL) was added 4 N HCl in 1,4-dioxane (5 mL) and stirred at RT for 1 h. The reaction mixture was concentrated, added diethyl ether thereto, and the residue was collected by filtration to get the title compound (0.17 g, 85%). LC-MS: 221 $[M+H]^+$

[0133] Step-3: N-(4-((5-Fluoropyrimidin-2-yl)oxy)benzyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 1)

To a solution of 2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.11 g, 0.62 mmol) in DMF (5 mL) were added HATU (0.32 g, 0.84 mmol) and DIPEA (0.39 g, 3.0 mmol) and stirred at RT for 10 min. Then (4-((5-fluoropyrimidin-2-yl)oxy)phenyl)methanamine hydrochloride (0.14 g, 0.56 mmol) was added thereto, and the mixture was stirred at RT for 16 h. The reaction mixture was added into ice cold water, and the precipitate formed was collected by filtration and dried to afford the title compound (0.09 g, 42%). LC-MS: 380 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.83-10.80 (d, 2H), 8.91-8.88 (t, 1H), 8.65 (s, 2H), 7.52-7.49 (dd, 1H), 7.43 (s, 1H), 7.30-7.28 (d, 2H), 7.09-7.07 (d, 2H), 6.92-6.90 (d, 1H), 4.40-4.39 (d, 2H).

[0134] Example-2

[Chem.23]



[0135] Step-1: 4-Isopropoxybenzonitrile

To a stirred solution of 4-hydroxybenzonitrile (0.20 g, 1.68 mmol) in acetone (4 mL) was added K_2CO_3 (0.7 g, 5.03 mmol) followed by 2-bromopropane (0.62 g, 5.03 mmol) and stirred at 55°C for 12 h. The reaction mass was filtered through Celite and the filtrate was concentrated to get a crude compound. The crude compound was purified by combi flash column chromatography using 10% EtOAc in hexane as an eluent to afford the title compound (0.24 g, 88.6%). LC-MS: 162 $[M+H]^+$

[0136] Step-2: (4-Isopropoxyphenyl)methanamine

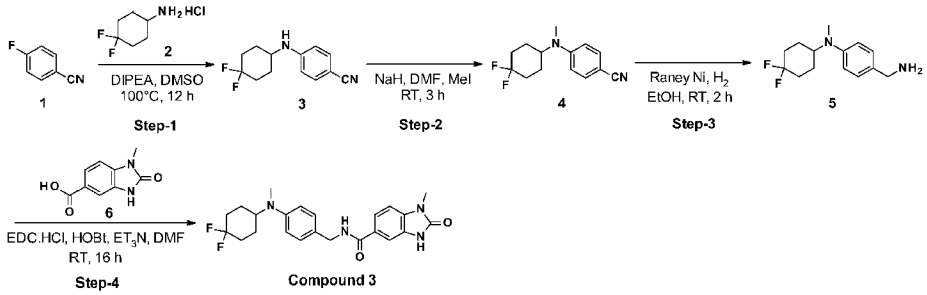
To a solution of 4-isopropoxybenzonitrile (0.19 g, 1.17 mmol) in EtOH (8 mL) was added Raney nickel (0.20 g) followed by 7 M methanolic ammonia (0.50 mL) and stirred at RT for 2 h under hydrogen bladder pressure. The reaction mass was filtered through Celite and the filtrate was concentrated to afford the title compound (0.11 g, 56.4%). LC-MS: 166 $[M+H]^+$

[0137] Step-3: N-(4-Isopropoxybenzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide trifluoroacetate (Compound 2)

To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.13 g, 0.67 mmol) in DMF (6 mL) were added EDC.HCl (0.13 g, 0.67 mmol) and HOBt (0.06 g, 0.44 mmol), and stirred at RT for 10 min. Then (4-isopropoxyphenyl)methanamine (0.11 g, 0.68 mmol) was added thereto followed by triethylamine (0.41 g, 4.05 mmol), and the mixture was stirred at RT for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. This was purified by preparative HPLC using Method A to afford the title compound as a TFA salt (0.06 g, 19.6%). LC-MS: 340 $[M+H]^+$; ^{1}H-NMR (400 MHz, CD_3OD) δ 8.80-8.77 (bs, 1H), 7.65-7.63 (dd, 1H), 7.56 (bs, 1H), 7.25-7.23 (d, 2H), 7.15-7.13 (d, 1H), 6.85-6.83 (d, 2H), 4.58-4.55 (m, 1H), 4.49-4.47 (d, 2H), 3.39 (s, 3H), 1.27-1.26 (d, 6H).

[0138] Example-3

[Chem.24]



[0139] Step-1: 4-((4,4-Difluorocyclohexyl)amino)benzonitrile

To a stirred solution of 4-fluorobenzonitrile (0.20 g, 1.65 mmol) in DMSO (10 mL) was added DIPEA (0.45 g, 3.48 mmol) followed by 4,4-difluorocyclohexan-1-amine hydrochloride (0.29 g, 1.69 mmol) and stirred at 100°C for 12 h. The reaction mixture was concentrated to remove DIPEA then poured into ice cold water, and the solid separated was collected by filtration and dried to afford the title compound (0.25 g, 64%). LC-MS: 237 $[M+H]^+$

[0140] Step-2: 4-((4,4-Difluorocyclohexyl)(methyl)amino)benzonitrile

To a stirred solution of 4-((4,4-difluorocyclohexyl)amino)benzonitrile (0.32 g, 1.35 mmol) in DMF (3 mL) was added NaH (60% dispersion in mineral oil) (0.07 g, 1.75 mmol) followed by dropwise addition of iodomethane (0.23 g, 1.62 mmol) at 0°C and stirred at RT for 3 h. The reaction mixture was poured into ice cold water, and the solid separated was collected by filtration and dried to afford the title compound (0.30 g, 88.7%). LC-MS: 251 $[M+H]^+$

[0141] Step-3: 4-(Aminomethyl)-N-(4,4-difluorocyclohexyl)-N-methylaniline

To a solution of 4-((4,4-difluorocyclohexyl)(methyl)amino)benzonitrile (0.30 g, 1.20 mmol) in EtOH (5 mL) was added Raney nickel (0.30 g) and stirred under hydrogen bladder pressure for 2 h at RT. The reaction mass was filtered through Celite and the filtrate was concentrated to afford the title compound (0.28 g, 92.1%). LC-MS: 255 $[M+H]^+$

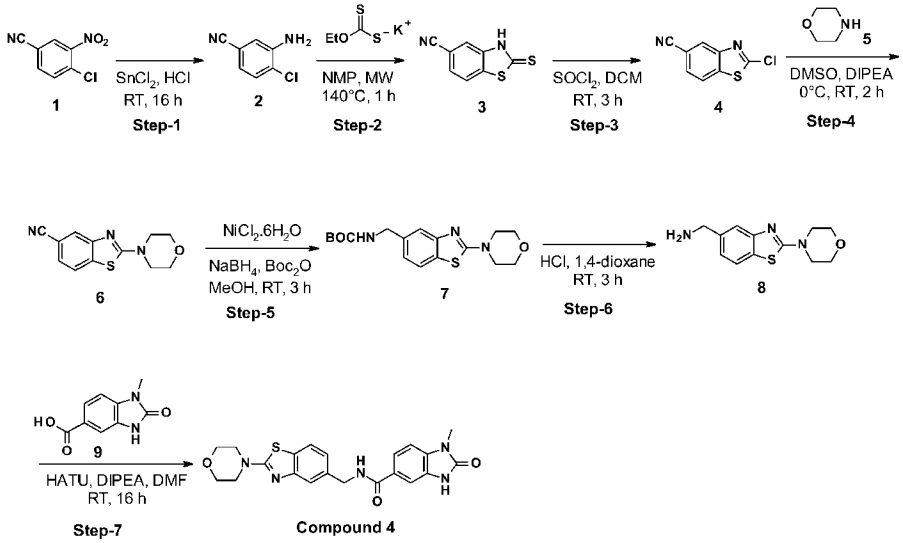
[0142] Step-4: N-(4-((4,4-Difluorocyclohexyl)(methyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide trifluoroacetate (Compound 3)

To a solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.24 g, 1.25 mmol) in DMF (5 mL) were added EDC.HCl (0.26 g, 1.36 mmol) and HOBt (0.07 g, 0.52 mmol), and stirred at RT for 10 min. Then 4-(aminomethyl)-N-(4,4-difluorocyclohexyl)-N-methylaniline (0.27 g, 1.06 mmol) was added thereto followed by triethylamine (0.32 g, 3.16 mmol), and the mixture was stirred at RT for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound.

This was purified by preparative HPLC using Method A to afford the title compound as a TFA salt (0.02 g, 3.48%). LC-MS: 429 $[M+H]^+$; ^{1}H-NMR (400 MHz, CD_3OD) δ 7.66-7.63 (dd, 1H), 7.57 (d, 1H), 7.47-7.45 (d, 2H), 7.28 (bs, 2H), 7.16-7.14 (dd, 1H), 4.55 (s, 2H), 3.79-3.76 (m, 1H), 3.40 (s, 3H), 3.11 (s, 3H), 2.13-1.68 (m, 8H).

[0143] Example-4

[Chem.25]



[0144] Step-1: 3-Amino-4-chlorobenzonitrile

To a solution of 4-chloro-3-nitrobenzonitrile (2.00 g, 10.9 mmol) in 37% HCl (100 mL) was added $SnCl_2$ (2.07 g, 10.9 mmol) and stirred at RT for 16 h. The reaction mixture was quenched with sodium bicarbonate solution, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (1.50 g, 90%). LC-MS: 153 $[M+H]^+$

[0145] Step-2: 2-Thioxo-2,3-dihydrobenzothiazole-5-carbonitrile

To a solution of 3-amino-4-chlorobenzonitrile (2.00 g, 13.10 mmol) in NMP (10 mL) was added potassium ethylxanthate (3.15 g 19.6 mmol) and stirred at 140°C in microwave for 1 h. The reaction mixture was added into ice cold water, and the precipitate formed was collected by filtration and dried to afford the title compound (1.80 g, 72%). LC-MS: 191 $[M-H]^-$

[0146] Step-3: 2-Chlorobenzothiazole-5-carbonitrile

To a stirred solution of 2-thioxo-2,3-dihydrobenzothiazole-5-carbonitrile (2.00 g, 10.4 mmol) in DCM (15 mL) was added thionyl chloride (5.00 g, 42.0 mmol) dropwise at 10°C and stirred at RT for 3 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, washed with water, dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (2.00 g, 98.7%). The compound obtained was taken to the next step without any further purification.

[0147] Step-4: 2-Morpholinobenzothiazole-5-carbonitrile

To a stirred solution of 2-chlorobenzothiazole-5-carbonitrile (0.50 g, 2.57 mmol) in DMSO (10 mL) was added DIPEA (0.66 g, 5.13 mmol) followed by morpholine (0.36 g, 4.13 mmol) and stirred at RT for 2 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (0.50 g, 79.3%). LC-MS: 246 $[M+H]^+$

[0148] Step-5: tert-Butyl ((2-morpholinobenzothiazol-5-yl)methyl)carbamate

To a stirred solution of 2-morpholinobenzothiazole-5-carbonitrile (0.50 g, 2.03 mmol) in MeOH (10 mL), was added $NiCl_2.6H_2O$ (0.39 g, 1.63 mmol) followed by dropwise addition of di-tert-butyl dicarbonate (1.12 g, 5.09 mmol) at 0°C and stirred for 5 min. Then $NaBH_4$ (0.30 g, 7.93 mmol) was added thereto in portions by maintaining the same temperature. After stirring for 3 h at RT, the reaction mass was concentrated to remove the solvent. The residue was diluted with EtOAc, washed with water, dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (0.22 g, 31%). LC-MS: 350 $[M+H]^+$

[0149] Step-6: (2-Morpholinobenzothiazol-5-yl)methanamine hydrochloride

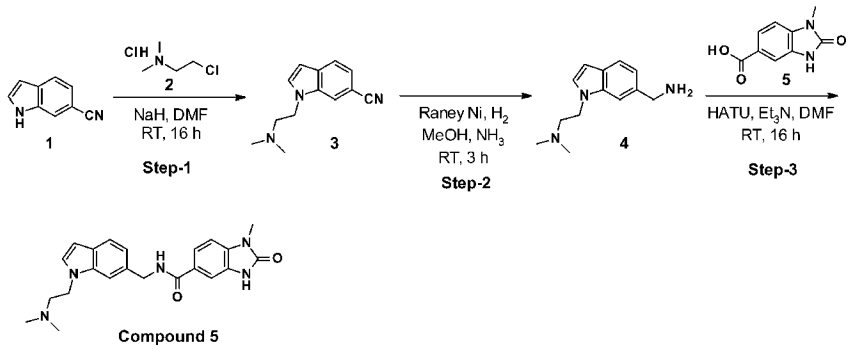
To a solution of tert-butyl ((2-morpholinobenzothiazol-5-yl)methyl)carbamate (0.22 g, 0.63 mmol) in 1,4-dioxane (4 mL) was added 4 N HCl in 1,4-dioxane (4 mL) and stirred for 3 h at RT. The reaction mixture was then concentrated, added diethyl ether, and the solid was collected by filtration to get the title compound (0.15 g, 83%) LC-MS: 250 $[M+H]^+$

[0150] Step-7:
1-Methyl-N-((2-morpholinobenzothiazol-5-yl)methyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide trifluoroacetate (Compound 4)

To a stirred solution of
1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.10 g, 0.52 mmol) in DMF (6 mL) were added HATU (0.27 g, 0.72 mmol) and DIPEA (0.24 g, 1.80 mmol), and stirred at RT for 10 min. Then
(2-morpholinobenzothiazol-5-yl)methanamine hydrochloride (0.15 g, 0.52 mmol) was added thereto and the mixture was stirred at RT for 16 h. The reaction mixture was added into ice cold water, and the precipitate formed was collected by filtration and dried. The crude compound was further purified by preparative HPLC using Method A to afford the title compound as a TFA salt (0.03 g, 12.5%). LC-MS: 424 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.09 (s, 1H), 8.98-8.95 (t, 1H), 7.72-7.70 (d, 1H), 7.67-7.64 (dd, 1H), 7.54 (s, 1H), 7.40 (s, 1H), 7.17-7.15 (d, 1H), 7.07-7.05 (d, 1H), 4.51-4.50 (d, 2H), 3.73-3.71 (t, 4H), 3.53-3.51 (t, 4H), 3.31 (s,3H).

[0151] Example-5

[Chem.26]



[0152] Step-1: 1-(2-(Dimethylamino)ethyl)-1H-indole-6-carbonitrile

To a stirred solution of 1H-indole-6-carbonitrile (1.00 g, 7.03 mmol) in DMF (6 mL) was added NaH (60% dispersion in mineral oil) (0.32 g, 8.00 mmol) followed by 2-chloro-N,N-dimethylethan-1-amine hydrochloride (1.02 g, 7.03 mmol) and stirred at RT for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get the title compound (1.3 g, 86.6%). LC-MS: 214 $[M+H]^+$

[0153] Step-2: 2-(6-(Aminomethyl)-1H-indol-1-yl)-N,N-dimethylethan-1-amine

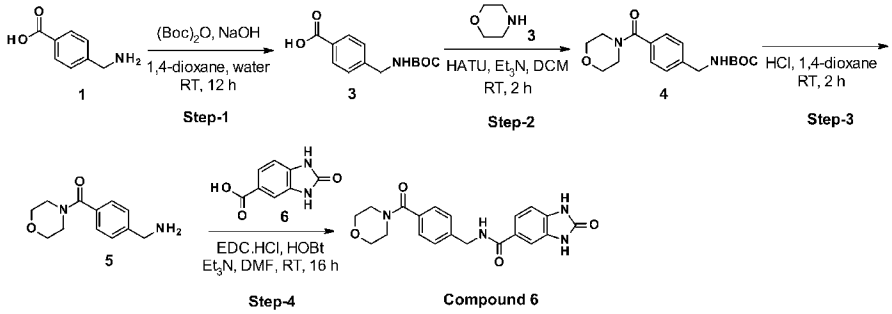
To a solution of 1-(2-(dimethylamino)ethyl)-1H-indole-6-carbonitrile (0.25 g, 1.17 mmol) in MeOH (3 mL) was added Raney nickel (0.25 g) followed by 7 M methanolic ammonia (1 mL) and stirred at RT for 3 h under hydrogen bladder pressure. The reaction mass was filtered through Celite and the filtrate was concentrated to afford the title compound (0.25 g, 98%). LC-MS: 218 $[M+H]^+$

[0154] Step-3: N-((1-(2-(Dimethylamino)ethyl)-1H-indol-6-yl)methyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide trifluoroacetate (Compound 5)

To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.24 g, 1.34 mmol) in DMF (6 mL) were added HATU (0.74 g, 1.91 mmol) and triethylamine (0.64 g, 6.37 mmol), and stirred at RT for 10 min. Then 2-(6-(aminomethyl)-1H-indol-1-yl)-N,N-dimethylethan-1-amine (0.27 g, 1.24 mmol) was added thereto and stirred at RT for 16 h. The reaction mixture was added into ice cold water, and the precipitate formed was collected by filtration and dried. The crude compound was further purified by preparative HPLC using Method A to afford the title compound as a TFA salt (0.02 g, 3.9%). LC-MS: 392 $[M+H]^+$; ^{1}H-NMR (400 MHz, CD_3OD) δ 7.69-7.66 (dd, 1H), 7.60-7.56 (m, 2H), 7.50 (s, 1H), 7.29-7.28 (d, 1H), 7.18-7.14 (t, 2H), 6.54-6.53 (d, 1H), 4.7 (s, 2H), 4.62-4.59 (t, 2H), 3.64-3.61 (t, 2H) 3.42 (s, 3H), 2.95-2.89 (m, 6H).

[0155] Example-6

[Chem.27]



[0156] Step-1: 4-(((tert-Butoxycarbonyl)amino)methyl)benzoic acid

To a stirred solution of 4-(aminomethyl)benzoic acid (2.00 g, 13.23 mmol) in 1,4-dioxane (32 mL) and water (16 mL) was added NaOH (0.79 g, 19.84 mmol) followed by di-tert-butyl dicarbonate (2.88 g, 13.23 mmol), and stirred at RT for 12 h. The reaction mixture was concentrated, and the mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the title compound (2.90 g, 87.30%). LC-MS: 250 $[M-H]^-$

[0157] Step-2: tert-Butyl (4-(morpholine-4-carbonyl)benzyl)carbamate

To a solution of 4-(((tert-butoxycarbonyl)amino)methyl)benzoic acid (0.45 g, 1.79 mmol) in DCM (5 mL) were added HATU (0.81 g, 2.14 mmol) and triethylamine (0.36 g, 3.58 mmol). The reaction mass was stirred for 10 min at RT followed by addition of morpholine (0.17 g, 1.96 mmol). After stirring for 2 h at RT, the reaction mixture was quenched with ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (0.55 g, 96%). LC-MS: 321 $[M+H]^+$

[0158] Step-3: (4-(Aminomethyl)phenyl)(morpholino)methanone

To a solution of tert-butyl (4-(morpholine-4-carbonyl)benzyl)carbamate (0.55 g, 1.71 mmol) in 1,4-dioxane (5 mL) was added 4 N HCl in 1,4-dioxane (5 mL) and stirred at RT for 2 h. The reaction mixture was then concentrated, added diethyl ether, and the solid was collected by filtration to get the title compound (0.36 g, 95%). LC-MS: 221 $[M+H]^+$

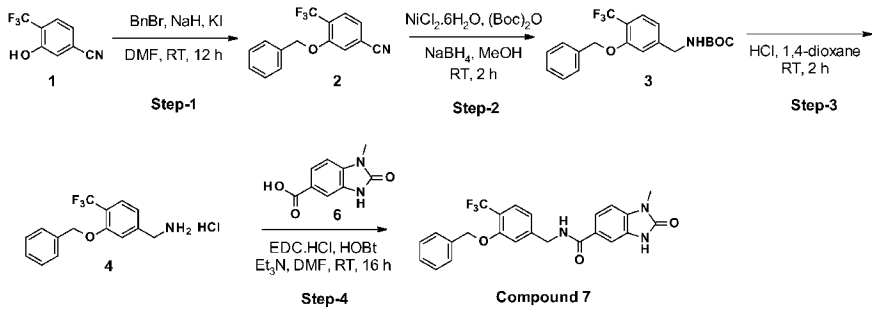
[0159] Step-4: N-(4-(Morpholine-4-carbonyl)benzyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide trifluoroacetate (Compound 6)

To a solution of 2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.145 g, 0.82 mmol) in DMF (4 mL) were added EDC.HCl (0.19 g, 1.01 mmol) and HOBt (0.13 g, 1.01 mmol), and stirred at RT for 10 min. Then (4-(aminomethyl)phenyl)(morpholino)methanone (0.18 g, 0.82 mmol) was added thereto followed by triethylamine (0.42 g, 4.20 mmol), and the mixture was stirred at RT for 16 h. The reaction mixture was poured into ice cold water, extracted with

EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. This was purified by preparative HPLC using Method A to afford the title compound as a TFA salt (0.06 g, 14.4%). LC-MS: 381 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.89-10.86 (d, 2H), 8.98-8.95 (t, 1H), 7.58-7.56 (d, 1H), 7.49 (bs, 1H), 7.37-7.35 (m, 4H), 6.98-6.96 (d, 1H), 4.49-4.47(d, 2H), 3.7-3.4 (m, 8H).

[0160] Example-7

[Chem.28]



[0161] Step-1: 3-(Benzyloxy)-4-(trifluoromethyl)benzonitrile

To a stirred solution of 3-hydroxy-4-(trifluoromethyl)benzonitrile (0.60 g, 3.20 mmol) in DMF (10 mL) was added KI (0.11 g, 0.66 mmol) followed by NaH (60% dispersion in mineral oil) (0.13 g, 3.25 mmol). Then benzyl bromide (0.66 g, 3.84 mmol) was added thereto and stirred at RT for 12 h. The reaction mixture was quenched with ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get a crude compound. The crude compound was purified by combi flash column chromatography using 2% EtOAc in hexane as an eluent to afford the title compound (0.50 g, 56%). LC-MS: 276 $[M-H]^-$

[0162] Step-2 tert-Butyl (3-(benzyloxy)-4-(trifluoromethyl)benzyl)carbamate

To a solution of 3-(benzyloxy)-4-(trifluoromethyl)benzonitrile (0.50 g, 1.80 mmol) in MeOH (10 mL) was added $NiCl_2.6H_2O$ (0.21 g, 0.90 mmol) followed by dropwise addition of di-tert-butyl dicarbonate (0.79 g, 3.60 mmol) at 0°C and stirred for 5 min. Then $NaBH_4$ (0.08 g, 2.11 mmol) was added thereto in portions by maintaining the same temperature. After stirring for 2 h at RT, the reaction mass was concentrated to remove the solvent, diluted with EtOAc and filtered on Celite bed. The filtrate was washed with water, dried over anhydrous Na_2SO_4 and concentrated to afford a crude compound. The crude compound was purified by combi flash column chromatography using 8% EtOAc in hexane as an eluent to afford the title compound (0.35 g, 51%). LC-MS: 380 $[M-H]^-$

[0163] Step-3: (3-(Benzyloxy)-4-(trifluoromethyl)phenyl)methanamine hydrochloride

To a solution of tert-butyl (3-(benzyloxy)-4-(trifluoromethyl)benzyl)carbamate (0.35 g, 0.91 mmol) in 1,4-dioxane (5 mL) was added 4 N HCl in 1,4-dioxane (5 mL) and stirred for 2 h at RT. The reaction mixture was then concentrated, added diethyl

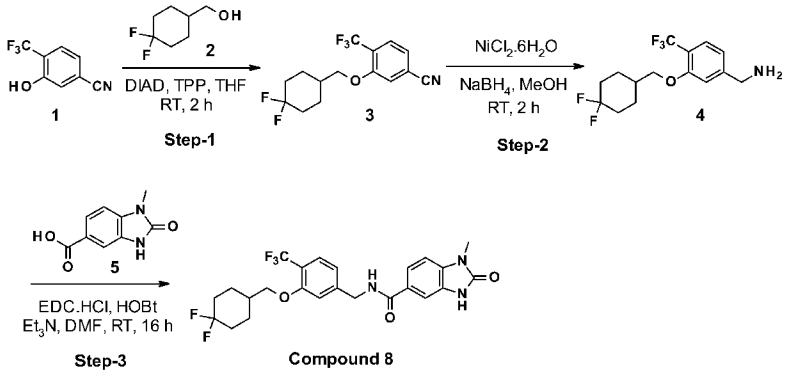
ether and filtered to get the title compound (0.28 g, 96%). LC-MS: 282 $[M+H]^+$

[0164] Step-4: N-(3-(Benzyloxy)-4-(trifluoromethyl)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 7)

To a solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.10 g, 0.52 mmol) in DMF (2 mL) were added EDC.HCl (0.12 g, 0.62 mmol) and HOBt (0.08 g, 0.59 mmol), and stirred at RT for 10 min. Then (3-(benzyloxy)-4-(trifluoromethyl)phenyl)methanamine hydrochloride (0.15 g, 0.47 mmol) was added thereto followed by triethylamine (0.16 g, 1.56 mmol) and the mixture was stirred at RT for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash column chromatography using 40% EtOAc in hexane as an eluent to afford the title compound (0.01 g, 4.7%). LC-MS: 456 $[M+H]^+$; ^{1}H-NMR (400 MHz, CD_3OD) δ 7.68-7.63 (d, 1H), 7.58-7.57 (m, 1H), 7.53-7.51 (d, 1H), 7.42-7.36 (m, 2H), 7.27-7.21 (m, 3H), 7.17-7.16 (m, 2H), 7.01-6.99 (d, 1H), 5.19 (s, 2H), 4.56 (s, 2H), 3.41 (s, 3H).

