DUAL-ACTING ANGIOTENSIN AND ENDOTHELIN RECEPTOR ANTAGONISTS

FIELD

[0001] Provided herein are methods of treating idiopathic pulmonary fibrosis (IPF), and other diseases, comprising administering a therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist (DARA), or a pharmaceutically acceptable salt thereof, to a patient in need thereof. Provided herein are also pharmaceutical composition that are suitable for such administration.

BACKGROUND

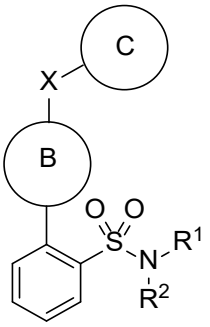
[0002] Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial lung disease of unknown cause. IPF affects the lung interstitium, the tissue residing between the alveoli which is dense with capillaries in order to facilitate gas exchange during respiration. Recurrent, subclinical epithelial injury superimposed on accelerated epithelial aging leads to aberrant repair of the injured alveolus and deposition of interstitial fibrosis by myofibroblasts. Fibrosis of the lung interstitium leads to inefficient gas exchange, causing progressive and irreversible decline in lung function, leading to cough, dyspnea, low forced vital lung capacity, and impaired quality of life. While certain risk factors have been identified, including environmental exposures, smoking, gastroesophageal reflux disease, certain infections, and genetic predisposition, the specific route of pathogenesis for idiopathic pulmonary fibrosis is currently unknown.

[0003] Current management for IPF includes treatment with nintedanib, a tyrosine kinase inhibitor, or pirfenidone, an inhibitor of TGF-β production, collagen synthesis, and fibroblast proliferation. While these treatments slow IPF progression, they do not stop or reverse the damage caused by the disease. Side effects of these treatments include diarrhea, gastrointestinal distress, nausea, disinterest in eating, and photosensitivity, which limit patient tolerability of treatment, and cause approximately 30% of patients to discontinue treatment within 2 years.

[0004] A need exists for therapeutic agents for treating idiopathic pulmonary fibrosis, and other diseases amenable to treatment with dual-acting angiotensin and endothelin receptor antagonists (DARAs).

SUMMARY

[0005] Provided herein are compounds of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.



I

wherein R^1, R^2, X, Ring B, and Ring C are as described in the detailed description. The compounds are useful in treating idiopathic pulmonary fibrosis (IPF), and other diseases amenable to treatment with dual-acting angiotensin and endothelin receptor antagonists (DARAs).

[0006] Also provided is a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable excipient.

[0007] Provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

[0008] Further provided herein is a method for treating hypertension, portal hypertension, hypertension secondary to treatment with erythropoietin and low renin hypertension, pulmonary arterial hypertension (PAH), disorders related to renal, glomerular and mesangial cell function, acute (ischemic, nephrotoxic, or glomerulonephritis) and chronic (diabetic, hypertensive or immune-mediated) renal failure, diabetic nephropathy, glomerular injury, renal damage secondary to old age or related to dialysis, nephrosclerosis (hypertensive nephrosclerosis), nephrotoxicity (including nephrotoxicity related to imaging and contrast agents and to cyclosporine), renal ischemia, primary vesicoureteral reflux, proteinuric glomerular diseases, glomerulosclerosis, focal segmental glomerulosclerosis (FSGS),kidney disease such as chronic kidney disease (CKD), disorders related to paracrine and endocrine function, diabetic nephropathy, hypertension-induced nephropathy, IGA-induced nephropathy, endotoxemia or endotoxin shock, hemorrhagic shock, in alleviation of pain associated cancer, such as the pain associated with prostate cancer, and bone pain associated with bone cancer, in the prevention and/or reduction of end-organ damage associated with the cell-proliferative effects of endothelin, hypoxic and ischemic disease, for example, cardiac, renal and cerebral ischemia and reperfusion (such as that occurring following cardiopulmonary bypass surgery), coronary and cerebral vasospasm, myocardial infarction; therapy for peripheral vascular disease (e.g., Raynaud's disease, intermittent claudication and Takayasu's disease); treatment of cardiac hypertrophy (e.g., hypertrophic

cardiomyopathy); treatment of primary pulmonary hypertension (e.g., plexogenic, embolic) in adults and in the newborn and pulmonary hypertension secondary to heart failure, radiation and chemotherapeutic injury, or other trauma; treatment of central nervous system vascular disorders, such as stroke, migraine and subarachnoid hemorrhage; treatment of central nervous system behavioral disorders; treatment of gastrointestinal diseases such as ulcerative colitis, Crohn's disease, gastric mucosal damage, ulcer, inflammatory bowel disease and ischemic bowel disease; treatment of gall bladder or bile duct-based diseases such as cholangitis; pancreatitis; cell growth; benign prostatic hypertrophy; restenosis following angioplasty or following any procedure including transplantation and stenting; congestive heart failure including inhibition of fibrosis; inhibition of left ventricular dilatation, remodeling and dysfunction; treatment of hepatotoxicity and sudden death; sickle cell disease including the initiation and/or evolution of the pain crises of this disease; hypertension resulting from hemangiopericytoma; early and advanced liver disease and injury including attendant complications (e.g., hepatotoxicity, fibrosis and cirrhosis); treatment of spastic diseases of the urinary tract and/or bladder; hepatorenal syndrome; immunological diseases involving vasculitis such as lupus, systemic sclerosis, mixed cryoglobulinemia; fibrosis associated with renal dysfunction and hepatotoxicity, metabolic and neurological disorders; cancer; insulin-dependent and non-insulin-dependent diabetes mellitus; neuropathy; retinopathy; epilepsy; hemorrhagic and ischemic stroke; bone remodeling; psoriasis; and chronic inflammatory diseases such as arthritis, rheumatoid arthritis, osteoarthritis, sarcoidosis and eczematous dermatitis (all types of dermatitis); disorders involving bronchoconstriction and disorders of chronic or acute pulmonary inflammation such as chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS); sexual dysfunction; Alzheimer's dementia, senile dementia and vascular dementia; comprising administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or a composition described herein, to a patient in need thereof.

DETAILED DESCRIPTION

[0009] The following description sets forth exemplary embodiments of the present technology. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

Definitions

[0010] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0011] It is noted here that as used in this specification and the appended claims, the singular forms "a" "an" and "the" and the like include plural referents unless the context clearly dictates otherwise.

[0012] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -C(O)NH_2 is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line or a dashed line drawn through a line in a structure indicates a specified point of attachment of a group. Unless chemically or structurally required, no directionality or stereochemistry is indicated or implied by the order in which a chemical group is written or named.

[0013] The prefix "C_{u-v}" indicates that the following group has from u to v carbon atoms. For example, "C_{1-6} alkyl" indicates that the alkyl group has from 1 to 6 carbon atoms.

[0014] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. In certain embodiments, the term "about" includes the indicated amount ± 10%. In other embodiments, the term "about" includes the indicated amount ± 5%. In certain other embodiments, the term "about" includes the indicated amount ± 1%. Also, to the term "about X" includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0015] "Alkyl" refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (i.e., C_{1-20} alkyl), 1 to 12 carbon atoms (i.e., C_{1-12} alkyl), 1 to 8 carbon atoms (i.e., C_{1-8} alkyl), 1 to 6 carbon atoms (i.e., C_{1-6} alkyl) or 1 to 4 carbon atoms (i.e., C_{1-4} alkyl). Examples of alkyl groups include, e.g., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, "butyl" includes n-butyl (i.e., -$(CH_2)_3CH_3$), sec-butyl (i.e., -$CH(CH_3)CH_2CH_3$), isobutyl (i.e., -$CH_2CH(CH_3)_2$) and tert-butyl (i.e., -$C(CH_3)_3$); and "propyl" includes n-propyl (i.e., -$(CH_2)_2CH_3$), and isopropyl (i.e., -$CH(CH_3)_2$).

[0016] Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent "alkyl" group, a divalent "aryl" group, etc., may also be referred to as an "alkylene" group or an "alkylenyl" group, an "arylene" group, or an "arylenyl" group, respectively. Also, unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, e.g., arylalkyl or aralkyl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

[0017] "Alkenyl" refers to an alkyl group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkenyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkenyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkenyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkenyl). Examples of alkenyl groups include, e.g., ethenyl, propenyl, and butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

[0018] "Alkynyl" refers to an alkyl group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkynyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkynyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkynyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkynyl). The term "alkynyl" also includes those groups having one triple bond and one double bond.

[0019] "Alkoxy" refers to the group "alkyl-O-". Examples of alkoxy groups include, e.g., methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy.

[0020] "Alkoxyalkyl" refers to the group "alkyl-O-alkyl".

[0021] "Alkylthio" refers to the group "alkyl-S-". "Alkylsulfinyl" refers to the group "alkyl-S(O)-". "Alkylsulfonyl" refers to the group "alkyl-$S(O)_2$-". "Alkylsulfonylalkyl" refers to -alkyl-$S(O)_2$-alkyl.

[0022] "Acyl" refers to a group -$C(O)R^y$, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include, e.g., formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethyl-carbonyl, and benzoyl.

[0023] "Amido" refers to both a "C-amido" group which refers to the group -$C(O)NR^yR^z$ and an "N-amido" group which refers to the group -$NR^yC(O)R^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein, or R^y and R^z are taken together to form a cycloalkyl or heterocyclyl; each of which may be optionally substituted, as defined herein.

[0024] "Amino" refers to the group -NR^yR^z wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0025] "Aminoalkyl" refers to the group "-alkyl-NR^yR^z," wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0026] "Amidino" refers to -$C(NR^y)(NR^z{}_2)$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0027] "Aryl" refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (i.e., C_{6-20} aryl), 6 to 12 carbon ring atoms (i.e., C_{6-12} aryl), or 6 to 10 carbon ring atoms (i.e., C_{6-10} aryl). Examples of aryl groups include, e.g., phenyl, naphthyl, fluorenyl and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl. If one or more aryl groups are fused with a heterocyclyl, the resulting ring system is heterocyclyl.

[0028] "Arylalkyl" or "Aralkyl" refers to the group "aryl-alkyl-".

[0029] "Carbamoyl" refers to both an "O-carbamoyl" group which refers to the group $-O-C(O)NR^yR^z$ and an "N-carbamoyl" group which refers to the group $-NR^yC(O)OR^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0030] "Carboxyl ester" or "ester" refer to both $-OC(O)R^x$ and $-C(O)OR^x$, wherein R^x is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0031] "Cyanoalkyl" refers to refers to an alkyl group as defined above, wherein one or more (e.g., one to three) hydrogen atoms are replaced by a cyano (-CN) group.

[0032] "Cycloalkyl" refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond) and carbocyclic fused ring systems having at least one sp^3 carbon atom (i.e., at least one non-aromatic ring). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl). Monocyclic groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic groups include, for example, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, octahydropentalenyl, and the like. Further, the term cycloalkyl is intended to encompass any non-aromatic ring which may be fused to an aryl ring, regardless of the attachment to the remainder of the molecule. Still further, cycloalkyl also includes "spirocycloalkyl" when there are two positions for substitution on the same carbon atom, for example spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl.

[0033] "Cycloalkoxy" refers to "-O-cycloalkyl."

[0034] "Cycloalkylalkyl" refers to the group "cycloalkyl-alkyl-".

[0035] "Cycloalkylalkoxy" refers to "-O-alkyl-cycloalkyl."

[0036] "Guanidino" refers to -$NR^yC(=NR^z)(NR^yR^z)$, wherein each R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0037] "Hydrazino" refers to -$NHNH_2$.

[0038] "Imino" refers to a group -$C(NR^y)R^z$, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0039] "Imido" refers to a group -$C(O)NR^yC(O)R^z$, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0040] "Halogen" or "halo" refers to atoms occupying group VIIA of the periodic table, such as fluoro, chloro, bromo, or iodo.

[0041] "Haloalkyl" refers to an unbranched or branched alkyl group as defined above, wherein one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two ("di") or three ("tri") halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0042] "Haloalkoxy" refers to an alkoxy group as defined above, wherein one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a halogen.

[0043] "Hydroxyalkyl" refers to an alkyl group as defined above, wherein one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a hydroxy group.

[0044] "Heteroalkyl" refers to an alkyl group in which one or more (e.g., one to five or one to three) of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group, provided the point of attachment to the remainder of the molecule is through a carbon atom. The term "heteroalkyl" includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, -NR^y-, -O-, -S-, -S(O)-, -$S(O)_2$-, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl,

heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkyl groups include, e.g., ethers (e.g., $-CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_2OCH_3$, etc.), thioethers (e.g., $-CH_2SCH_3$, $-CH(CH_3)SCH_3$, $-CH_2CH_2SCH_3$, $-CH_2CH_2SCH_2CH_2SCH_3$, etc.), sulfones (e.g., $-CH_2S(O)_2CH_3$, $-CH(CH_3)S(O)_2CH_3$, $-CH_2CH_2S(O)_2CH_3$, $-CH_2CH_2S(O)_2CH_2CH_2OCH_3$, etc.), and amines (e.g., $-CH_2NR^yCH_3$, $-CH(CH_3)NR^yCH_3$, $-CH_2CH_2NR^yCH_3$, $-CH_2CH_2NR^yCH_2CH_2NR^yCH_3$, etc., where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). As used herein, heteroalkyl includes 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

[0045] "Heteroalkylene" refers to a divalent alkyl group (i.e., alkylene) in which one or more (e.g., one to five or one to three) of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group. "Heteroalkylene" groups must have at least one carbon and at least one heteroatomic group within the chain. The term "heteroalkylene" includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, $-NR^y-$, -O-, -S-, -S(O)-, $-S(O)_2-$, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkylene groups include, e.g., $-CH_2OCH_2-$, $-CH(CH_3)OCH_2-$, $-CH_2CH_2OCH_2-$, $-CH_2CH_2OCH_2CH_2OCH_2-$, $-CH_2SCH_2-$, $-CH(CH_3)SCH_2-$, $-CH_2CH_2SCH_2-$, $-CH_2CH_2SCH_2CH_2SCH_2-$, $-CH_2S(O)_2CH_2-$, $-CH(CH_3)S(O)_2CH_2-$, $-CH_2CH_2S(O)_2CH_2-$, $-CH_2CH_2S(O)_2CH_2CH_2OCH_2-$, $-CH_2NR^yCH_2-$, $-CH(CH_3)NR^yCH_2-$, $-CH_2CH_2NR^yCH_2-$, $-CH_2CH_2NR^yCH_2CH_2NR^yCH_2-$, etc., where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). As used herein, heteroalkylene includes 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom. As used herein, the term "heteroalkylene" does not include groups such as amides or other functional groups having an oxo present on one or more carbon atoms.

[0046] "Heteroaryl" refers to an aromatic group having a single ring, multiple rings or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (i.e., C_{1-20} heteroaryl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heteroaryl), or 3 to 8 carbon ring atoms (i.e., C_{3-8} heteroaryl); and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. In certain instances, heteroaryl includes 5-10 membered ring systems, 5-7 membered ring systems, or 5-6 membered ring systems, each independently having 1 to 4 ring heteroatoms, 1

to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. Examples of heteroaryl groups include, e.g., acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinolinyl, isoquinolinyl, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl, and imidazo[1,5-a]pyridinyl, where the heteroaryl can be bound via either ring of the fused system. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

[0047] "Heteroarylalkyl" refers to the group "heteroaryl-alkyl-".

[0048] "Heterocyclyl" refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. The term "heterocyclyl" includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged or spiro, and may comprise one or more (e.g., one to three or one or two) oxo (=O) or N-oxide ($-O^-$) moieties. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to an aryl or heteroaryl ring, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 2 to 20 ring carbon atoms (i.e., C_{2-20} heterocyclyl), 2 to 12 ring carbon atoms (i.e., C_{2-12} heterocyclyl), 2 to 10 ring carbon atoms (i.e., C_{2-10} heterocyclyl), 2 to 8 ring carbon atoms (i.e., C_{2-8} heterocyclyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heterocyclyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} heterocyclyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} heterocyclyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur or oxygen. Examples of heterocyclyl groups include, e.g., azetidinyl, azepinyl, benzodioxolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzopyranyl, benzodioxinyl, benzopyranonyl, benzofuranonyl, dioxolanyl, dihydropyranyl, hydropyranyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, furanonyl, imidazolinyl, imidazolidinyl, indolinyl,

indolizinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, oxiranyl, oxetanyl, phenothiazinyl, phenoxazinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, tetrahydropyranyl, trithianyl, tetrahydroquinolinyl, thiophenyl (i.e., thienyl), tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl and 1,1-dioxo-thiomorpholinyl. The term "heterocyclyl" also includes "spiroheterocyclyl" when there are two positions for substitution on the same carbon atom. Examples of the spiro-heterocyclyl rings include, e.g., bicyclic and tricyclic ring systems, such as 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.4]octanyl and 6-oxa-1-azaspiro[3.3]heptanyl. Examples of the fused-heterocyclyl rings include, but are not limited to, 1,2,3,4-tetrahydroisoquinolinyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridinyl, indolinyl, and isoindolinyl, where the heterocyclyl can be bound via either ring of the fused system.

[0049] "Heterocyclylalkyl" refers to the group "heterocyclyl-alkyl-".

[0050] "Oxime" refers to the group $-CR^y(=NOH)$ wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0051] "Sulfonyl" refers to the group $-S(O)_2R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl, and toluenesulfonyl.

[0052] "Sulfinyl" refers to the group $-S(O)R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfinyl are methylsulfinyl, ethylsulfinyl, phenylsulfinyl, and toluenesulfinyl.

[0053] "Sulfonamido" refers to the groups $-SO_2NR^yR^z$ and $-NR^ySO_2R^z$, where R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0054] The terms "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term "optionally substituted" refers to any one or more (e.g., one to five or one to three) hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[0055] In certain embodiments, R^y and R^z as used herein are optionally substituted. In certain embodiments, R^y and R^z as used herein are unsubstituted.

[0056] The term "substituted" used herein means any of the above groups (i.e., alkyl, alkenyl, alkynyl, alkylene, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, aryl, heterocyclyl, heteroaryl, and/or heteroalkyl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atom such as, but not limited to alkyl, alkenyl, alkynyl, alkoxy, alkylthio, acyl, amido, amino, amidino, aryl, aralkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkylalkyl, guanadino, halo, haloalkyl, haloalkoxy, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydrazine, hydrazone, imino, imido, hydroxy, oxo, oxime, nitro, sulfonyl, sulfinyl, alkylsulfonyl, alkylsulfinyl, sulfinic acid, sulfonic acid, sulfonamido, thiol, thioxo, N-oxide, or $-Si(R^y)_3$ wherein each R^y is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl.