[0165] Example-8

[Chem.29]



[0166] Step-1: 3-((4,4-Difluorocyclohexyl)methoxy)-4-(trifluoromethyl)benzonitrile

To a stirred solution of 3-hydroxy-4-(trifluoromethyl)benzonitrile (0.50 g, 2.67 mmol) in THF (10 mL) was added TPP (1.05 g, 4.00 mmol) followed by ((4,4-difluorocyclohexyl)methanol (0.60 g, 4.00 mmol) and stirred at RT for 10 min. Then DIAD (0.81 g, 4.00 mmol) was added thereto, and the reaction mixture was stirred at RT for 2 h. The reaction mixture was concentrated, washed with pentane, and the obtained solid was collected by filtration and dried to get a crude compound. The crude compound was purified by combi flash column chromatography using 30% EtOAc in hexane as an eluent to afford the title compound (0.50 g, 58.6%). LC-MS: 320 $[M+H]^+$

[0167] Step-2: (3-((4,4-Difluorocyclohexyl)methoxy)-4-(trifluoromethyl)phenyl)methanamine

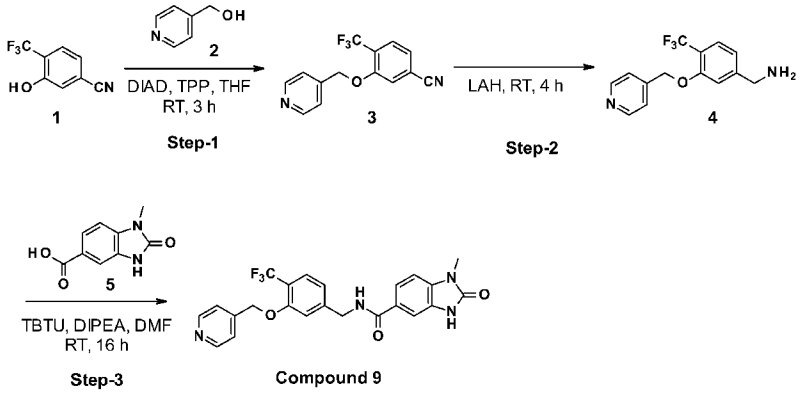
To a solution of 3-((4,4-difluorocyclohexyl)methoxy)-4-(trifluoromethyl)benzonitrile (0.50 g, 1.56 mmol) in MeOH (10 mL) was added $NiCl_2.6H_2O$ (0.19 g, 0.79 mmol). Then $NaBH_4$ (0.09 g, 2.38 mmol) was added thereto in portions by maintaining the same temperature. After stirring for 2 h at RT, the reaction mass was concentrated to remove the solvent. The residue was diluted with EtOAc and filtered on Celite bed. The filtrate was washed with water, dried over anhydrous Na_2SO_4 and concentrated to afford the title crude compound (0.41 g, 81%). LC-MS: 324 $[M+H]^+$

[0168] Step-3: N-(3-((4,4-Difluorocyclohexyl)methoxy)-4-(trifluoromethyl)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 8)

To a solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.30 g, 1.56 mmol) in DMF (15 mL) were added EDC.HCl (0.36 g, 1.87 mmol) and HOBt (0.25 g, 1.87 mmol), and stirred at RT for 10 min. Then (3-((4,4-difluorocyclohexyl)methoxy)-4-(trifluoromethyl)phenyl)methanamine (0.40 g, 1.24 mmol) was added thereto followed by triethylamine (0.47 g, 4.68 mmol) and the mixture was stirred at RT for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash column chromatography using 80% EtOAc in hexane as an eluent to afford the title compound (0.12 g, 19.5%). LC-MS: 498 $[M+H]^+$; ^{1}H-NMR (400 MHz, CD_3OD) δ 7.67-7.65 (dd, 1H), 7.58-7.57 (d, 1H), 7.51-7.49 (d, 1H), 7.17-7.15 (d, 1H), 7.11 (s, 1H), 7.01-6.99 (d, 1H), 4.58 (s, 2H), 3.94-3.93 (d, 2H), 3.4 (s, 3H), 2.04-1.99 (bs, 2H), 1.92-1.69 (m, 5H), 1.48-1.42 (m, 2H).

[0169] Example-9

[Chem.30]



[0170] Step-1: 3-(Pyridin-4-ylmethoxy)-4-(trifluoromethyl)benzonitrile

To a stirred solution of 3-hydroxy-4-(trifluoromethyl)benzonitrile (0.50 g, 2.67 mmol) in THF (10 mL) was added TPP (1.05 g, 4.00 mmol) followed by pyridin-

4-ylmethanol (0.44 g, 4.00 mmol) and stirred at RT for 10 minutes. Then DIAD (0.81 g, 4.00 mmol) was added thereto, and the reaction mixture was stirred at RT for 3 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash column chromatography using 30% EtOAc in hexane as an eluent to afford the title compound (0.65 g, 87.50%). LC-MS: 279 $[M+H]^+$

[0171] Step-2: (3-(Pyridin-4-ylmethoxy)-4-(trifluoromethyl)phenyl)methanamine

To a stirred solution of 3-(pyridin-4-ylmethoxy)-4-(trifluoromethyl)benzonitrile (0.35 g, 1.25 mmol) in THF (3 mL) was added dropwise solution of LAH (2 M solution in THF) (0.07 g, 1.80 mmol) at 0°C. After stirring for 4 h at RT, the reaction mass was quenched with saturated NH_4Cl solution at 0°C and diluted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (0.24 g, 68%). LC-MS: 283 $[M+H]^+$

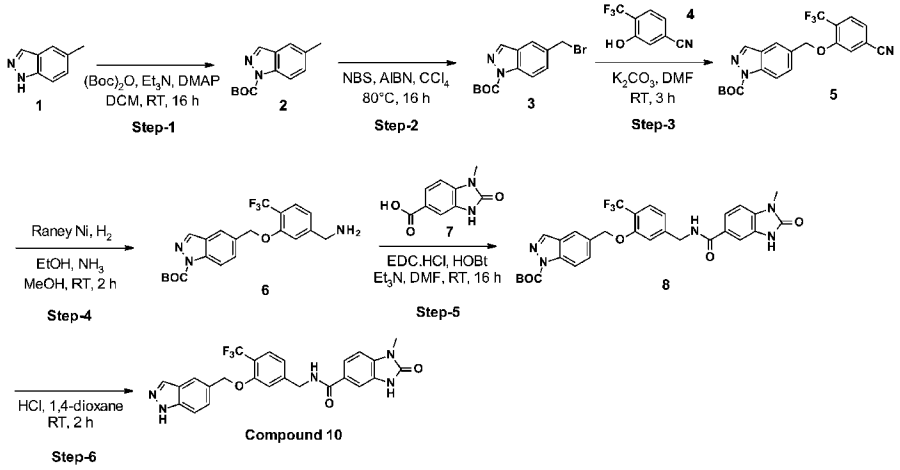
[0172] Step-3:

1-Methyl-2-oxo-N-(3-(pyridin-4-ylmethoxy)-4-(trifluoromethyl)benzyl)-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 9)

To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.23 g, 1.19 mmol) in DMF (5 mL) was added TBTU (0.42 g, 1.31 mmol). Then (3-(pyridin-4-ylmethoxy)-4-(trifluoromethyl)phenyl)methanamine (0.24 g, 0.85 mmol) was added thereto followed by DIPEA (0.46 g, 3.59 mmol) and the mixture was stirred at RT for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash column chromatography using 10% MeOH in DCM as an eluent to afford the title compound (0.02 g, 6.5%). LC-MS: 457 $[M+H]^+$; ^{1}H-NMR (400 MHz, CD_3OD) δ 8.45-8.44 (d, 2H), 7.63-7.61 (dd, 1H), 7.58-7.55 (m, 2H), 7.47-7.45 (d, 2H), 7.18 (s, 1H), 7.15 (bs, 1H), 7.07-7.05 (d, 1H), 5.29 (s, 2H), 4.58 (s, 2H), 3.41 (s, 3H).

[0173] Example-10

[Chem.31]



[0174] Step-1: tert-Butyl 5-methyl-1H-indazole-1-carboxylate

To a stirred solution of 5-methyl-1H-indazole (3.00 g, 22.70 mmol) in DCM (25 mL) was added triethylamine (8.04 g, 79.44 mmol) followed by DMAP (1.63 g, 13.24 mmol) at 0°C. Then di-tert-butyl dicarbonate (8.67 g, 39.72 mmol) was added thereto and stirred at RT for 16 h. The reaction mixture was concentrated to remove the solvent. The crude residue was purified by combi flash column chromatography using 10% EtOAc in hexane as an eluent to afford the title compound (2.30 g, 43.62%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 8.01-7.99 (d, 1H), 7.44 (s, 1H), 7.31-7.29 (d, 1H), 2.42 (s, 3H), 1.67 (s, 9H).

[0175] Step-2: tert-Butyl 5-(bromomethyl)-1H-indazole-1-carboxylate

To a stirred solution of tert-butyl 5-methyl-1H-indazole-1-carboxylate (2.10 g, 9.04 mmol) in CCl_4 (10 mL) was added AIBN (0.15 g, 0.90 mmol) followed by NBS (1.77 g, 9.94 mmol) at 0°C and stirred at 80°C for 16 h. The reaction mass quenched with sodium thiosulphate, diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. This was purified by combi flash column chromatography using 11% EtOAc in hexane as an eluent to afford the title compound (1.80 g, 63.98%). ^{1}H-NMR (400 MHz, CD_3OD) δ 8.18-8.15 (m, 2H), 7.75 (s, 1H), 7.58-7.56 (d, 1H), 4.63 (s, 2H), 1.73 (s, 9H).

[0176] Step-3: tert-Butyl 5-((5-cyano-2-(trifluoromethyl)phenoxy)methyl)-1H-indazole-1-carboxylate

To a stirred solution of 3-hydroxy-4-(trifluoromethyl)benzonitrile (0.15 g, 0.80 mmol) in DMF (5 mL) was added K_2CO_3 (0.17 g, 1.2 mmol) followed by tert-butyl 5-(bromomethyl)-1H-indazole-1-carboxylate (0.30 g, 0.96 mmol) and stirred at RT for 3 h. The reaction mixture was concentrated to remove the solvent then poured into ice cold water, and the solid separated was collected by filtration and dried. This was purified by combi flash column chromatography using 30% EtOAc in hexane as an eluent to afford the title compound (0.25 g, 74.80%). LC-MS: 416 $[M-H]^-$

[0177] Step-4: tert-Butyl 5-((5-(aminomethyl)-2-(trifluoromethyl)phenoxy)methyl)-1H-indazole-1-carboxylate

To a solution of tert-butyl 5-((5-cyano-2-(trifluoromethyl)phenoxy)methyl)-1H-indazole-1-carboxylate (0.25 g, 0.60 mmol) in EtOH (4 mL) was added Raney nickel (0.25 g) followed by 7 M methanolic ammonia (1 mL) and stirred at RT for 2 h under hydrogen bladder pressure. The reaction mass was filtered through Celite and the filtrate was concentrated to afford the title compound (0.18 g, 71.4%). LC-MS: 422 $[M+H]^+$

[0178] Step-5: tert-Butyl 5-((5-((1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamido)methyl)-2-(trifluoromethyl)phenoxy)methyl)-1H-indazole-1-carboxylate

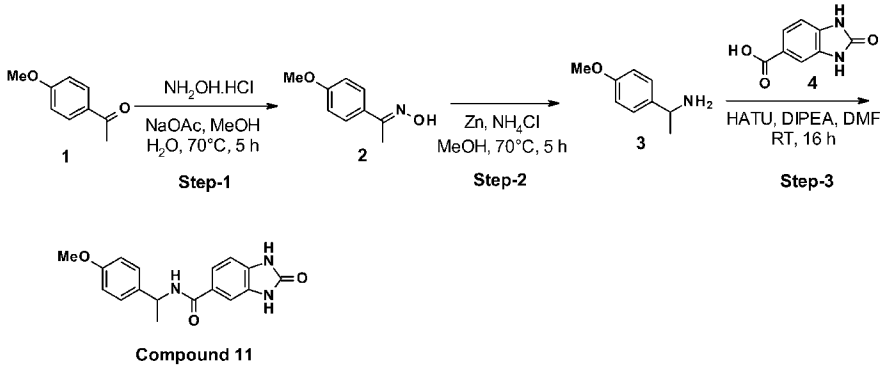
To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.07 g, 0.36 mmol) in DMF (3mL) were added EDC.HCl (0.09 g, 0.46 mmol) and HOBt (0.06 g, 0.44 mmol), and stirred at RT for 10 min. Then tert-butyl 5-((5-(aminomethyl)-2-(trifluoromethyl)phenoxy)methyl)-1H-indazole-1-carboxylate (0.16 g, 0.39 mmol) followed by triethylamine (0.12 g, 1.17 mmol) were added thereto, and the mixture was stirred at RT for 16 h. The reaction mixture was added into ice cold water, and the precipitate formed was collected by filtration and dried. This was purified by combi flash column chromatography using 5% MeOH in DCM as an eluent to afford the title compound (0.06 g, 28.03%). LC-MS: 594 $[M-H]^-$

[0179] Step-6: N-(3-((1H-Indazol-5-yl)methoxy)-4-(trifluoromethyl)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 10)

To a solution of tert-butyl 5-((5-((1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamido)methyl)-2-(trifluoromethyl)phenoxy)methyl)-1H-indazole-1-carboxylate (0.03 g, 0.05 mmol) in 1,4-dioxane (1 mL) was added 4 N HCl in 1,4-dioxane (1 mL) and stirred at RT for 2 h. The reaction mixture was then concentrated, added diethyl ether and the solid was collected by filtration to get title compound (0.02 g, 80%). LC-MS: 496 $[M+H]^+$; ^{1}HNMR (400 MHz, CD_3OD) δ 8.19 (bs, 1H), 7.87 (s, 1H), 7.61-7.53 (m, 5H), 7.24 (s, 1H), 7.15-7.12 (d, 1H), 7.03-7.00 (d, 1H), 5.32 (s, 2H), 4.57 (s, 2H), 3.42 (s, 3H).

[0180] Example-11

[Chem.32]



[0181] Step-1: (E)-1-(4-Methoxyphenyl)ethan-1-one oxime

To a stirred solution of 1-(4-methoxyphenyl)ethan-1-one (1.00 g, 6.65 mmol) in MeOH (5 mL) and water (1 mL) was added hydroxylamine hydrochloride (0.69 g, 9.90 mmol) followed by sodium acetate (1.09 g, 13.00 mmol) and stirred at 70°C for 5 h. The reaction mass was concentrated to remove MeOH. The residue was diluted with EtOAc, washed with water, dried over anhydrous Na_2SO_4 and concentrated to afford the crude title compound (1.00 g, 91%). LC-MS: 166 $[M+H]^+$

[0182] Step-2: 1-(4-Methoxyphenyl)ethan-1-amine

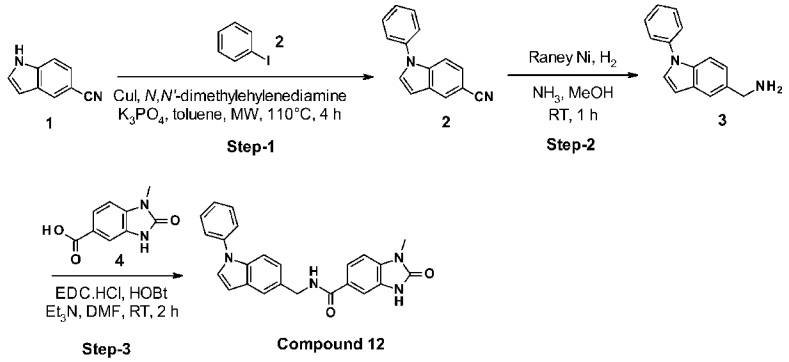
To a stirred solution of (E)-1-(4-methoxyphenyl)ethan-1-one oxime (0.25 g, 1.50 mmol) in MeOH (3 mL) was added ammonium chloride (0.40 g, 7.50 mmol) followed by zinc dust (0.98 g, 15.00 mmol) and stirred at 70°C for 5 h. The reaction mass was quenched with 10% NaOH solution, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (0.20 g, 88.50%). LC-MS: 152 $[M+H]^+$

[0183] Step-3: N-(1-(4-Methoxyphenyl)ethyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 11)

To a stirred solution of 2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.15 g, 0.84 mmol) in DMF (3 mL) was added HATU (0.48 g, 1.26 mmol) and stirred at RT for 10 min. Then 1-(4-methoxyphenyl)ethan-1-amine (0.19 g, 1.26 mmol) was added thereto followed by DIPEA (0.33 g, 2.55 mmol) and the mixture was stirred at RT for 16 h. The residue was diluted with EtOAc, washed with water, dried over anhydrous Na_2SO_4 and concentrated. This was purified by combi flash column chromatography using 4% MeOH in DCM as an eluent to afford the title compound (0.03 g, 11.4%). LC-MS: 312 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.86-10.82 (d, 2H), 8.60-8.58 (d, 1H), 7.55-7.53 (d, 1H), 7.46 (s, 1H), 7.30-7.28 (d, 2H), 6.95-6.93 (d, 1H), 6.88-6.86 (d, 2H), 5.12-5.09 (m, 1H), 3.72 (s, 3H), 1.44-1.42 (d, 3H).

[0184] Example-12

[Chem.33]



[0185] Step-1: 1-Phenyl-1H-indole-5-carbonitrile

To a stirred solution of 1H-indole-5-carbonitrile (1.00 g, 7.03 mmol) in toluene (10 mL) were added copper iodide (0.13 g, 0.70 mmol) and potassium phosphate (1.49 g, 7.03 mmol). The reaction mass was purged with argon for 10 min. Then N,N'-dimethylethane-1,2-diamine (0.12 g, 1.40 mmol) was added thereto followed by iodobenzene (1.72 g, 8.44 mmol). Again, the reaction mass was degassed with argon for 15 minutes, and then stirred at 110°C for 4 h in microwave. The reaction mixture was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a crude compound. This was purified by combi flash column chromatography using 20% EtOAc in hexane as an eluent to afford the title compound (0.18 g, 11.73%). ^{1}H-NMR (400 MHz, DMSO-D_6) δ 8.22 (s, 1H), 7.88-7.87 (d, 1H), 7.67-7.55 (m, 5H), 7.53-7.50 (d, 1H), 7.49-7.45 (m, 1H), 6.87-6.86 (d, 1H).

[0186] Step-2: (1-Phenyl-1H-indol-5-yl)methanamine

To a solution of 1-phenyl-1H-indole-5-carbonitrile (0.18 g, 0.82 mmol) in MeOH (5 mL) was added Raney nickel (0.18 g) followed by 7 M methanolic ammonia (2 mL) and stirred at RT for 1 h under hydrogen bladder pressure. The reaction mass was filtered through Celite and the filtrate was concentrated to afford the title compound (0.17 g, 92.8%). ^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.62-7.61 (d, 1H), 7.58-7.57 (m, 6H), 7.39-7.37 (m, 1H), 7.18-7.16 (d, 1H), 6.64-6.63 (d, 1H), 3.79 (s, 2H).

[0187] Step-3:

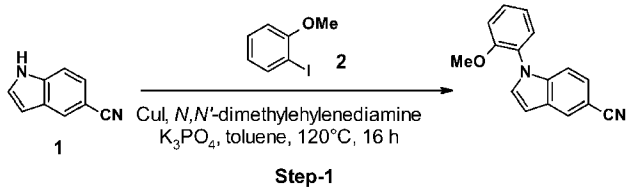
1-Methyl-2-oxo-N-((1-phenyl-1H-indol-5-yl)methyl)-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 12)

To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.18 g, 0.94 mmol) in DMF (3 mL) were added EDC.HCl (0.22 g, 1.15 mmol) and HOBt (0.15 g, 1.12 mmol), and stirred at RT for 10 min. Then (1-phenyl-1H-indol-5-yl)methanamine (0.17 g, 0.76 mmol) was added thereto followed by triethylamine (0.28 g, 2.8 mmol) and the mixture was stirred at RT for 2 h. The reaction mixture was diluted with water,

extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a crude compound. This was purified by combi flash column chromatography using 60% EtOAc in hexane as an eluent to afford the title compound (0.02 g, 6.6%). LC-MS: 397 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.07 (s, 1H), 8.98-8.93 (m, 1H), 7.64-7.63 (m, 2H), 7.58-7.57 (m, 5H), 7.55 (s, 2H), 7.40-7.36 (m, 1H), 7.2-7.18 (d, 1H), 7.16-7.14 (d, 1H), 6.68-6.66 (d, 1H), 4.56-4.55 (d, 2H), 3.30 (s, 3H).

[0188] Preparation-1

[Chem.34]



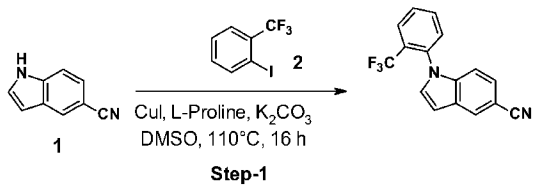
Step-1

[0189] Step-1: 1-(2-Methoxyphenyl)-1H-indole-5-carbonitrile

To a stirred solution of 1H-indole-5-carbonitrile (0.25 g, 1.76 mmol) in toluene (5 mL) were added copper iodide (0.07 g, 0.36 mmol) and potassium phosphate (0.75 g, 3.53 mmol). The reaction mass was purged with argon for 10 min. Then N,N'-dimethylethane-1,2-diamine (0.08 g, 0.87 mmol) was added thereto followed by 1-iodo-2-methoxybenzene (0.49 g, 2.11 mmol). The reaction mass was again degassed with argon for 15 min and stirred at 120°C for 16 h. The reaction mixture was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a crude compound. This was purified by combi flash column chromatography using 30% EtOAc in hexane as an eluent to afford the title compound (0.05 g, 11.46%). LC-MS: 249 $[M+H]^+$

[0190] Preparation-2

[Chem.35]



Step-1

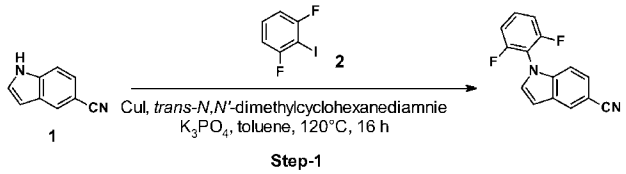
[0191] Step-1: 1-(2-(Trifluoromethyl)phenyl)-1H-indole-5-carbonitrile

To a solution of 1H-indole-5-carbonitrile (0.05 g, 0.35 mmol) in DMSO (2 mL) was added copper iodide (0.02 g, 0.10 mmol) and potassium carbonate (0.19 g, 1.4 mmol). Then L-proline (0.02 g, 0.17 mmol) was added thereto followed by 1-iodo-2-(trifluoromethyl)benzene (0.11 g, 0.4 mmol) and stirred at 110°C for 16 h. The reaction mixture was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a crude

compound. This was purified by combi flash column chromatography using 20% EtOAc in hexane as an eluent to afford the title compound (0.01g, 10%). LC-MS: 287 $[M+H]^+$

[0192] Preparation-3

[Chem.36]



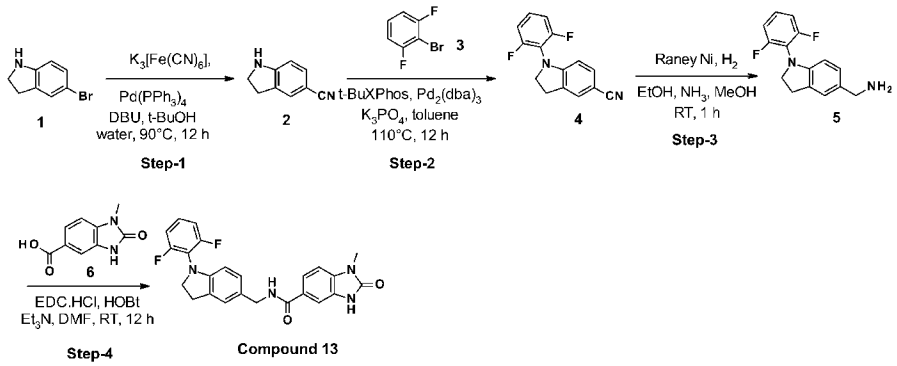
Step-1

[0193] Step-1: 1-(2,6-Difluorophenyl)-1H-indole-5-carbonitrile

To a solution of 1H-indole-5-carbonitrile (0.05 g, 0.35 mmol) in toluene (3 mL) were added copper iodide (0.01 g, 0.05 mmol) and potassium phosphate (0.22 g, 1.04 mmol). Then trans-N,N′-dimethylcyclohexane-1,2-diamine (0.02 g, 0.14 mmol) was added followed by 1,3-difluoro-2-iodobenzene (0.13 g, 0.54 mmol) and stirred at 120°C for 16 h. The reaction mixture was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a crude compound. This was purified by combi flash column chromatography using 30% EtOAc in hexane as an eluent to afford the title compound (0.02 g, 22.50%).

[0194] Example-13

[Chem.37]



[0195] Step-1: Indoline-5-carbonitrile

To a stirred solution of 5-bromoindoline (2.00 g, 10.10 mmol) in t-BuOH (5 mL) and water (5 mL) were added DBU (0.38 g, 2.50 mmol) and potassium hexa-cyanoferrate(II) trihydrate (1.71 g, 4.03 mmol). The reaction mass was degassed with argon for 15 min. Then tetrakis(triphenylphosphine)palladium (0.58 g, 0.50 mmol) was added thereto and stirred at 90°C for 12 h. The reaction mixture was poured into ice cold water, and the solid separated was collected by filtration and dried to get a crude compound. The crude compound was purified by combi flash column chromatography using 20% EtOAc in hexane as an eluent to afford the title compound (0.56 g, 38.80%). LC-MS: 145 $[M+H]^+$

[0196] Step-2: 1-(2,6-Difluorophenyl)indoline-5-carbonitrile

To a stirred solution of indoline-5-carbonitrile (2.5 g, 17.34 mmol) in toluene (10 mL) were added tripotassium phosphate (7.36 g, 34.67 mmol) and 2-bromo-1,3-difluorobenzene (10.03 g, 51.97 mmol). The reaction mass was degassed with argon for 15 min. Then t-BuXPhos (0.74 g, 1.73 mmol) was added thereto followed by $Pd_2(dba)_3$ (0.79 g, 0.86 mmol) and stirred at 110°C for 12 h. The reaction mass was concentrated and purified by combi flash column chromatography using 10% EtOAc in hexane as an eluent to afford the title compound (0.90 g, 20.27%). LC-MS: 257 $[M+H]^+$

[0197] Step-3: (1-(2,6-Difluorophenyl)indolin-5-yl)methanamine

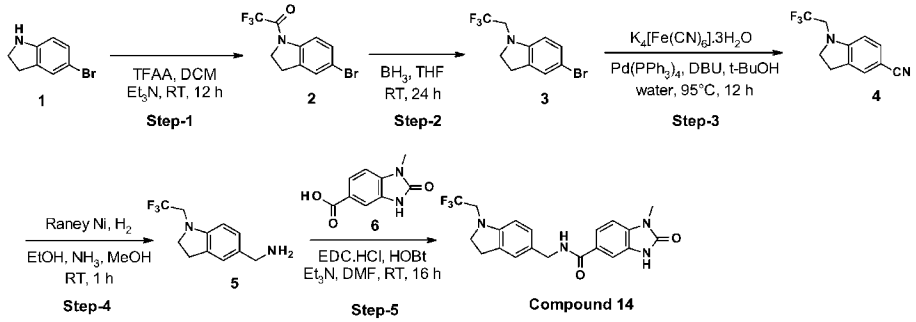
To a stirred solution of 1-(2,6-difluorophenyl)indoline-5-carbonitrile (0.80 g, 3.12 mmol) in EtOH (20 mL) was added Raney nickel (0.80 g) followed by 7 M methanolic ammonia (1 mL) and stirred at RT for 1 h under hydrogen bladder pressure. The reaction mixture was filtered through Celite and the filtrate was concentrated to get the title compound (0.70 g, 86.20%). LC-MS: 261 $[M+H]^+$

[0198] Step-4: N-((1-(2,6-Difluorophenyl)indolin-5-yl)methyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 13)

To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.52 g, 2.68 mmol) in DMF (20 mL) were added EDC.HCl (0.62 g, 3.22 mmol), HOBt (0.44 g, 3.22 mmol), triethylamine (0.82 g, 8.06 mmol) and (1-(2,6-difluorophenyl)indolin-5-yl)methanamine (0.70 g, 2.68 mmol). The reaction mass was stirred at RT for 12 h and quenched with water, and the solid precipitated was collected by filtration and dried. The crude compound was purified by washing with DCM/ hexane (1:1 ratio) to get the title compound (0.45 g, 38.46%). LC-MS: 435 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.07 (s, 1H), 8.81-8.80 (m, 1H), 7.65-7.63 (d, 1H), 7.53 (s, 1H), 7.34-7.30 (m, 1H), 7.22-7.18 (m, 2H), 7.15-7.12 (m, 2H), 6.95-6.93 (d, 1H), 6.12-6.10 (d, 1H), 4.35-4.34 (m, 2H), 3.89-3.85 (t, 2H), 3.30 (s, 3H), 3.16-3.11 (t, 2H).