[0057] In certain embodiments, "substituted" includes any of the above alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl groups in which one or more (e.g., one to five or one to three) hydrogen atoms are independently replaced with deuterium, halo, cyano, nitro, azido, oxo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NR^gR^h$, $-NR^gC(=O)R^h$, $-NR^gC(=O)NR^gR^h$, $-NR^gC(=O)OR^h$, $-NR^gS(=O)_{1-2}R^h$, $-C(=O)R^g$, $-C(=O)OR^g$, $-OC(=O)OR^g$, $-OC(=O)R^g$, $-C(=O)NR^gR^h$, $-OC(=O)NR^gR^h$, $-OR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-OS(=O)_{1-2}R^g$, $-S(=O)_{1-2}OR^g$, $-NR^gS(=O)_{1-2}NR^gR^h$, $=NSO_2R^g$, $=NOR^g$, $-S(=O)_{1-2}NR^gR^h$, $-SF_5$, $-SCF_3$, or $-OCF_3$. In certain embodiments, "substituted" also means any of the above groups in which one or more (e.g., one to five or one to three) hydrogen atoms are replaced with $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^gR^h$, $-CH_2SO_2R^g$, or $-CH_2SO_2NR^gR^h$. In the foregoing, R^g and R^h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and/or heteroarylalkyl. In certain embodiments, "substituted" also means any of the above groups in which one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, N-heterocyclyl, heterocyclylalkyl, heteroaryl, and/or heteroarylalkyl, or two of R^g and R^h and R^i are taken together with the atoms to which they are attached to form a heterocyclyl ring optionally substituted with oxo, halo or alkyl optionally substituted with oxo, halo, amino, hydroxyl, or alkoxy.

[0058] Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to ((substituted aryl)substituted aryl)substituted aryl. Similarly, the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5

fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term "substituted" may describe other chemical groups defined herein.

[0059] In certain embodiments, as used herein, the phrase "one or more" refers to one to five. In certain embodiments, as used herein, the phrase "one or more" refers to one to three.

[0060] Any compound or structure given herein, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. These forms of compounds may also be referred to as "isotopically enriched analogs." Isotopically labeled compounds have structures depicted herein, except that one or more (e.g., one to five or one to three) atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

[0061] The term "isotopically enriched analogs" includes "deuterated analogs" of compounds described herein in which one or more (e.g., one to five or one to three) hydrogens is/are replaced by deuterium, such as a hydrogen on a carbon atom. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound when administered to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more (e.g., one to five or one to three) hydrogens have been replaced by deuterium.

[0062] Deuterium labelled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F, ^{3}H, ^{11}C labeled compound may be useful for PET or SPECT or other imaging studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-

isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in a compound described herein.

[0063] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0064] In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0065] "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0066] The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like. Salts derived from organic acids include, e.g., acetic acid, propionic acid, gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines (i.e., NH_2(alkyl)), dialkyl amines (i.e., $HN(alkyl)_2$), trialkyl amines (i.e., $N(alkyl)_3$), substituted alkyl amines (i.e., NH_2(substituted alkyl)),

di(substituted alkyl) amines (i.e., HN(substituted alkyl)$_2$), tri(substituted alkyl) amines (i.e., N(substituted alkyl)$_3$), alkenyl amines (i.e., NH$_2$(alkenyl)), dialkenyl amines (i.e., HN(alkenyl)$_2$), trialkenyl amines (i.e., N(alkenyl)$_3$), substituted alkenyl amines (i.e., NH$_2$(substituted alkenyl)), di(substituted alkenyl) amines (i.e., HN(substituted alkenyl)$_2$), tri(substituted alkenyl) amines (i.e., N(substituted alkenyl)$_3$, mono-, di- or tri-cycloalkyl amines (i.e., NH$_2$(cycloalkyl), HN(cycloalkyl)$_2$, N(cycloalkyl)$_3$), mono-, di- or tri- arylamines (i.e., NH$_2$(aryl), HN(aryl)$_2$, N(aryl)$_3$) or mixed amines, etc. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0067] The term "hydrate" refers to the complex formed by the combining of a compound described herein and water.

[0068] A "solvate" refers to an association or complex of one or more solvent molecules and a compound of the disclosure. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, dimethylsulfoxide, ethyl acetate, acetic acid and ethanolamine.

[0069] Some of the compounds exist as tautomers. Tautomers are in equilibrium with one another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown and regardless of the nature of the equilibrium among tautomers, the compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

[0070] The compounds of the invention, or their pharmaceutically acceptable salts include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0071] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention

contemplates various stereoisomers and mixtures thereof and includes "enantiomers," which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

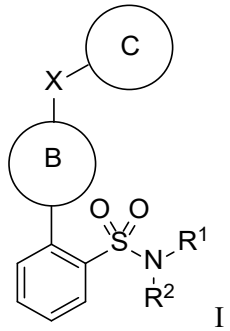
[0072] "Diastereomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0073] Relative centers of the compounds as depicted herein are indicated graphically using the "thick bond" style (bold or parallel lines) and absolute stereochemistry is depicted using wedge bonds (bold or parallel lines).

[0074] "Prodrugs" means any compound which releases an active parent drug according to a structure described herein *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound described herein are prepared by modifying functional groups present in the compound described herein in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds described herein wherein a hydroxy, amino, carboxyl, or sulfhydryl group in a compound described herein is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate and benzoate derivatives), amides, guanidines, carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds described herein and the like. Preparation, selection and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985; and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, each of which are hereby incorporated by reference in their entirety.

[0075] "Idiopathic pulmonary fibrosis" or "IPF" refers to a chronic, progressive fibrosing interstitial pneumonia of the lungs.

[0076] In some embodiments, provided is a compound of Formula I:



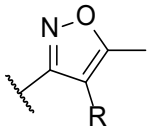
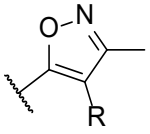
I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

X is $-CH_2-$;

Ring B is C_{5-10} cycloalkyl, 4- to 9-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein each cycloalkyl, heterocyclyl, or heteroaryl is independently optionally substituted with one to six Z^1;

Ring C is 4- to 9-membered heterocyclyl or 5- to 10-membered heteroaryl; wherein the 4- to 9-membered heterocyclyl or 5- to 10-membered heteroaryl is independently optionally substituted with one to six Z^1;

R^1 is  or  , where R is C_{1-6} alkyl or halo;

R^2 is hydrogen or alkoxyalkyl;

each Z^1 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxyalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-C(O)N(R^{10})_2$, $-NR^{10}C(O)R^{10}$, $-OC(O)N(R^{10})_2$, $-NR^{10}C(O)OR^{10}$, $-S(O)_{0-2}R^{10}$, $-NR^{10}S(O)_{1-2}R^{10}$, $-NR^{10}C(O)N(R^{10})_2$, or $-NR^{10}S(O)_{1-2}N(R^{10})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{10} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each Z^{1a} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10a}$, $-N(R^{10a})_2$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-OC(O)R^{10a}$, $-C(O)N(R^{10a})_2$, $-NR^{10}C(O)R^{10a}$, $-OC(O)N(R^{10a})_2$, $-NR^{10a}C(O)OR^{10a}$, $-S(O)_{0-2}R^{10a}$, $-NR^{10a}S(O)_{1-2}R^{10a}$, $-NR^{10a}C(O)N(R^{10a})_2$, or $-NR^{10a}S(O)_{1-2}N(R^{10a})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

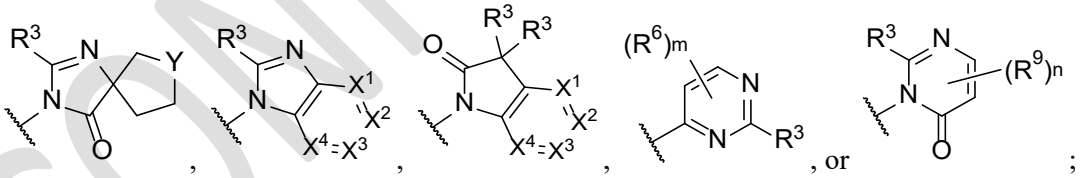
each R^{10a} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, -OH, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C_{1-6} alkyl, -L-C_{2-6} alkenyl, -L-C_{2-6} alkynyl, -L-C_{1-6} haloalkyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, $-S(O)_2-$, -N(C_{1-6} alkyl)-, -N(C_{2-6} alkenyl)-, -N(C_{2-6} alkynyl)-, -N(C_{1-6} haloalkyl)-, -N(C_{3-10} cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C_{1-6} alkyl)-, -C(O)N(C_{2-6} alkenyl)-, -C(O)N(C_{2-6} alkynyl)-, -C(O)N(C_{1-6} haloalkyl)-, -C(O)N(C_{3-10} cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -OC(O)NH-, -OC(O)N(C_{1-6} alkyl)-, -OC(O)N(C_{2-6} alkenyl)-, -OC(O)N(C_{2-6} alkynyl)-, -OC(O)N(C_{1-6} haloalkyl)-, -OC(O)N(C_{3-10} cycloalkyl)-, -OC(O)N(heterocyclyl)-, -OC(O)N(aryl)-, -OC(O)N(heteroaryl)-, -NHC(O)-, -N(C_{1-6} alkyl)C(O)-, -N(C_{2-6} alkenyl)C(O)-, -N(C_{2-6} alkynyl)C(O)-, -N(C_{1-6} haloalkyl)C(O)-, -N(C_{3-10} cycloalkyl)C(O)-, -N(heterocyclyl)C(O)-, -N(aryl)C(O)-, -N(heteroaryl)C(O)-, -NHC(O)O-, -N(C_{1-6} alkyl)C(O)O-, -N(C_{2-6} alkenyl)C(O)O-, -N(C_{2-6} alkynyl)C(O)O-, -N(C_{1-6} haloalkyl)C(O)O-, -N(C_{3-10} cycloalkyl)C(O)O-, -N(heterocyclyl)C(O)O-, -N(aryl)C(O)O-, -N(heteroaryl)C(O)O-, -NHC(O)NH-, -NHS(O)-, $-NHS(O)_2NH$, -S(O)NH-, $-S(O)_2NH$, -NHS(O)NH-, or $-NHS(O)_2NH$-;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five halo, cyano, hydroxy, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl.

[0077] In some embodiments, provided is a compound of Formula I, wherein Ring C is:



where

Y is $-CH_2-$ or $-S(O)_2-$;

X^1, X^2, X^3, and X^4 are independently chosen from CR^4 and N, provided that at least three of X^1, X^2, X^3, and X^4 are CR^4;

R^3 is C_{1-6} alkyl, C_{3-7} cycloalkyl, or (C_{3-7} cycloalkyl)alkyl;

each R^4 is independently hydrogen, halo, C_{1-6} alkyl optionally substituted with 1 to 3 halo, C_{1-6} alkoxy optionally substituted with 1 to 3 halo, cyano, $-N(R^5)_2$, $-NH-S(O)_2-R^5$, $-C(O)OR^5$, or $-C(O)NR^5{}_2$;

each R^5 is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each R^6 is independently C_{1-6} alkyl optionally substituted with $-C(O)NR^7_2$;

each R^7 is independently hydrogen, C_{1-6} alkyl, 4- to 11-membered heterocyclyl, C_{3-7} cycloalkyl, 5- to 9-membered heteroaryl, or C_{6-10} aryl, wherein each heterocyclyl contains from 1 to 3 heteroatoms selected from O, N, NR^8, and S, and wherein each heteroaryl contain from 1 to 3 heteroatoms selected from O, N, and NR^8;

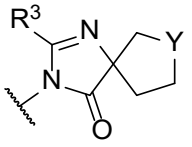
or two R^7, together with the nitrogen to which they attach, form a 4- to 9-membered heterocyclyl optionally containing 1 to 2 additional heteroatoms selected from O, NR^8, and S;

each R^8 is independently hydrogen, C_{1-6} alkyl, or C_{3-7} cycloalkyl;

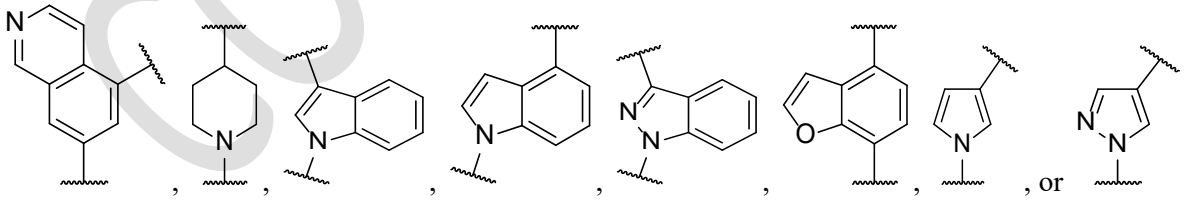
each R^9 is independently $-C(O)NR^7_2$ or C_{1-6} alkyl optionally substituted with $-C(O)NR^7_2$;

m is 0, 1, or 2; and

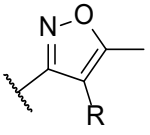
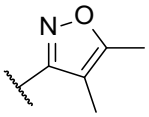
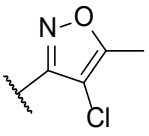
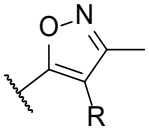
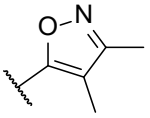
n is 0, 1, or 2.

[0078] In some or any embodiments presented herein, the moiety  comprises stereoisomers and all such stereoisomers and mixtures of stereoisomers are included within the scope of embodiments presented herein.

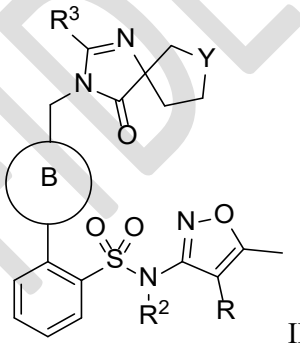
[0079] In some embodiments, provided is a compound of Formula I, Ring B is:



optionally substituted with C_{1-6} alkyl or C_{1-6} alkoxyalkyl,.

[0080] In some embodiments, provided is a compound of Formula I, wherein R^1 is  . In some embodiments, provided is a compound of Formula I, wherein R^1 is  . In some embodiments, provided is a compound of Formula I, wherein R^1 is  . In some embodiments, provided is a compound of Formula I, wherein R^1 is  . In some embodiments, provided is a compound of Formula I, wherein R^1 is  .

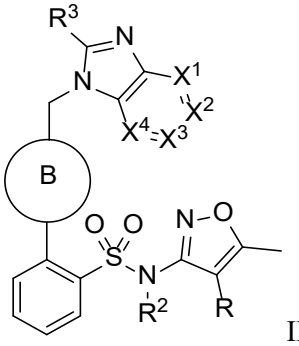
[0081] In some embodiments, provided is a compound represented by Formula II:



II

wherein R, R^2, R^3, Y, and Ring B are each independently as defined herein.

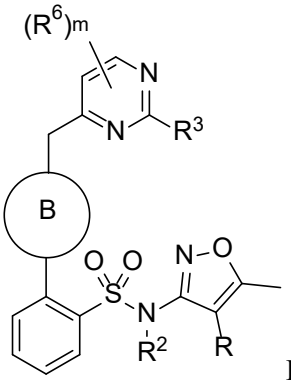
[0082] In some embodiments, provided is a compound represented by Formula III:



III

wherein R, R^2, R^3, X^1, X^2, X^3, X^4, and Ring B are each independently as defined herein.

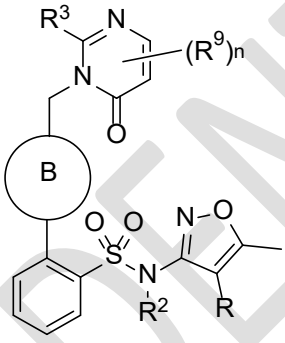
[0083] In some embodiments, provided is a compound represented by Formula IV:



IV

wherein m, R, R^2, R^3, R^6, and Ring B are each independently as defined herein.

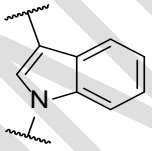
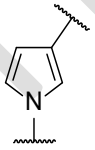
[0084] In some embodiments, provided is a compound represented by Formula V:

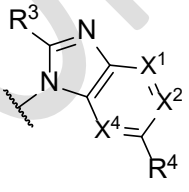
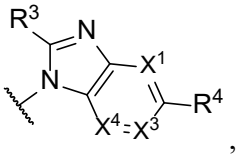
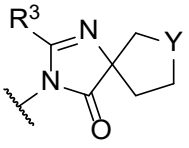


V

wherein n, R, R^2, R^3, R^9, and Ring B are each independently as defined herein.

[0085] In some embodiments of Formula I

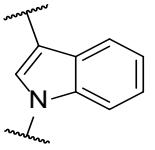
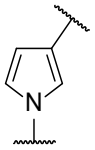
ring B is selected from  and  ; and

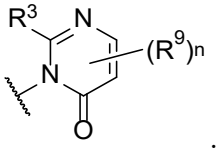
ring C is selected from  ,  , and  .

[0086] In some embodiments, Y is CH_2. In some embodiments, Y is $S(O)_2$.

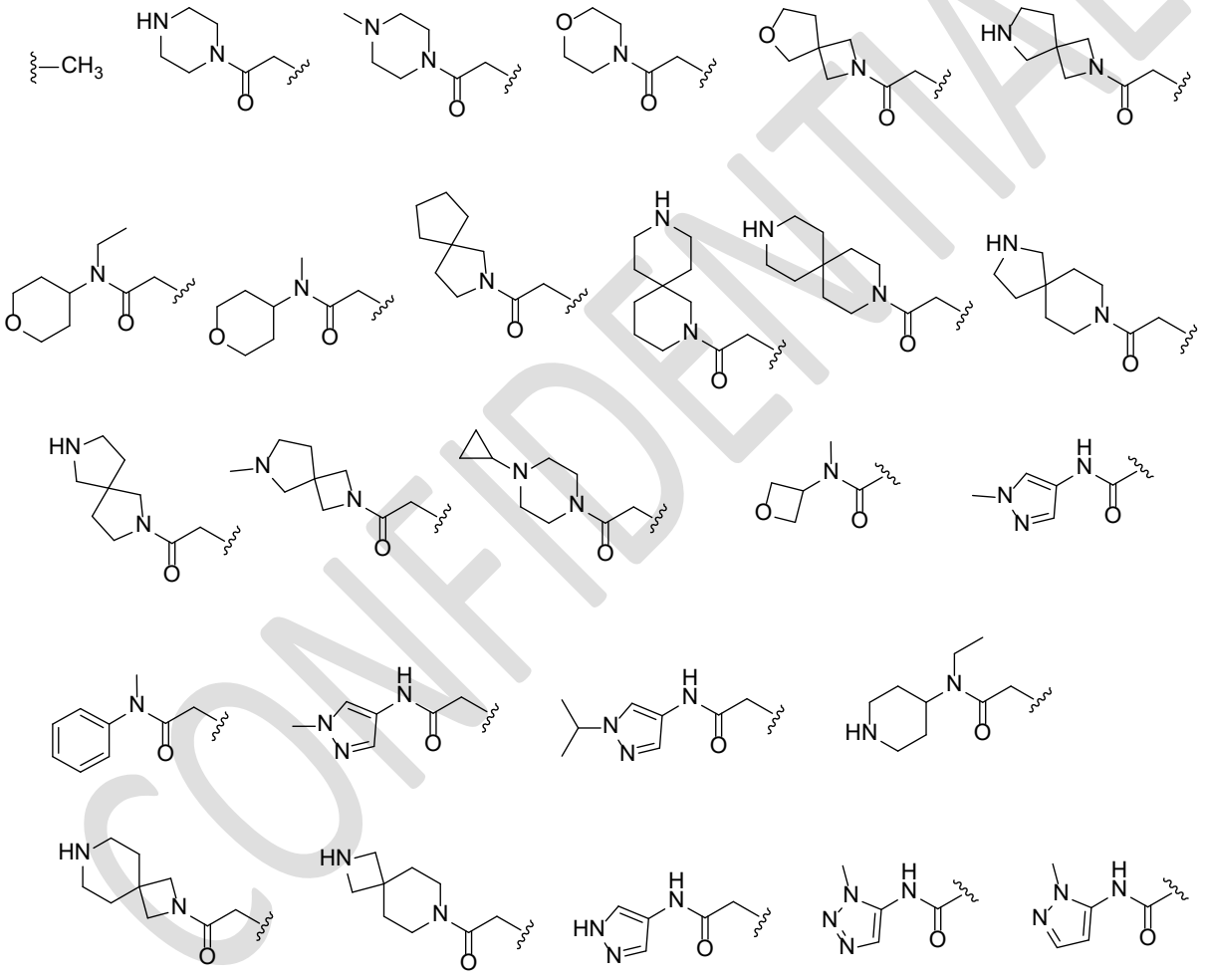
[0087] In some embodiments, R^4 is selected from $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ haloalkyl, halo, cyano, $-OR^{10}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})_2$, and $-NR^{10}S(O)_{1\text{-}2}R^{10}$. In some embodiments, R^4 is selected from $-CH_3$, $-CH_2CH_3$, $-CF_3$, -CN, halo, $-OCH_3$, $-OCF_3$, -C(O)OH, and $-C(O)NH_2$.

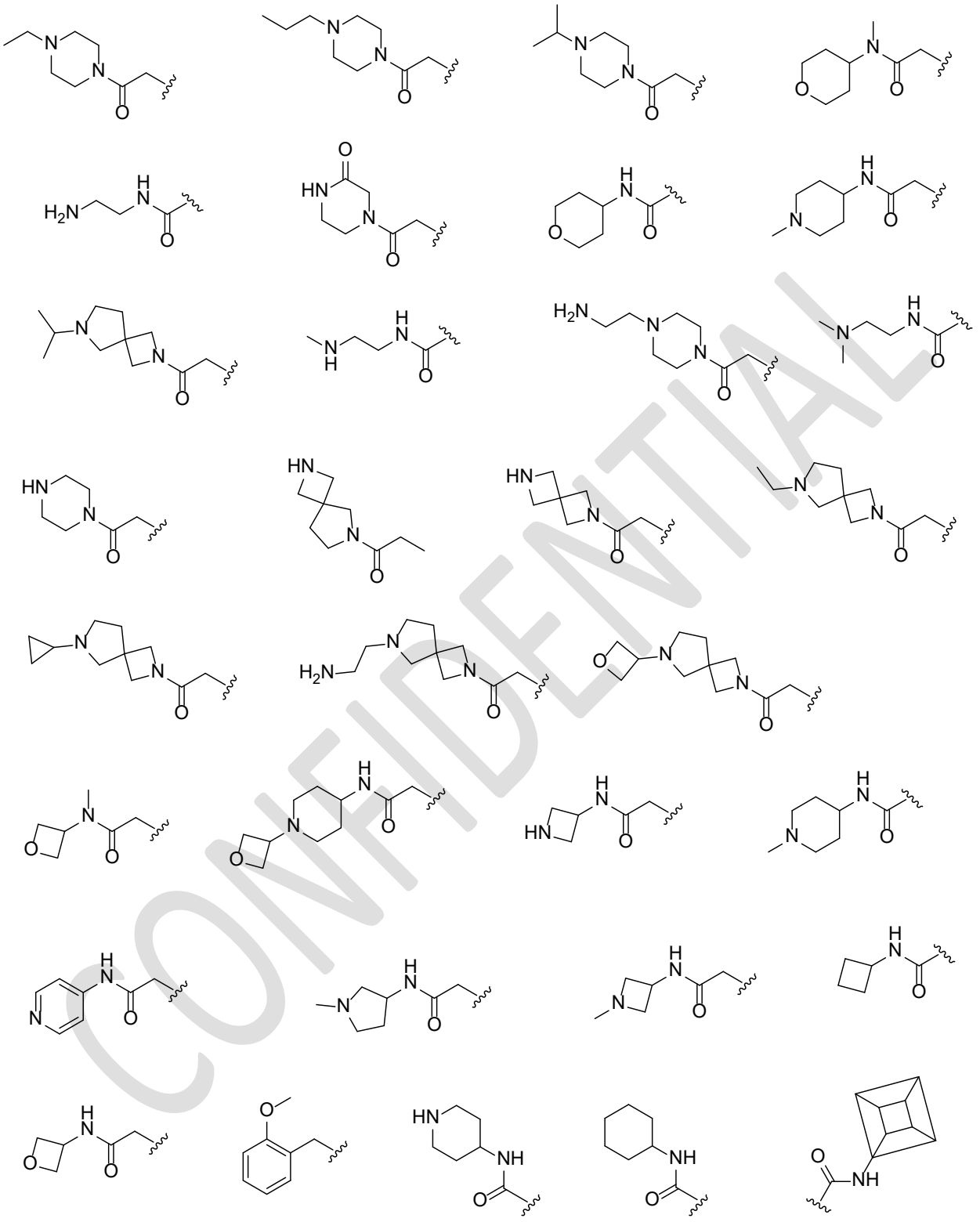
[0088] In some embodiments of Formula I

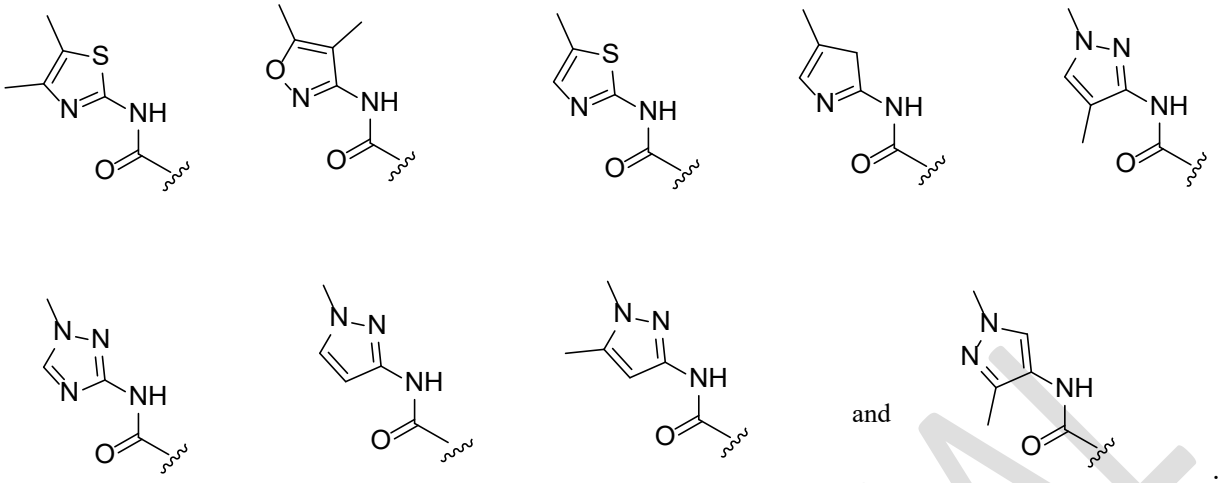
ring B is selected from  and  ; and

ring C is  .

[0089] In some embodiments, R^9 is selected from







.

[0090] In some embodiments, R^3 is selected from

. In some embodiments, R^3 is selected from

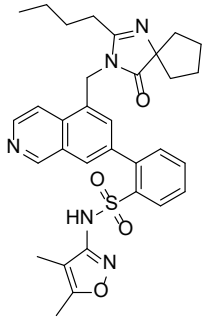
[0091]

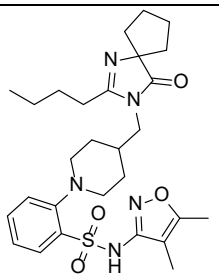
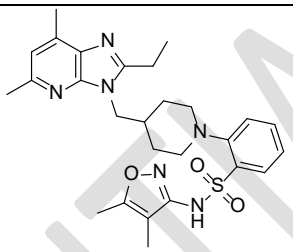
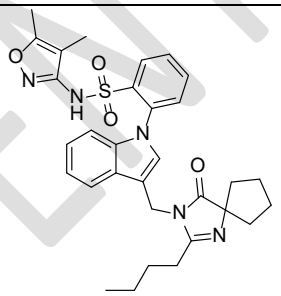
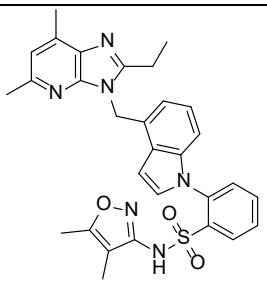
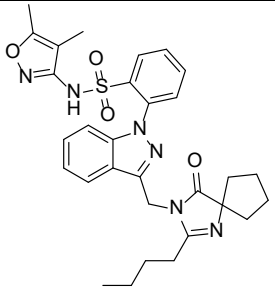
.

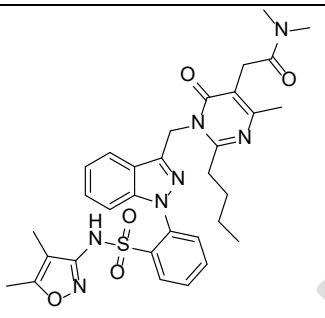
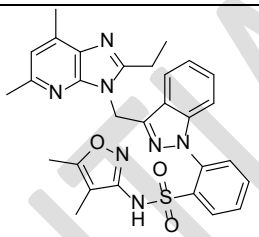
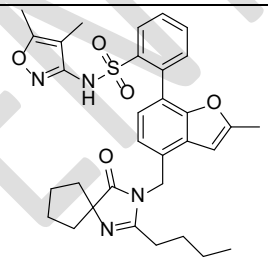
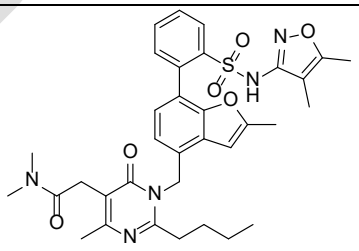
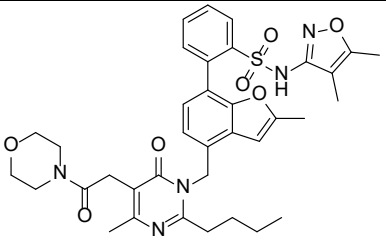
[0092] In some embodiments, R^2 is hydrogen. In some embodiments, n is 1 or 2.

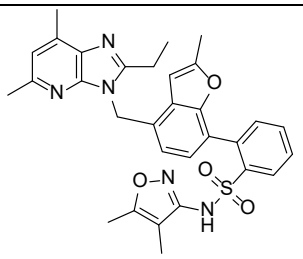
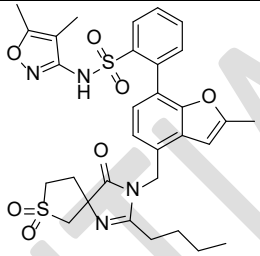
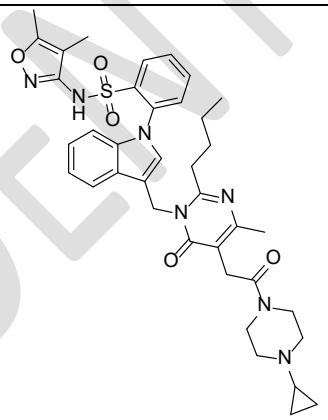
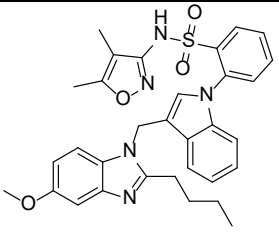
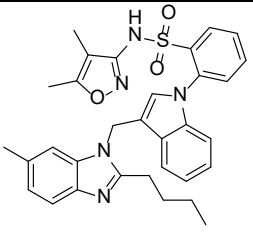
[0093] Provided herein is a compound selected from Table 1, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

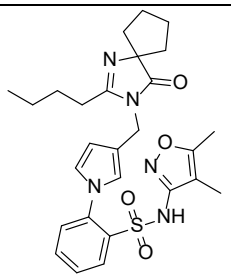
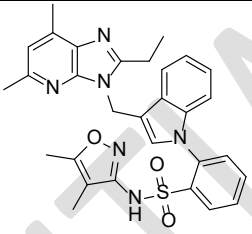
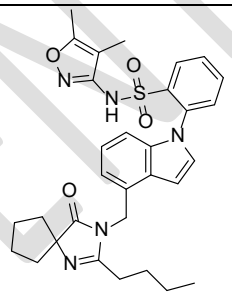
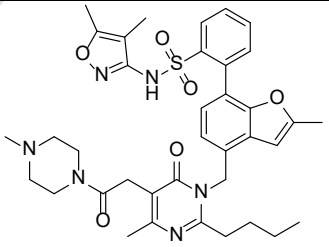
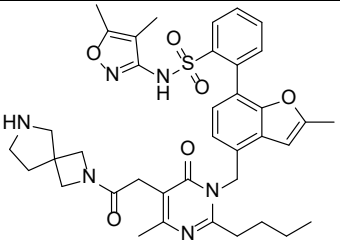
TABLE 1

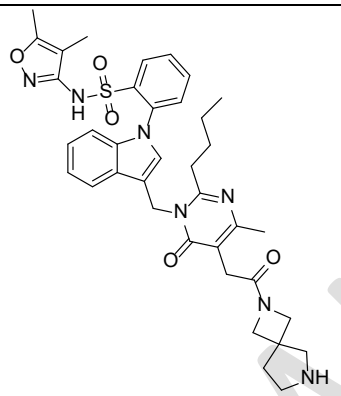
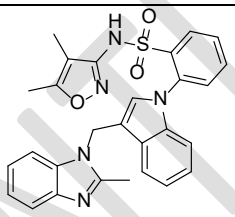
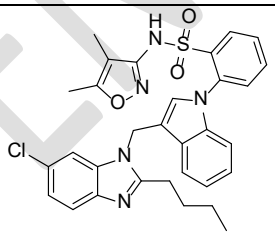
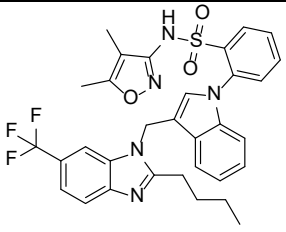
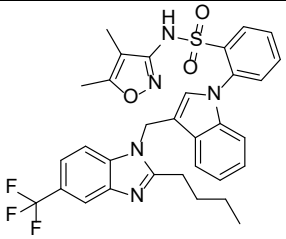
Compound Number	Structure
1	

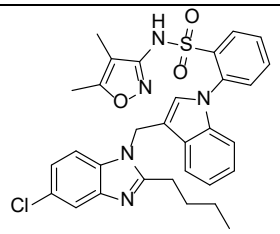
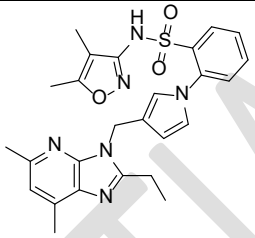
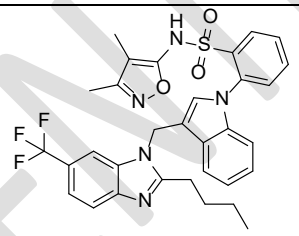
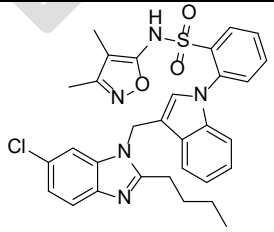
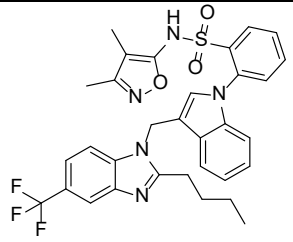
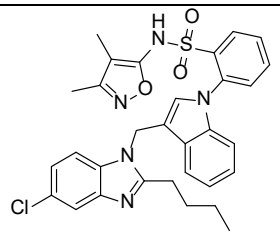
Compound Number	Structure
2	
3	
4	
5	
6	

Compound Number	Structure
7	
8	
9	
10	
11	

Compound Number	Structure
12	
13	
14	
15	
16	

Compound Number	Structure
17	
18	
19	
20	
21	

Compound Number	Structure
22	
23	
24	
25	
26	

Compound Number	Structure
27	
28	
29	
30	
31	
32	

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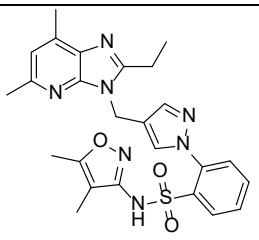
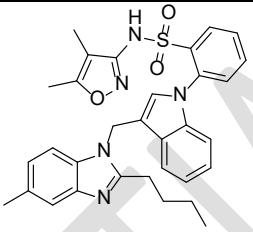
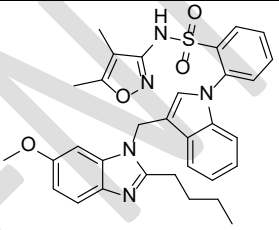
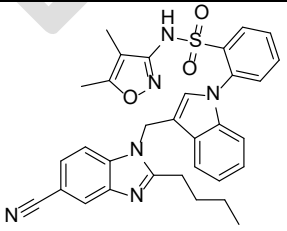
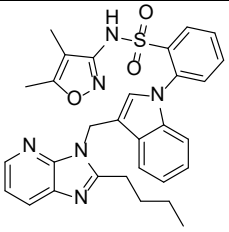
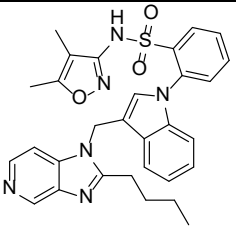
33	
34	
35	
36	
37	
38	

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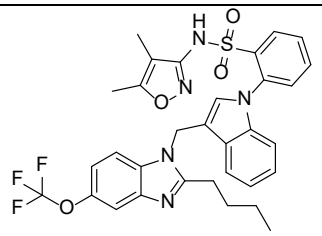
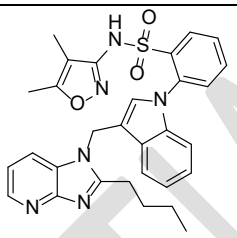
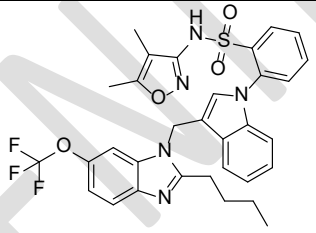
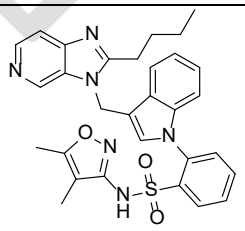
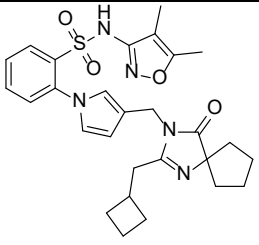
39	
40	
41	
42	
43	