[0199] Example-14

[Chem.38]



[0200] Step-1: 1-(5-Bromoindolin-1-yl)-2,2,2-trifluoroethan-1-one

To a stirred solution of 5-bromoindoline (1.00 g, 5.05 mmol) in DCM (10 mL) was added triethylamine (1.53 g, 15.14 mmol) followed by TFAA (1.27 g, 6.06 mmol) and stirred at RT for 12 h. The reaction mass was quenched with water, extracted with DCM, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a crude compound. The crude compound was purified by combi flash column using 20% EtOAc in hexane as an eluent to get the title compound (1.00 g, 67.34%). ^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.98-7.96 (d, 1H), 7.58 (s, 1H), 7.48-7.45 (dd, 1H), 4.31-4.27 (t, 2H), 3.27-3.23 (t, 2H).

[0201] Step-2: 5-Bromo-1-(2,2,2-trifluoroethyl)indoline

To a stirred solution of 1-(5-bromoindolin-1-yl)-2,2,2-trifluoroethan-1-one (0.80 g, 2.72 mmol) in THF (40 mL) was added borane in THF (11.69 g, 136.00 mmol) at 10°C and stirred at RT for 24 h. The reaction mixture was quenched with MeOH and concentrated to get a crude compound, which was purified by combi flash column using 20% EtOAc in hexane as an eluent to get the title compound (0.20 g, 26.25%), LC-MS: 279 $[M-H]^-$

[0202] Step-3: 1-(2,2,2-Trifluoroethyl)indoline-5-carbonitrile

To a stirred solution of 5-bromo-1-(2,2,2-trifluoroethyl)indoline (0.25 g, 0.89 mmol) in t-BuOH (5 mL) and water (5 mL) were added DBU (0.27 g, 1.78 mmol) and potassium hexacyanoferrate(II) trihydrate (0.19 g 0.44 mmol). The reaction mass was degassed with argon for 15 min. Then tetrakis(triphenylphosphine)palladium (0.52 g, 0.44 mmol) was added thereto and stirred at 95°C for 12 h. The reaction mass was quenched with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a crude compound. The crude compound was purified by combi flash column using 20% EtOAc in hexane as an eluent to get the title compound (0.10 g, 49.75%), LC-MS: 227 $[M+H]^+$

[0203] Step-4: (1-(2,2,2-Trifluoroethyl)indolin-5-yl)methanamine

To a stirred solution of 1-(2,2,2-trifluoroethyl)indoline-5-carbonitrile (0.10 g, 0.44 mmol) in EtOH (5 mL) was added Raney nickel (0.10 g) followed by 7 M methanolic ammonia (1 mL) and stirred at RT for 1 h under hydrogen bladder

pressure. The reaction mixture was filtered through Celite and concentrated under reduced pressure to get the title compound (0.10 g, 99.0%), LC-MS: 214 $[M-NH_2]^+$

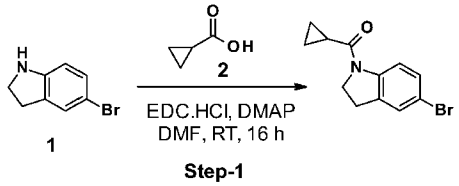
[0204] Step-5:

1-Methyl-2-oxo-N-((1-(2,2,2-trifluoroethyl)indolin-5-yl)methyl)-2,3-dihydro-1H-benzimidazole-5-carboxamide formate (Compound 14)

To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.08 g, 0.43 mmol) in DMF (4 mL) were added triethylamine (0.22 g, 2.17 mmol), EDC.HCl (0.08 g, 0.43 mmol), HOBt (0.03 g, 0.22 mmol) and (1-(2,2,2-trifluoroethyl)indolin-5-yl)methanamine (0.10 g, 0.43 mmol). Then the reaction mass was stirred at RT for 16 h. The reaction mass was quenched with ice cold water, and the solid precipitated was collected by filtration and dried to get a crude compound. This was further purified by preparative HPLC using Method B to afford the title compound as a formic acid salt (0.01 g, 5.70%) LC-MS: 405 $[M+H]^+$; ^{1}H-NMR (400 MHz, CD_3OD) δ 7.63-7.61 (dd, 1H), 7.55-7.51 (d, 1H), 7.14-7.12 (d, 1H), 7.09 (bs, 1H), 7.05-7.03 (d, 1H), 6.51-6.49 (d, 1H), 4.43 (s, 2H), 3.74-3.67 (q, 2H), 3.57-3.46 (t, 2H), 3.39 (s, 3H), 3.0-2.9 (t, 2H).

[0205] Preparation-4

[Chem.39]



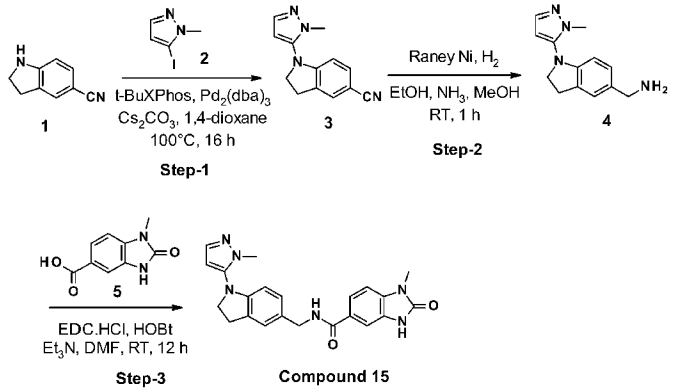
Step-1

[0206] Step-1: (5-Bromoindolin-1-yl)(cyclopropyl)methanone

To a stirred solution of cyclopropane carboxylic acid (0.13 g, 1.51 mmol) in DMF (5 mL) was added EDC.HCl (0.51 g, 2.66 mmol) followed by DMAP (0.17 g, 1.38 mmol). The reaction mass was stirred at RT for 10 min, then 5-bromoindoline (0.25 g, 0.1.26 mmol) was added thereto and stirred at RT for 16 h. The reaction mixture was diluted with cold water, and the solid precipitated was collected by filtration and dried to get the title compound (0.33 g, 98.50%). LC-MS: 266 $[M+H]^+$

[0207] Example-15

[Chem.40]



[0208] Step-1: 1-(1-Methyl-1H-pyrazol-5-yl)indoline-5-carbonitrile

To a stirred solution of indoline-5-carbonitrile (0.69 g, 4.8 mmol) in DMF (15 mL) were added cesium carbonate (4.69 g, 14.40 mmol) and 5-iodo-1-methyl-1H-pyrazole (1.00 g 4.8 mmol). The reaction mass was degassed with argon for 15 min. Then t-BuXPhos (0.74 g, 1.74 mmol) was added thereto followed by $Pd_2(dba)_3$ (0.79 g, 0.86 mmol) and stirred at 100°C for 16 h. The reaction mass was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash using 50% EtOAc in hexane as an eluent to get the title compound (0.40 g, 37.03%), LC-MS: 225 $[M+H]^+$

[0209] Step-2: (1-(1-Methyl-1H-pyrazol-5-yl)indolin-5-yl)methanamine

To a stirred solution of 1-(1-methyl-1H-pyrazol-5-yl)indoline-5-carbonitrile (0.25 g, 1.11 mmol) in EtOH (6 mL) was added Raney nickel (0.25 g) followed by 7 M methanolic ammonia (1 mL) and stirred at RT for 1 h under hydrogen bladder pressure. The reaction mixture was filtered through Celite and the filtrate was concentrated to get the crude title compound (0.25 g, 98.4%), LC-MS: 229 $[M+H]^+$

[0210] Step-3:

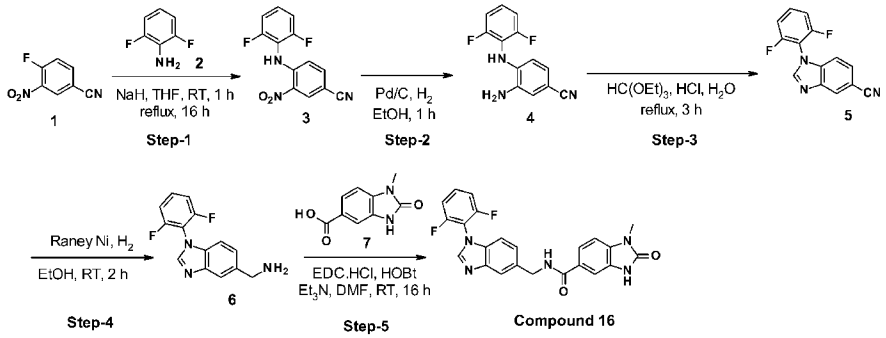
1-Methyl-N-((1-(1-methyl-1H-pyrazol-5-yl)indolin-5-yl)methyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide formate (Compound 15)

To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.19 g, 0.99 mmol) in DMF (5 mL) were added triethylamine (0.55 g, 5.47 mmol), EDC.HCl (0.19 g, 0.99 mmol), HOBt (0.07 g, 0.49 mmol) and (1-(1-methyl-1H-pyrazol-5-yl)indolin-5-yl)methanamine (0.25 g, 1.09 mmol). The reaction mass was stirred at RT for 12 h. The reaction mass quenched with cold water, and the solid precipitated was collected by filtration and dried to get a crude compound. This was further purified by preparative HPLC using Method B to afford the pure title compound as a formic acid salt (0.11 g, 24.70%). LC-MS: 403 $[M+H]^+$; ^{1}

H-NMR (400 MHz, DMSO-D_6) δ 11.04 (s, 1H), 8.82-8.79 (d, 1H), 7.61-7.59 (dd, 1H), 7.49-7.48 (d, 1H), 7.4-7.39 (d, 2H), 7.12-7.10 (m, 2H), 6.96-6.94 (d, 1H), 6.28-6.26 (d, 1H), 6.04-6.03 (d, 1H), 4.33-4.31 (d, 2H), 3.70-3.65 (m, 5H), 3.27 (s, 3H), 3.07-3.03 (t, 2H).

[0211] Example-16

[Chem.41]



[0212] Step-1: 4-((2,6-Difluorophenyl)amino)-3-nitrobenzonitrile

To a stirred solution of 4-fluoro-3-nitrobenzonitrile (1.50 g, 9.03 mmol) in THF (30 mL) was added NaH (60% dispersion in mineral oil) (0.43 g, 10.83 mmol) at 0°C and stirred at RT for 1 h. Then 2,6-difluoroaniline (1.17 g, 9.03 mmol) was added thereto and refluxed for 16 h. The reaction mixture was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated. The obtained residue was purified by combi flash column chromatography using 20% EtOAc in hexane as an eluent to afford the title compound (1.70 g, 68.50%). LC-MS: 274 $[M-H]^-$

[0213] Step-2: 3-Amino-4-((2,6-difluorophenyl)amino)benzonitrile

To a stirred solution of 4-((2,6-difluorophenyl)amino)-3-nitrobenzonitrile (0.60 g, 2.18 mmol) in EtOH (14 mL) was added Pd/C (0.24 g) and stirred under hydrogen bladder pressure for 1 h at RT. The reaction mass was filtered through Celite, and the filtrate was concentrated to afford the title compound (0.52 g 97.30%). LC-MS: 244 $[M-H]^-$

[0214] Step-3: 1-(2,6-Difluorophenyl)-1H-benzimidazole-5-carbonitrile

To a stirred solution of 3-amino-4-((2,6-difluorophenyl)amino)benzonitrile (0.20 g, 0.816 mmol) in triethyl orthoformate (5 mL) was added 37% HCl (0.5 mL) and reflux at 85°C for 3 h. The reaction mixture was concentrated and purified by column chromatography using 40% EtOAc in hexane as an eluent to afford the title compound (0.18 g, 86.53%). LC-MS: 256 $[M+H]^+$

[0215] Step-4: (1-(2,6-Difluorophenyl)-1H-benzimidazol-5-yl)methanamine

To a stirred solution of 1-(2,6-difluorophenyl)-1H-benzimidazole-5-carbonitrile (0.15 g, 0.58 mmol) in EtOH (5 mL) was added Raney nickel (0.15 g) and stirred at RT for 2 h under hydrogen bladder pressure. The reaction mass was filtered through

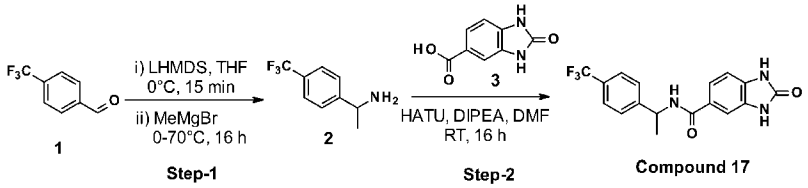
Celite and concentrated to afford the title compound (0.15 g, 98.60%). LC-MS: 260 $[M+H]^+$

[0216] Step-5: N-((1-(2,6-Difluorophenyl)-1H-benzimidazol-5-yl)methyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide trifluoroacetate (Compound 16)

To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.14 g, 0.72 mmol) in DMF (4 mL) was added EDC.HCl (0.17 g, 0.87 mmol) followed by HOBt (0.12 g, 0.87 mmol) and stirred at RT for 10 min. Then (1-(2,6-difluorophenyl)-1H-benzimidazol-5-yl)methanamine (0.13 g, 0.51 mmol) was added thereto followed by triethylamine (0.22 g, 2.18 mmol) and the mixture was stirred at RT for 16 h. The reaction mixture was diluted with ice cold water, and the solid precipitated was collected by filtration and dried. This was further purified by preparative HPLC using Method A to afford the title compound as a TFA Salt (0.02 g, 6.10%). LC-MS: 434 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.10 (s, 1H), 9.06-9.00 (t, 1H), 8.58 (s, 1H), 7.74-7.66 (m, 3H), 7.56-7.48 (m, 3H), 7.36-7.34 (dd, 1H), 7.33-7.29 (d, 1H), 7.18-7.16 (d, 1H), 4.76-4.59 (bs, 2H), 3.31 (s, 3H).

[0217] Example-17

[Chem.42]



[0218] Step-1: 1-(4-(Trifluoromethyl)phenyl)ethan-1-amine

To a stirred solution of 4-(trifluoromethyl)benzaldehyde (2.0 g, 11.48 mmol) in THF (20 mL) was added LiHMDS (2.30 g, 13.74 mmol) at 0°C and stirred for 15 min. Then 3 M methyl magnesium bromide (2.73 g, 22.88 mmol) in THF was added at 0°C and stirred at 70°C for 16 h. The reaction mixture was quenched with saturated ammonium chloride solution, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated. This was purified by combi flash column chromatography using 30% EtOAc in hexane as an eluent to afford the title compound (0.30 g, 13.8%). LC-MS: 190 $[M+H]^+$.

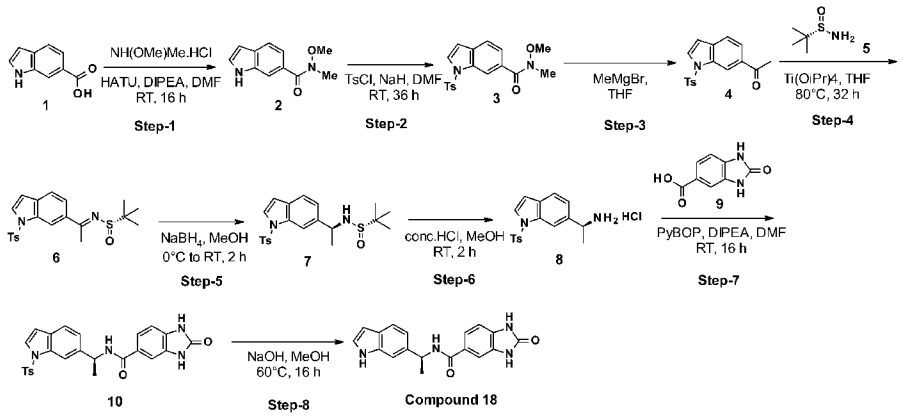
[0219] Step-2: 2-Oxo-N-(1-(4-(trifluoromethyl)phenyl)ethyl)-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 17)

To a stirred solution of 2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.15 g, 0.84 mmol) in DMF (2 mL) was added HATU (0.48 g, 1.26 mmol) followed

by DIPEA (0.43 g, 3.36 mmol) and stirred at RT for 10 min. Then 1-(4-(trifluoromethyl)phenyl)ethan-1-amine (0.12 g, 0.64 mmol) was added thereto and the mixture was stirred at RT for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash column chromatography using 2% MeOH in DCM as an eluent to afford the title compound. (0.03 g, 13%). LC-MS: 350 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.89-10.85 (m, 2H), 8.77-8.75 (d, 1H), 7.69-7.67 (d, 2H), 7.60-7.55 (m, 3H), 7.48 (s, 1H), 6.97-6.95 (d, 1H), 5.19 (m, 1H), 1.49-1.47 (d, 3H).

[0220] Example-18

[Chem.43]



[0221] Step-1: N-Methoxy-N-methyl-1H-indole-6-carboxamide

To a stirred solution of 1H-indole-6-carboxylic acid (10.0 g, 62.0 mmol) in DMF (100 mL) were added HATU (47.18 g, 0.12 mol) and DIPEA (40.09 g, 0.31 mol), and stirred at RT for 10 min. Then N,O-dimethylhydroxylamine hydrochloride (18.15 g, 0.19 mol) was added thereto and stirred at RT for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash column chromatography using 5% MeOH in DCM as an eluent to afford the title compound (10.0 g, 78.9%). LC-MS: 205 $[M+H]^+$

[0222] Step-2: N-Methoxy-N-methyl-1-tosyl-1H-indole-6-carboxamide

To a stirred solution of N-methoxy-N-methyl-1H-indole-6-carboxamide (6.80 g, 33.30 mmol) in DMF (100 mL) was added NaH (60% dispersion in mineral oil) (1.59 g, 39 mmol). Then p-toluenesulfonyl chloride (8.25 g, 43.0 mmol) was added thereto and stirred at RT for 36 h. The reaction mixture was poured into ice cold water, and the solid separated was collected by filtration and dried to afford the title compound (6.50 g, 54.5%). LC-MS: 359 $[M+H]^+$

[0223] Step-3: 1-(1-Tosyl-1H-indol-6-yl)ethan-1-one

To a stirred solution of N-methoxy-N-methyl-1-tosyl-1H-indole-6-carboxamide

(6.50 g, 18.13 mmol) in THF (65 mL) was added 3 M methyl magnesium bromide (6.49 g, 54.40 mmol) in THF at 0°C and stirred at RT for 1 h. The reaction mixture was quenched with ammonium chloride solution, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated. This was purified by combi flash column chromatography using 30% EtOAc in hexane as an eluent to afford the title compound (3.75 g, 66.13%). LC-MS: 314 $[M+H]^+$

[0224] Step-4:

(S,E)-2-Methyl-N-(1-(1-tosyl-1H-indol-6-yl)ethylidene)propane-2-sulfinamide

To a stirred solution of 1-(1-tosyl-1H-indol-6-yl)ethan-1-one (1.00 g, 3.19 mmol) in THF (10 mL) was added titanium isopropoxide (2.72 g, 9.57 mmol) followed by (S)-2-methylpropane-2-sulfinamide (0.77 g, 6.35 mmol) and stirred at 60°C for 32 h. The reaction mixture was diluted with water, solid separated was filtered, and the filtrate was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude compound was purified by combi flash column chromatography using 30% EtOAc in hexane as an eluent to afford the title compound (0.80 g, 60.24%). LC-MS: 418 $[M+H]^+$

[0225] Step-5: (S)-2-Methyl-N-((S)-1-(1-tosyl-1H-indol-6-yl)ethyl)propane-2-sulfinamide

To a stirred solution of (S,E)-2-methyl-N-(1-(1-tosyl-1H-indol-6-yl)ethylidene)propane-2-sulfinamide (0.40 g, 0.96 mmol) in MeOH (4 mL) was added $NaBH_4$ (0.09 g, 2.40 mmol) in portions at 0°C and stirred at RT for 2 h. The reaction mass was quenched with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a crude compound, which was purified by combi flash column using 30% EtOAc in hexane as an eluent to get the title compound (0.23 g, 57.35%). LC-MS: 419 $[M+H]^+$

[0226] Step-6: (S)-1-(1-Tosyl-1H-indol-6-yl)ethan-1-amine hydrochloride

To a solution of (S)-2-methyl-N-((S)-1-(1-tosyl-1H-indol-6-yl)ethyl)propane-2-sulfinamide (0.23 g, 0.55 mmol)) in MeOH (3 mL) was added aqueous 37% HCl (3 mL) and stirred at RT for 2 h. The reaction mixture was concentrated to get the title compound (0.17 g, 98.83%). ^{1}H-NMR (400 MHz, DMSO-D_6) δ 8.37 (bs, 2H), 8.11 (s, 1H), 7.97-7.95 (d, 2H), 7.84-7.83 (d, 1H), 7.66-7.64 (d, 1H), 7.40-7.36 (m, 3H), 6.84-6.83 (d, 1H), 4.60-4.57 (m, 1H), 2.32 (s, 3H), 1.54-1.52 (d, 3H).

[0227] Step-7:

(S)-2-Oxo-N-(1-(1-tosyl-1H-indol-6-yl)ethyl)-2,3-dihydro-1H-benzimidazole-5-carboxamide

To a solution of 2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.09 g, 0.50 mmol) in DMF (3 mL) was added PyBOP (0.52 g, 1.00 mmol) followed by

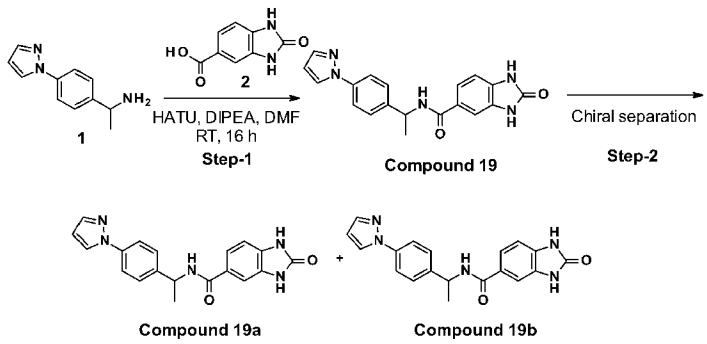
DIPEA (0.32 g, 2.47 mmol) and stirred at RT for 10 min. Then (S)-1-(1-tosyl-1H-indol-6-yl)ethan-1-amine hydrochloride (0.17 g, 0.50 mmol) was added thereto and stirred at RT for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get the crude title compound. (0.12 g, 50.63%). LC-MS: 473 $[M-H]^-$

[0228] Step-8: (S)-N-(1-(1H-Indol-6-yl)ethyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 18)

To a solution of (S)-2-oxo-N-(1-(1-tosyl-1H-indol-6-yl)ethyl)-2,3-dihydro-1H-benzimidazole-5-carboxamide (0.12 g, 0.25 mmol) in MeOH (3 mL) was added NaOH (0.10 g, 2.52 mmol) and stirred at 60°C for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash column chromatography using 4% MeOH in DCM as an eluent to afford the title compound. (0.07 g, 86.42%). LC-MS: 321 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.00 (s, 1H), 10.87-10.84 (d, 2H), 8.68-8.66 (d, 1H), 7.58-7.56 (dd, 1H), 7.49-7.44 (m, 2H), 7.36 (s, 1H), 7.28-7.27 (m, 1H), 7.05-7.03 (dd, 1H), 6.96-6.94 (d, 1H), 6.35 (bs, 1H), 5.25-5.22 (m, 1H), 1.51-1.50 (d, 3H).

[0229] Example-19

[Chem.44]



[0230] Step-1: N-(1-(4-(1H-Pyrazol-1-yl)phenyl)ethyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 19)

To a solution of 2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.38 g, 2.13 mmol) in DMF (10 mL) was added HATU (1.22 g, 3.20 mmol) followed by DIPEA (1.10 g, 8.54 mmol) and stirred at RT for 10 min. Then 1-(4-(1H-pyrazol-1-yl)phenyl)ethan-1-amine (0.40 g, 2.13 mmol) was added thereto and stirred at RT for 16 h. The reaction mixture was added into ice cold water, and the precipitate formed was collected by filtration and dried to afford the title compound

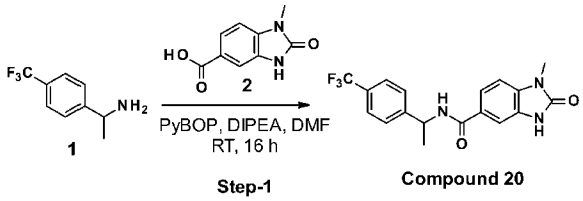
(0.30 g, 40.43%). LC-MS: 348 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.87-10.83 (d, 2H), 8.71-8.69 (d, 1H), 8.43-8.42 (d, 1H), 7.76-7.70 (m, 3H), 7.56-7.54 (dd, 1H), 7.48-7.46 (m, 3H), 6.96-6.94 (d, 1H), 6.51-6.50 (t, 1H), 5.20-5.15 (m, 1H), 1.48-1.46 (d, 3H).

[0231] Step-2: N-(1-(4-(1H-Pyrazol-1-yl)phenyl)ethyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Isomer separation) (Compound 19a and Compound 19b)

Racemic mixture of N-(1-(4-(1H-pyrazol-1-yl)phenyl)ethyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (0.30 g) was separated using preparative HPLC Method C. After separation, each isomer was basified with 10% $NaHCO_3$ solution, and the solid was collected by filtration and dried to afford the title compound (isomer-1: Compound 19a) as 15 mg; LC-MS: 348 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.90-10.86 (d, 2H), 8.73-8.71 (d, 1H), 8.45-8.44 (d, 1H), 7.78-7.76 (d, 2H), 7.71 (s, 1H), 7.56 (d, 1H), 7.50-7.48 (m, 3H), 6.97-6.95 (d, 1H), 6.52 (s, 1H), 5.19 (m, 1H), 1.50-1.48 (d, 3H); and (isomer-2: Compound 19b) as 25 mg. LC-MS: 348.0 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.90-10.86 (d, 2H), 8.72-8.70 (d, 1H), 8.44-8.43 (d, 1H), 7.78-7.76 (d, 2H), 7.71 (s, 1H), 7.56 (d, 1H), 7.50-7.48 (m, 3H), 6.97-6.95 (d, 1H), 6.52 (s, 1H), 5.19 (m, 1H), 1.50-1.48 (d, 3H).