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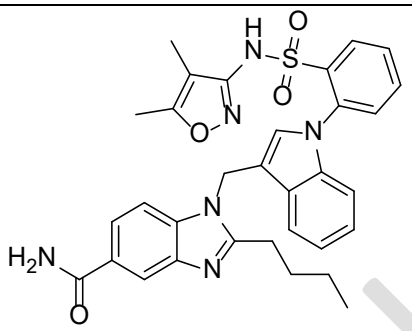
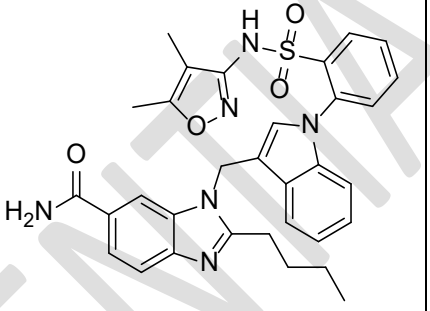
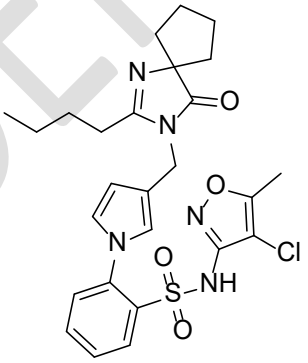
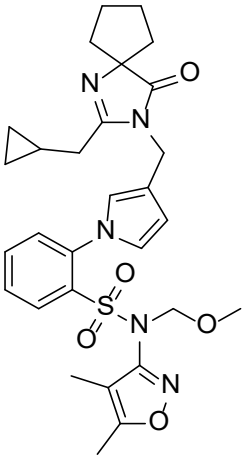
44	
45	
46	
47	

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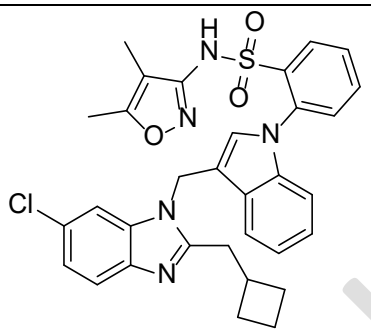
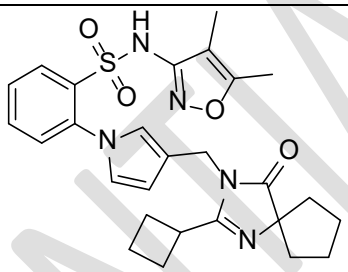
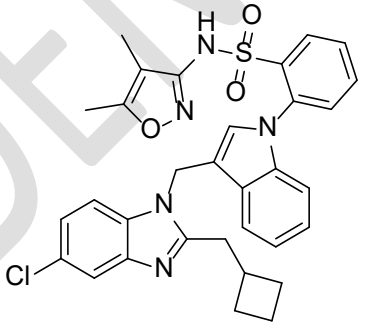
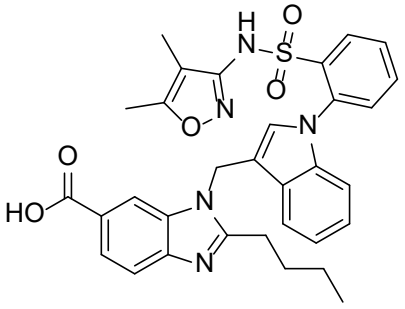
48	
49	
50	
51	

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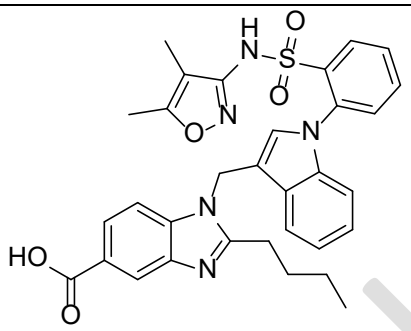
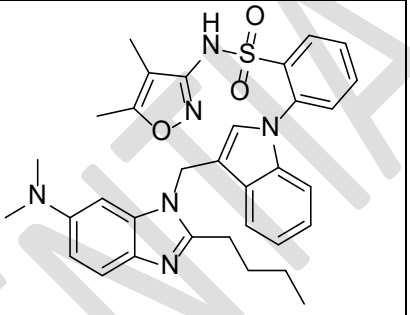
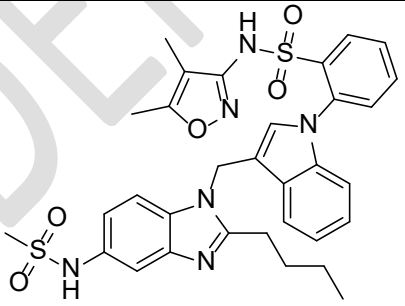
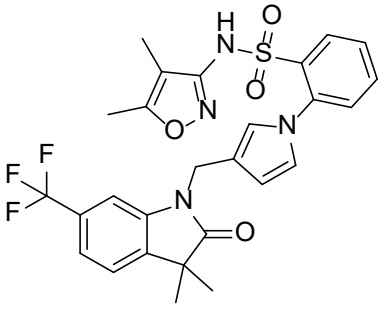
52	
53	
54	
55	

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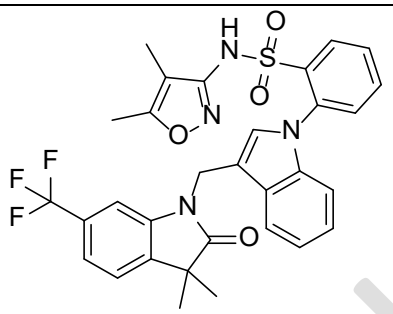
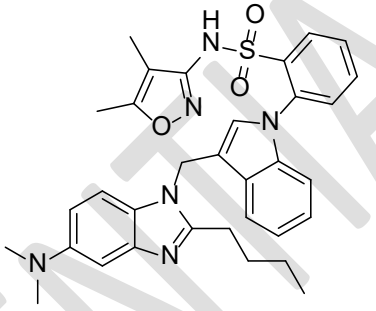
56	
57	

[0094] Provided herein is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable carrier.

Methods of Treatment

[0095] As used herein, the term "administration" refers to introducing an agent into a patient. For example, a therapeutic amount can be administered to the patient, which can be determined by the treating physician, medical professional, or the like. In some embodiments, an oral route of administration is preferred. The related terms and phrases "administering" and "administration of," when used in connection with a compound or tablet (and grammatical equivalents) refer both to direct administration, which may be administration to a patient by a medical professional or by self-administration by the patient, and/or to indirect administration, which may be the act of prescribing a drug. Administration entails delivery to the patient of the drug.

[0096] "Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more

clinical symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (e.g., metastasis) of the disease or condition); and/or c) relieving the disease, that is, causing the regression of clinical symptoms (e.g., ameliorating the disease state, providing partial or total remission of the disease or condition, enhancing effect of another medication, delaying the progression of the disease, increasing the quality of life and/or prolonging survival. In one embodiment, treating does not encompass preventing.

[0097] "Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0098] "Subject" or "patient" refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation, or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal. In certain embodiments, the subject is a human.

[0099] The term "therapeutically effective amount" or "effective amount" of a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof means an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration of symptoms or slowing of disease progression. For example, a therapeutically effective amount may be an amount sufficient to decrease a symptom of a disease or condition of as described herein. The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one of ordinary skill in the art.

[0100] The term "dose" or "dosage" refers to the total amount of an active agent (e.g., the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof) administered to a patient in a single day (24-hour period). The desired dose can be administered once daily. In some embodiments, the desired dose may be administered in one, two, three, four or more sub-doses at appropriate intervals throughout the day, where the cumulative amount of the sub-doses equals the amount of the desired dose administered in a single day. The terms "dose" and "dosage" are used interchangeably herein.

[0101] The methods described herein may be applied to cell populations *in vivo* or *ex vivo*. "*In vivo*" means within a living individual, as within an animal or human. In this context, the methods described herein may be used therapeutically in an individual. "*Ex vivo*" means outside of a living individual. Examples of ex vivo

cell populations include in vitro cell cultures and biological samples including fluid or tissue samples obtained from individuals. Such samples may be obtained by methods well known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine and saliva. In this context, the compounds and compositions described herein may be used for a variety of purposes, including therapeutic and experimental purposes. For example, the compounds and compositions described herein may be used *ex vivo* to determine the optimal schedule and/or dosing of administration of a compound of the present disclosure for a given indication, cell type, individual, and other parameters. Information gleaned from such use may be used for experimental purposes or in the clinic to set protocols for *in vivo* treatment. Other *ex vivo* uses for which the compounds and compositions described herein may be suited are described below or will become apparent to those skilled in the art. The selected compounds may be further characterized to examine the safety or tolerance dosage in human or non-human subjects. Such properties may be examined using commonly known methods to those skilled in the art.

[0102] Provided herein are methods of treating idiopathic pulmonary fibrosis (IPF), comprising administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, to a patient in need thereof.

[0103] It is contemplated that in treating patients with a DARA agent such as compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, certain side effects associated with known therapy may be avoided. For example, diarrhea, gastrointestinal distress, nausea, and photosensitivity like adverse events are not reported with approved endothelin receptor antagonists, and diarrhea and dyspepsia are infrequently reported adverse drug reactions associated with approved angiotensin antagonists. Thus in one embodiment is provided methods of treating idiopathic pulmonary fibrosis in a patient in need thereof, comprising administering a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and having reduced side effects in said patient, selected from diarrhea, gastrointestinal distress, nausea, photosensitivity, and combinations thereof. This reduction is compared to current IPF therapies, e.g. nintedanib.

[0104] Also provided herein are methods of treating idiopathic pulmonary fibrosis, comprising administering a composition, comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable carrier, to a patient in need thereof.

[0105] In some embodiments, the therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or

prodrug thereof, treats idiopathic pulmonary fibrosis in a patient in need thereof by suppressing lung epithelial inflammation and fibrosis.

[0106] In some embodiments, the therapeutically effective amount of compound of Formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, treats idiopathic pulmonary fibrosis in a patient in need thereof by suppressing lung myofibroblast phenotypic transition.

[0107] The compounds of formula I, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, are antagonists of both endothelin and angiotensin, and are useful in the treatment of conditions associated with increased ET levels and/or increased angiotensin levels and treatment of all endothelin-dependent or angiotensin -dependent disorders. In some embodiments, the compounds provided herein are useful for treating hypertension, and also in treatment of portal hypertension, hypertension secondary to treatment with erythropoietin, low renin hypertension, and pulmonary arterial hypertension (PAH),.

[0108] In some embodiments, the compounds provided herein are useful in the treatment of disorders related to renal, glomerular, and mesangial cell function, including acute (such as ischemic, nephrotoxic, or glomerulonephritis) and chronic (such as diabetic, hypertensive or immune-mediated) renal failure, diabetic nephropathy, glomerular injury, renal damage secondary to old age or related to dialysis, nephrosclerosis (especially hypertensive nephrosclerosis), nephrotoxicity (including nephrotoxicity related to imaging and contrast agents and to cyclosporine), renal ischemia, primary vesicoureteral reflux, proteinuric glomerular diseases, glomerulosclerosis, focal segmental glomerulosclerosis (FSGS),kidney disease such as chronic kidney disease (CKD) and the like. In some embodiments, the compounds provided herein are useful in the treatment of disorders related to paracrine and endocrine function, diabetic nephropathy, hypertension-induced nephropathy, IGA-induced nephropathy, endotoxemia or endotoxin shock, hemorrhagic shock, in alleviation of pain associated with cancer, such as the pain associated with prostate cancer, and bone pain associated with bone cancer, in the prevention and/or reduction of end-organ damage associated with the cell-proliferative effects of endothelin, hypoxic and ischemic disease, for example, cardiac, renal and cerebral ischemia, and reperfusion (such as that occurring following cardiopulmonary bypass surgery), coronary and cerebral vasospasm, and the like.

[0109] In some embodiments, the compounds provided herein are useful as anti-arrhythmic agents; anti-anginal agents; anti-fibrillatory agents; anti-asthmatic agents; anti-atherosclerotic; and anti-arteriosclerotic agents (including anti-transplantation arteriosclerotic agents); additives to cardioplegic solutions for cardiopulmonary bypasses; adjuncts to thrombolytic therapy; and anti-diarrheal agents. The compounds of this invention may be useful in therapy for myocardial infarction; therapy for peripheral vascular disease

(e.g., Raynaud's disease, intermittent claudication, and Takayasu's disease); treatment of cardiac hypertrophy (e.g., hypertrophic cardiomyopathy); treatment of primary pulmonary hypertension (e.g., plexogenic, embolic) in adults and in newborns, and pulmonary hypertension secondary to heart failure, radiation, and chemotherapeutic injury, or other trauma; treatment of central nervous system vascular disorders, such as stroke, migraine, and subarachnoid hemorrhage; treatment of central nervous system behavioral disorders; treatment of gastrointestinal diseases such as ulcerative colitis, Crohn's disease, gastric mucosal damage, ulcer, inflammatory bowel disease, and ischemic bowel disease; treatment of gall bladder or bile duct-based diseases such as cholangitis; treatment of pancreatitis; regulation of cell growth; treatment of benign prostatic hypertrophy; restenosis following angioplasty or following any procedure including transplantation and stenting; therapy for congestive heart failure including inhibition of fibrosis; inhibition of left ventricular dilatation, remodeling, and dysfunction; treatment of hepatotoxicity and sudden death; treatment of sickle cell disease including the initiation and/or evolution of the pain crises of this disease; treatment of the deleterious consequences of ET-producing tumors, such as hypertension resulting from hemangiopericytoma; treatment of early and advanced liver disease and injury including attendant complications (e.g., hepatotoxicity, fibrosis and cirrhosis); treatment of spastic diseases of the urinary tract and/or bladder; treatment of hepatorenal syndrome; treatment of immunological diseases involving vasculitis such as lupus, systemic sclerosis, mixed cryoglobulinemia; and treatment of fibrosis associated with renal dysfunction and hepatotoxicity. The compounds of this invention are useful in therapy for metabolic and neurological disorders; cancer; insulin-dependent and non-insulin-dependent diabetes mellitus; neuropathy; retinopathy; epilepsy; hemorrhagic and ischemic stroke; bone remodeling; psoriasis; and chronic inflammatory diseases, such as arthritis, rheumatoid arthritis, osteoarthritis, sarcoidosis, and eczematous dermatitis (all types of dermatitis).

[0110] In some embodiments, the compounds described herein are useful in the treatment of disorders involving bronchoconstriction, and disorders of chronic or acute pulmonary inflammation, such as chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS), sexual dysfunction in both men (erectile dysfunction, for example, due to diabetes mellitus, spinal cord injury, radical prostatectomy, psychogenic etiology, or any other cause) and women by improving blood flow to the genitalia, especially, the corpus cavernosum.

[0111] In some embodiments, the compounds described herein are useful in the treatment of dementia, including Alzheimer's dementia, senile dementia, and vascular dementia, and in the reduction of general morbidity and/or mortality as a result of any of the conditions described above.

[0112] In some embodiments, the patient is 50 years of age or older. In some embodiments, the patient is less than 50 years of age.

[0113] In some embodiments, the patient is a smoker. In some embodiments, the patient is not a smoker.

[0114] In some embodiments, the patient also suffers from gastroesophageal reflux disease (GERD). In some embodiments, the patient does not also suffer from gastroesophageal reflux disease.

[0115] In some embodiments, the patient requires supplemental oxygen. In some embodiments, the patient does not require supplemental oxygen.

[0116] In some embodiments, the patient has a genetic mutation in one or more of the MUC5B, TERT, TERC, RTEL1, PARN, SFTPC, or SFTPA2 genes.

[0117] In some embodiments, the patient has a genetic mutation in the MUC5B gene. In some embodiments, the patient has a genetic mutation in the TERT gene. In some embodiments, the patient has a genetic mutation in the TERC gene. In some embodiments, the patient has a genetic mutation in the RTEL1 gene. In some embodiments, the patient has a genetic mutation in the PARN gene. In some embodiments, the patient has a genetic mutation in the SFTPC gene. In some embodiments, the patient has a genetic mutation in the SFTPA2 gene. In some embodiments, the patient has a genetic mutation in more than one gene, said gene selected from the MUC5B, TERT, TERC, RTEL1, PARN, SFTPC, and SFTPA2 genes.

[0118] In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is administered once daily. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is administered over two doses in a day.

[0119] In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is formulated for oral administration. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is in tablet form or capsule form. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is formulated as an amorphous solid dispersion.

[0120] In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is formulated for parenteral administration.

[0121] In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is formulated for inhalation.

[0122] In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is about 50 mg/day to about 1000 mg/day. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is about 100 mg/day to about 900 mg/day. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is about 200 mg/day to about 800 mg/day. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is about 400 mg/day to about 600 mg/day.

[0123] In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is about 200 mg/day. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is about 400 mg/day. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is about 600 mg/day. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is about 800 mg/day.

[0124] In some embodiments, the dual-acting angiotensin and endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is dosed at about 400 mg/day to a patient in need thereof, in order to treat idiopathic pulmonary fibrosis, while reducing the occurrence of at least one known side effect of currently known IPF therapies, including, but not limited to, diarrhea, gastrointestinal distress, nausea, disinterest in eating, and photosensitivity.

[0125] In some embodiments, methods provided herein further comprise administering one or more of an additional therapeutic agent. In some embodiments, the additional therapeutic agent is an anti-inflammatory agent.

[0126] In some embodiments, the anti-inflammatory agent is a corticosteroid, such as beclomethasone, betamethasone, budesonide, clobetasol, flunisolide, fluocinolone, fluocinonide, fluticasone, halobetasol, hydrocortisone, methylprednisone, mometasone, prednisolone, prednisone, and triamcinolone. In some embodiments, the anti-inflammatory agent is a non-steroidal anti-inflammatory (NSAIDs), such as a non-selective COX inhibitor or a selective COX-2 inhibitor. Non-selective COX inhibitors include, but are not limited to, salicylic acid derivates (e.g., aspirin, sodium salicylates, choline magnesium trisalicylate, salsalate, diflunisal, sulfasalazine, mesalamine, and olsalazine), para-aminophenol derivatives (e.g., acetaminophen), indole and indene acetic acids (e.g., tolmetin, diclofenac, and ketorolac), heteroaryl acetic acids (e.g.,

flurbiprofen, ketoprofen, fenprofen, ibuprofen, naproxen, and oxaprozin), anthranilic acids or fenamates (e.g., mefenamic acid and meclofenamic acid), enolic acids (e.g., piroxicam and meloxicam), and alkanones (e.g., nabumetone). Selective COX-2 inhibitors include, but are not limited to, diaryl-substituted pyrazoles (e.g., celecoxib), indole acetic acids (e.g., etodolac), and sulfonanilides (e.g., nimesulide).