[0232] Example-20

[Chem.45]



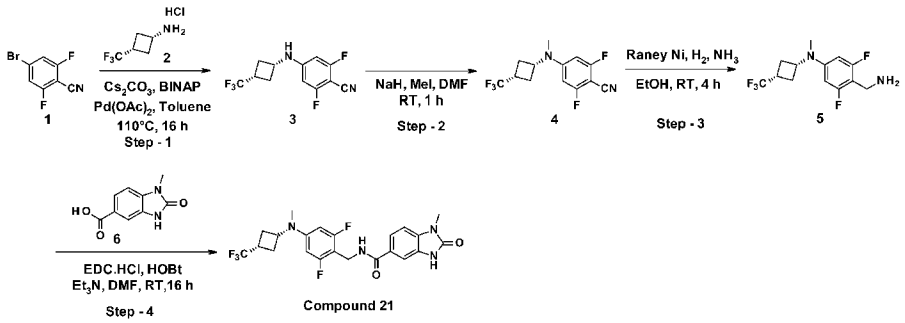
[0233] Step-1: 1-Methyl-2-oxo-N-(1-(4-(trifluoromethyl)phenyl)ethyl)-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 20)

To a solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.10 g, 0.52 mmol) in DMF (4 mL) was added PyBOP (0.54 g, 1.04 mmol) followed by DIPEA (0.33 g, 2.55 mmol) and stirred at RT for 10 min. Then 1-(4-(trifluoromethyl)phenyl)ethan-1-amine (0.09 g, 0.47 mmol) was added thereto and stirred at RT for 16 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash column chromatography using 4% MeOH in DCM as an eluent to afford the title compound. (0.07 g, 41%). LC-MS: 364 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.12 (s, 1H), 8.83-8.81 (d, 1H),

7.70-7.65 (m, 3H), 7.60-7.58 (m, 2H), 7.54 (s, 1H), 7.17-7.15 (d, 1H), 5.23-5.19 (m, 1H), 3.31 (s, 3H), 1.50-1.48 (d, 3H).

[0234] Example-21

[Chem.46]



[0235] Step-1: 2,6-Difluoro-4-((cis-3-(trifluoromethyl)cyclobutyl)amino)benzonitrile

To a stirred solution of 4-bromo-2,6-difluorobenzonitrile (0.50 g, 2.29 mmol) in toluene (7 mL) was added cesium carbonate (1.49 g, 4.57 mmol) followed by cis-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride (0.40 g 2.29 mmol). The reaction mass was degassed with argon for 15 min. Then BINAP (71 mg, 0.11 mmol) was added thereto followed by $Pd(OAc)_2$ (26 mg, 0.11 mmol) and stirred at 110°C for 16 h. The reaction mass was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash chromatography using 20% EtOAc in hexane as an eluent to get the title compound (0.40 g, 63.13%), LC-MS: 275 $[M-H]^-$

[0236] Step-2: 2,6-Difluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzonitrile

To a stirred solution of 2,6-difluoro-4-((cis-3-(trifluoromethyl)cyclobutyl)amino)-benzonitrile (0.40 g, 1.44 mmol) in DMF (6 mL) was added NaH (60% dispersion in mineral oil) (0.09 g, 2.17 mmol) followed by dropwise addition of iodomethane (0.31 g, 2.17 mmol) at 0°C and stirred at RT for 1 h. The reaction mass was diluted with ice water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash chromatography using 10% EtOAc in hexane as an eluent to get the title compound (0.40 g, 95.69%), LC-MS: 291 $[M+H]^+$.

[0237] Step-3:

4-(Aminomethyl)-3,5-difluoro-N-methyl-N-(cis-3-(trifluoromethyl)cyclobutyl)aniline

To a stirred solution of 2,6-difluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)-amino)benzonitrile (0.32 g, 1.10 mmol) in EtOH (6 mL) was added Raney nickel (0.07 g, 1.10 mmol) followed by 7 M methanolic ammonia (2 mL) and stirred at RT for 4 h under hydrogen bladder pressure. The reaction mass was filtered through Celite, and the filtrate was concentrated to afford the title crude compound (0.31 g, 95.6%).

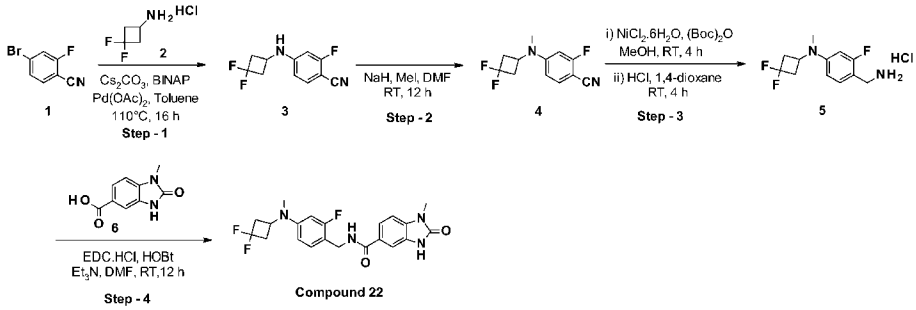
LC-MS: 295 $[M+H]^+$.

[0238] Step-4: N-(2,6-Difluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 21)

To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.15 g, 0.78 mmol) in DMF (6 mL) was added EDC.HCl (0.15 g, 0.78 mmol) followed by HOBt (0.07g, 0.52 mmol) and stirred at RT for 10 min. Then 4-(aminomethyl)-3,5-difluoro-N-methyl-N-(cis-3-(trifluoromethyl)cyclobutyl)aniline (0.23 g, 0.78 mmol) was added thereto followed by triethylamine (0.47 g, 4.68 mmol) and the mixture was stirred at RT for 16 h. The reaction mixture was poured into ice cold water, and the solid formed was collected by filtration and dried. This was washed with pentane to get the title compound (0.08 g, 23.56%). LC-MS: 469 $[M+H]^+$; ^{1}H-NMR (400 MHz, CD_3OD) δ 7.95-7.57 (dd, 1H), 7.51-7.50 (d, 1H), 7.12-7.10 (d, 1H), 6.41-6.36 (m, 2H), 4.86 (s, 2H), 4.16-4.08 (m,1H), 3.38 (s, 3H), 2.87-2.74 (m, 4H), 2.52-2.45 (m, 2H), 2.26-2.15 (m, 2H).

[0239] Example-22

[Chem.47]



[0240] Step-1: 4-((3,3-Difluorocyclobutyl)amino)-2-fluorobenzonitrile

To a stirred solution of 4-bromo-2-fluorobenzonitrile (1.0 g, 5.0 mmol) in toluene (20 mL) was added 3,3-difluorocyclobutan-1-amine hydrochloride (0.72 g, 5.0 mmol) followed by cesium carbonate (3.26 g, 10 mmol). The reaction mass was degassed with argon for 15 min. Then BINAP (0.16 g, 0.25 mmol) was added thereto followed by Pd $(OAc)_2$ (0.05 g, 0.25 mmol) and stirred at 110°C for 16 h. The reaction mass was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash chromatography using 10% EtOAc in hexane as an eluent to get the title compound (0.90 g, 80.35 %). LCMS: 225 $[M-H]^-$

[0241] Step-2: 4-((3,3-Difluorocyclobutyl)(methyl)amino)-2-fluorobenzonitrile

To a stirred solution of 4-((3,3-difluorocyclobutyl)amino)-2-fluorobenzonitrile (0.90 g, 3.98 mmol) in DMF (10 mL) was added sodium hydride (0.23 g, 5.92 mmol)

followed by dropwise addition of iodomethane (0.84 g, 5.92 mmol) and stirred at RT for 12 h. The reaction mass was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. The crude compound was purified by combi flash chromatography using 10% EtOAc in hexane as an eluent to get the title compound (0.80 g, 83.70 %). ^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.61-7.57 (t, 1H), 6.85-6.80 (d, 1H), 6.75- 6.72 (d, 1H), 4.28-4.26 (m, 1H), 3.06-2.99 (m, 2H), 2.90 (s, 3H), 2.83-2.76 (s, 2H).

[0242] Step-3: 4-(Aminomethyl)-N-(3,3-difluorocyclobutyl)-3-fluoro-N-methylaniline hydrochloride

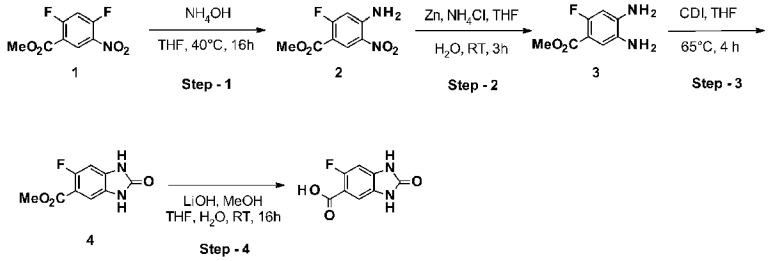
To a stirred solution of 4-((3,3-difluorocyclobutyl)(methyl)amino)-2-fluorobenzonitrile (0.60 g, 2.50 mmol) in MeOH (10 mL) was added $NiCl_2.6H_2O$ (0.08 g, 0.37 mmol) followed by dropwise addition of di-tert-butyl dicarbonate (1.09 g, 5.0 mmol) at 0°C and stirred for 5 min. Then $NaBH_4$ (0.66 g, 17.48 mmol) was added in portions thereto by maintaining the same temperature. After stirring at RT for 4 h, the reaction mass was concentrated to remove the solvent. The residue was diluted with EtOAc, washed with water, dried over anhydrous Na_2SO_4 and concentrated. This was purified by combi flash column chromatography using 20% EtOAc in hexane as an eluent. This was taken with 1,4-dioxane (2 mL) and 4 M HCl in 1,4-dioxane (2 mL) was added thereto then stirred at RT for 4 h. The reaction mixture was concentrated and washed with ether to get the title compound (0.34 g, 55.7%). LCMS: 228 $[M-NH_2]^+$.

[0243] Step-4: N-(4-((3,3-Difluorocyclobuyl)(methyl)amino)-2-fluorobenzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 22)

To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.10 g, 0.53 mmol) in DMF (8 mL) was added EDC.HCl (0.10 g, 0.53 mmol) followed by HOBt (0.03 g, 0.26 mmol) and stirred at RT for 10 min. Then 4-(aminomethyl)-N-(3,3-difluorocyclobutyl)-3-fluoro-N-methylaniline (0.13 g, 0.53 mmol) was added thereto followed by triethylamine (0.26 g, 2.66 mmol) and the mixture was stirred at RT for 12 h. The reaction mixture was poured into ice cold water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get a crude compound. This was washed with pentane to get the title compound (0.07 g, 31.1%). LC-MS: 419 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.10 (s, 1H), 8.79 (bs, 1H), 7.65-7.63 (d, 1H), 7.52 (s, 1H), 7.21-7.14 (q, 2H), 6.65-6.62 (m, 2H), 4.39-4.38 (d, 2H), 3.93-3.92 (d, 1H), 3.31 (s, 3H), 3.05-2.95 (m, 2H), 2.80 (s, 3H), 2.74-2.61 (m, 2H).

[0244] Preparation-5

[Chem.48]



[0245] Step-1: Methyl 4-amino-2-fluoro-5-nitrobenzoate

To a stirred solution of methyl 2,4-difluoro-5-nitrobenzoate (2.50 g, 11.51 mmol) in THF (20 mL) was added NH_4OH (0.59 g, 16.85 mmol) and stirred at 40°C for 16 h. The reaction mixture was concentrated to remove THF then poured into ice cold water, and the solid separated was collected by filtration and dried to afford the title compound (2.30 g, 93.3%). LC-MS: 215 $[M+H]^+$.

[0246] Step-2: Methyl 4,5-diamino-2-fluorobenzoate

To a stirred solution of methyl 4-amino-2-fluoro-5-nitrobenzoate (2.30 g, 10.74 mmol) in THF (15 mL) and water (7 mL) was added ammonium chloride (5.74 g, 107.4 mmol) followed by zinc dust (4.91 g, 75.18 mmol) and stirred at RT for 3 h. The reaction mass was diluted with EtOAc and filtered on Celite bed. The filtrate was washed with water, dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (1.90 g, 96.1%). LC-MS: 185 $[M+H]^+$.

[0247] Step-3: Methyl 6-fluoro-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate

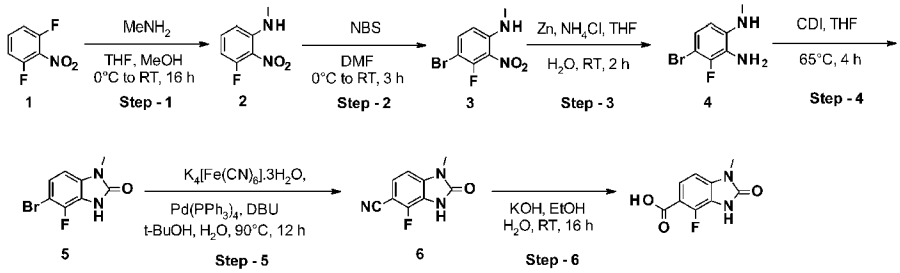
To a stirred solution of methyl 4,5-diamino-2-fluorobenzoate (1.80 g, 9.77 mmol) in THF (36 mL) was added CDI (2.22 g, 13.68 mmol) and stirred at 65°C for 4 h. The reaction mixture was concentrated to remove THF then poured into ice cold water, and the solid separated was collected by filtration and dried to afford the title compound (1.90 g, 92.54%). LC-MS: 211 $[M+H]^+$

[0248] Step-4: 6-Fluoro-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid

To a stirred solution of methyl 6-fluoro-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate (1.90 g, 9.04 mmol) in THF (15 mL), MeOH (10 mL) and water (6 mL) was added LiOH (1.30 g, 54.23 mmol) and stirred at RT for 16 h. The reaction mixture was concentrated to remove THF and MeOH, diluted with water and acidified with 1 N HCl. The precipitate formed was collected by filtration and dried to get the title compound (1.70 g, 96.04%). LC-MS: 197 $[M+H]^+$

[0249] Preparation-6

[Chem.49]



[0250] Step-1: 3-Fluoro-N-methyl-2-nitroaniline

To a stirred solution of 1,3-difluoro-2-nitrobenzene (2.0 g, 12.57 mmol) in MeOH (30 mL) was added 2 M methanamine (0.47 g, 15.13 mmol) in THF at 0°C and stirred at RT for 16 h. The reaction mass was concentrated to remove the solvent. The residue was diluted with EtOAc, washed with water, dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (2.10 g, 98%). LC-MS: 171 $[M+H]^+$.

[0251] Step-2: 4-Bromo-3-fluoro-N-methyl-2-nitroaniline

To a stirred solution of 3-fluoro-N-methyl-2-nitroaniline (2.0 g, 11.75 mmol) in DMF (30 mL) was added NBS (2.09 g, 11.75 mmol) at 0°C and stirred at RT for 3 h. The reaction mixture was diluted with water, and the solid formed was collected by filtration and dried to afford the title compound (2.10 g, 72%). LC-MS: 251 $[M+H]^+$.

[0252] Step-3: 4-Bromo-3-fluoro-N^1-methylbenzene-1,2-diamine

To a stirred solution of 4-bromo-3-fluoro-N-methyl-2-nitroaniline (0.90 g, 3.61 mmol) in THF (12 mL) and water (3 mL) was added ammonium chloride (1.16 g, 21.68 mmol) followed by zinc dust (0.71 g, 10.84 mmol) and stirred at RT for 2 h. The reaction mixture was filtered and the filtrate was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (0.75 g, 95%). LC-MS: 219 $[M+H]^+$.

[0253] Step-4: 5-Bromo-4-fluoro-1-methyl-1,3-dihydro-2H-benzimidazol-2-one

To a stirred solution of 4-bromo-3-fluoro-N^1-methylbenzene-1,2-diamine (0.75 g, 3.42 mmol) in THF (8 mL) was added CDI (1.10 g, 6.78 mmol) and stirred at 65°C for 3 h. The reaction mixture was concentrated to remove THF then poured into ice cold water, and the solid formed was collected by filtration and dried to afford the title compound (0.80 g, 95.5%). LC-MS: 245 $[M+H]^+$.

[0254] Step-5: 4-Fluoro-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carbonitrile

To a stirred solution of 5-bromo-4-fluoro-1-methyl-1,3-dihydro-2H-benzimidazol-2-one (1.00 g, 4.08 mmol) in t-BuOH (5 mL) and water (5 mL) was added DBU (0.12 g, 0.81 mmol) and potassium hexacyanoferrate(II) trihydrate (0.69 g, 1.63 mmol). The reaction mass was degaussed with argon for 15 min. Then tetrakis(triphenylphosphine)palladium (0.47 g, 0.40 mmol) was added thereto and stirred at 90°C for 12 h. The reaction mixture was

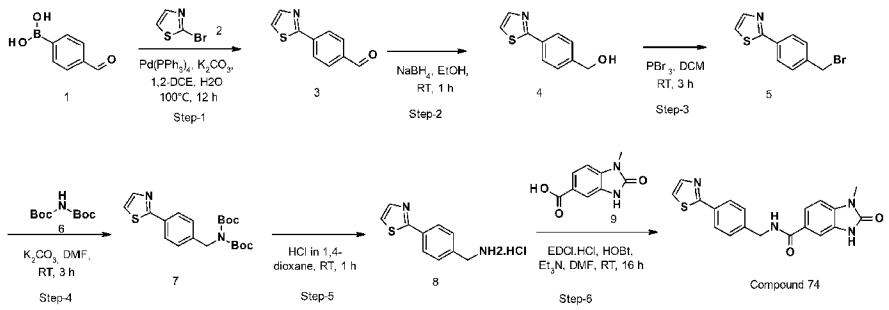
poured into ice cold water, and the solid separated was collected by filtration and dried to afford the title compound (0.63 g, 80.76%). LC-MS: 190 [M-H]$^-$.

[0255] Step-6: 4-Fluoro-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid

To a stirred solution of 4-fluoro-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carbonitrile (1.0 g, 5.23 mmol) in water (1 mL) and EtOH (12 mL) was added KOH (1.17 g, 20.9 mmol) and stirred at RT for 16 h. Then the reaction mixture was concentrated, diluted with water and acidified with 1 N HCl. The precipitate formed was collected by filtration and dried to get the title compound (0.80 g, 87%). LC-MS: 211 [M+H] $^+$.

[0256] Example-74

[Chem.50]



[0257] Step-1: 4-(Thiazol-2-yl)benzaldehyde

To a stirred solution of (4-formylphenyl)boronic acid (1 g, 6.66 mmol) in 1,2-dichloroethane (5mL) and water (2 mL) was added 2-bromothiazole (1.20 g, 7.31 mmol) followed by potassium carbonate (0.40 g, 2.89 mmol). The reaction mass was degassed with argon for 15 min. Then tetrakis(triphenylphosphine)palladium (0.77 g, 0.66 mmol) was added thereto and stirred at 100°C for 12 h. The reaction mass was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get the crude compound. The crude compound was purified by combi flash column chromatography using 50% EtOAc in n-hexane as an eluent to get the title compound (0.90 g, 71.42%).

LC-MS: 190 [M+H] $^+$.

[0258] Step-2: (4-(Thiazol-2-yl)phenyl)methanol

To a stirred solution of 4-(thiazol-2-yl)benzaldehyde (0.9 g, 4.75 mmol) in EtOH (10 mL) was added $NaBH_4$ (0.09 g, 2.38 mmol) at 0°C and stirred at RT for 1 h. The reaction mass was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get the crude compound. The crude compound was purified by combi flash column chromatography using 30% EtOAc in n-hexane as an eluent to get the title compound (0.62 g, 68.28%).

LC-MS: 192 [M+H] $^+$.

[0259] Step-3: 2-(4-(Bromomethyl)phenyl)thiazole

To a stirred solution of (4-(thiazol-2-yl)phenyl)methanol (0.3 g, 1.56 mmol) in DCM (20 mL) was added PBr_3 (0.21 g, 0.78 mmol) at 0°C and stirred at RT for 3 h. The reaction mass was diluted with DCM, washed with $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated to get the title compound (0.3 g, 75.75%).
LC-MS: 254 $[M+H]^+$.

[0260] Step-4: tert-Butyl N-(tert-butoxycarbonyl)-N-(4-(thiazol-2-yl)benzyl)carbamate

To a stirred solution of 2-(4-(bromomethyl)phenyl)thiazole (0.3 g, 1.18 mmol) in DMF (5 mL) was added potassium carbonate (0.32 g, 2.35 mmol) followed by dropwise addition of di-tert-butyl dicarbonate (0.26 g, 1.19 mmol) at 0°C and stirred at RT for 3 h. The reaction mass was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get the title compound (0.41 g, 89.13%).
LC-MS: 391 $[M+H]^+$.

[0261] Step-5: (4-(Thiazol-2-yl)phenyl)methanamine hydrochloride

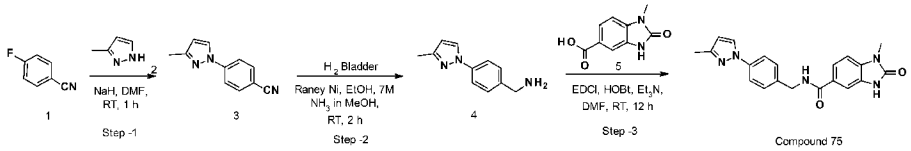
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-(thiazol-2-yl)benzyl)carbamate (0.4 g, 1.02 mmol) in 1,4-dioxane (2 mL) was added 4 M HCl in 1,4-dioxane (2mL) at 0°C and stirred at RT for 1 h. The reaction mixture was concentrated, washed with diethyl ether and dried to get the title compound (0.23 g, 99.13%).
LCMS: 191 $[M+H]^+$.

[0262] Step-6:
1-Methyl-2-oxo-N-(4-(thiazol-2-yl)benzyl)-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 74)

To a stirred solution of 1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.20 g, 1.01 mmol) in DMF (6 mL) was added EDC.HCl (0.19 g, 1.01 mmol) followed by HOBt (0.54 g, 0.40 mmol) and stirred at RT for 10 min. Then (4-(thiazol-2-yl)phenyl)methanamine hydrochloride (0.23 g, 1.01 mmol) was added thereto followed by triethylamine (0.61 g, 6.06 mmol) and stirred at RT for 16 h. The reaction mixture was diluted with ice cold water, and the solid precipitated was collected by filtration and dried. This was further purified by preparative HPLC using Method B to afford the title compound (0.05 g, 14%).
LC-MS: 365 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.11 (s, 1H), 9.03-9.00 (t, 1H), 7.93-7.91 (m, 3H), 7.77-7.76 (d, 1H), 7.69-7.67 (dd, 1H), 7.56-7.55 (d, 1H), 7.45-7.43 (d, 2H), 7.18-7.16 (d, 1H), 4.53-4.51 (d, 2H), 3.32 (s, 3H).

[0263] Example-75

[Chem.51]



[0264] Step-1: 4-(3-Methyl-1H-pyrazol-1-yl)benzonitrile

To a stirred solution of 3-methyl-1H-pyrazole (0.17 g, 2.07 mmol) in DMF (5 mL) was added NaH (60% dispersion in mineral oil) (0.08 g, 2.07 mmol) followed by 4-fluorobenzonitrile (0.25 g, 2.07 mmol) at 0°C and stirred at RT for 1 h. The reaction mass was quenched with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get the crude compound. The crude compound was purified by combi flash column chromatography using 10% EtOAc in n-hexane as an eluent to get the title compound (0.25 g, 66.1%).

LC-MS: 184 $[M+H]^+$.

[0265] Step-2: (4-(3-Methyl-1H-pyrazol-1-yl)phenyl)methanamine

To a stirred solution of 4-(3-methyl-1H-pyrazol-1-yl)benzonitrile (0.25 g, 1.36 mmol) in EtOH (2 mL) was added Raney nickel (0.25 g, 4.26 mmol) followed by 7 M methanolic ammonia (8 mL) and stirred at RT for 2 h under hydrogen bladder pressure. The reaction mass was filtered through Celite and the filtrate was concentrated to afford the title compound (0.25 g, 98.4%).

LC-MS: 188 $[M+H]^+$.

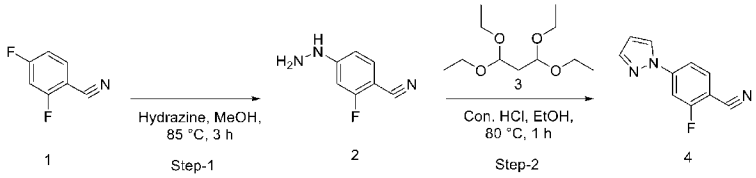
[0266] Step-3:
1-Methyl-N-(4-(3-methyl-1H-pyrazol-1-yl)benzyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide (Compound 75)

To a stirred solution of
1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.26 g, 1.34 mmol) in DMF (6 mL) was added EDC.HCl (0.26 g, 1.38 mmol) followed by HOBt (0.05 g, 0.37 mmol) and stirred at RT for 10 min. Then
(4-(3-methyl-1H-pyrazol-1-yl)phenyl)methanamine (0.25 g, 1.34 mmol) was added thereto followed by triethylamine (0.76 g, 7.47 mmol) and stirred at RT for 12 h. The reaction mixture was diluted with ice cold water, and the solid precipitated was collected by filtration and dried. This was further purified by preparative HPLC using Method B to afford the title compound (0.02 g, 4.14%).

LC-MS: 362 $[M+H]^+$; ^{1}H-NMR (400 MHz, CD_3OD) δ 8.02-8.01 (d, 1H), 7.71-7.62 (dd, 1H), 7.65-7.62 (m, 3H), 7.49-7.47 (d, 2H), 7.17-7.15 (d, 1H), 6.31-6.30 (d, 1H), 4.62 (s, 2H), 3.44 (s, 3H), 2.35 (s, 3H).

[0267] Preparation-7

[Chem.52]



1 2 3 4

[0268] Step-1: 2-Fluoro-4-hydrazinylbenzonitrile

To a stirred solution of 2,4-difluorobenzonitrile (1.00 g, 7.18 mmol) in MeOH (20 mL) was added hydrazine (0.23 g, 7.18 mmol) and stirred at 85°C for 3 h. The reaction mass was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get the title compound (0.75 g, 69.03%).

LC-MS: 152 $[M+H]^-$

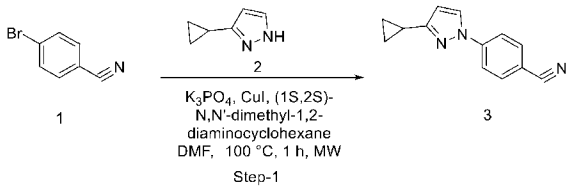
[0269] Step-2: 2-Fluoro-4-(1H-pyrazol-1-yl)benzonitrile

To a stirred solution of 2-fluoro-4-hydrazinylbenzonitrile (0.70 g, 4.63 mmol) in EtOH (20 mL) was added 1,1,3,3-tetraethoxypropane (1.02 g, 4.63 mmol) followed by dropwise addition of conc. HCl (0.01 g, 0.46 mmol) at 0°C and stirred at 80°C for 1 h. The reaction mass was concentrated and neutralized with $NaHCO_3$. The precipitate formed was collected by filtration and dried to get the crude compound, which was purified by combi flash column chromatography using 20% EtOAc in n-hexane as an eluent to get the title compound (0.30 g, 34.61%).

LC-MS: 188 $[M+H]^+$.