[0127] In some embodiments, the additional therapeutic agent is an immunosuppressive agent. Non-limiting examples of immunosuppressive agents include methotrexate, cyclophosphamide, mizoribine, chlorambucil, cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, sirolimus, deoxyspergualin, leflunomide, and its malononitriloamide analogs.

[0128] It is understood that modifications which do not substantially affect the activity of the various embodiments of this disclosure are also included within the definition of the disclosure provided herein. Accordingly, the following examples are intended to illustrate but not limit the present disclosure.

Kits

[0129] Provided herein are also kits that include a compound of the disclosure, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, and suitable packaging. In certain embodiments, a kit further includes instructions for use. In one aspect, a kit includes a compound of the disclosure, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof, and a label and/or instructions for use of the compounds in the treatment of the indications, including the diseases or conditions, described herein.

[0130] Provided herein are also articles of manufacture that include a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers or prodrug thereof in a suitable container. The container may be a vial, jar, ampoule, preloaded syringe and intravenous bag.

Pharmaceutical Compositions and Modes of Administration

[0131] Compounds provided herein are usually administered in the form of pharmaceutical compositions. Thus, provided herein are also pharmaceutical compositions that contain one or more of the compounds described herein a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or prodrug thereof and one or more pharmaceutically acceptable vehicles selected from carriers, adjuvants and excipients. Suitable pharmaceutically acceptable vehicles may include, for example, inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. See, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0132] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical composition may be administered by various methods including, for example, rectal, buccal, intranasal, and transdermal routes. In certain embodiments, the pharmaceutical composition may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[0133] One mode for administration is parenteral, for example, by injection. The forms in which the pharmaceutical compositions described herein may be incorporated for administration by injection include, for example, aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[0134] Oral administration may be another route for administration of the compounds described herein. Administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0135] Some examples of suitable excipients include, e.g., lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0136] The compositions that include at least one compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Another formulation for use in the methods disclosed herein employ transdermal delivery devices (“patches”). Such transdermal patches may be used to provide

continuous or discontinuous infusion of the compounds described herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0137] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0138] The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0139] Compositions for inhalation or insufflation may include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described herein. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. In other embodiments, compositions in pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

Dosing

[0140] The specific dose level of a compound of the present application for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the subject undergoing therapy. For example, a

dosage may be expressed as a number of milligrams of a compound described herein per kilogram of the subject's body weight (mg/kg). Dosages of between about 0.1 and 150 mg/kg may be appropriate. In some embodiments, about 0.1 and 100 mg/kg may be appropriate. In other embodiments a dosage of between 0.5 and 60 mg/kg may be appropriate. In some embodiments, a dosage of from about 0.0001 to about 100 mg per kg of body weight per day, from about 0.001 to about 50 mg of compound per kg of body weight, or from about 0.01 to about 10 mg of compound per kg of body weight may be appropriate. Normalizing according to the subject's body weight is particularly useful when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject.

Synthesis of the Compounds

[0141] The compounds may be prepared using the methods disclosed herein and routine modifications thereof, which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of typical compounds described herein may be accomplished as described in the following examples. If available, reagents and starting materials may be purchased commercially, e.g., from Sigma Aldrich or other chemical suppliers.

[0142] It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[0143] Additionally, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in Wuts, P. G. M., Greene, T. W., & Greene, T. W. (2006). Greene's protective groups in organic synthesis. Hoboken, N.J., Wiley-Interscience, and references cited therein.

[0144] Furthermore, the compounds of this disclosure may contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this disclosure, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like.

[0145] The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989) organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

Abbreviations

Abbreviation	**Meaning**
δ	chemical shift (ppm)
ABC	Ammonium bicarbonate
AGTR1	Angiotensin-II receptor type 1
B_2Pin_2	bis(pinacolato)diboron
DCM	dichloromethane
DEA	diethylamine
DIBAL-H	diisobutylaluminum hydride
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
d_6-DMSO	deuterated dimethylsulfoxide
EDNRA	Endothelin-1 receptor type-A
EtOAc	ethyl acetate
g	grams
GPCR	G-protein coupled receptors
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
h	hour(s)
HPLC	high performance liquid chromatography

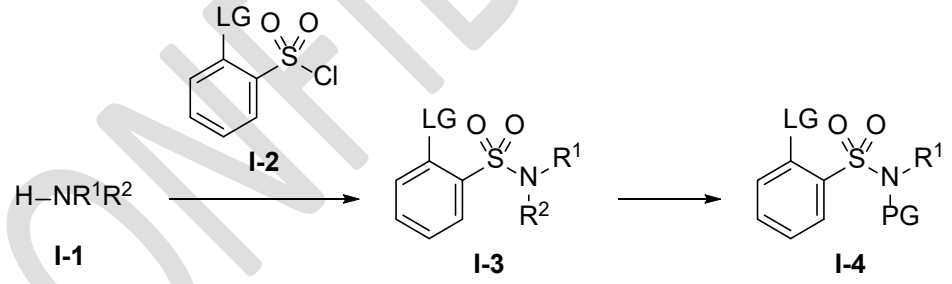
IC50	half maximal inhibitory concentration
L	liter
LC	liquid chromatography
LCMS	liquid chromatography – mass spectrometry
M	molar
MeOH	methanol
mg	milligrams
MHz	megahertz
min	minute(s)
mL	milliliter
mmol	millimole
µM	micromolar
MOMCl	chloromethyl methyl ether
MsCl	methanesulfonyl chloride
NBS	N-bromosuccinimide
nM	nanomolar
N	normal
$PdCl_2$(dppf)	1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
rt	room temperature
Rt	retention time
secs	seconds
SFC	supercritical fluid chromatography
t-Bu	tert-butyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TsCl	4-toluenesulfonyl chloride

UPLC	ultra performance liquid chromatography
UV	ultraviolet
NMR abbreviations	s = singlet
	d = doublet
	t = triplet
	q = quartet
	br = broad
	m = multiplet

General Synthesis

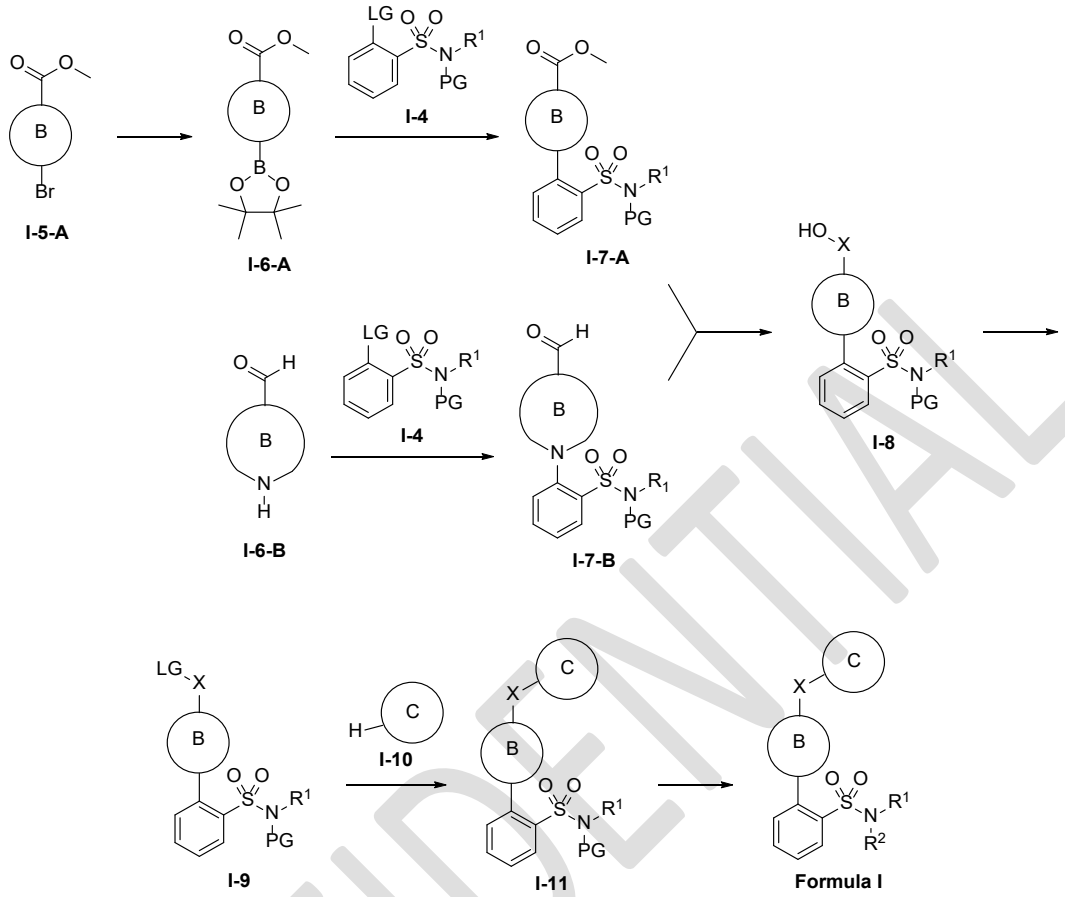
[0146] The following reactions shown in Schemes I and II illustrate a general method which can be employed for the synthesis of compounds disclosed herein. In Schemes I and II, each R^1, R^2, X, Ring A, and Ring B are independently as defined herein, LG is a leaving group (e.g., halo, such as bromo or chloro), and PG is an amine protecting group (e.g., methoxymethyl).

Scheme I



[0147] Referring to Scheme I, compound I-3 can be provided by contacting heteroaryl amine, compound I-1, with 2-halobenzenesulfonyl chloride, compound I-2, under standard basic conditions, including, but not limited to, pyridine, 4-dimethylaminopyridine, and the like. Protecting compound I-3 with an appropriate amine protecting group, including, but not limited to, a methyoxymethyl ether group, under conditions known to those of skill in the art can provide compound I-4. The use of methoxymethyl ether is illustrative only, and other conventional amine protecting groups, such as benzyl, 9-fluorenylmethoxycarbonyl (Fmoc), benzyloxycarbonyl (Cbz), p-nitrobenzyloxycarbonyl, and the like could be used.

Scheme II



[0148] Referring to Scheme II, forming phenyl-Ring B bicycle compounds of formula I-7-A, when the attachment point in Ring B is a carbon atom, proceed through general synthetic pathway A. Boronic ester compounds of formula I-6-A can be prepared by contacting bromo compounds of formula I-5-A with bis(pinacolato)diboron in the presence of a suitable catalyst, including, but not limited to, $PdCl_2(dppf)$, $PdCl_2(PPh_3)_2$, and the like, under conditions known to those of skill in the art. Suzuki coupling of boronic ester compounds of formula I-6-A with protected aryl sulfonamide compounds of formula I-4, in the presence of a suitable catalyst, including, but not limited to, $PdCl_2(dppf)$, $PdCl_2(PPh_3)_2$, and the like, under conditions known to those of skill in the art, can provide for bicyclic sulfonamide compounds of formula I-7-A.

[0149] Forming phenyl-Ring B bicycle compounds of formula I-7-B, when the attachment point in Ring B is a nitrogen atom, proceed through general synthetic pathway B. Bicyclic sulfonamide compounds of formula I-7-B can be prepared by contacting cyclic amine compounds of formula I-6-B with protected aryl sulfonamide compounds of formula I-4, in the presence of a suitable base, such as sodium hydride, cesium carbonate, potassium carbonate, and the like, under conditions known to those of skill in the art.

[0150] The ester of bicyclic compounds of Formula I-7-A, or the aldehyde of bicyclic compounds of formula I-7-B, can be reduced in the presence of a suitable reducing agent, such as diisobutyl aluminum hydride, sodium borohydride, and the like, to provide for bicyclic alcohol compounds of formula I-8. Conversion of the primary alcohol of compounds of formula I-8 to a suitable leaving group in compounds of formula I-9 can be accomplished by contacting compounds of formula I-8 with a suitable reagent to activate the alcohol to an S_N2 displacement from a selected nucleophile, including, but not limited to, the Appel reaction using triphenylphoshine and a carbon tetrahalide, methanesulfonyl chloride and a bulky base (e.g., DIPEA, etc.), and the like, under conditions known to those of skill in the art. Amine alkylation of Ring C in compounds of formula I-10 with bicyclic compounds of formula I-9 can then be accomplished in the presence of a base, such as sodium hydride, cesium carbonate, potassium carbonate, and the like. Finally, deprotection of the sulfonamide amine of compounds of formula I-11 to provide for compounds of formula I can be accomplished by treatment with various deprotecting agents, such as trifluoroacetic acid, hydrochloric acid, and the like, depending on the amine protecting group employed.

[0151] Appropriate starting materials and reagents for the reactions shown in Schemes I and II can be purchased or prepared by methods known to one of skill in the art (e.g., see Examples below). For any compound shown in Schemes I and II, it should be understood that various derivatives can be provided by functional group interconversion at any step. In some embodiments, the various substituents of Formula I-1, I-2, I-3, I-4, I-5-A, I-6-A, I-6-B, I-7-A, I-7-B, I-8, I-9, I-10, or I-11 are as defined herein. However, derivatization of compounds I-1, I-2, I-3, I-4, I-5-A, I-6-A, I-6-B, I-7-A, I-7-B, I-8, I-9, I-10, or I-11 prior to reacting in any step, and/or further derivatization of the resulting reaction product, provides various compounds of Formula I. Upon each reaction completion, each of the intermediate or final compounds can be recovered, and optionally purified, by conventional techniques such as neutralization, extraction, precipitation, chromatography, filtration, and the like. Other modifications to arrive at compounds of this disclosure are within the skill of the art.

[0152] Furthermore, the compounds of this disclosure may contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this disclosure, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like. It should be appreciated that various isomers of Formula I can be separated as well.

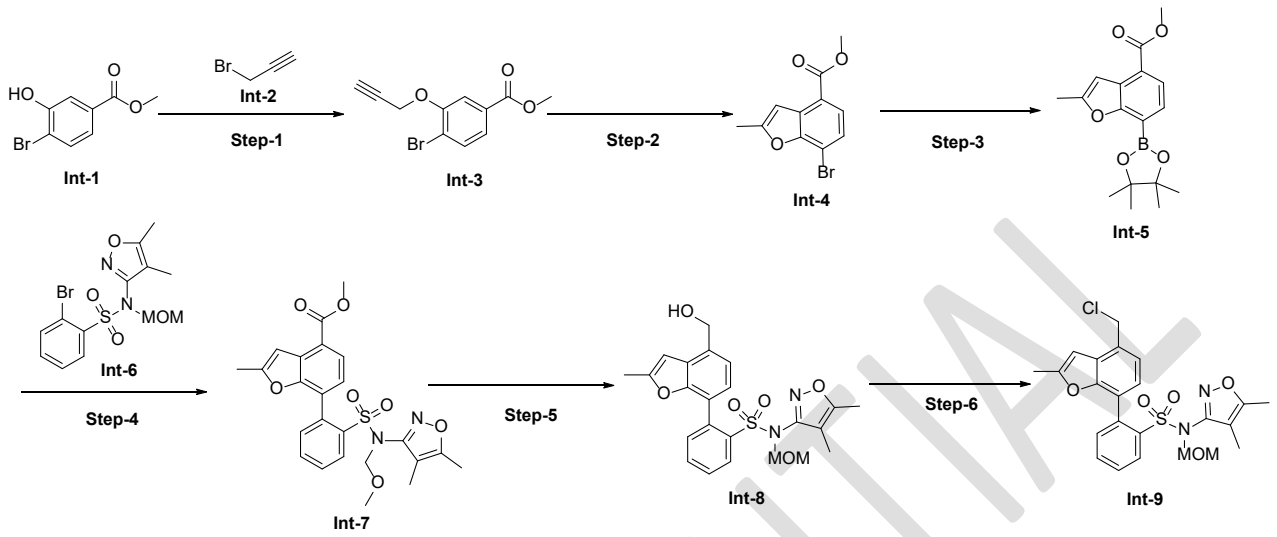
EXAMPLES

[0153] The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques to function well in the practice of the disclosure, and thus can be considered to constitute specific modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

General Experimental Methods

[0154] All commercially available reagents used were procured from either local suppliers or Sigma-Aldrich, Alfa Aesar, Fluorochem, etc. and were used as such. Thin-layer chromatography was performed on pre-coated TLC silica gel 60 F254 plates on aluminum (Merck). TLC was visualized in UV-254 and 360 nm, iodine on silica gel. Column chromatography was performed using 230-400 mesh silica gel. Automated purifications were done using Teledyne ISCO Combi flash companion and Grace Reversal unless otherwise noted; all reactions were carried out under atmosphere of argon in dried glassware using standard techniques. Unless stated, analytical or laboratory grade solvents were used without further drying/purification. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 500 MHz, Varian 400 MHz and 300 MHz spectrometers. Chemical shifts are reported in ppm with TMS as reference. Data are reported as follows: chemical shift, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (in Hz) and number of protons. LCMS spectra were recorded using Agilent 1290 series, Mass 6150 quadru pole LCMS, Software: Chemstation; and LCMS run method specifications are column: Acquity UPLC BEH C18 (50 X 2.1 mm, 1.7 µm), Mobile phase: B: 0.1% formic acid in water, mobile phase A: 0.1% formic acid in acetonitrile, Gradient: Time (min)/% A: 0/2, 0.2/2, 1.5/98, 2.6/98, 2.61/2,3.2/2, Column Temp: 45 °C, Flow rate: 0.8 mL min^{-1}.

Example 1, Intermediate 9: Synthesis of 2-(4-(chloromethyl)-2-methylbenzofuran-7-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide (Int-9)



Step-1: Synthesis of methyl 4-bromo-3-(prop-2-yn-1-yloxy) benzoate (Int-3)

[0155] To a stirred solution of methyl 4-bromo-3-hydroxybenzoate (10 g, 43.283 mmol) in CH_3CN (150 mL) was added propargyl bromide (5.785 ml, 64.924 mmol) and K_2CO_3 (11.962 g, 86.565 mmol) at room temperature. The reaction mixture was stirred for 16 h at rt. After completion of the reaction (monitored by LCMS and TLC), the reaction mixture was diluted with ice cold water (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford the title compound (8.5 g, 72.98%), LCMS; $[M+H]^+$: 271.15.