[0270] Preparation-8

[Chem.53]



1 2 3

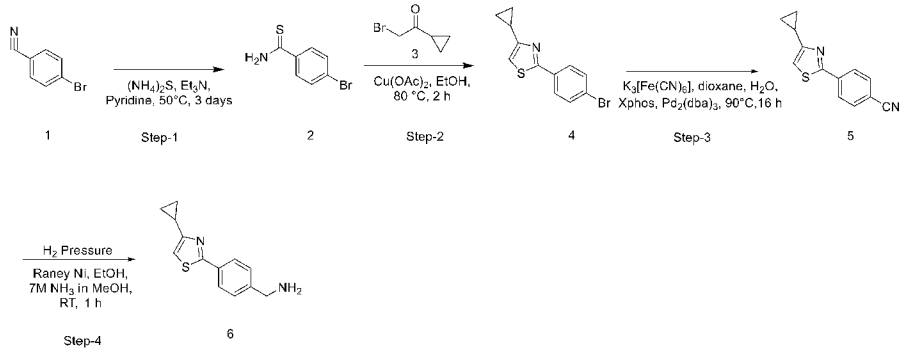
[0271] Step-1: 4-(3-Cyclopropyl-1H-pyrazol-1-yl)benzonitrile

To a stirred solution of 4-bromobenzonitrile (0.60 g, 3.29 mmol) in DMF (15 mL) was added 3-cyclopropyl-1H-pyrazole (0.36 g, 3.29 mmol) followed by addition of K_3PO_4 (2.35g, 11.09 mmol). Then (1S,2S)-N, N'-dimethylcyclohexane-1,2-diamine (0.05 g, 0.33 mmol) was added thereto followed by copper (I) iodide (0.63 g, 3.29 mmol) and the mixture was stirred at 100°C in microwave for 1 h. The reaction mixture was filtered and diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get the crude compound. The crude compound was purified by combi flash column chromatography using 25% EtOAc in n-hexane as an eluent to get the title compound (0.22 g, 31.89%).

LC-MS: 210 $[M+H]^+$.

[0272] Preparation-9

[Chem.54]



[0273] Step-1: 4-Bromobenzothioamide

To a stirred solution of 4-bromobenzonitrile (2.00 g, 10.98 mmol) in pyridine (20 mL) was added ammonium sulfide (2.17 g, 16.48 mmol) followed by triethylamine (1.22 g, 12.08 mmol) and stirred at 50°C for 3 days. The reaction mass was diluted with EtOAc, washed with 0.1 N HCl, dried over anhydrous Na_2SO_4 and concentrated to get the title compound (2.30 g, 97.87%).

LC-MS: 216 $[M+H]^-$

[0274] Step-2: 2-(4-Bromophenyl)-4-cyclopropylthiazole

To a stirred solution of 4-bromobenzothioamide (1.0 g, 4.62 mmol) in EtOH (6 mL) was added 2-bromo-1-cyclopropylethan-1-one (0.75 g, 4.62 mmol) followed by addition of copper (II) acetate monohydrate (0.04 g, 0.23 mmol) and stirred at 80°C for 2 h. The reaction mass was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to get the title compound (1.20 g, 93.75%).

LC-MS: 280 $[M+H]^+$.

[0275] Step-3: 4-(4-Cyclopropylthiazol-2-yl)benzonitrile

To a stirred solution of 2-(4-bromophenyl)-4-cyclopropylthiazole (0.50 g, 1.78 mmol) in 1,4-dioxane (6 mL) and water (2 mL) were added potassium acetate (0.35 g, 3.56 mmol) and potassium ferricyanide (0.29 g, 0.89 mmol). The reaction mass was degassed with argon for 15 min. Then 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (0.01 g, 0.03 mmol) was added thereto followed by $Pd_2(dba)_3$ (0.01 g, 0.01 mmol) and stirred at 90°C for 16 h. The reaction mass was filtered and washed with EtOAc dried over anhydrous Na_2SO_4 and concentrated to get the title compound (0.37 g, 92.03%).

LCMS: 227 $[M+H]^+$.

[0276] Step-4: (4-(4-Cyclopropylthiazol-2-yl)phenyl)methanamine

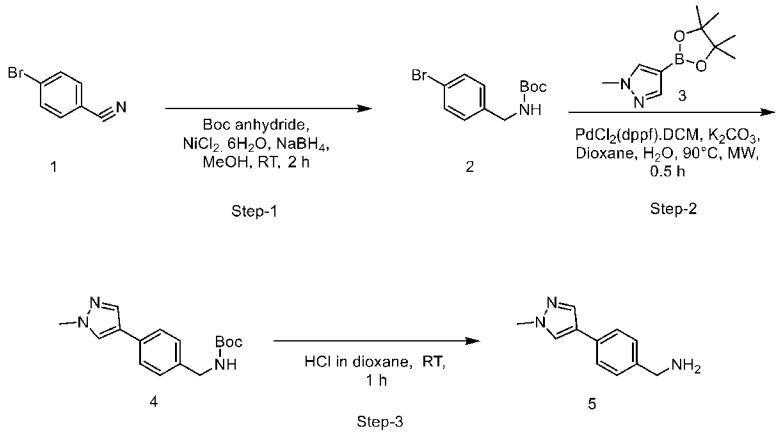
To a stirred solution of 4-(4-cyclopropylthiazol-2-yl)benzonitrile (0.15 g, 0.66 mmol) in EtOH (3 mL) was added Raney nickel (0.15 g, 8.51 mmol) followed by 7 M methanolic ammonia (6 mL) and stirred at RT for 1 h under hydrogen bladder

pressure. The reaction mass was filtered through Celite and the filtrate was concentrated to afford the title compound (0.10 g, 65.78%).

LC-MS: 231 $[M+H]^+$.

[0277] Preparation-10

[Chem.55]



[0278] Step-1: tert-Butyl (4-bromobenzyl)carbamate

To a stirred solution of 4-bromobenzonitrile (0.5 g, 2.75 mmol) in MeOH (100 mL) was added $NiCl_2.6H_2O$ (0.07 g, 0.27 mmol) followed by dropwise addition of di-tert-butyl dicarbonate (1.2 g, 5.49 mmol) at 0°C and stirred for 5 min. Then $NaBH_4$ (0.52 g, 13.74 mmol) was added thereto in portions by maintaining the same temperature. After stirring at RT for 2 h, the reaction mass was concentrated to remove solvent. The residue was diluted with EtOAc, washed with water, dried over anhydrous Na_2SO_4 and concentrated to get the title compound (0.65 g, 82.7%).

^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.54-7.49 (d, 2H), 7.42-7.40 (t, 1H), 7.22-7.18 (d, 2H), 4.13-4.09 (d, 2H), 1.41 (s, 9H).

[0279] Step-2: tert-Butyl (4-(1-methyl-1H-pyrazol-4-yl)benzyl)carbamate

To a stirred solution of tert-butyl (4-bromobenzyl)carbamate (1.0 g, 3.50 mmol) in 1,4-dioxane (3 mL) and water (0.5 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.72 g, 3.50 mmol) followed by potassium carbonate (1.0 g, 7.30 mmol). The reaction mass was degassed with argon for 15 min. Then [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) DCM complex (0.14 g, 0.01 mmol) was added and stirred at 90°C for 30 min under microwave irradiation. The reaction mass was diluted with EtOAc and filtered on Celite bed. The filtrate was washed with water, dried over anhydrous Na_2SO_4 and concentrated to get the crude compound. The crude compound was purified by combi flash column chromatography using 50% EtOAc in n-hexane as an eluent to get the title compound (0.36 g, 35.87%).

LCMS: 288 $[M+H]^+$

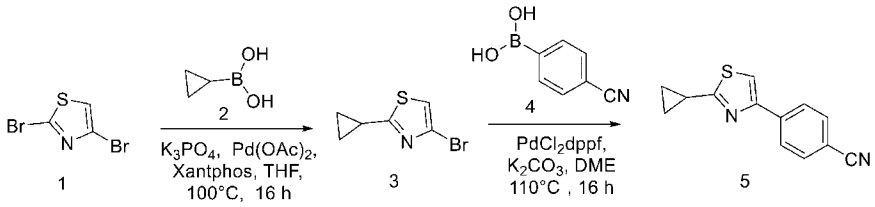
[0280] Step-3: (4-(1-methyl-1H-pyrazol-4-yl)phenyl)methanamine hydrochloride

To a stirred solution of tert-Butyl (4-(1-methyl-1H-pyrazol-4-yl)benzyl)carbamate (0.36 g, 1.25 mmol) in 1,4-dioxane (4 mL) was added 4 M HCl in 1,4-dioxane (4 mL), and then stirred at RT for 1 h. The reaction mixture was concentrated and washed with n-pentane to get the title compound (0.27 g, 96.42%).

LCMS: 188 $[M+H]^+$.

[0281] Preparation-11

[Chem.56]



[0282] Step-1: 4-Bromo-2-cyclopropylthiazole

To a stirred solution of 2,4-dibromothiazole (0.25 g, 1.03 mmol) in THF (3 mL) was added cyclopropylboronic acid (0.11 g, 1.24 mmol) followed by K_3PO_4 (0.66 g, 3.08 mmol). The reaction mass was degassed with argon for 15 min. Then 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.04 g, 0.07 mmol) was added thereto followed by $Pd(OAc)_2$ (0.02 g, 0.07 mmol) and stirred at 100°C for 16 h. The reaction mass was diluted with EtOAc and filtered on Celite bed. The filtrate was concentrated to get the crude compound. The crude compound was purified by combi flash column chromatography using 10% EtOAc in n-hexane as an eluent to get the title compound (0.20 g, 95.23%). LC-MS: 206 $[M+H]^+$

[0283] Step-2: 4-(2-Cyclopropylthiazol-4-yl)benzonitrile

To a stirred solution of 4-bromo-2-cyclopropylthiazole (0.25 g, 1.23 mmol) in 1,2-dimethoxyethane (5 mL) was added (4-cyanophenyl)boronic acid (0.2 g, 1.35 mmol) followed by potassium carbonate (0.51 g, 3.67 mmol). The reaction mass was degassed with argon for 15 min. Then [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) DCM complex (0.07 g, 0.08 mmol) was added thereto and stirred at 110°C for 16 h. The reaction mass was diluted with EtOAc and filtered on Celite bed. The filtrate was washed with water, dried over anhydrous Na_2SO_4 and concentrated to get the crude compound. The crude compound was purified by combi flash chromatography using 30% EtOAc in n-hexane as an eluent to get the title compound (0.2 g, 72.15%).

^{1}H-NMR (400 MHz, CD_3Cl_3) δ 8.02-7.99 (d, 2H), 7.72-7.69 (d, 2H), 7.40 (s, 1H), 2.40-2.36 (m, 1H), 1.23-1.15 (m, 4H).

[0284] Prep HPLC methods:

-Method A: Column-LUNA C18 (250mm x 19mm), 5.0μ; Eluent-A 0.05% TFA in water, B-ACN, gradient-10% B at 0 min, 20% B at 2 min, 50% B at 10 min, 70% B at 15 min), Flow: 18mL/min

-Method B: Column- Waters, Xselect, c18 (250mm x 21.2mm), 5.0μ; Eluent-A 0.05% HCOOH in water, B-ACN, gradient-10% B at 0 min, 30% B at 2 min, 70% B at 8 min), Flow: 13mL/min

-Method-C: Column: Chiralpak IA (250 x 20 x 5μm), Dilution: IPA:DCM (90:10)+TFA; Eluent-A- 0.1 % TFA in hexane, B- EtOH (100%), Isocratic-A:B(50:50), Flow: 15mL/min

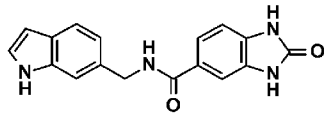
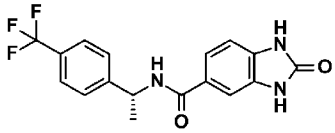
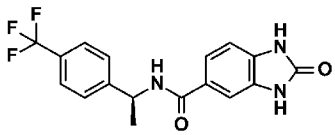
[0285] Examples-23 to 96

Compounds of Examples (Ex.)-23 to 96 shown in Tables 2 to 51 were prepared according to a similar manner to that of the referred Example and step. For example, the term “E1-S3” in the column “Ref.” of the table shows that the compound was prepared according to a similar manner to that of referred “E”xample-“1” - “S”tep-“3” above. Likewise, the term “P9-S3” in the column “Ref.” of the table shows that the compound was prepared according to a similar manner to that of referred “P”reparation-“9” - “S”tep-“3” above. It is understood that compounds can be obtained as a free form or a salt form due to isolation condition.

[0286] The compound having a chemical structural formula with "HCl" in the vicinity thereof represents that the compound was isolated as hydrochloride.

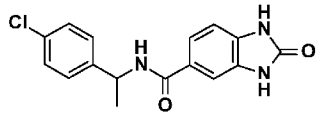
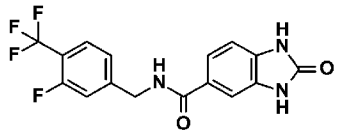
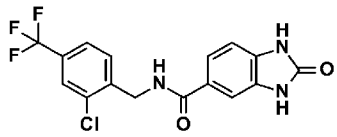
[0287]

[Table 2]

Ex	Ref.	Structure	LC-MS, NMR
23	E1-S3	 (Compound 23)	LC-MS: 307 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.00 (bs, 1H), 10.90-10.84 (d, 2H), 8.90-8.88 (t, 1H), 7.59-7.56 (dd, 1H), 7.50 (s, 1H), 7.47-7.45 (d, 1H), 7.31 (s, 1H), 7.28-7.27 (t, 1H), 6.97-6.65 (d, 2H) 6.36 (s, 1H), 4.54-4.52 (d, 2H).
24	E11-S3	 (Compound 24)	LC-MS: 350 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.89-10.85 (m, 2H), 8.79-8.77 (d, 1H), 7.69-7.67 (d, 2H), 7.60-7.55 (m, 3H), 7.49-7.48 (d, 1H), 6.97-6.95 (d, 1H), 5.19 (m, 1H), 1.49-1.47 (d, 3H).
25	E11-S3	 (Compound 25)	LC-MS: 350 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.89-10.85 (m, 2H), 8.80-8.78 (d, 1H), 7.69-7.67 (d, 2H), 7.60-7.55 (m, 3H), 7.49-7.48 (d, 1H), 6.97-6.95 (d, 1H), 5.19 (m, 1H), 1.49-1.47 (d, 3H).

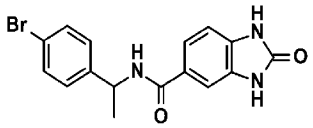
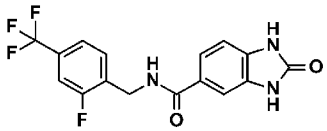
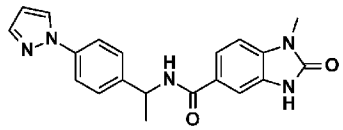
[0288]

[Table 3]

Ex	Ref.	Structure	LC-MS, NMR
26	E11-S3	 (Compound 26)	LC-MS: 316 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.89-10.84 (d, 2H), 8.71-8.69 (d, 1H), 7.57-7.54 (dd, 1H), 7.48 (s, 1H), 7.41-7.26 (m, 4H), 6.97-6.95 (d, 1H), 5.15-5.11 (m, 1H), 1.46-1.44 (d, 3H).
27	E1-S3	 (Compound 27)	LC-MS: 354 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.90-10.87 (d, 2H), 9.04-9.00 (t, 1H), 7.75-7.71 (t, 1H), 7.57-7.54 (dd, 1H), 7.47-7.46 (d, 1H), 7.40-7.37 (d, 1H), 7.33-7.30 (d, 1H), 6.97-6.95 (d, 1H), 4.52-4.50 (d, 2H).
28	E1-S3	 (Compound 28)	LC-MS: 370 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.88-10.83 (d, 2H), 8.98-8.96 (t, 1H), 7.81 (s, 1H), 7.66-7.64 (d, 1H), 7.54-7.52 (dd, 1H), 7.48-7.46 (m, 2H), 6.94-6.92 (d, 1H), 4.50-4.49 (d, 2H).

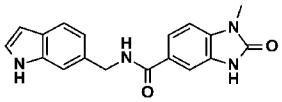
[0289]

[Table 4]

Ex	Ref.	Structure	LC-MS, NMR
29	E11-3	 (Compound 29)	LC-MS: 362 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.89-10.85 (m, 2H), 8.71-8.69 (d, 1H), 7.57-7.47 (m, 4H), 7.35-7.33 (d, 2H), 6.97-6.95 (d, 1H), 5.12-5.09 (m, 1H), 1.45-1.43 (d, 3H).
30	E1-S3	 (Compound 30)	LC-MS: 354 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.90-10.80 (m, 2H), 8.99-8.96 (t, 1H), 7.66-7.64 (d, 1H), 7.57-7.55 (m, 3H), 7.48 (s, 1H), 6.98-6.96 (d, 1H), 4.55-4.53 (d, 2H).
31	E11-3	 (Compound 31)	LC-MS: 362 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.03 (s, 1H), 8.74-8.72 (d, 1H), 8.44-8.43 (d, 1H), 7.78-7.76 (d, 2H), 7.71 (s, 1H), 7.68-7.66 (d, 1H), 7.54 (s, 1H), 7.51-7.49 (d, 2H), 7.16-7.14 (d, 1H), 6.52 (s, 1H), 5.22-5.18 (m, 1H), 1.51-1.49 (d, 3H), 3.30 (s, 3H).

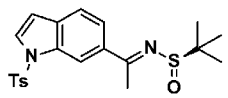
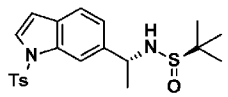
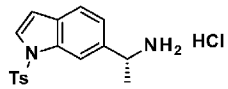
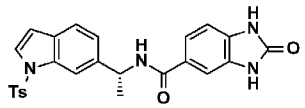
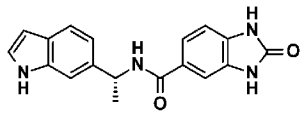
[0290]

[Table 5]

Ex	Ref.	Structure	LC-MS, NMR
32	E1-S3	 (Compound 32)	LC-MS: 321 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.08 (bs, 1H), 11.00 (bs, 1H), 8.95-8.92 (t, 1H), 7.68-7.66 (d, 1H), 7.55 (s, 1H), 7.47-7.45 (d, 1H), 7.32-7.28 (m, 2H), 7.16-7.14 (d, 1H), 6.98-6.96 (d, 1H), 6.36 (bs, 1H), 4.55-4.54 (d, 2H), 3.30 (s, 3H).

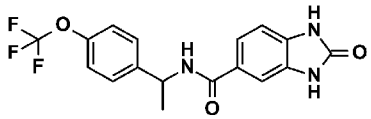
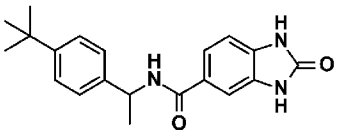
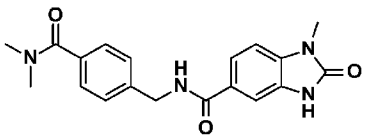
[0291]

[Table 6]

Ex	Ref.	Structure	LC-MS, NMR
33	E18-S4		LC-MS: 417 [M+H] $^{+}$.
	E18-S5		LC-MS: 419 [M+H] $^{+}$.
	E18-S6		^{1}H-NMR (400 MHz, DMSO-D_6) δ 8.37 (bs, 2H), 8.11 (s, 1H), 7.97-7.95 (d, 2H), 7.84-7.83 (d, 1H), 7.66-7.64 (d, 1H), 7.40-7.36 (m, 3H), 6.84-6.83 (d, 1H), 4.60-4.56 (m, 1H), 2.32 (s, 3H), 1.54-1.52 (d, 3H).
	E18-S7		LC-MS: 475 [M+H] $^{+}$.
	E18-S8	 (Compound 33)	LC-MS: 321 [M+H] $^{+}$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.99 (s, 1H), 10.86-10.83 (d, 2H), 8.67-8.65 (d, 1H), 7.58-7.55 (dd, 1H), 7.49-7.44 (m, 2H), 7.36 (s, 1H), 7.28-7.27 (m, 1H), 7.05-7.03 (dd, 1H), 6.95-6.93 (d, 1H), 6.35-6.34 (bs, 1H), 5.25-5.22 (m, 1H), 1.51-1.49 (d, 3H).

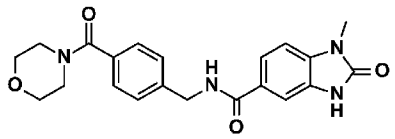
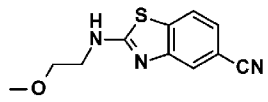
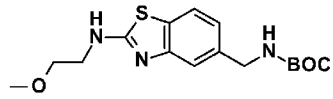
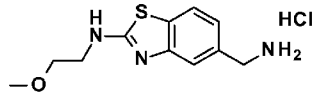
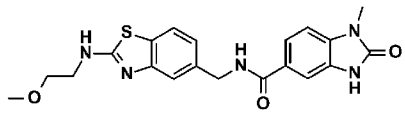
[0292]

[Table 7]

Ex	Ref.	Structure	LC-MS, NMR
34	E11-S3	 (Compound 34)	LC-MS: 366 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.90-10.84 (d, 2H), 8.73-8.71 (d, 1H), 7.57-7.55 (d, 1H), 7.50-7.48 (m, 3H), 7.33-7.30 (d, 2H), 6.97-6.95 (d, 1H), 5.19-5.15 (m, 1H), 1.47-1.46 (d, 3H).
35	E11-S3	 (Compound 35)	LC-MS: 338 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 10.90-10.84 (d, 2H), 8.65-8.63 (d, 1H), 7.56-7.54 (d, 1H), 7.47 (s, 1H), 7.34-7.28 (m, 4H), 6.96-6.94 (d, 1H), 5.13-5.11 (m, 1H), 1.45-1.43 (d, 3H), 1.23 (s, 9H).
36	E6-S4	 (Compound 36)	LC-MS: 353 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.69-7.67 (dd, 1H), 7.60 (d, 1H), 7.46-7.39 (m, 4H), 7.19-7.17 (d, 1H), 4.62 (s, 2H), 3.42 (s, 3H), 3.09 (s, 3H), 3.00 (s, 3H).

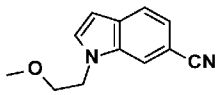
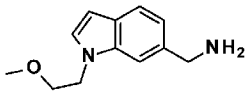
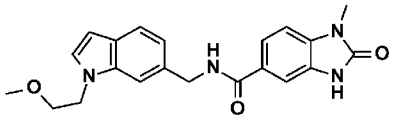
[0293]

[Table 8]

Ex	Ref.	Structure	LC-MS, NMR
37	E6-S4	 (Compound 37)	LC-MS: 393 $[M-H]^-$. ^{1}H-NMR (400 MHz, CD_3OD) δ 9.15 (bs, 1H), 7.94-7.92 (d, 1H), 7.59 (s, 1H), 7.47 (d, 2H), 7.42-7.41 (m, 3H), 4.65 (s, 1H), 3.63 (bs, 4H), 3.51-3.45 (m, 4H), 3.08 (s, 3H).
38	E4-S4		LC-MS: 234 $[M+H]^+$.
	E4-S5		LC-MS: 338 $[M+H]^+$.
	E4-S6		LC-MS: 238 $[M+H]^+$.
	E4-S7	 (Compound 38)	LC-MS: 412 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.70-7.68 (d, 2H), 7.61 (s, 1H), 7.50 (s, 1H), 7.32-7.30 (d, 1H), 7.19-7.17 (d, 1H), 4.66 (s, 2H), 3.68-3.64 (m, 4H), 350-3.31 (m, 6H).

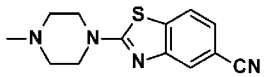
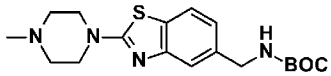
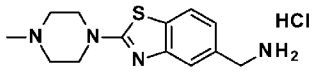
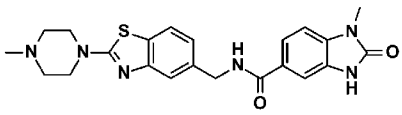
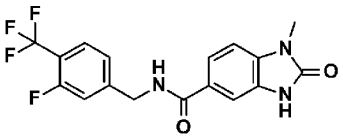
[0294]

[Table 9]

Ex	Ref.	Structure	LC-MS, NMR
39	E5-S1		LC-MS: 201 $[M+H]^+$.
	E5-S2		LC-MS: 188 $[M-NH_2]^+$.
	E5-S3  (Compound 39)		LC-MS: 379 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.07 (s, 1H), 8.92-8.89 (t, 1H), 7.66-7.64 (d, 1H), 7.54 (s, 1H), 7.48-7.46 (d, 1H), 7.41 (s, 1H), 7.31-7.30 (d, 1H), 7.16-7.14 (d, 1H), 7.02 (d, 1H), 6.37 (d, 1H), 4.57-4.55 (d, 2H), 4.29-4.27 (t, 2H), 3.65-3.63 (t, 2H), 3.30 (s, 3H), 3.20 (s, 3H).

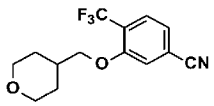
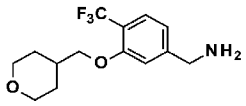
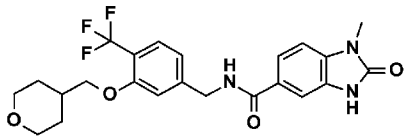
[0295]

[Table 10]

Ex	Ref.	Structure	LC-MS, NMR
40	E4-S4		LC-MS: 259 $[M+H]^+$.
	E4-S5		LC-MS: 363 $[M+H]^+$.
	E4-S6		LC-MS: 263 $[M+H]^+$.
	E4-S7	 (Compound 40)	LC-MS: 437 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.67-7.65 (d, 2H), 7.59 (d, 1H), 7.54 (s, 1H), 7.20-7.12 (m, 2H), 4.63 (s, 2H), 4.30 (bs, 2H), 3.65 (m, 6H), 3.40 (s, 3H), 2.96 (s, 3H).
41	E7-S4	 (Compound 41)	LC-MS: 368 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.10 (bs, 1H), 9.08 (t, 1H), 7.78-7.72 (t, 1H), 7.66-7.62 (d, 1H), 7.53 (s, 1H), 7.43-7.38 (d, 1H), 7.38-7.32 (d, 1H), 7.18 (d, 1H), 4.55-4.53 (d, 2H), 3.31 (s, 3H).

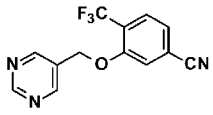
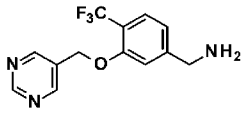
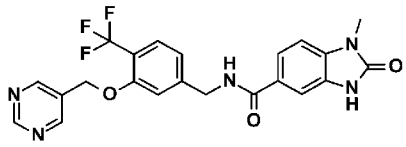
[0296]

[Table 11]

Ex	Ref.	Structure	LC-MS, NMR
42	E8-S1		^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.84-7.81 (d, 2H), 7.58-7.56 (dd, 1H), 4.07-4.05 (d, 2H), 3.89-3.86 (dd, 2H), 3.36-3.32 (m, 2H), 2.05-1.95 (m, 1H), 1.65-1.62 (d, 2H), 1.37-1.36 (m, 2H).
	E8-S2		LC-MS: 290 $[M+H]^+$.
	E8-S3	 (Compound 42)	LC-MS: 464 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.05 (bs, 1H), 9.02-8.97 (bs, 1H), 7.63 (d, 1H), 7.56-7.53 (m, 2H), 7.19-7.14 (t, 2H), 7.00-6.98 (d, 1H), 4.51-4.49 (d, 2H), 3.95-3.93 (d, 2H), 3.88-3.86 (d, 2H), 3.32-3.31 (d, 5H), 2.00 (bs, 1H), 1.65-1.62 (d, 2H), 1.37 (m, 2H).

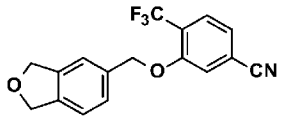
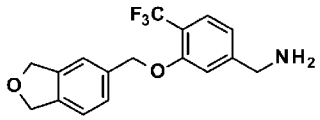
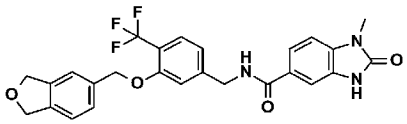
[0297]

[Table 12]

Ex	Ref.	Structure	LC-MS, NMR
43	E8-S1		LC-MS: 280 $[M+H]^+$.
	E8-S2		LC-MS: 284 $[M+H]^+$.
	E8-S3 (Compound 43)		LC-MS: 458 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.10 (s, 1H), 9.18 (s, 1H), 9.06-9.02 (m, 1H), 8.88 (s, 2H), 7.70-7.60 (m, 2H), 7.54 (s, 1H), 7.40-7.36 (s, 1H), 7.20-7.15 (d, 1H), 7.10-7.05 (d, 1H), 5.33 (s, 2H), 4.56-4.51 (d, 2H), 3.32 (s, 3H).

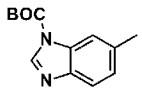
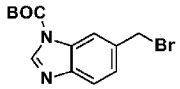
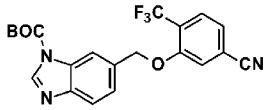
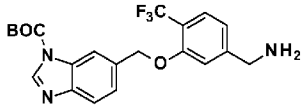
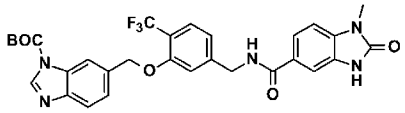
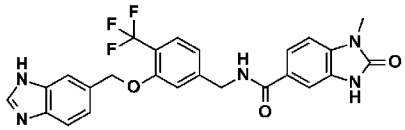
[0298]

[Table 13]

Ex	Ref.	Structure	LC-MS, NMR
44	E10-S3		LC-MS: 318 $[M-H]^-$.
	E10-S4		LC-MS: 324 $[M+H]^+$.
	E10-S5  (Compound 44)		LC-MS: 498 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.64-7.62 (dd, 1H), 7.56 (bs, 1H), 7.54-7.52 (dd, 1H), 7.29-7.27 (m, 2H), 7.18-7.14 (t, 3H), 7.02-7.00 (d, 1H), 5.21 (s, 2H), 4.97 (s, 2H), 4.94 (s, 2H), 4.56 (s, 2H), 3.42 (s, 3H).

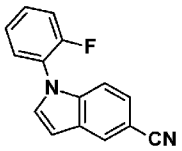
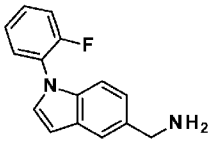
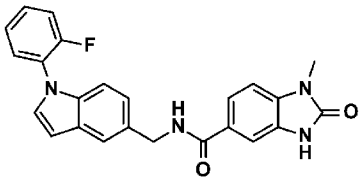
[0299]

[Table 14]

Ex	Ref.	Structure	LC-MS, NMR
45	E10-S1		LC-MS: 233 $[M+H]^+$.
	E10-S2		LC-MS: 311 $[M+H]^+$.
	E10-S3		LC-MS: 416 $[M-H]^-$.
	E10-S4		LC-MS: 422 $[M+H]^+$.
	E10-S5		LC-MS: 594 $[M-H]^-$.
	E10-S6	 (Compound 45)	LC-MS: 496 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 7.97-7.96 (bs, 1H), 7.82-7.80 (m, 1H), 7.72-7.70 (m, 1H), 7.66-7.60 (m, 2H), 7.57-7.56 (d, 1H), 7.27 (bs, 1H), 7.20-7.18 (d, 1H), 7.11-7.09 (d, 1H), 5.46 (s, 2H), 4.62 (s, 2H), 3.45 (s, 3H).

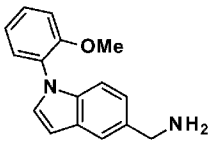
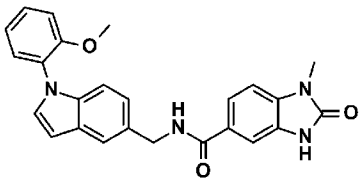
[0300]

[Table 15]

Ex	Ref.	Structure	LC-MS, NMR
46	E12-S1		^{1}H-NMR (400 MHz, DMSO-D_6) δ 8.24 (s, 1H), 7.81-7.80 (d, 1H), 7.69-7.68 (t, 1H), 7.59-7.58 (m, 3H), 7.56-7.54 (t, 1H), 7.38-7.37 (d, 1H), 6.89-6.88 (dd, 1H).
	E12-S2		LC-MS: 224 $[M-NH_2]^+$.
	E12-S3	 (Compound 46)	LC-MS: 415 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.08 (bs, 1H), 8.96-8.93 (t, 1H), 7.70-7.66 (dd, 1H), 7.59 (s, 2H), 7.55-7.50 (m, 4H), 7.40 (m, 1H), 7.18-7.16 (t, 3H), 6.70-6.68 (d, 1H), 4.58-4.55 (d, 2H), 3.31 (s, 3H).

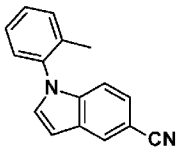
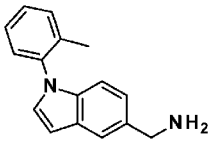
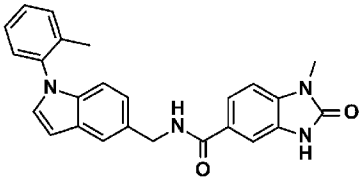
[0301]

[Table 16]

Ex	Ref.	Structure	LC-MS, NMR
47	E12-S2		LC-MS: 236 $[M-NH_2]^+$.
	E12-S3	 (Compound 47)	LC-MS: 427 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.63-7.60 (m, 1H), 7.55 (m, 2H), 7.37-7.35 (m, 1H), 7.29-7.27 (m, 1H), 7.21-7.20 (d, 1H), 7.17-7.15 (d, 1H), 7.13-7.08 (m, 1H), 7.07-7.05 (d, 1H), 7.02-7.00 (m, 2H), 6.53-6.52 (d, 1H), 4.63 (s, 2H), 3.70 (s, 3H) 3.34 (s, 3H).

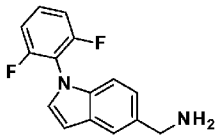
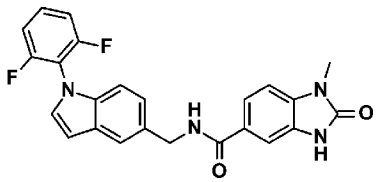
[0302]

[Table 17]

Ex	Ref.	Structure	LC-MS, NMR
48	E12-S1		^{1}H-NMR (400 MHz, DMSO-D_6) δ 8.21 (s, 1H), 7.71-7.70 (d, 1H), 7.50-7.46 (m, 3H), 7.45-7.36 (m, 2H), 7.10-7.08 (dd, 1H), 6.84-6.83 (d, 1H), 1.97 (s, 3H).
	E12-S2		LC-MS: 220 $[M-NH_2]^+$.
	E12-S3	 (Compound 48)	LC-MS: 411 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.66-7.62 (m, 1H), 7.52-7.57 (d, 2H), 7.40-7.30 (m, 3H), 7.26-7.24 (d, 1H), 7.21-7.20 (d, 1H), 7.16-7.12 (m, 2H), 6.90-6.88 (d, 1H), 6.60-6.59 (d, 1H), 4.65 (s, 2H), 3.39 (s, 3H), 1.98 (s, 3H).

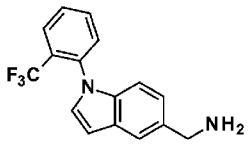
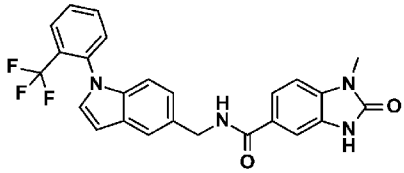
[0303]

[Table 18]

Ex	Ref.	Structure	LC-MS, NMR
49	E12-S2		LC-MS: 242 $[M-NH_2]^+$.
	E12-S3	 (Compound 49)	LC-MS: 433 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.03 (s, 1H), 8.90 (t, 1H), 7.62-7.61 (m, 1H), 7.56 (m, 2H), 7.51-7.48 (m, 2H), 7.40-7.36 (t, 2H), 7.14-7.10 (m, 2H), 7.05-6.95 (d, 1H), 6.69-6.68 (d, 1H), 4.52-4.51 (d, 2H), 3.27 (s, 3H).

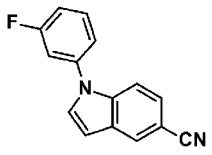
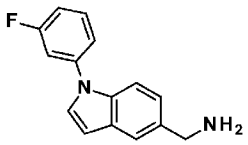
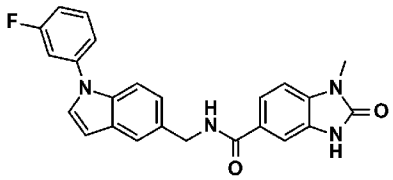
[0304]

[Table 19]

Ex	Ref.	Structure	LC-MS, NMR
50	E12-S2		LC-MS: 274 $[M-NH_2]^+$.
	E12-S3	 (Compound 50)	LC-MS: 465 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.05 (s, 1H), 8.95 (t, 1H), 8.01-7.99 (d, 1H), 7.90-7.85 (t, 1H), 7.80-7.75 (m, 1H), 7.68-7.65 (dd, 1H), 7.57-7.52 (m, 3H), 7.42-7.41 (m, 1H), 7.16-7.10 (t, 2H), 6.89-6.86 (d, 1H), 6.65-6.64 (d, 1H), 4.54 (s, 2H), 3.30 (s, 3H).

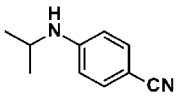
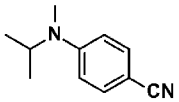
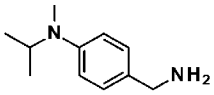
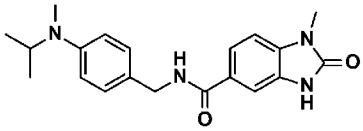
[0305]

[Table 20]

Ex	Ref.	Structure	LC-MS, NMR
51	E12-S1		^{1}H-NMR (400 MHz, DMSO-D_6) δ 8.23 (s, 1H), 7.72-7.65 (m, 1H), 7.64-7.62 (m, 2H), 7.52-7.49 (m, 2H), 7.47-7.38 (d, 1H), 7.15-7.13 (d, 1H), 6.87-6.86 (d, 1H).
	E12-S2		LC-MS: 224 $[M-NH_2]^+$.
	E12-S3	 (Compound 51)	LC-MS: 415 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.04 (s, 1H), 8.93 (t, 1H), 7.66-7.65 (m, 2H), 7.62-7.55 (m, 2H), 7.52 (bs, 1H), 7.47-7.43 (t, 2H), 7.20-7.18 (m, 2H), 7.13-7.11 (d, 2H), 6.67-6.66 (d, 1H), 4.53-4.52 (d, 2H), 3.27 (s, 3H).

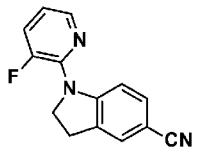
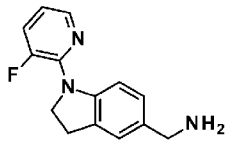
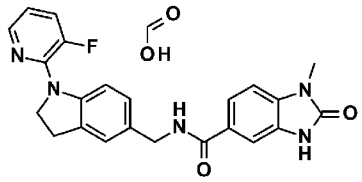
[0306]

[Table 21]

Ex	Ref.	Structure	LC-MS, NMR
52	E3-S1		LC-MS: 161 $[M+H]^+$.
	E3-S2		LC-MS: 175 $[M+H]^+$.
	E3-S3		LC-MS: 179 $[M+H]^+$.
	E3-S4 (Compound 52)		LC-MS: 353 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.06 (s, 1H), 8.80-8.77 (t, 1H), 7.64-7.61 (dd, 1H), 7.51 (d, 1H), 7.14-7.11 (m, 3H), 6.73-6.71 (d, 2H), 4.33-4.31 (d, 2H), 4.08-4.01 (m, 1H), 3.30 (s, 3H), 2.62 (s, 3H), 1.08-1.06 (d, 6H).

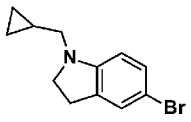
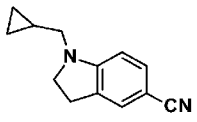
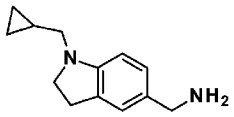
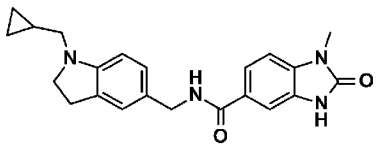
[0307]

[Table 22]

Ex	Ref.	Structure	LC-MS, NMR
53	E13-S2		LC-MS: 240 $[M+H]^+$.
	E13-S3		LC-MS: 227 $[M-NH_2]^+$.
	E13-S4	 (Compound 53)	LC-MS: 418 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.05 (s, 1H), 8.85-8.82 (t, 1H), 8.49 (s, 1H), 8.10-8.08 (d, 1H), 7.67-7.60 (m, 2H), 7.50 (s, 1H), 7.18-7.10 (m, 3H), 7.02-6.98 (m, 2H), 4.36-4.34 (d, 2H), 4.12-4.07 (m, 2H), 3.27 (s, 3H), 3.09-3.05 (t, 2H).

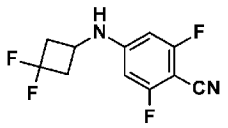
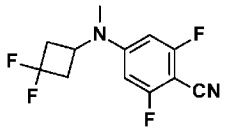
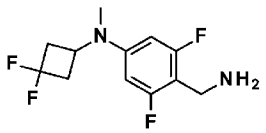
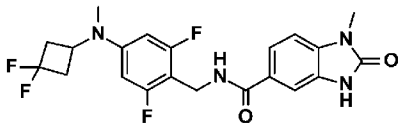
[0308]

[Table 23]

Ex	Ref.	Structure	LC-MS, NMR
54	E14-S2		LC-MS: 252 $[M+H]^+$.
	E14-S3		LC-MS: 199 $[M+H]^+$.
	E14-S4		LC-MS: 186 $[M-NH_2]^+$.
	E14-S5  (Compound 54)		LC-MS: 377 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.03 (s, 1H), 8.74-8.71 (t, 1H), 7.60-7.58 (d, 1H), 7.48 (s, 1H), 7.11-7.09 (d, 1H), 7.97 (s, 1H), 6.91-6.89 (d, 1H), 6.41-6.39 (d, 1H), 4.28-4.26 (d, 2H), 3.34 (m, 1H), 3.32 (m, 1H), 3.36-3.34 (m, 3H), 2.84-2.79 (m, 4H), 0.92-0.80 (m, 1H), 0.47-0.43 (m 2H), 0.17-0.11 (m, 2H).

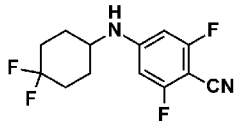
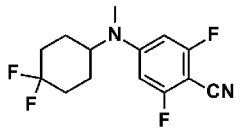
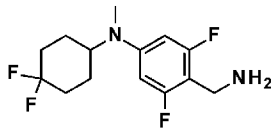
[0309]

[Table 24]

Ex	Ref.	Structure	LC-MS, NMR
55	E21-S1		LC-MS: 243 $[M-H]^-$.
	E21-S2		^{1}H-NMR (400 MHz, DMSO-D_6) δ 6.78-6.75 (d, 2H), 4.34-4.29 (m, 1H), 3.08-2.98 (m, 2H), 2.96 (s, 3H), 2.89-2.76 (m, 2H).
	E21-S3		LC-MS: 246 $[M-NH_2]^+$.
	E21-S4	 (Compound 55)	LC-MS: 437 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.04 (s, 1H), 8.62-8.60 (t, 1H), 7.49-7.48 (dd, 2H), 7.15-7.11 (d, 1H), 6.52-6.45 (d, 2H), 4.38-4.37 (d, 2H), 4.08-4.04 (m, 1H), 3.30 (s, 3H), 3.08-2.94 (m, 2H), 2.83 (s, 3H), 2.74-2.65 (m, 2H).

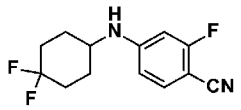
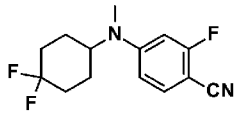
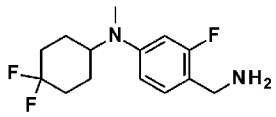
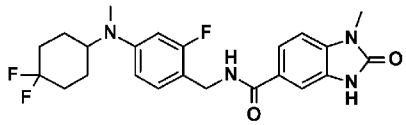
[0310]

[Table 25]

Ex	Ref.	Structure	LC-MS, NMR
56	E21-S1		LC-MS: 271 $[M-H]^-$.
	E21-S2		LC-MS: 287 $[M+H]^+$.
	E21-S3		LC-MS: 274 $[M-NH_2]^+$.
	E21-S4	 (Compound 56)	LC-MS: 465 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.05 (s, 1H), 8.59-8.56 (t, 1H), 7.61-7.59 (dd, 1H), 7.49-7.48 (d, 1H), 7.13-7.11 (d, 1H), 6.52-6.48 (d, 2H), 4.37-4.36 (d, 2H), 3.93-3.87 (m, 1H), 3.30 (s, 3H), 2.70 (s, 3H), 2.08-2.04 (m, 4H), 1.70-1.67 (m, 4H).

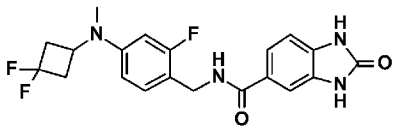
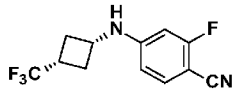
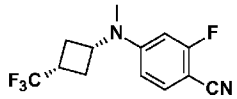
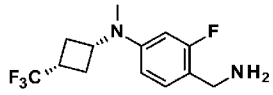
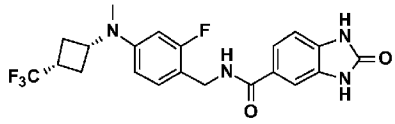
[0311]

[Table 26]

Ex	Ref.	Structure	LC-MS, NMR
57	E22-S1		LC-MS: 253 $[M-H]^-$.
	E22-S2		LC-MS: 269 $[M+H]^+$.
	E22-S3		LC-MS: 256 $[M-NH_2]^+$.
	E22-S4	 (Compound 57)	LC-MS: 447 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.07 (s, 1H), 8.77-8.74 (t, 1H), 7.65-7.62 (dd, 1H), 7.52-7.51 (d, 1H), 7.19-7.13 (m, 2H), 6.64-6.60 (m, 2H), 4.37-4.36 (d, 2H), 3.89-3.86 (m, 1H), 3.31 (s, 3H), 2.67 (s, 3H), 2.11-2.03 (m, 4H), 1.72-1.66 (m, 4H).

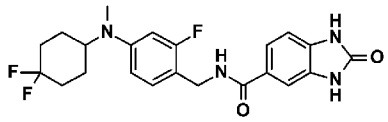
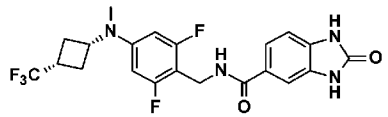
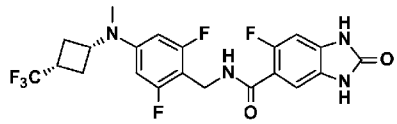
[0312]

[Table 27]

Ex	Ref.	Structure	LC-MS, NMR
58	E22-S4	 (Compound 58)	LC-MS: 405 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.60-7.56 (m, 2H), 7.29-7.25 (t, 1H), 7.11-7.08 (d, 1H), 6.65-6.58 (m, 2H), 4.53 (s, 2H), 3.95-3.85 (m, 1H), 3.02-2.92 (m, 2H), 2.87 (s, 3H), 2.68 -2.52 (m, 2H).
59	E22-S1		LC-MS: 257 $[M-H]^-$.
	E22-S2		LC-MS: 273 $[M+H]^+$.
	E22-S3		LC-MS: 260 $[M-NH_2]^+$.
	E22-S4	 (Compound 59)	LC-MS: 437 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.60-7.56 (m, 2H), 7.26-7.22 (t, 1H), 7.10-7.08 (d, 1H), 6.63-6.55 (m, 2H), 4.53 (s, 2H), 4.14-4.06 (m, 1H), 2.85 (s, 3H), 2.84-2.78 (m, 1H), 2.52 -2.49 (m, 2H), 2.24-2.21 (m, 2H).

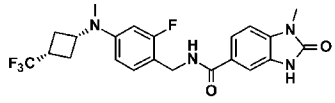
[0313]

[Table 28]

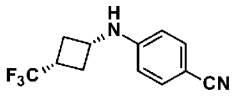
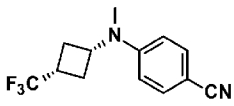
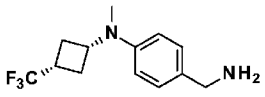
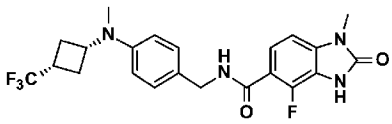
Ex	Ref.	Structure	LC-MS, NMR
60	E22-S4	 (Compound 60)	LC-MS: 433 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.60-7.56 (m, 2H), 7.23-7.21 (t, 1H), 7.10-7.08 (d, 1H), 6.65-6.56 (m, 2H), 4.52 (s, 2H), 3.86-3.79 (m, 1H), 2.77 (s, 3H), 2.13-1.79 (m, 8H).
61	E21-S4	 (Compound 61)	LC-MS: 455 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.56-7.52 (m, 2H), 7.08-7.06 (d, 1H), 6.43-6.40 (d, 2H), 4.54 (s, 2H), 4.20-4.10 (m, 1H), 2.88 (s, 3H), 2.86-2.80 (m, 1H), 2.56-2.51 (m, 2H), 2.29-2.25 (m, 2H).
62	E21-S4	 (Compound 62)	LC-MS: 473 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.38-7.37 (d, 1H), 6.90-6.86 (d, 1H), 6.43-6.40 (d, 2H), 4.57 (s, 2H), 4.20-4.10 (m, 1H), 2.88 (s, 3H), 2.86-2.80 (m, 1H), 2.56-2.51 (m, 2H), 2.30-2.26 (m, 2H).

[0314]

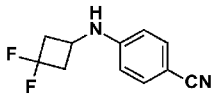
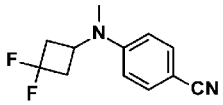
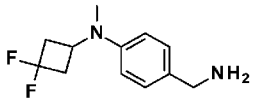
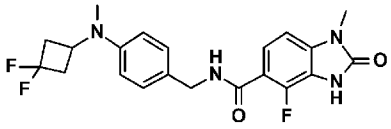
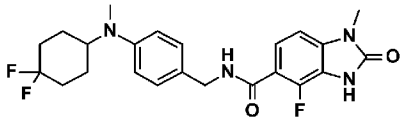
[Table 29]

Ex	Ref.	Structure	LC-MS, NMR
63	E22-S4	 (Compound 63)	LC-MS: 451 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.67-7.66 (dd, 1H), 7.59-7.58 (d, 1H), 7.27-7.22 (t, 1H), 7.18-7.16 (d, 1H), 6.63-6.55 (m, 2H), 4.53 (s, 2H), 4.09-4.05 (m, 1H), 3.43 (s, 3H), 2.85 (s, 3H), 2.83-2.81 (m, 1H), 2.54-2.47 (m, 2H), 2.24-2.21 (m, 2H).

[0315] [Table 30]

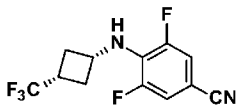
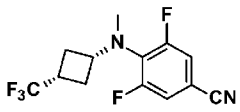
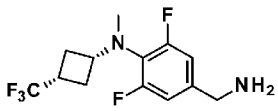
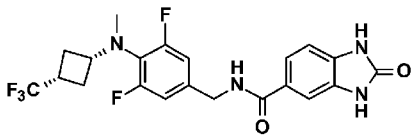
Ex	Ref.	Structure	LC-MS, NMR
64	E3-S1		LC-MS: 241 $[M+H]^+$.
	E3-S2		LC-MS: 255 $[M+H]^+$.
	E3-S3		LC-MS: 259 $[M+H]^+$.
	E3-S4	 (Compound 64)	LC-MS: 451 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.52-7.48 (m, 1H), 7.27-7.25 (d, 2H), 7.04-7.02 (d, 1H), 6.88-6.85 (d, 2H), 4.50 (s, 2H), 4.09-3.97 (m, 1H), 3.44 (s, 3H), 2.90-2.75 (m, 4H), 2.50-2.47 (m, 2H), 2.21-2.18 (m, 2H).

[0316] [Table 31]

Ex	Ref.	Structure	LC-MS, NMR
65	E3-S1		LC-MS: 209 $[M+H]^+$.
	E3-S2		LC-MS: 223 $[M+H]^+$.
	E3-S3		LC-MS: 227 $[M+H]^+$.
	E3-S4	 (Compound 65)	LC-MS: 419 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.52-7.48 (m, 1H), 7.30-7.27 (d, 2H), 7.04-7.02 (d, 1H), 6.89-6.87 (d, 2H), 4.51 (s, 2H), 3.80-3.78 (m, 1H), 3.43 (s, 3H), 2.91-2.89 (m, 2H), 2.88 (s, 3H), 2.61-2.50 (m, 2H).
66	E3-S4	 (Compound 66)	LC-MS: 447 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.52-7.48 (m, 1H), 7.26-7.24 (d, 2H), 7.04-7.02 (d, 1H), 6.89-6.87 (d, 2H), 4.49 (s, 2H), 3.85-3.75 (m, 1H), 3.43 (s, 3H), 2.77 (s, 3H), 2.13-1.79 (m, 8H).

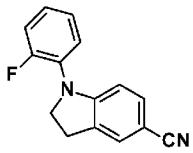
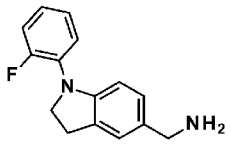
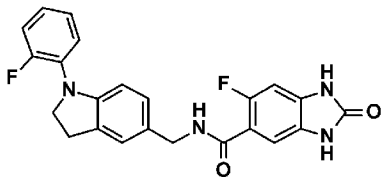
[0317]

[Table 32]

Ex	Ref.	Structure	LC-MS, NMR
67	E3-S1		LC-MS: 277 $[M+H]^+$.
	E3-S2		LC-MS: 291 $[M+H]^+$.
	E3-S3		LC-MS: 295 $[M+H]^+$.
	E3-S4 (Compound 67)		LC-MS: 455 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.64-7.59 (m, 2H), 7.13-7.11 (d, 1H), 6.96-6.94 (d, 2H), 4.52 (s, 2H), 3.80-3.76 (m, 1H), 2.74-2.67 (m, 4H), 2.30-2.28 (m, 2H), 2.04-2.01 (m, 2H).