Step-2: Synthesis of methyl 7-bromo-2-methylbenzofuran-4-carboxylate (Int-4)

[0156] To a stirred solution of methyl 4-bromo-3-(prop-2-yn-1-yloxy) benzoate (10 g, 37.441 mmol) in N, N-diethyl aniline (100 mL) was added CsF (8.5 g, 56.16 mmol). The reaction mixture was heated to 220 °C and stirred for 6 h at the same temperature. After completion of the reaction (monitored by TLC/LCMS), the reaction mixture was diluted with ice cold water (30 mL), and acidified to pH-4-5 with 6N hydrochloric acid. The aqueous phase was extracted with ethyl acetate (3 x 100 mL), and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude material thus obtained was purified by combi flash chromatography by using a mixture of ethyl acetate and petroleum ether (20 to 60%) to afford the title compound (6.5 g, 64.5%), LCMS; $[M+H]^+$: 270.12.

Step-3: Synthesis of methyl 2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzofuran-4-carboxylate (Int-5)

[0157] To a stirred solution of methyl 7-bromo-2-methylbenzofuran-4-carboxylate (6.5 g, 24.15 mmol) in 1,4 dioxane (60 mL), were added bis(pinacolato)diboron (7.3 g, 28.986 mmol) and KOAc (5.9 g, 60.388 mmol). The reaction mixture was degassed with argon gas for 10 min, then $PdCl_2$(dppf).dcm (1.97 g,

2.416 mmol) was added. The resulting reaction mixture was heated to 110 °C and stirred for 3 h. After completion of the reaction (monitored by TLC/LCMS), the reaction mixture was diluted with water (150 mL) and extracted into ethyl acetate (2 x 200 mL). The combined organic layers were washed with water, brine solution, dried over sodium sulfate, filtered, and filtrate was concentrated under reduced pressure. The crude material thus obtained was purified by combi flash chromatography by using a mixture of ethyl acetate and petroleum ether (20 to 60%) to afford the title compound (4.7 g, 61%), LCMS; $[M+H]^+$: 317.4.

Step-4: Synthesis of methyl 7-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)sulfamoyl)phenyl)-2-methylbenzofuran-4-carboxylate (Int-7)

[0158] To a stirred solution of 2-bromo-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl) benzenesulfonamide (3 g, 7.995 mmol) in 1,4 Dioxane (30 mL) and water (5 mL), was added methyl 2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzofuran-4-carboxylate (3.792 g, 11.992 mmol), K_2CO_3 (3.314 g, 23.985 mmol), and $PdCl_2$dppf.dcm (0.979 g, 1.199 mmol). The resulting reaction mixture was heated to 110 °C and stirred for 4 h. After completion of the reaction, the reaction mixture was diluted with water (80 mL) and extracted with ethyl acetate (2 x 250 mL). The combined organic extracts were washed with water, brine solution, dried over sodium sulfate, filtered, and filtrate was concentrated. The crude material thus obtained was purified by combi flash chromatography by using a mixture of ethyl acetate and petroleum ether (20 to 60%) to afford the title compound (3.8 g, 64%), LCMS; $[M+H]^+$: 485.27.

Step-5: Synthesis N-(4,5-dimethylisoxazol-3-yl)-2-(4-(hydroxymethyl)-2-methylbenzofuran-7-yl)-N-(methoxymethyl) benzenesulfonamide (Int-8)

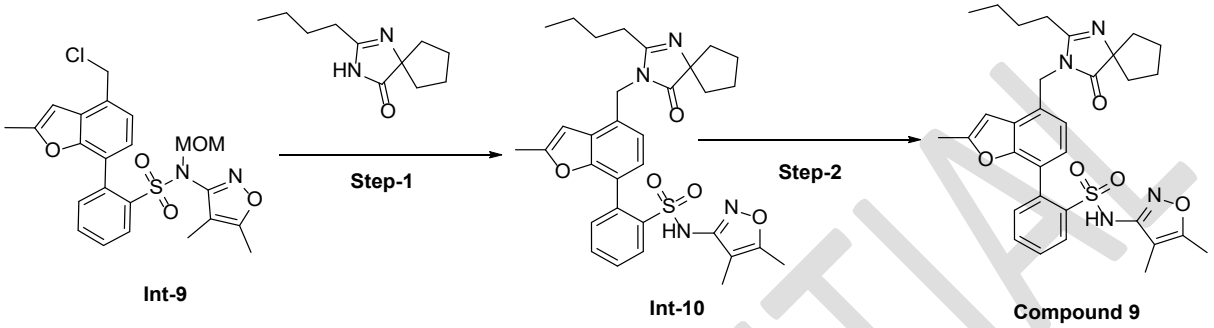
[0159] To a stirred solution of methyl 7-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl) sulfamoyl) phenyl)-2-methylbenzofuran-4-carboxylate (1.2 g, 2.479 mmol) in DCM (25 mL) was added DIBAL-H (1.5 M in toluene, 3.5 mL, 7.482 mmol) at -70 °C. The reaction mixture was allowed to warm to rt and stirred for 4-5 h. After completion of the reaction (monitored by TLC/LCMS), the reaction mixture was cooled to 0 °C and quenched with saturated ammonium chloride (20 mL) solution and stirred at rt for 5-6 h. The resulting mixture was diluted with water (100 mL) and extracted with DCM (2x 50 mL). The combined organic layers were washed with water, brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude material thus obtained was purified by combi flash chromatography by using a mixture of ethyl acetate and petroleum ether (20 to 60%) to afford the title compound (0.72 g, 64%), LCMS; $[M+H]^+$: 457.1.

Step-6: Synthesis of 2-(4-(chloromethyl)-2-methylbenzofuran-7-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl) benzenesulfonamide (Int-9)

[0160] To a stirred solution of N-(3,4-dimethylisoxazol-5-yl)-2'-(ethoxymethyl)-4'-(hydroxymethyl)-N-(methoxymethyl)-[1,1'-biphenyl]-2-sulfonamide (0.25 g, 0.55 mmol) in DCM (15 mL), was added DIPEA (0.48 mL, 2.74 mmol) and methane sulfonyl chloride (0.13 mL, 1.64 mmol) at 0 °C. The resulting reaction mixture was stirred at rt for 2 h. After completion of the reaction (monitored by LCMS/TLC), the reaction mixture was diluted with ice cold water (5 mL) and extracted with DCM (2x20 mL). The combined organic

layers were dried over sodium sulfate and concentrated under reduced pressure to afford the title compound (230 mg, 88.4%), LCMS; $[M+H]^+$: 475.13.

Example 2: Synthesis of 2-(4-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-2-methylbenzofuran-7-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Compound 9):



Step-1: Synthesis of 2-(4-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-2-methylbenzofuran-7-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Int-10)

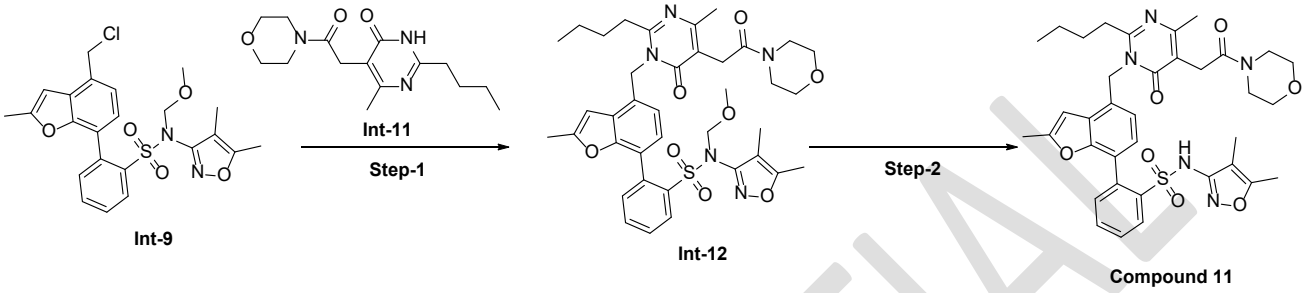
[0161] To a stirred solution of 2-butyl-1,3-diazaspiro [4.4] non-1-en-4-one (146 mg, 0.758 mmol) in DMF (6 mL) was added sodium hydride (45.48 mg, 1.90 mmol) at 0 °C. The resulting reaction mixture was stirred at rt for 30 minutes at the same temperature. To this reaction mixture was added 2-(4-(chloromethyl)-2-methylbenzofuran-7-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl) benzenesulfonamide (300 mg, 0.632 mmol), and the reaction mixture was allowed to warm to rt and was stirred for 16 h. After completion of reaction (monitored by TLC/LCMS), the reaction mixture was diluted with ice cold water (50 mL) and extracted with 10% MeOH in DCM (2 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude material thus obtained was purified by automated flash chromatography by using a mixture of ethyl acetate and petroleum ether (20 to 60%) (silica gel) to afford the title compound (310 mg, 81%), LCMS; $[M+H]^+$: 732.36.

Step-2: Synthesis of 2-(4-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-2-methylbenzofuran-7-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Compound 9)

[0162] 2-(4-((2-Butyl-4-oxo-1,3-diazaspiro[4.4] non-1-en-3-yl)methyl)-2-methylbenzofuran-7-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide (0.2 g, 0.32 mmol) was dissolved in TFA (2 mL) and heated to 60 °C for 2 h. After completion of the reaction (monitored by TLC/LCMS), the reaction mixture concentrated under reduced pressure. The crude material thus obtained was diluted with ice cold water (20 mL) and sodium bicarbonate solution (20 mL). The aqueous phase was extracted with DCM (2 x 25 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude material thus obtained was purified by combi flash chromatography by using a mixture of ethyl acetate and petroleum

ether (20 to 60%) to afford **Compound 9** (7.4 mg, 4%), LCMS;
$[M+H]^+$: 589.31.

Example 3: Synthesis of 2-(4-((2-butyl-4-methyl-5-(2-morpholino-2-oxoethyl)-6-oxopyrimidin-1(6H)-yl) methyl)-2-methylbenzofuran-7-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Compound 11)



Step-1: Preparation of (2'-(N-(3,4-dimethylisoxazol-5-yl)-N-(methoxymethyl) sulfamoyl)-2-(ethoxymethyl)-[1,1'-biphenyl]-4-yl)methyl methane sulfonate (Int-12)

[0163] To a stirred solution of 2-(4-(chloromethyl)-2-methylbenzofuran-7-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide (251 mg, 0.53 mmol) and 2-butyl-6-methyl-5-(2-morpholino-2-oxoethyl)pyrimidin-4(3H)-one (37 mg , 0.53 mmol) in dioxane (15 mL) was added cesium carbonate (207 mg, 0.63 mmol). The resulting reaction mixture was heated to 100 °C and stirred for 16 h at the same temperature. After completion of the reaction (monitored by TLC/LCMS), the reaction mixture was diluted with ice cold water (50 mL) and extracted with 10% MeOH in DCM (2 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude material thus obtained was purified by automated flash chromatography (silica gel) by using a mixture of ethyl acetate and petroleum ether (20 to 60%) to afford the title compound (240 mg, 62%), LCMS; $[M+H]^+$: 732.36.

Step-2: Preparation of 2-(4-((2-butyl-4-methyl-5-(2-morpholino-2-oxoethyl)-6-oxopyrimidin-1(6H)-yl)methyl)-2-methylbenzofuran-7-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Compound 11)

[0164] To a stirred solution of 2-(4-((2-butyl-4-methyl-5-(2-morpholino-2-oxoethyl)-6-oxopyrimidin-1(6H)-yl)methyl)-2-methylbenzofuran-7-yl)-N-(4,5-dimethylisoxazol-3-yl)-N (methoxymethyl) benzenesulfonamide (200 mg, 0.27 mmol) in ethanol (2.5 mL), was added conc. HCl solution (2 mL). The resulting reaction mixture was heated to 60 °C and stirred at same temperature for 3 h. After completion of the reaction (monitored by TLC/LCMS), the reaction mixture was concentrated, and the crude material was diluted with ice cold water (20 mL) and sodium bicarbonate solution (20 mL). The aqueous phase was extracted with DCM (2 x 25mL), and the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude material thus obtained was purified by preparative HPLC

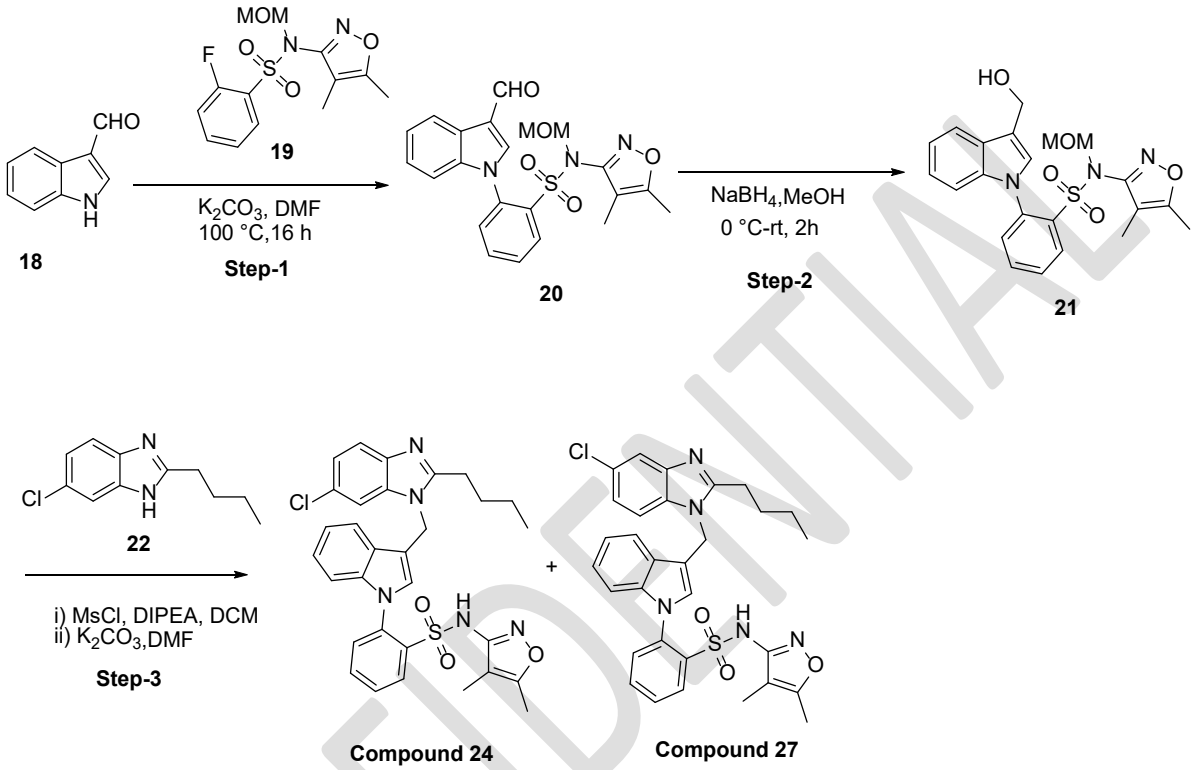
using X-select CSH C18 (250*19*5u) column and mobile phase A: 0.1% formic acid in H_2O. Mobile phase B: - acetonitrile as eluent to afford **Compound 11** (48 mg, 25%), LCMS; $[M+H]^+$: 688.37, Purity: 98.90%.

[0165] The following compounds were synthesized using the procedure demonstrated for **Compound 11**.

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
9	589.31	δ ppm 10.4 (s, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.71-7.67 (m, 2H), 7.34 (dd, *J* = 2.0, 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.60 (s, 1H), 4.96 (s, 2H), 2.49 (m, 2H), 2.92(s, 3H), 2.18 (s, 3H), 1.95-1.79 (m, 8H), 1.52-1.46 (m, 5H), 1.28-1.23 (m, 2H), 0.79 (t, *J* = 7.6 Hz, 3H).
10	646.32	δ ppm 8.05 (m, 1H), 7.34 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.11 (m, 1H), 6.61 (d, *J* = 1.2 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H) , 5.47 (s, 2H), 3.57 (s, 2H), 3.10 (s, 3H), 2.84 (s, 3H), 2.63 (q, *J* = 8.0 Hz, 2H), 2.27 (s, 3H), 2.17 (s, 3H), 1.98 (s, 3H) 1.54 (m, 2H), 1.30 (s, 3H), 1.25 (q, *J* = 7.6 Hz, 2H), 0.78 (t, *J* = 7.2 Hz, 3H).
11	688.37	δ ppm 10.4 (s, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 7.65 (m, 2H), 7.32 (d, *J* =7.2 Hz, 1H), 6.98 (d, *J* = 6.8 Hz, 1H), 6.70-6.67 (m, 2H), 5.50 (s, 2H), 3.61-3.54 (m, 8H), 3.45 (m, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.28 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H), 1.57-1.51 (m, 2H), 1.47 (s, 3H), 1.27-1.21 (m, 2H), 0.79 (t, *J* = 7.6 Hz, 3H).
12	570.30	δ ppm 10.38 (s, 1H), 8.13-8.11 (m, 1H), 8.69-7.65 (m, 2H), 7.35-7.33 (m, 1H), 7.11 (s, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.72 (t, *J* = 1.2 Hz, 2H), 7.29 (s, 1H), 5.74 (s, 2H), 2.91 (d, *J* = 7.2 Hz, 2H), 2.56 (s, 6H), 2.28 (s, 3H), 2.12 (s, 3H), 1.49 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 3H).

13	639.27	δ ppm 10.40 (s, 1H), 8.14 (dd, *J* =8.0, 2.0 Hz, 1H), 7.71-7.65 (m, 2H), 7.35 (dd, *J* =7.2, 1.6 Hz, 1H), 6.98 (q, *J* = 7.6 Hz, 2H), 6.61 (d, *J* = 1.2 Hz, 1H), 4.94 (s, 2H), 3.54-3.50 (m, 1H), 3.43-3.22 (m, 3H), 2.42-2.39 (m, 3H), 2.29 (s, 3H), 2.18 (s, 4H), 1.52-1.48 (m, 5H), 1.26 (q, *J* = 7.2 Hz, 2H), 0.80 (t, *J* = 7.6 Hz, 3H).
20	701.40	δ ppm 10.51 (bs, 1H), 8.13 (dd, *J* = 2.4, 7.6 Hz, 1H), 7.69-7.61 (m, 2H), 7.32 (dd, *J* = 2.0, 7.6 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.70-6.67 (m, 2H), 5.50 (s, 2H), 3.60 (s, 4H), 3.48 (s, 2H), 2.63 (t, *J* = 7.6 Hz 2H), 2.43 (bs, 2H), 2.35 (bs, 2H), 2.28 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H), 1.57-1.54 (m, 2H), 1.48 (m, 3H), 1.27-1.21 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H).
21	713.41	δ ppm 8.70 (bs, 1H), 8.08-8.01 (m, 1H), 7.41-7.39 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.17-7.15 (m, 1H), 6.59 (s, 1H) ,6.51 (d, *J* = 8.0 Hz, 1H), 5.47 (d, *J* = 6.1 Hz, 2H), 4.21 (d, *J* = 8.8 Hz, 1H), 4.1 (d, *J* = 8.4 Hz, 1H) ,3.80 (d, *J* = 7.2 Hz, 2H), 3.44 (d, *J* =7.2 Hz, 1H), 3.31 (s, 1H), 3.18-3.06 (m, 4H), 2.67-2.65 (m, 2H), 2.3 (s, 3H), 2.28 (s, 3H), 2.08-2.07 (m, 2H), 2.02 (s, 3H), 1.6-1.56 (m, 2H), 1.31-1.23 (m, 6H), 0.79 (t, *J* = 7.2 Hz, 3H).

Example 4: Synthesis of 2-(3-((2-butyl-5-chloro-1H-benzo[d]imidazol-1-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Compound 27) and 2-(3-((2-butyl-6-chloro-1H-benzo[d]imidazol-1-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Compound 24)



Step-1: Synthesis of N-(4,5-dimethylisoxazol-3-yl)-2-(3-formyl-1H-indol-1-yl)-N-(methoxymethyl) benzenesulfonamide (20)

[0166] To a stirred solution of 1H-indole-3-carbaldehyde (4.8 g, 33.10 mmol) in in DMF (50 mL), was added N-(4,5-dimethylisoxazol-3-yl)-2-fluoro-N-(methoxy methyl) benzene sulfonamide (21 g, 66.20 mmol) and potassium carbonate (9.12 g, 66.20 mmol). The resulting reaction mixture was stirred at 110 °C for 16 h. After completion of the reaction (monitored by the TLC/LCMS), the reaction mixture was diluted with ice cold water (100 mL), extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material thus obtained was purified by column chromatography using EtOAc and petroleum ether as eluent to afford the title compound. (6 g, 41 %) LCMS; $[M+H]^+$: 439.48.

Step-2: Synthesis of N-(4,5-dimethylisoxazol-3-yl)-2-(3-(hydroxymethyl)-1H-indol-1-yl)-N-(methoxymethyl) benzenesulfonamide (21)

[0167] To a stirred solution of N-(4,5-dimethylisoxazol-3-yl)-2-(4-formyl-1H-indol-1-yl)-N-(methoxymethyl) benzene sulfonamide (0.48 g, 1.09 mmol) in MeOH (30 mL), was added $NaBH_4$ (0.08 g, 2.18 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 2 h. After completion of

the reaction (monitored by TLC), the volatiles were evaporated under reduced pressure, diluted with ice cold water (10 mL), extracted with EtOAc (2 x 20mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material was used as such for the next step without further purification. (0.4 g, 83 %), LCMS; $[M+H]^+$: 441.50.

Step-3: Synthesis of 2-(3-((2-butyl-5-chloro-1H-benzo[d]imidazol-1-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Compound 27) and 2-(3-((2-butyl-6-chloro-1H-benzo[d]imidazol-1-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Compound 24)

[0168] To a stirred solution of N-(4,5-dimethylisoxazol-3-yl)-2-(3-(hydroxymethyl)-1H-indol-1-yl)-N-(methoxymethyl)benzenesulfonamide (0.5 g, 1.13 mmol) in DCM (5 mL), was added methanesulfonyl chloride (0.13 mL, 1.70 mmol) and DIPEA (0.62 mL, d = 0.742g/mL, 3.39 mmol). The resulting reaction mixture was stirred at rt for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ice cold water (30 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with dried over sodium sulfate, concentrated under reduced pressure. The crude material thus obtained was used for next step without further purification.

[0169] To a stirred solution of (1-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)sulfamoyl)phenyl)-1H-indol-3-yl)methyl methanesulfonate (0.35 g, 0.67 mmol) in DMF (15 mL), was added 2-butyl-6-chloro-1H-benzo[d]imidazole (0.14 g, 0.67 mmol) and Cs_2CO_3 (0.66 g, 2.02 mmol). The resulting reaction mixture was stirred at 110 °C for 8 h. After completion of the reaction (monitored by LCMS), the reaction mixture was diluted with ice cold water (30 mL) extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material thus obtained was purified by Prep-HPLC using Cogent C18(150*20*5µ) column, mobile phase A: 10 mM ABC in water, Mobile phase B: Acetonitrile. The pure fractions were collected and concentrated under reduced pressure, lyophilized to afford the title compounds (70 mg) as a mixture. The mixture was further used for regio isomeric separation using preparative chiral SFC using Chiralpak-IF (250X4.6X5µ) column, CO_2 and 0.5% DEA in MeOH as eluent to afford the title compounds 2-(3-((2-butyl-5-chloro-1H-benzo[d]imidazol-1-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (**Compound 27**) (0.017 g, 4%), LCMS; $[M+H]^{+:}$ 588.27; Rt = 4.55, and 2-(3-((2-butyl-6-chloro-1H-benzo[d]imidazol-1-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (**Compound 24**) (0.019 g, 4%), LCMS; $[M+H]^+$: 588.30, Rt = 3.28.

[0170] The following compounds were synthesized using the procedure demonstrated for **Compound 24** using advanced intermediate 21. **Compound 6**, **Compound 7**, **Compound 8** were synthesized using Indazole-3-carboxaldehyde.

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
4	574.33	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.75 (bs, 1H), 8.17 (dd, *J* = 4.0 Hz, 1H), 7.73 (t, *J* = 6.4 Hz, 2H), 7.52-7.50 (m, 2H), 7.46-7.41 (m, 2H), 7.05 (t, *J* = 3.6 Hz, 2H), 6.81-6.78 (m, 1H), 4.83 (s, 3H), 2.54-2.49 (m, 2H), 2.12 (s, 2H), 1.83-1.80 (m, 6H), 1.60-1.57 (m, 3H), 1.15-1.44 (m, 3H), 1.29-1.23 (m, 2H), 0.80 (t, *J* = 8.0 Hz, 3H).
5	554.67	^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.13 (m, 2H), 7.57 (s, 1H), 7.48 (s, 2H), 7.19 (bs, 1H), 6.95 (s, 1H), 6.82 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 3.2 Hz, 1H), 6.35 (d, *J* = 7.2 Hz, 1H), 5.72 (s, 2H), 2.78 (q, *J* = 5.6 Hz, 2H), 2.52 (s, 3H), 2.51 (s, 3H), 1.95 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 2H).
6	574.70	^{1}H NMR (400 MHz, DMSO-d6): δ ppm 10.21 (s, 1H), 8.13 (dd, *J* = 1.2, 6.4 Hz, 1H), 7.80-7.69 (bs, 3H), 7.57 (bs, 1H), 7.36 (bs, 1H), 7.20 (bs, 1H), 5.07 (s, 2H), 2.50 (s, 2H), 2.18 (s, 3H), 1.81 (bs, 6H), 1.72-1.59 (m, 5H), 1.50 (m, 2H), 1.27 (m, 2H), 0.75 (t, *J* = 7.0 Hz, 3H).
7	631.75	^{1}H NMR (400 MHz, DMSO-d6): δ ppm 10.00 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.90-7.57 (m, 4H), 7.41-7.09 (m, 3H), 5.67 (s, 2H), 3.43 (s, 2H), 3.04 (s, 3H), 2.90 (bs, 2H), 2.81 (s, 3H), 2.20 (s, 3H), 2.07 (s, 3H), 1.65-1.54 (m, 5H), 1.27 (m, 2H), 0.79 (t, *J* = 7.2 Hz, 3H).
8	555.66	^{1}H NMR (400 MHz, DMSO-d6): δ ppm 10.05 (s, 1H), 8.07 (dd, *J* = 1.2, 6.4 Hz, 1H), 7.90-7.86 (m, 2H), 7.77 (t, *J* = 1.2 Hz, 1H), 7.61 (dd, *J* = 0.8,7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.21 (m, 2H), 7.08 (s, 1H), 5.96 (s, 2H), 3.04 (d, *J* = 6.4 Hz, 2H), 2.58 (s, 3H), 2.50 (s, 3H), 2.21 (s, 3H), 1.62 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
15	583.71	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.50 (s, 1H), 8.12 (m, 1H), 7.75 (s, 1H), 7.60 (m, 2H), 7.44 (m, 2H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.14 (m, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.92-6.86 (m, 2H), 6.82(d, *J* = 7.2 Hz, 1H), 6.78 (dd, *J* = 2.0, 8.4 Hz, 1H), 5.50 (s, 2H), 3.75 (s, 3H), 2.97 (t, *J* = 7.6 Hz, 2H), 1.96 (s, 3H), 1.73 (m, 2H), 1.39 (m, 2H), 1.29 (s, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); Rt = 6.46 min.
16	567.71	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.81 (s, 1H), 8.15 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.63 (bs, 2H), 7.49 (s, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 2H), 6.96 (m, 3H), 6.81 (d, *J* = 7.2 Hz, 1H), 5.54 (s, 2H), 2.94 (t, *J* = 7.6 Hz, 2H), 2.40 (s, 3H), 2.08 (s, 3H), 1.73 (m, 2H), 1.44-1.34 (m, 5H), 0.85 (t, *J* = 7.2 Hz, 3H); Rt = 15.75 min.
18	598.72	^{1}H NMR (400 MHz, DMSO-d6, at 90 °C): δ ppm 8.17 (dd, *J* = 6.8, 9.2 Hz, 1H), 7.58 (m, 3H), 7.50 (m, 3H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.95 (m, 3H), 6.79 (m, 3H), 5.59 (s, 2H), 2.91 (q, *J* = 5.6 Hz, 2H), 2.58 (s, 3H), 2.50 (s, 3H), 1.38 (t, *J* = 5.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 4H).
19	573.71	^{1}H NMR (400 MHz, DMSO-d6): δ ppm 10.65 (s, 1H), 8.20 (dd, *J* = 6.8, 9.2 Hz, 1H), 7.79 (m, 2H), 7.39 (m, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.67 (q, *J* = 3.2 Hz, 2H), 4.97 (m, 2H), 2.36 (t, *J* = 6.8 Hz, 2H), 2.13 (s, 3H), 1.87 (bs, 6H), 1.68 (bs, 2H), 1.48 (m, 5H), 1.24 (m, 2H), 0.82 (t, *J* = 7.2 Hz, 3H).
24	588.30	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.75 (s, 1H), 8.16 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.70 (bs, 2H), 7.54 (d, *J* = 6.8 Hz, 1H), 7.39-7.29 (m, 3H), 7.15 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.01 (m, 2H), 6.79 (m, 1H), 5.62 (s, 2H), 2.94 (t, *J* = 7.6 Hz, 2H), 2.12 (s, 3H), 1.74 (m, 2H), 1.50 (s, 3H), 1.37 (s, 2H), 0.84 (t, *J* = 7.2 Hz, 3H).

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
25	621.68	^{1}H NMR (400 MHz, DMSO-d_6 at 90 °C): δ ppm 10.75 (s, 1H), 8.17 (d, *J* = 6.8 Hz, 1H), 7.97 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.61 (m, 2H), 7.30 (d, *J* = 6.8 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 6.98 (m, 2H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.68 (s, 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.04 (s, 3H), 2.07 (s, 3H), 1.77 (m, 2H), 1.41 (m, 5H), 0.84 (t, *J* = 7.2 Hz, 3H). Rt = 2.98 min.
26	621.68	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.70 (s, 1H), 8.15 (m, 1H), 7.96 (s, 1H), 7.66 (bs, 2H), 7.58-7.46 (m, 2H), 7.33-7.27 (m, 2H), 7.02-6.95 (m, 2H), 6.80 (m, 1H), 5.67 (s, 2H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.08 (m, 3H), 1.75 (m, 2H), 1.42 (m, 4H), 1.33 (m, 1H), 0.84 (t, *J* =7.2 Hz, 3H). Rt = 3.77 min.
27	588.27	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.75 (s, 1H), 8.16 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.74 (m, 3H), 7.70 (bs, 2H), 7.60 (d, *J* = 6.8 Hz, 1H), 7.36 (m, 3H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.18-7.15 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.03 (m, 2H), 6.79 (dd, *J* = 1.2, 6.8 Hz, 1H), 5.62 (s, 2H), 2.95 (t, *J* = 7.6 Hz, 2H), 2.15 (s, 3H), 1.73 (m, 2H), 1.55 (s, 3H), 1.39 (m, 2H), 0.85 (t, *J* =7.2 Hz, 3H). Rt = 4.55 min
29	621.68	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.20 (s, 2H), 8.10 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.74 (d, *J* = 6.8 Hz, 1H), 7.65 (s, 1H), 7.46 (m, 3H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.19 (dd, *J* = 2.8, 4.0 Hz, 1H), 6.99-6.88 (m, 3H), 5.71 (s, 2H), 3.05 (t, *J* = 7.6 Hz, 2H), 2.91 (q, *J* = 7.2 Hz, 3H), 1.82 (s, 3H), 1.41 (m, 2H), 1.37 (s, 2H), 1.23 (t, *J* = 7.6 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 3H). The compound isolated as DEA salt. Rt = 11.91 min.
30	588.12	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.11 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.87 (d, *J* = 6.8 Hz, 2H), 7.67 (s, 1H), 7.55-7.45 (m, 3H), 7.22 (m, 2H), 7.15 (dd, *J* = 2.8, 4.0 Hz, 1H), 6.99-6.89 (m, 3H), 5.59 (s, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 2.86 (q, *J* = 7.2 Hz, 3H), 1.82 (s, 3H), 1.72 (m, 2H), 1.40 (m, 2H), 1.14 (t, *J* = 7.6 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); The compound isolated as DEA salt, Rt = 8.67 min.
31	621.68	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.50 (s, 1H), 9.46 (s, 1H), 8.20-8.11 (m, 1H), 8.00 (d, *J* = 8 Hz, 1H), 7.87 (s, 1H), 7.79 (s, 1H), 7.50 (m, 3H), 7.25 (m, 2H), 6.90 (m, 3H), 5.56 (s, 2H), 4.81-4.78(m, 2H), 3.23 (s, 2H), 3.10 (t, *J* =

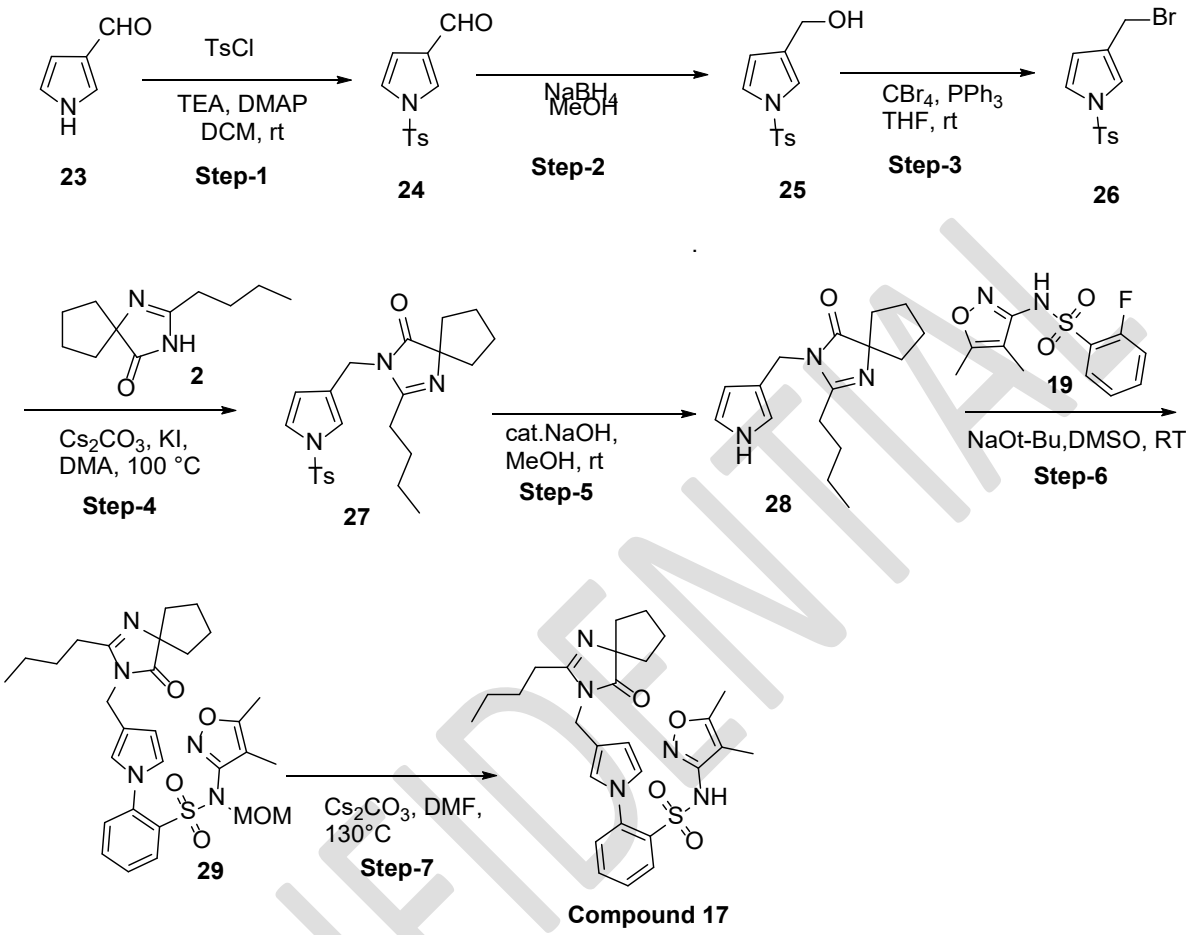
Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
		7.6 Hz, 2H), 2.94 (q, *J* = 7.6 Hz, 2H), 1.81 (m, 3H), 1.43 (m, 2H), 1.40 (s, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); Rt = 16.00 min.
32	588.12	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.13 (dd, *J* = 1.2, 8 Hz, 1H), 7.81 (d, *J* = 6.8 Hz, 1H), 7.78 (s, 1H), 7.56 (d, *J* = 6.8 Hz, 1H), 7.50 (m, 2H), 7.24 (m, 2H), 7.15 (dd, *J* = 2.8, 4.0 Hz, 1H), 6.97-6.89 (m, 3H), 5.58 (s, 2H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.88 (q, *J* = 7.2 Hz, 3H), 1.83 (s, 3H), 1.75 (m, 2H), 1.42 (m, 2H), 1.38 (s, 3H), 1.23 (t, *J* = 7.6 Hz, 5H), 0.85 (t, *J* = 7.2 Hz, 3H). The compound isolated as DEA salt. Rt = 11.12 min.
34	567.71	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.72 (s, 1H), 8.14 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.58 (m, 4H), 7.32 (s, 1H), 7.25 (m, 2H), 6.95 (m, 3H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.54 (s, 2H), 2.94 (t, *J* = 7.6 Hz, 2H), 2.38 (s, 3H), 2.05 (s, 3H), 1.72 (m, 2H), 1.41-1.34 (m, 5H), 0.85 (t, *J* = 7.2 Hz, 3H); Rt = 19.09 min.
35	583.71	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.50 (s, 1H), 8.12 (m, 1H), 7.75 (s, 1H), 7.45 (m, 2H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.25 (m, 2H), 7.13 (m, 1H), 6.92 (m, 2H), 6.92 (m, 2H), 6.83 (m, 1H), 6.73 (dd, *J* = 2.0, 8.4 Hz, 1H), 5.51 (s, 2H), 3.79 (s, 3H), 2.97 (t, *J* = 8.0 Hz, 2H), 1.95 (s, 3H), 1.73 (m, 2H), 1.39 (m, 2H), 1.29 (s, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); Rt = 5.05 min.
36	579.33	^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 10.71 (s, 1H), 8.15 (dd, *J* = 1.6, 7.6 Hz, 1H), 8.07 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 1.6, 8.4 Hz, 4H), 7.32-7.25 (m, 2H), 6.98 (t, *J* = 7.6 Hz, 2H), 6.80 (d, *J* =7.6 Hz, 1H), 5.67 (s, 2H), 3.03 (t, *J* = 6.8 Hz, 2H), 2.07 (d, *J* = 4.4 Hz, 3H), 1.76 (t, *J* = 7.2 Hz, 2H), 1.43-1.36 (m, 5H), 0.87 (t, *J* = 7.2 Hz, 3H); Rt = 4.66 min.
37	554.67	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.73 (s, 1H), 8.41 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.18 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.98 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.77 (m, 2H), 7.56 (m, 2H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.26 (q, *J* = 4.8 Hz, 1H), 6.97 (m, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 5.63 (s, 2H), 2.97 (m, 2H), 2.13 (s, 3H), 1.70 (m, 3H), 1.70 (m, 2H), 1.50 (s, 3H), 1.35 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H). The compound isolated as DEA salt. Rt = 5.22 min.