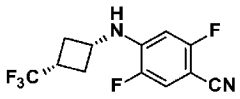
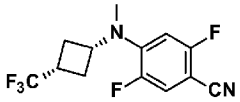
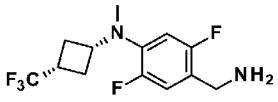
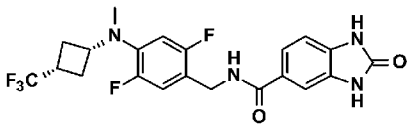
[0318]

[Table 33]

Ex	Ref.	Structure	LC-MS, NMR
68	E13-S2		LC-MS: 239 $[M+H]^+$.
	E13-S3		LC-MS: 226 $[M-NH_2]^+$.
	E13-S4	 (Compound 68)	LC-MS: 421 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.44-7.39 (m, 2H), 7.22-7.10 (m, 4H), 7.05-7.04 (d, 1H), 6.92-6.89 (d, 1H), 6.51-6.48 (dd, 1H), 4.50 (s, 2H), 3.95-3.90 (t, 2H), 3.17-3.15 (t, 2H).

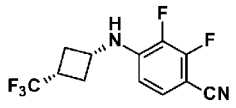
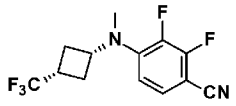
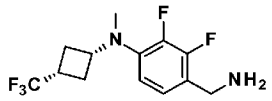
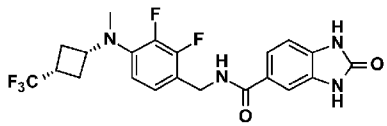
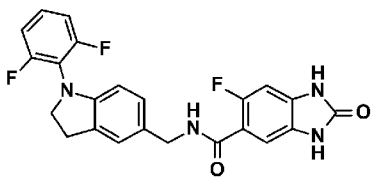
[0319]

[Table 34]

Ex	Ref.	Structure	LC-MS, NMR
69	E3-S1		LC-MS: 277.1 $[M+H]^+$.
	E3-S2		LC-MS: 291.0 $[M+H]^+$.
	E3-S3		LC-MS: 295.1 $[M+H]^+$.
	E3-S4 (Compound 69)		LC-MS: 455 $[M+H]^+$; ^{1}H-NMR (400 MHz, CD_3OD) δ 7.62-7.57 (m, 2H), 7.12-7.06 (m, 2H), 6.74-6.69 (dd, 1H), 4.53 (s, 2H), 3.85-3.75 (m, 1H), 2.85-2.75 (m, 1H), 2.72 (s, 3H), 2.46-2.43 (m, 2H), 2.12-2.08(m, 2H).

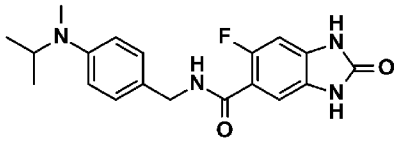
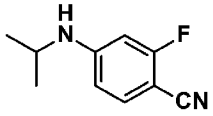
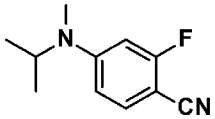
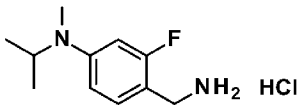
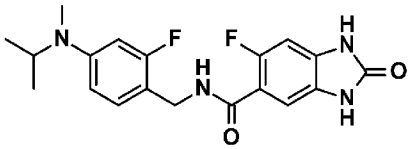
[0320]

[Table 35]

Ex	Ref.	Structure	LC-MS, NMR
70	E3-S1		LC-MS: 277 $[M+H]^+$.
	E3-S2		LC-MS: 291 $[M+H]^+$.
	E3-S3		LC-MS: 295 $[M+H]^+$.
	E3-S4	 (Compound 70)	LC-MS: 455 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.62-7.57 (m, 2H), 7.11-7.09 (m, 2H), 6.74-6.70 (m, 1H), 4.60 (s, 2H), 3.81-3.79 (m, 1H), 2.81-2.79 (m, 1H), 2.73 (s, 3H), 2.45-2.42 (m, 2H), 2.10-2.07(m, 2H).
71	E13-S4	 (Compound 71)	LC-MS: 439 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.43-7.41 (d, 1H), 7.29-7.25 (m, 1H), 7.18 (bs, 1H), 7.09-7.00 (d, 3H), 6.91-6.88 (d, 1H), 6.18-6.14(m, 1H), 4.51 (s, 2H), 3.96-3.91 (m, 2H), 3.22-3.18 (m, 2H).

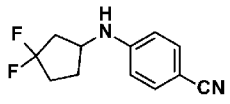
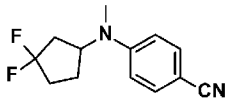
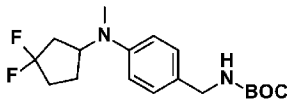
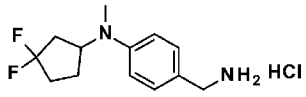
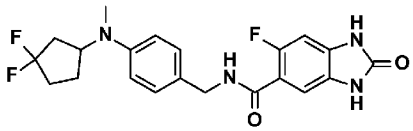
[0321]

[Table 36]

Ex	Ref.	Structure	LC-MS, NMR
72	E3-S4	 (Compound 72)	LC-MS: 357 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.65-7.59 (m, 4H), 7.44-7.43 (d, 1H), 6.94-6.92 (d, 1H), 4.67 (s, 2H), 4.00-3.93 (m, 1H), 3.34 (s, 3H), 1.41-1.30 (m, 6H).
73	E3-S1		LC-MS: 179 $[M+H]^+$.
	E3-S2		LC-MS: 193 $[M+H]^+$.
	E3-S3		LC-MS: 180 $[M-NH_2]^-$.
	E3-S4	 (Compound 73)	LC-MS: 375 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.42-.7.40 (d, 1H), 7.24-7.21 (t, 1H), 6.91-6.90 (d, 1H), 6.61-6.50 (dd, 2H), 4.52 (s, 2H), 4.12-4.10 (m, 1H), 2.73 (s, 3H), 1.18-1.17 (d, 6H).

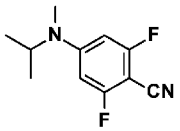
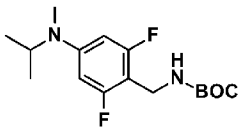
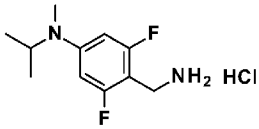
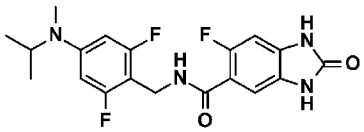
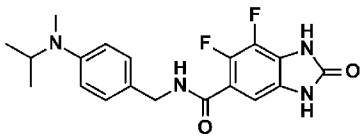
[0322]

[Table 37]

Ex	Ref.	Structure	LC-MS, NMR
76	E3-S1		LC-MS: 221 $[M-H]^-$.
	E3-S2		LC-MS: 235 $[M-H]^-$.
	E4-S2		LC-MS: 339 $[M-H]^-$.
	E4-S3		LC-MS: 239 $[M-H]^-$.
	E4-S4	 (Compound 76)	LC-MS: 419 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.42-7.41 (d, 1H), 7.26-7.24 (d, 2H), 6.92-6.88 (m, 3H), 4.50 (s, 2H), 4.40-4.36 (m, 1H), 2.80 (s, 3H), 2.40-1.90 (m, 6H).

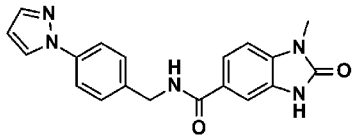
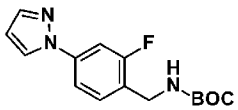
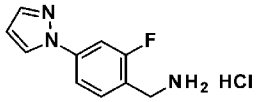
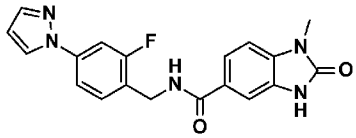
[0323]

[Table 38]

Ex	Ref.	Structure	LC-MS, NMR
77	E3-S1		LC-MS: 211 $[M+H]^+$.
	E4-S2		LC-MS: 315 $[M+H]^+$.
	E4-S3		LC-MS: 198 $[M-NH_2]^+$.
	E4-S4	 (Compound 77)	LC-MS: 393 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.39-7.37 (d, 1H), 6.89-6.86 (d, 1H), 6.40-6.35 (dd, 2H), 4.55 (s, 2H), 4.10-4.05 (m, 1H), 2.75 (s, 3H), 1.20-1.18 (d, 6H).
78	E4-S4	 (Compound 78)	LC-MS: 375 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.66-7.60 (m, 4H), 7.21-7.19 (m, 1H), 4.67 (s, 2H), 3.98-3.95 (m, 1H), 3.30 (s, 3H), 1.44-1.26 (d, 6H).

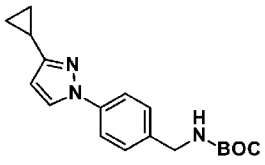
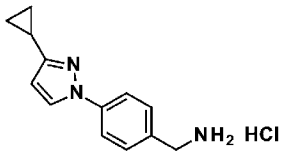
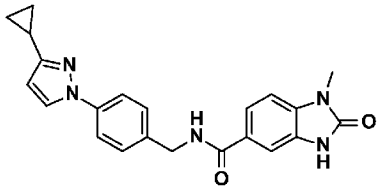
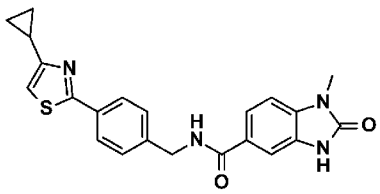
[0324]

[Table 39]

Ex	Ref.	Structure	LC-MS, NMR
79	E4-S4	 (Compound 79)	LC-MS: 348 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.10 (s, 1H), 9.00-8.98 (t, 1H), 8.46-8.45 (d, 1H), 7.80-7.78 (m, 2H), 7.73-7.72 (d, 1H), 7.69-7.66 (m, 1H), 7.55 (s, 1H), 7.44-7.42 (d, 2H), 7.18-7.16 (d, 1H), 6.54-6.52 (m, 1H), 4.51-4.49 (d, 2H), 3.31 (s, 3H).
80	E4-S2		LC-MS: 292 $[M+H]^+$.
	E4-S3		LC-MS: 192 $[M+H]^+$.
	E4-S4	 (Compound 80)	LC-MS: 366 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.10 (s, 1H), 8.97-8.94 (t, 1H), 8.53-8.52 (d, 1H), 7.76-7.66 (m, 4H), 7.55-7.54 (d, 1H), 7.49-7.45 (t, 1H), 7.18-7.16 (d, 1H), 6.57-6.55 (m, 1H), 4.52-4.51 (d, 2H), 3.31 (s, 3H).

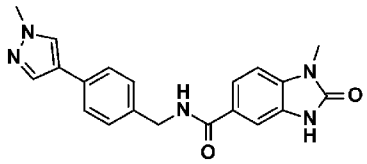
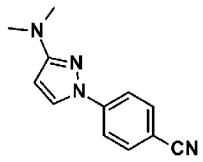
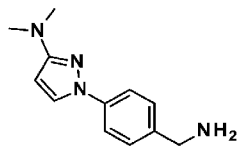
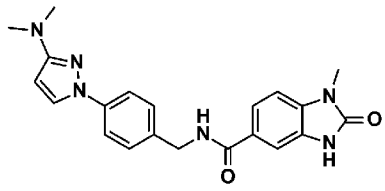
[0325]

[Table 40]

Ex	Ref.	Structure	LC-MS, NMR
81	E4-S2		LC-MS: 314 $[M+H]^+$.
	E4-S3		LC-MS: 214 $[M+H]^+$.
	E4-S4 (Compound 81)		LC-MS: 388 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.04-8.03 (d, 1H), 7.71-7.62 (m, 4H), 7.49-7.47 (m, 2H), 7.20-7.18 (d, 1H), 6.18-6.17 (d, 1H), 4.62 (s, 2H), 3.44 (s, 3H), 2.04-2.0 (m, 1H), 1.00-0.96 (m, 2H), 0.80-0.76 (m, 2H).
82	E4-S4 (Compound 82)		LC-MS: 405 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.90-7.88 (d, 2H), 7.72-7.70 (d, 1H), 7.63 (s, 1H), 7.47-7.45 (d, 2H), 7.20-7.18 (d, 1H), 7.05 (s, 1H), 4.64 (s, 2H), 3.44 (s, 3H), 2.13-2.11 (m, 1H), 0.98-0.93 (m, 4H).

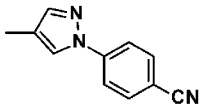
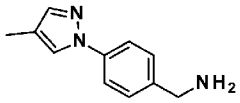
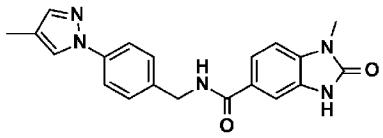
[0326]

[Table 41]

Ex	Ref.	Structure	LC-MS, NMR
83	E4-S4	 (Compound 83)	LC-MS: 362 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.07 (s, 1H), 8.93-8.90 (t, 1H), 8.09 (s, 1H), 7.82 (s, 1H), 7.67-7.65 (dd, 1H), 7.55-7.50 (m, 3H), 7.30-7.28 (d, 2H), 7.17-7.15 (d, 1H), 4.45-4.44 (d, 2H), 3.85 (s, 3H), 3.31 (s, 3H).
84	E85-S1		LC-MS: 213 $[M+H]^+$.
	E85-S2		LC-MS: 217 $[M+H]^+$.
	E4-S4	 (Compound 84)	LC-MS: 391 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.98-7.97 (d, 1H), 7.71-7.69 (dd, 1H), 7.65-7.61 (m, 3H), 7.44-7.42 (dd, 2H), 7.20-7.18 (d, 1H), 5.98-5.97 (d, 1H), 4.60 (s, 2H), 3.44 (s, 3H), 2.93 (s, 6H).

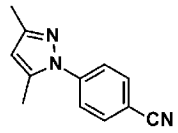
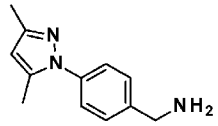
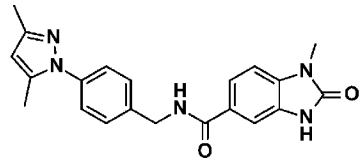
[0327]

[Table 42]

Ex	Ref.	Structure	LC-MS, NMR
85	E85-S1		LC-MS: 184 $[M+H]^+$.
	E85-S2		LC-MS: 188 $[M+H]^+$.
	E4-S4  (Compound 85)		LC-MS: 362 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.08 (s, 1H), 8.97-8.96 (t, 1H), 8.22 (s, 1H), 7.73-7.71 (m, 2H), 7.68-7.65 (m, 1H), 7.55-7.54 (m, 2H), 7.41-7.39 (d, 2H), 7.17-7.15 (d, 1H), 4.49-4.47 (d, 2H), 3.31 (s, 3H), 2.09 (s, 3H).

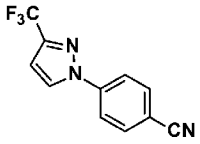
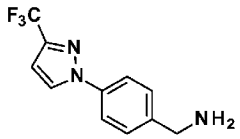
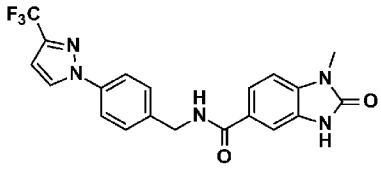
[0328]

[Table 43]

Ex	Ref.	Structure	LC-MS, NMR
86	E85-S1		LC-MS: 198 $[M+H]^+$.
	E85-S2		LC-MS: 202 $[M+H]^+$.
	E4-S4	 (Compound 86)	LC-MS: 376 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.73-7.70 (dd, 1H), 7.64-7.63 (d, 1H), 7.54-7.52 (m, 2H), 7.42-7.40 (m, 2H), 7.21-7.19 (d, 1H), 6.07 (s, 1H), 4.66 (s, 2H), 3.44 (s, 3H), 2.27-2.25 (m, 6H).

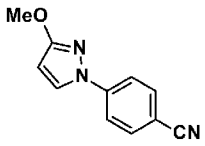
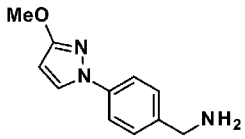
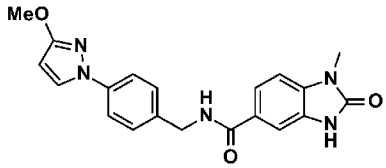
[0329]

[Table 44]

Ex	Ref.	Structure	LC-MS, NMR
87	E85-S1		^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.07-8.06 (m, 1H), 7.91-7.89 (m, 2H), 7.83-7.81 (m, 2H), 6.82-6.81 (d, 1H).
	E85-S2		LC-MS: 242 $[M+H]^+$.
	E4-S4	 (Compound 87)	LC-MS: 416 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.37-8.36 (m, 1H), 7.81-7.79 (d, 2H), 7.72-7.70 (dd, 1H), 7.63-7.62 (d, 1H), 7.60-7.54 (d, 2H), 7.21-7.19 (d, 1H), 6.83-6.82 (d, 1H), 4.66 (s, 2H), 3.44 (s, 3H).

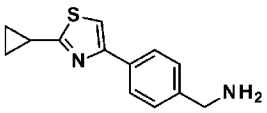
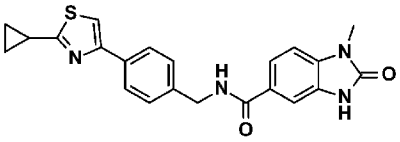
[0330]

[Table 45]

Ex	Ref.	Structure	LC-MS, NMR
88	E85-S1		LC-MS: 200 $[M+H]^+$.
	E85-S2		LC-MS: 204 $[M+H]^+$.
	E4-S4  (Compound 88)		LC-MS: 378 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.01-8.00 (d, 1H), 7.71-7.69 (dd, 1H), 7.66-7.62 (m, 3H), 7.46-7.44 (d, 2H), 7.20-7.18 (d, 1H), 5.95-5.94 (d, 1H), 4.61 (s, 2H), 3.94 (s, 3H), 3.44 (s, 3H).

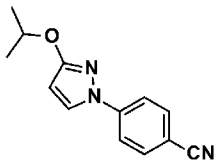
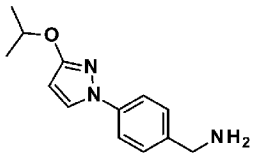
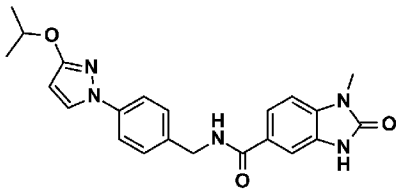
[0331]

[Table 46]

Ex	Ref.	Structure	LC-MS, NMR
89	E85-S2		LC-MS: 231 $[M+H]^+$.
	E4-S4	 (Compound 89)	LC-MS: 405 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.87-7.85 (d, 2H), 7.71-7.69 (dd, 1H), 7.63-7.62 (d, 1H), 7.51 (s, 1H), 7.43-7.41 (d, 2H), 7.20-7.18 (d, 1H), 4.62 (s, 2H), 3.44 (s, 3H), 2.43-2.39 (m, 1H), 1.22-1.17 (m, 2H), 1.09-1.07 (m, 2H).

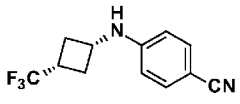
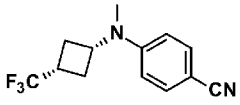
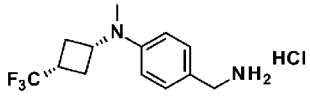
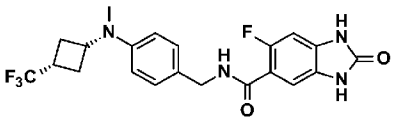
[0332]

[Table 47]

Ex	Ref.	Structure	LC-MS, NMR
90	E85-S1		LC-MS: 228 $[M+H]^+$.
	E85-S2		LC-MS: 232 $[M+H]^+$.
	E4-S4  (Compound 90)		LC-MS: 406 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-D_6) δ 11.11 (bs, 1H), 8.96-8.95 (t, 1H), 8.27-8.26 (d, 1H), 7.67-7.64 (m, 3H), 7.55 (s, 1H), 7.39-7.37 (d, 2H), 7.17-7.15 (d, 1H), 5.98-5.97 (d, 1H), 4.80-4.77 (m, 1H), 4.47-4.46 (d, 2H), 3.26 (s, 3H), 1.32-1.28 (d, 6H).

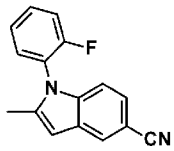
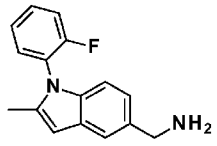
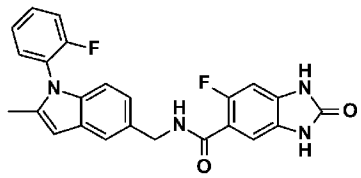
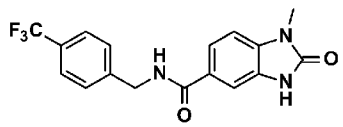
[0333]

[Table 48]

Ex	Ref.	Structure	LC-MS, NMR
91	E3-S1		LC-MS: 241 $[M+H]^+$
	E3-S2		LC-MS: 255 $[M+H]^+$
	E22-S3		LC-MS: 259 $[M+H]^+$
	E22-S4 (Compound 91)		LC-MS: 437 $[M+H]^+$ ^{1}H-NMR (400 MHz, CD_3OD) δ 7.66-7.60 (m, 4H), 7.44-7.43 (d, 1H), 6.94-6.92 (d, 1H), 4.66 (s, 2H), 4.38-4.34 (m, 1H), 3.25 (s, 3H), 2.98-2.95 (m, 1H), 2.50-2.40 (m, 4H).

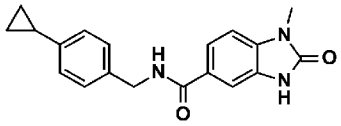
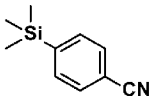
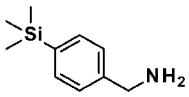
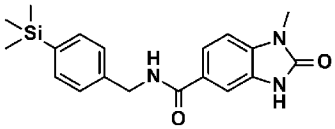
[0334]

[Table 49]

Ex	Ref.	Structure	LC-MS, NMR
92	E12-S1		LC-MS: 251 $[M+H]^+$
	E22-S3		LC-MS: 238 $[M-NH_2]^+$
	E22-S4	 (Compound 92)	LC-MS: 433 $[M+H]^+$ ^{1}H-NMR (400 MHz, CD_3OD) δ 7.58-7.56 (m, 1H), 7.55 (s, 1H), 7.44-7.41 (m, 4H), 7.12-7.09 (dd, 1H), 6.92-6.89 (m, 2H), 6.41 (s, 1H), 4.67 (s, 2H), 2.26 (s, 3H).
93	E4-S4	 (Compound 93)	LC-MS: 350 $[M+H]^+$ ^{1}H-NMR (400 MHz, CD_3OD) δ 7.72-7.70 (dd, 1H), 7.66-7.62 (m, 3H), 7.57-7.54 (m, 2H), 7.21-7.19 (d, 1H), 4.67 (d, 2H), 3.44 (s, 3H).

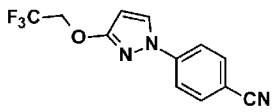
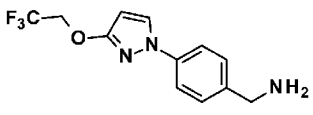
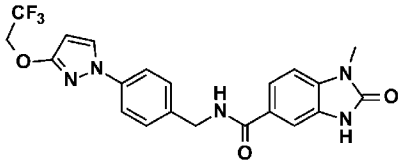
[0335]

[Table 50]

Ex	Ref.	Structure	LC-MS, NMR
94	E4-S4	 (Compound 94)	LC-MS: 322 $[M+H]^+$ ^{1}H-NMR (400 MHz, CD_3OD) δ 7.69-7.66 (dd, 1H), 7.60-7.59 (d, 1H), 7.25-7.23 (d, 2H), 7.19-7.17 (d, 1H), 7.07-7.04 (d, 2H), 4.54 (s, 2H), 3.44 (s, 3H), 1.93-1.89 (m, 1H), 0.97-0.92 (m, 2H), 0.68-0.64 (m, 2H).
95	P9-S3		^{1}H-NMR (400 MHz, DMSO-D_6) δ 7.81-7.79 (d, 2H), 7.73-7.71 (d, 2H), 0.27 (s, 9H).
	P9-S4		LC-MS: 180 $[M+H]^+$
	E4-S4	 (Compound 95)	LC-MS: 354 $[M+H]^+$ ^{1}H-NMR (400 MHz, CD_3OD) δ 7.68-7.67 (dd, 1H), 7.62-7.61 (d, 1H), 7.52-7.50 (d, 2H), 7.36-7.34 (d, 2H), 7.19-7.17 (d, 1H), 4.59 (s, 2H), 3.44 (s, 3H), 0.27 (s, 9H).

[0336]

[Table 51]

Ex	Ref.	Structure	LC-MS, NMR
96	E75-S1		LC-MS: 268 $[M+H]^+$
	E75-S2		LC-MS: 255 $[M-NH_2]^+$
	E75-S3	 (Compound 96)	LC-MS: 446 $[M+H]^+$ ^{1}H-NMR (400 MHz, CD_3OD) δ 8.09-8.08 (d, 1H), 7.69-7.63 (m, 4H), 7.48-7.46 (d, 2H), 7.21-7.19 (d, 1H), 6.04-6.03 (d, 1H), 4.80-4.76 (q, 2H), 4.61 (s, 2H), 3.44 (s, 3H).

[0337] <Biological Assays>

Example 97 KIT Tyrosine Kinase Assay

An in vitro assay utilizing the recombinant human KIT tyrosine kinase protein was developed to measure compound inhibition of KIT. KIT tyrosine kinase activity was measured by the ADP-Glo Kinase Assay system with poly (Glu4-Tyr) peptide substrate. Kinase Assay was performed in white 384-well plates and the luminescence was measured by Victor X5 Multilabel Counter (Perkin Elmer).

[0338] Materials and Method

Recombinant intracellular domain of human KIT protein was purchased from Carna Biosciences (Kobe, Japan). Poly (Glu4-Tyr) peptide was purchased from Sigma-Aldrich (St. Louis, Missouri, USA). ADP-Glo Kinase Assay reagent was purchased from Promega (Madison, Wisconsin, USA). Each test compound was dissolved in 100% DMSO to prepare 10 mM stock solutions. Stock solutions were diluted to 400 μM, then serially diluted 1:3 in 100% DMSO to make a 9-point serial dilution. To prepare compound working solutions, each serially diluted solution was further diluted 1:8 with Assay Buffer, consisting of 50 mM Tris-HCl pH 7.5, 20 mM $MgCl_2$, 0.01% Tween-20, 2 mM $MnCl_2$, 50 μM Dithiothreitol (DTT).

[0339] Recombinant KIT protein was diluted to 1 μM with Assay Buffer. Poly (Glu4-Tyr) peptide and ATP were diluted to 300 microgram/mL and 250 μM, re-

spectively, with Assay Buffer, then mixed to make the substrate solution. In a 384-well plate, 2 μL of working compounds and 5 μL of recombinant KIT protein were mixed and incubated for 30 minutes at room temperature. After the preincubation, 3 μL of substrate/ATP mixture was added and incubated for 1 hour at room temperature. The tyrosine phosphorylation by KIT kinase was quantified by ADP-Glo kinase assay kit following the manufacturer's protocol. Briefly, the phosphorylation reaction was terminated by adding 10 μL ADP-Glo reagent and incubated for 60 minutes at room temperature. 20 μL of Kinase Detection Reagent was added to each well and luminescence was measured by plate reader. The assay control for this experiment was 2.5% DMSO and Assay Buffer was used as the blank.

[0340] Half maximal inhibitory concentration (IC50) was calculated by a Four Parameters Logistic Regression model using GraphPad Prism (GraphPad Software). The value without recombinant KIT protein and without test compound was used as a negative control (assay background). The value with recombinant KIT protein without test compound was a positive control (100% activity).

[0341] The Table 52 below lists inhibitory effects of representative compounds of the present invention against KIT.

[0342]

[Table 52]

Compound No.	KIT IC50 (μM)	Compound No.	KIT IC50 (μM)	Compound No.	KIT IC50 (μM)
1	6.917	32	0.295	65	0.281
2	0.095	33	0.189	66	0.029
3	0.025	34	0.101	67	0.186
4	0.336	35	0.083	68	0.011
5	65%@10μM	36	21.73	69	0.085
6	3.761	37	55%@100μM	70	0.154
7	0.064	38	0.526	71	0.010
8	0.057	39	0.615	72	0.035
9	0.056	40	4.506	73	0.050
10	0.096	41	0.198	74	0.275
11	2.304	42	0.116	75	0.072
12	0.354	43	0.096	76	0.023
13	0.030	44	0.170	77	0.027
14	0.025	45	0.093	78	0.049
15	0.027	46	0.033	79	0.104
16	0.538	47	0.057	80	0.155
17	0.353	48	0.031	81	0.032
18	23.29	49	0.024	82	0.038
19	0.213	50	0.147	83	0.282
19a	0.067	51	0.045	84	0.559
19b	5.385	52	0.046	85	1.026
20	0.073	53	0.046	86	65%@10uM
21	0.016	54	0.039	87	0.183
22	0.042	55	0.049	88	0.052
23	0.153	56	0.033	89	0.046
24	1.124	57	0.028	90	0.029
25	>100	58	0.025	91	0.037
26	1.456	59	0.029	92	0.037
27	0.419	60	0.048	93	0.096
28	20.61	61	0.023	94	0.047
29	2.063	62	0.023	95	0.047
30	0.630	63	0.017	96	0.024
31	0.205	64	0.038		

[0343] Notably, the representative compounds of the present invention showed selective inhibitory activities against KIT while not exhibiting significant inhibition against other kinases.

[0344] Example 98 SCF-dependent M-07e Cell Proliferation Assay

SCF-dependent cell proliferation assay was developed to measure the inhibitory potency of the compounds in M-07e cells, which express wild-type human KIT protein. The assay was performed in 96-well plates and the IC50 of each KIT inhibitor was determined by CellTiter Glo Assay reagent and Victor X5 Multilabel Counter (Perkin Elmer).

[0345] Materials and Methods

M-07e cells were purchased from AcceGen Biotechnology. Cells were maintained with M-07e Growth medium: RPMI-1640 containing 20% FBS, 100 U/mL

penicillin and 100 microgram/mL streptomycin, 10 ng/mL rhGM-CSF, 10 ng/mL rhSCF. M-07e cells were seeded at a density of 5000 cells/90μL/well in 96-well plates. Test compounds were dissolved in 100% DMSO to make 20 mM stock solution and serially diluted 1:3 with 100% DMSO to make an 11-point dilution series with concentrations from 15 mM to 0.024 μM. The serially diluted compounds were then each diluted 1:50 with culture medium to obtain assay compound solutions containing 2% DMSO. Ten μL of assay compound solutions were added to the 90 μL of culture cell suspension in the 96-well plate, with a final DMSO concentration of 0.2%. The plates were then incubated in a 5% CO_2 incubator at 37°C for 3 days. To obtain Day Zero Controls for background calculation, cells were seeded at 5000 cells/100 μL in a new 96-well plate and processed on the same day. Both Day Zero controls and 3 day culture plates were then treated as follows. 100 μL of CellTiter Glo Assay reagent was added to each well and the plate was incubated at room temperature for 15 min on a shaker at 200-300 RPM. Then 100 μL of cell lysate samples were transferred to white wall 96-well plates and luminescence was measured by a plate reader. The luminescence of Day Zero Control was subtracted from the luminescence intensity of 3 day culture readings. The assay control for this experiment was cells treated with 0.2% DMSO in culture medium and wells with 100 μL of culture medium (0.2% DMSO without cells) were used as the blank for data analysis.

[0346] The IC50 value of each compound was determined by using % inhibition by normalizing inhibition in DMSO treated control wells to 0% using the following formula method:

% inhibition=100-[(Blanks subtracted L of experimental wells)/(Blanks subtracted L of 0.2% DMSO control wells)×100]

*Where L is luminescence

[0347] Plot percent inhibition in proliferation of triplicates against the respective concentrations of compound and fit the dose response curve using the sigmoidal dose response equation to generate the IC50 in GraphPad Prism 8 software.

[0348] The Table 53 below lists inhibitory effects of representative compounds of the present invention against the M-07e cells.

[0349]

[Table 53]

Compound No.	M-07e IC50 (μM)
2	0.657
3	0.080
8	1.497
9	1.604
10	3.736
12	0.431
13	0.056
14	0.173
15	0.717
21	0.049
22	0.099
27	1.325
41	0.458
42	1.110
43	5.667
46	0.275
47	2.181
48	0.722
49	0.146
51	0.988
52	0.065
53	0.303
54	0.818
55	1.464
56	0.049
57	0.025
58	0.515

Compound No.	M-07e IC50 (μM)
59	0.043
60	0.335
61	0.122
62	0.314
63	0.025
64	0.180
66	0.061
68	0.532
69	3.501
71	0.174
72	0.028
73	0.047
75	0.410
76	0.153
77	0.515
78	0.241
81	0.186
82	0.586
89	0.252
90	0.161
91	0.082
92	0.279
93	0.156
94	0.333
95	0.197
96	0.164

[0350] Example 99 GIST Cell Proliferation Assay

Gastrointestinal stromal tumors (GIST) are the most common adult sarcomas and the majority (85-90%) of GIST cases are caused by oncogenic mutations in the receptor tyrosine kinases (RTKs), KIT or PDGFRA, which result in constitutive activation of these receptors. Human GIST-derived cell line GIST-T1 which harboring a mutation in exon 11 of KIT was used for the measurement of inhibitory potency of the compounds.

[0351] Materials and Methods

GIST-T1 cells were purchased from Cosmo Bio (Tokyo, Japan) and cultured in 10% FBS containing DMEM. The assay was performed in 96-well plates and the IC50 of each compound was determined by CellTiter Glo Assay reagent and Victor X5 Multilabel Counter. Cells were seeded at a density of 2000 cells/90 μL/well in 96-well plates. Compound dilution, cell treatment and determination of IC50 were performed as described in the assay methods of M-07e Cell Proliferation Assay.

[0352] The Table 54 below lists inhibitory effects of representative compounds of the present invention against the GIST-T1 cells.

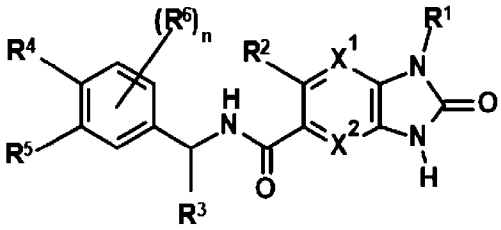
[0353] [Table 54]

Compound No.	GIST-T1 IC50 (μM)
4	1.740
7	1.084
12	0.177
17	0.566
19a	0.809
20	0.515
23	0.931
27	0.831
32	0.982
33	2.313
34	0.547
35	0.142
38	2.641
39	2.317
41	0.568
43	1.353

Claims

[Claim 1] A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by the following Formula (I):

[Chem.1]



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, C_{1-3}-alkyl, or C_{1-3}-deuteroalkyl,

R^2 is hydrogen, halogen, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, nitro, amino, or mono- or di-(C_{1-4}-alkyl)amino,

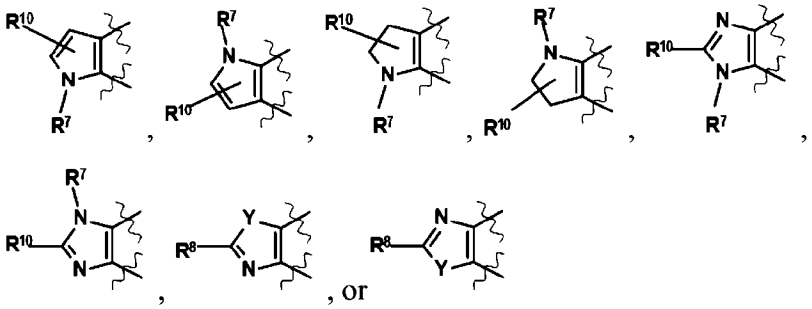
R^3 is hydrogen or C_{1-4}-alkyl,

R^4 is halogen, hydroxy, nitro, amino, mono- or di- or tri-(C_{1-4}-alkyl)silyl, R^A, -O-R^A, -N(R^A)(R^B), or -CO-N(R^A)(R^C), and

R^5 is hydrogen, halogen, hydroxy, nitro, amino, R^A, -O-R^A, -N(R^A)(R^B), or -CO-N(R^A)(R^C), or

R^4 and R^5 are taken together to form a group of the formula:

[Chem.2]



the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^7 is hydrogen or R^A,

R^8 is hydrogen or -N(R^A)(R^B),

X^1 and X^2 are each independently N or C-R^9,

R^9 is hydrogen, halogen, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, nitro, amino, or mono- or di-(C_{1-4}-alkyl)amino,

R^{10} is hydrogen, halogen, or C_{1-4}-alkyl,

Y is O or S,

n is an integer having a value of 0, 1, 2 or 3,

R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl, in which said C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino;

R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl, and

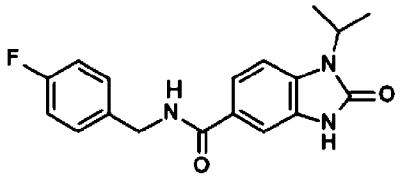
R^C is C_{1-4}-alkyl or C_{3-6}-cycloalkyl, or

R^A and R^B at the -N(R^A)(R^B), or R^A and R^C at the -CO-N(R^A)(R^C) are

taken together with the nitrogen atom to form an N-containing heterocyclic ring optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino,

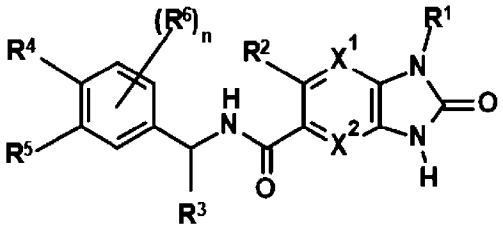
provided that the compound is not

[Chem.3]



[Claim 2] The pharmaceutical composition of claim 1, which is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by the following Formula (I):

[Chem.4]



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-3}-alkyl,

R^2 is hydrogen, halogen, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, nitro, amino, or mono- or di-(C_{1-4}-alkyl)amino,

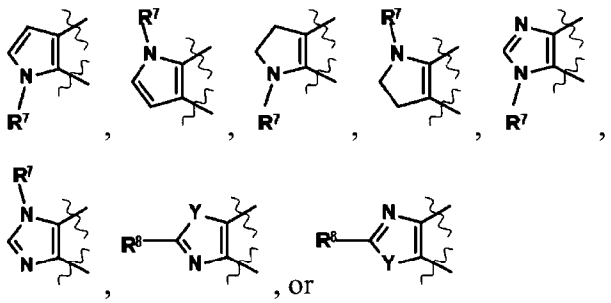
R^3 is hydrogen or C_{1-4}-alkyl,

R^4 is halogen, hydroxy, nitro, amino, R^A, -O-R^A, -N(R^A)(R^B), or -CO-N(R^A)(R^C), and

R^5 is hydrogen, halogen, hydroxy, nitro, amino, R^A, -O-R^A, -N(R^A)(R^B), or -CO-N(R^A)(R^C), or

R^4 and R^5 are taken together to form a group of the formula:

[Chem.5]



the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^7 is hydrogen or R^A,

R^8 is hydrogen or -N(R^A)(R^B),

X^1 and X^2 are each independently N or C-R^9,

R^9 is hydrogen, halogen, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, nitro, amino, or mono- or di-(C_{1-4}-alkyl)amino,

Y is O or S,

n is an integer having a value of 0, 1, 2 or 3,

R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl, in which said C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino;

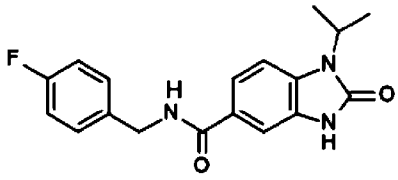
R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl, and

R^C is C_{1-4}-alkyl or C_{3-6}-cycloalkyl, or

R^A and R^B at the -N(R^A)(R^B), or R^A and R^C at the -CO-N(R^A)(R^C) are taken together with the nitrogen atom to form an N-containing heterocyclic ring optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino,

provided that the compound is not

[Chem.6]



.

[Claim 3] The pharmaceutical composition of claim 2, wherein R^1 is hydrogen, methyl, ethyl, or isopropyl, and R^3 is hydrogen or methyl.

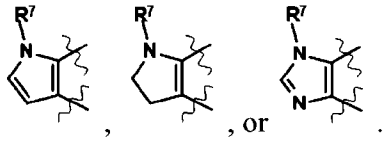
[Claim 4] The pharmaceutical composition of claim 3, wherein

R^4 is R^A, -O-R^A, or -N(R^A)(R^B), and

R^5 is hydrogen, halogen, or -O-R^A, or

R^4 and R^5 are taken together to form a group of the formula:

[Chem.7]



, , or .

[Claim 5] The pharmaceutical composition of any one of claims 2-4, wherein R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, phenyl, tetrahydropyranyl, piperidyl, piperazinyl, pyridyl, pyrimidyl, pyrazolyl, and indazolyl, in which said C_{3-6}-cycloalkyl, phenyl, tetrahydropyranyl, piperidyl, piperazinyl, pyridyl, pyrimidyl, pyrazolyl, and indazolyl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; phenyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with tetrahydropyranyl, piperidyl, or piperazinyl, each of which may be further substituted with halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, or mono- or di-(C_{1-4}-alkyl)amino; tetrahydropyranyl, piperidyl, or piperazinyl, each of which may be substituted with one or more groups selected from the group consisting of

halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; or pyridyl, pyrimidyl, pyrazolyl, or indazolyl, each of which may be substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; and R^B is methyl.

[Claim 6] The pharmaceutical composition of claim 5, wherein R^A is isopropyl; C_{3-6}-cycloalkyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl; phenyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl; or pyridyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl.

[Claim 7] The pharmaceutical composition of claim 1, wherein
R^4 is R^A, -O-R^A, or -N(R^A)(R^B),
R^5 is hydrogen or halogen,
R^A is C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-

alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; and

R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl.

[Claim 8] The pharmaceutical composition of claim 1, wherein the compound is selected from the group consisting of

N-((1-(2,6-Difluorophenyl)indolin-5-yl)methyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(4-(Isopropyl(methyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(2,6-Difluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(4-((3,3-Difluorocyclobutyl)(methyl)amino)-2-fluorobenzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(2,6-Difluoro-4-((4,4-difluorocyclohexyl)(methyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(4-((4,4-Difluorocyclohexyl)(methyl)amino)-2-fluorobenzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(2-Fluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(2-Fluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

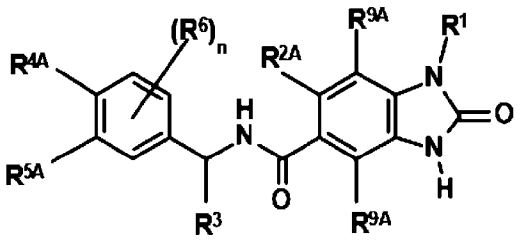
4-Fluoro-N-(4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide, and

N-(4-((4,4-Difluorocyclohexyl)(methyl)amino)benzyl)-4-fluoro-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

or a pharmaceutically acceptable salt thereof.

[Claim 9] A compound represented by the following Formula (Ia):

[Chem.8]



(Ia)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, C_{1-3}-alkyl, or C_{1-3}-deuteroalkyl,

R^{2A} is hydrogen or halogen,

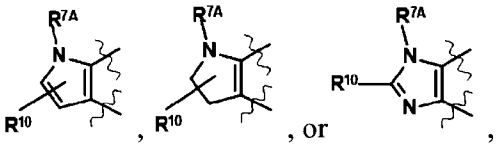
R^3 is hydrogen or C_{1-4}-alkyl,

R^{4A} is mono- or di- or tri-(C_{1-4}-alkyl)silyl, R^A, -O-R^A or -N(R^A)(R^B), and

R^{5A} is hydrogen, halogen, or -O-R^A, or

R^{4A} and R^{5B} are taken together to form a group of the formula:

[Chem.9]



the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^{7A} is R^A,

R^{9A} is hydrogen or halogen,

R^{10} is hydrogen, halogen, or C_{1-4}-alkyl,

n is an integer having a value of 0, 1, 2 or 3,

R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl, in which said C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more

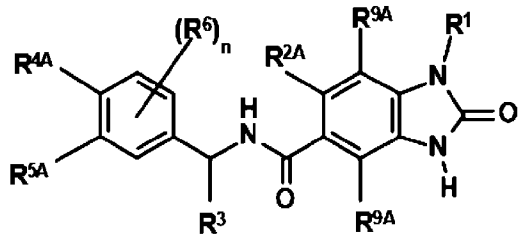
groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; and

R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl, or

R^A and R^B are taken together with the nitrogen atom to form an N-containing heterocyclic ring optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino.

[Claim 10] The compound of claim 9, which is a compound represented by the following Formula (Ia):

[Chem.10]



(Ia)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-3}-alkyl,

R^{2A} is hydrogen or halogen,

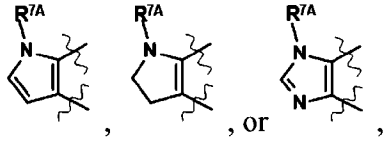
R^3 is hydrogen or C_{1-4}-alkyl,

R^{4A} is R^A, -O-R^A or -N(R^A)(R^B), and

R^{5A} is hydrogen, halogen, or -O-R^A, or

R^{4A} and R^{5B} are taken together to form a group of the formula:

[Chem.11]



the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^{7A} is R^A,

R^{9A} is hydrogen or halogen,

n is an integer having a value of 0, 1, 2 or 3,

R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl, in which said C_{3-6}-cycloalkyl, aryl, heterocyclyl, and heteroaryl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; and

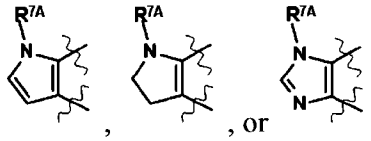
R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl, or

R^A and R^B are taken together with the nitrogen atom to form an N-containing heterocyclic ring optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino.

[Claim 11] The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen or methyl, and R^3 is hydrogen or methyl.

[Claim 12] The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^{4A} is -N(R^A)(R^B), and R^{5A} is hydrogen or halogen, or R^{4A} and R^{5B} are taken together to form a group of the formula:

[Chem.12]



, , or .

[Claim 13] The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^A is C_{1-4}-alkyl optionally substituted with one or more groups selected from the group consisting of halogen, -O-(C_{1-4}-alkyl), mono- or di-(C_{1-4}-alkyl)amino, C_{3-6}-cycloalkyl, phenyl, tetrahydropyranyl, piperidyl, piperazinyl, pyridyl, pyrimidyl, pyrazolyl, and indazolyl, in which said C_{3-6}-cycloalkyl, phenyl, tetrahydropyranyl, piperidyl, piperazinyl, pyridyl, pyrimidyl, pyrazolyl, and indazolyl may be further substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; phenyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with tetrahydropyranyl, piperidyl, or piperazinyl, each of which may be further substituted with halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, or mono- or di-(C_{1-4}-alkyl)amino; tetrahydropyranyl, piperidyl, or piperazinyl, each of which may be substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; or pyridyl, pyrimidyl, pyrazolyl, or indazolyl, each of which may be substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; and R^B is methyl.

[Claim 14] The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen or methyl,

R^{2A} is hydrogen or halogen,

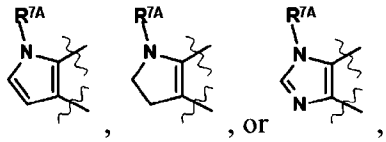
R^3 is hydrogen or methyl,

R^{4A} is -N(R^A)(R^B), and

R^{5A} is hydrogen, or halogen, or

R^{4A} and R^{5B} are taken together to form a group of the formula:

[Chem.13]



the wavy line indicates a point of attachment to the rest of molecule,

R^6 is hydrogen, halogen, or C_{1-4}-alkyl,

R^{7A} is R^A,

R^{9A} is hydrogen or halogen,

n is an integer having a value of 0, 1, 2 or 3,

R^A is isopropyl; C_{3-6}-cycloalkyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl; phenyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl; or pyridyl substituted with one or more groups selected from the group consisting of halogen, cyano, C_{1-4}-alkyl, and C_{1-4}-haloalkyl; and

R^B is methyl.

[Claim 15] The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein

R^{4A} is -O-R^A or -N(R^A)(R^B),

R^{5A} is hydrogen or halogen,

R^A is C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-

haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; and

R^B is hydrogen, C_{1-4}-alkyl, or C_{3-6}-cycloalkyl.

[Claim 16] The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein

R^{4A} is R^A,

R^{5A} is hydrogen or halogen, and

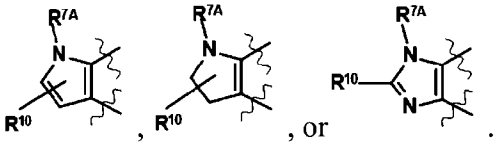
R^A is C_{3-6}-cycloalkyl optionally substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; aryl substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino, in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino; heterocyclyl substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, -O-(C_{1-4}-alkyl), C_{1-4}-

haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino; or heteroaryl substituted with one or more groups selected from the group consisting of halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), C_{3-6}-cycloalkyl, amino, and mono- or di-(C_{1-4}-alkyl)amino in which said C_{1-4}-alkyl may be further substituted with heterocyclyl optionally having halogen, cyano, hydroxy, C_{1-4}-alkyl, -O-(C_{1-4}-alkyl), C_{1-4}-haloalkyl, -O-(C_{1-4}-haloalkyl), amino, or mono- or di-(C_{1-4}-alkyl)amino.

[Claim 17] The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R^{4A} is R^A or -N(R^A)(R^B), and R^{5A} is -O-R^A.

[Claim 18] The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R^{4A} and R^{5B} are taken together to form a group of the formula:

[Chem.14]



, or .

[Claim 19] The compound of claim 9, wherein the compound is selected from the group consisting of

N-((1-(2,6-Difluorophenyl)indolin-5-yl)methyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(4-(Isopropyl(methyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(2,6-Difluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(4-((3,3-Difluorocyclobutyl)(methyl)amino)-2-fluorobenzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(2,6-Difluoro-4-((4,4-difluorocyclohexyl)(methyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(4-((4,4-Difluorocyclohexyl)(methyl)amino)-2-fluorobenzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(2-Fluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

N-(2-Fluoro-4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,

4-Fluoro-N-(4-(methyl(cis-3-(trifluoromethyl)cyclobutyl)amino)benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide, and

N-(4-((4,4-Difluorocyclohexyl)(methyl)amino)benzyl)-4-fluoro-1-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxamide,
or a pharmaceutically acceptable salt thereof.

[Claim 20] The pharmaceutical composition according to claim 1, which is a pharmaceutical composition for a treatment of a KIT mediated disease or condition.

[Claim 21] Use of the compound according to claim 9 or a pharmaceutically acceptable salt thereof for manufacturing a medicament for a treatment of a KIT mediated disease or condition.

[Claim 22] Use of the compound according to claim 9 or a pharmaceutically acceptable salt thereof for a treatment of a KIT mediated disease or condition.

[Claim 23] The compound according to 9 or a pharmaceutically acceptable salt thereof for a treatment of a KIT mediated disease or condition.

[Claim 24] A method of treating a KIT mediated disease or condition in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of one or more the pharmaceutical composition of any one of claims 1-8 or the compound of any one of claims 9-19, or a pharmaceutically acceptable salt thereof.

[Claim 25] The method of claim 24, wherein the KIT mediated disease or condition is a cancer, an autoimmune disease, an allergic disease, an inflammatory disease, fibrosis, a metabolic disorder, a neurodegenerative disease, bone loss, tumor angiogenesis, interstitial cystitis, pulmonary arterial hypertension (PAH), and primary pulmonary hypertension (PPH).

[Claim 26] The method of claim 25, wherein:
the cancer is selected from mastocytosis, mastocytoma, solid tumor, gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinoma, gastric carcinoma, testicular cancer, glioblastoma, astrocytoma, melanoma, mast cell tumor, neuroblastoma, sarcoma, and seminoma;
the autoimmune disease is selected from multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular pa-

narteritis, autoimmune enteropathy, and proliferative glomerulonephritis;
the allergic disease is selected from asthma, severe asthma, allergic rhinitis, chronic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, food allergy, seasonal allergy, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, and blood sucking parasitic infestation;
the inflammatory disease is selected from rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS), and eosinophilic esophagitis;
the fibrosis is selected from pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, and myelofibrosis;
the metabolic disorder is selected from diabetes mellitus and its chronic complications; obesity; type I diabetes or type II diabetes; hyperlipidemias and dyslipidemias; atherosclerosis; hypertension; and cardiovascular disease; and
the neurodegenerative disease is selected from Alzheimer's disease, Parkinson's disease, Huntington's disease, the prion diseases, motor neuron disease (MND), and amyotrophic lateral sclerosis (ALS).

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2023/042736

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4184 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2024	01/03/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Grassi, Damian

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Form PCT/ISA/210 (second sheet) (April 2005)

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A	WO 2005/021544 A2 (OSI PHARM INC [US]; CASTELHANO ARLINDO L [US] ET AL.) 10 March 2005 (2005-03-10)	1-26
A	WO 2007/076055 A2 (ENTREMED INC [US]; HEMBROUGH TODD A [US] ET AL.) 5 July 2007 (2007-07-05) page 147, last compound	1-26

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Information on patent family members

International application No
PCT/JP2023/042736

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