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
38	647.36	^{1}H NMR (400 MHz, DMSO-d6): δ ppm 10.94 (s, 1H), 8.85 (s, 1H), 8.28 (d, *J* = 5.6 Hz, 1H), 8.17-8.15 (m, 1H), 7.82 (d, *J* = 5.2 Hz, 1H), 7.53 (s, 1H), 7.36 (d, *J* = 6.4 Hz, 1H), 7.28 (d, *J* = 6.8 Hz, 1H), 7.02-6.94 (m, 2H), 6.80 (d, *J* = 7.2 Hz, 1H), 2.08 (s, 3H), 5.65 (s, 2H), 3.02 (t, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 1.80-1.72 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 2H). Rt = 4.17 min.
39	637.68	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.71 (s, 1H), 8.17 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.69 (bs, 2H), 7.53 (s, 2H), 7.32 (m, 2H), 7.13 (d, *J* = 8.4, 1H), 7.00 (m, 2H), 6.81 (d, *J* = 1.2 Hz, 2H), 5.64 (s, 2H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.11 (s, 3H), 1.74 (m, 2H), 1.48-1.35 (m, 5H), 0.85 (t, *J* = 7.2 Hz, 3H); Rt = 5.07 min.
40	554.67	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.28 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.22 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.19-7.92 (m, 2H), 7.45 (m, 2H), 7.17 (m, 3H), 7.22 (m, 2H), 7.11 (q, *J* = 4.8 Hz, 1H), 6.92 (m, 2H), 6.81 (d, *J* = 7.2 Hz, 1H), 5.59 (s, 2H), 3.10 (t, *J* = 7.6 Hz, 2H), 2.93 (q, *J* = 8 Hz, 3H), 1.94 (s, 3H), 1.83 (m, 2H), 1.46 (m, 2H), 1.23 (d, *J* = 4 Hz, 4H), 1.22 (q, *J* = 4.0 Hz, 6H), 0.85 (t, *J* = 7.2 Hz, 3H); The compound isolated as DEA salt; Rt = 3.89 min.
41	637.68	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.72 (s,1H), 8.16 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.81 (s, 1H), 7.79-7.65 (bs, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.56-7.47 (bs, 1H), 7.32 (d, *J* = 7.2 Hz, 2H), 7.12 (d, *J* = 1.2 Hz, 1H), 7.02-6.94 (m, 2H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.64 (s, 2H), 2.97 (t, *J* = 7.6 Hz, 2H), 2.78 (bs, 1H), 2.11 (s, 3H), 1.73 (m, 2H), 1.49-1.23 (bs, 4H), 0.85 (t, *J* = 7.2 Hz, 3H); Rt = 3.87 min.
42	555.18	^{1}H NMR (400 MHz, DMSO-d6): δ ppm 9.08 (s, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 8.17-8.15 (m, 1H), 7.68 (t, *J* = 7.6 Hz, 2H), 7.58-7.57 (m, 2H), 7.34-7.29 (m, 2H), 7.02-6.95 (m, 2H), 6.80-6.78 (m, 1H), 5.72 (s, 2H), 3.05 (t, *J* = 7.6 Hz, 5H), 2.08 (s, 3H), 1.82-1.74 (m, 2H), 1.44-1.37 (m, 6H), 0.89 (t, *J* = 7.6 Hz, 3H). Rt = 4.22 min.

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
44	597.32	^{1}H NMR (400MHz, DMSO-d6): δ ppm 8.13 - 8.10 (m, 2 H), 7.87 (s, 1H), 7.81 - 7.73 (m, 3 H), 7.47 - 7.41 (m, 2H), 7.20 (d, *J* = 6.8 Hz, 1H), 7.16 - 7.13 (m, 2H), 6.93 - 6.81 (m, 3H), 5.58 (s, 2H), 3.02 (t, *J* = 7.2 Hz, 2H), 1.94 (s, 3H), 1.79 - 1.72 (m, 2H), 1.43 -1.37 (m, 2H), 1.24 (m, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); Rt = 4.56 min.
45	597.28	^{1}H NMR (400MHz, DMSO-d6): δ ppm 10.70 (bs, 1H), 8.23 (s, 1H), 8.16 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.95 (s, 1H), 7.75-7.70 (m, 3H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.41-7.23 (m, 4H), 6.94 (m, 3H), 5.58 (s, 2H), 3.02 (t, *J* = 7.2 Hz, 2H), 1.94 (s, 3H), 1.79-1.72 (m, 2H), 1.43 -1.37 (m, 2H), 1.24 (m, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); Rt = 4.55 min.
48	600.27	^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.13-8.11 (m, 1H), 7.86 (d, *J* = 2.0 Hz, 1H), 7.7 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.48 (m, 2H), 7.19-7.23 (dd, *J* = 5.6, 2.4 Hz, 1H), 7.14 (m, 2H), 6.93-6.89 (m, 2H), 6.83 (dd, *J* = 6.8, 1.2 Hz, 1H), 5.56 (s, 2H), 3.17 (d, *J* = 7.6 Hz, 2H), 2.59 (m, 3H), 2.7 (s, 1H),2.1 (d, *J* = 6.4 Hz, 2H), 1.95 (s, 3H), 1.79-1.75 (m, 4H) 1.23 (s, 3H), 1.16 (s, 5H), 1.00 (m, 2H); Rt = 4.78 min.
50	600.27	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.15-8.12 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.48 (m, 2H), 7.19-7.15 (m, 3H), 6.93-6.89 (m, 2H), 6.83 (dd, *J* = 6.8, 1.2 Hz, 1H), 5.56 (s, 2H), 5.08-5.04 (m, 2H), 3.29 (s, 2H), 3.19 (d, *J* = 7.2 Hz, 2H), 2.58 (m, 2H), 2.06 (d, *J* = 7.2 Hz, 2H), 1.82-1.78 (m, 5H), 1.40-1.00 (m, 6H). Rt = 4.69 min.
51	598.26	^{1}H NMR (400 MHz, DMSO d6): δ ppm 12.70 (bs, 1H), 10.70 (bs, 1H), 8.28 (s, 1H), 8.16 (dd, *J* = 2.0, 7.6 Hz, 1H), 7.78 - 7.72 (m, 3H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 6.8 Hz, 3H), 7.03 - 6.96 (m, 2H), 6.77 (d, *J* = 7.2 Hz, 1H), 5.70 (d, *J* = 9.2 Hz, 2H), 2.97 (t, *J* = 7.2 Hz, 2 H), 2.12 (s, 3H), 1.78 (m, 2H), 1.48 (s, 3H), 1.43 -1.32 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H). Rt = 3.07 min.

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
52	598.26	^{1}H NMR (400 MHz, DMSO d6): δ ppm 12.60 (bs, 1H), 10.70 (bs, 1 H), 8.15-8.11 (m, 2 H), 7.84-7.59 (m, 5H), 7.25 (s, 2H), 6.95-6.93 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 5.62 (s, 2H), 3.02 (t, *J* = 7.2 Hz, 2H), 2.03 (s, 3H), 1.80 - 1.72 (m, 2 H), 1.42-1.35 (m, 5H), 0.88 (t, *J* = 7.2 Hz, 3H). Rt = 4.59 min.
54	647.49	^{1}H NMR (400 MHz, DMSO-d6): δ ppm 9.40 (s, 1H), 8.16 (dd, *J* = 2, 6 Hz ,1H) ,7.73-7.71 (m, 2H), 7.65 (d, *J* = 8.8, 1H), 7.41-7.33 (m, 4H), 7.06 (dd, *J* = 2 ,8.8 Hz, 1H), 7.02-6.97 (m ,2H), 6.80-6.78 (m, 1H), 5.58 (s, 2H), 2.95 (t, *J* = 7.2 Hz, 2H), 2.88 (s, 3H), 2.14 (s ,3H), 1.76-1.69 (m, 2H),1.52 (s, 3H), 1.41-1.32 (m, 2H), 0.87 (t, *J* =7.6 Hz, 3H).
56	609.46	^{1} H NMR (400 MHz, DMSO-d6): δ 10.63 (s, 1H), 8.18 (dd, *J* = 1.6, 7.2 Hz, 1H)**,** 7.73 (s, 1H)**,** 7.54 (d, *J* = 7.6 Hz, 2H)**,** 7.44 (s, 1H)**,** 7.31 (t, *J* = 8.4 Hz, 2H)**,** 7.04-6.94 (m, 2H), 6.73 (d, *J* = 7.2 Hz, 1H), 5.26 (d, *J* = 15.2 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 2H), 2.10 (s, 3H), 1.43 (s, 3H), 1.34 (s, 6H).

Example 5: Synthesis of 2-(3-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-3-yl) methyl)-1H-pyrrol-1-yl)-N-(4,5-dimethylisoxazol-3-yl) benzenesulfonamide (Compound 17)



Step-1: Synthesis of 1-tosyl-1H-pyrrole-3-carbaldehyde (24)

[0171] To a stirred solution of 1H-pyrrole-3-carbaldehyde (30 g, 0.31 mol) in DCM (200 mL), was added DMAP (1 g) and TEA (85 mL, 0.62 mol) at 0 °C. The reaction mixture was stirred at same temperature for 10 min, then was added 4-toluenesulfonyl chloride (62.4 g, 0.34 mol). The reaction mixture was allowed to warm to rt and stirred for 16 h. After completion of the reaction, the reaction mixture was diluted with ice cold water (200 mL), extracted with DCM (4x100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude residue thus obtained was purified by automated flash chromatography by using a mixture of ethyl acetate and petroleum ether (20 to 60%) to afford 1-tosyl-1H-pyrrole-3-carbaldehyde. (56 g, 71%), LCMS; $[M+H]^+$: 250.32.

Step-2: Synthesis of (1-tosyl-1H-pyrrol-3-yl) methanol (25)

[0172] To a stirred solution of 1-tosyl-1H-pyrrole-3-carbaldehyde (55 g, 0.22 mol) in MeOH (150 mL) at 0 °C, was added sodium borohydride (16.6 g, 0.44 mol). The reaction mixture was allowed to warm to rt and

stirred for 16 h. After completion of the reaction (monitored by TLC/LCMS), the reaction mixture was diluted with ice cold water and extracted with DCM (2x100 mL). The combined organic layers were washed with brine, concentrated under reduced pressure. The crude material thus obtained was purified by automated flash chromatography (silica gel) by using a mixture of ethyl acetate and petroleum ether (20 to 60%) to afford (1-tosyl-1H-pyrrol-3-yl) methanol. (34 g, 61%), LCMS; $[M+H]^+$: 252.72.

Step-3: synthesis of 3-(bromo methyl)-1-tosyl-1H-pyrrole (26)

[0173] To a stirred solution of (1-tosyl-1H-pyrrol-3-yl) methanol (45 g, 0.18 mol) in THF (450 mL), was added triphenylphosphine (93.9 g, 0.36 mol) and carbon tetrabromide (119 g, 0.36 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 16 h. After completion of the reaction, the reaction mixture was diluted with ice cold water and extracted with DCM (2x100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material thus obtained was purified by automated flash chromatography (silica gel) by using a mixture of ethyl acetate and petroleum ether (20 to 60%) to afford 3-(bromo methyl)-1-tosyl-1H-pyrrole. (30 g, 53%), LCMS; $[M+H]^+$: 315.14.

Step-4: synthesis of 2-butyl-3-((1-tosyl-1H-pyrrol-3-yl) methyl)-1,3-diazaspiro [4.4] non-1-en-4-one (27)

[0174] To a stirred solution of 3-(bromomethyl)-1-tosyl-1H-pyrrole (30 g, 95.5mmol) in DMF (300 mL), was added 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (20.4 g, 105.10 mmol) and cesium carbonate (93.3 g, 286.50 mmol) at rt and stirred for 4 h. After completion of the reaction, the reaction mixture was diluted with ice cold water (100 mL) and extracted with DCM (3x100 mL). The combined organic layers were washed with brine and concentrated under reduced pressure. The crude material thus obtained was purified by automated flash chromatography (silica gel) by using a mixture of ethyl acetate and petroleum ether (20 to 60%) to afford 2-butyl-3-((1-tosyl-1H-pyrrol-3-yl) methyl)-1,3-diazaspiro [4.4] non-1-en-4-one. (21 g, 51%), LCMS; $[M+H]^+$: 428.48.

Step-5: synthesis of 3-((1H-pyrrol-3-yl) methyl)-2-butyl-1,3-diazaspiro [4.4] non-1-en-4-one (28)

[0175] To a stirred solution of 2-butyl-3-((1-tosyl-1H-pyrrol-3-yl) methyl)-1,3-diazaspiro [4.4] non-1-en-4-one (21 g, 49.1 mmol) in MeOH (140 mL) at 0° C, was added 5 N aq NaOH (70 mL), allowed to warm to rt and stirred 16 h. After completion of the reaction, the solvent was evaporated under reduced pressure, the residue was diluted with water (100 mL). The aqueous phase was extracted with DCM (2 x 100 mL), washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure. The obtained crude was used as such for the next step without further purification. (11 g, 82%), LCMS; $[M+H]^+$: 315.37.

Step-6: Synthesis of 2-(3-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-3-yl) methyl)-1H-pyrrol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide (29)

[0176] To a stirred solution of 3-((1H-pyrrol-3-yl) methyl)-2-butyl-1,3-diazaspiro [4.4] non-1-en-4-one (13 g, 47.55 mmol) in DMSO (100 mL) at 0° C, was added sodium tert-butoxide (11.4 g, 118.75 mmol). The reaction was stirred at rt for 30 min, to this mixture was added N-(4,5-dimethylisoxazol-3-yl)-2-fluoro-

N-(methoxy methyl) benzene sulfonamide (12.8 g, 47.55 mmol). The resulting reaction mixture was stirred at rt for 16 h. After completion of the reaction, the reaction mixture was diluted with ice cold water (80 mL) and extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with brine solution, concentrated under reduced pressure. The crude material thus obtained was purified by chromatography (silica gel) to afford 2-(3-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-3-yl) methyl)-1H-pyrrol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)-N (methoxymethyl)benzenesulfonamide. (12 g, 44 %), LCMS; $[M+H]^+$: 568.67.

Step-7: synthesis of 2-(3-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-3-yl) methyl)-1H-pyrrol-1-yl)-N-(4,5-dimethylisoxazol-3-yl) benzene sulfone amide (Compound 17)

[0177] To a stirred solution of 2-(3-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-3-yl) methyl)-1H-pyrrol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl) benzenesulfonamide (10 g, 17.60 mmol) in DMF (100 mL), was added Cesium carbonate (17.2 g, 52.81 mmol). The reaction mixture was heated to 130 °C and stirred for 16 h. After completion of the reaction, the reaction mixture was cooled to rt, then filtered through celite bed washed with ethyl acetate (300 mL) and concentrated under reduced pressure. The crude material thus obtained was purified by Prep-HPLC using Cogent C18 (150*20*5µ) column, 10mM ABC in water and acetonitrile as mobile phase to afford 2-(3-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-3-yl) methyl)-1H-pyrrol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide. (3.5 g, 38%), LCMS; $[M+H]^+$: 524.41.

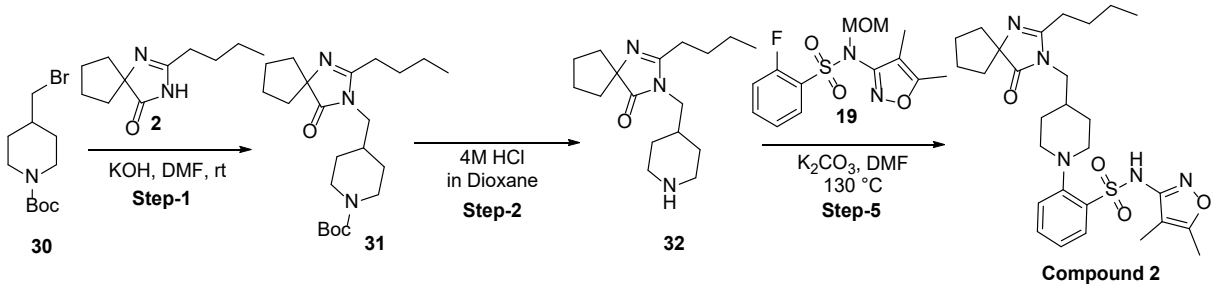
[0178] The following compounds were synthesized using procedure demonstrated for **Compound 17**. **Compound 33** was synthesized using similar procedure described for the synthesis of **Compound 17** by using corresponding starting material such as pyrazole-4-carboxaldehyde and using commercially available head group 2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine.

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
17	524.41	^{1}H NMR (DMSO-d6, 400 MHz): δ 10.81 (s, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 2.0 Hz, 2H), 5.99 (s, 1H), 4.50 (s, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.21 (s, 3H), 1.83-1.75 (m, 9H), 1.60 (t, *J* = 5.6 Hz, 2H), 1.57-1.49 (m, 2H), 1.30 (q, *J* = 7.6 Hz, 2H), 0.83 (t, *J* = 7.2 Hz, 3H).

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
28	505.30	^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 10.72 (s, 1H), 8.05 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.68 (t, *J* = 6.4 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.33-6.90 (m, 2H), 6.82 (s, 1H), 6.04-6.03 (m, 1H), 5.25 (s, 2H), 2.91-2.86 (q, *J* = 7.6 Hz, 2H), 2.53-2.48 (m, 6H), 2.18 (s, 3H), 1.69 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3H).
33	506.35	^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 10.18 (s, 1H), 8.90 (bs, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.44 (s, 3H), 6.91 (s, 1H), 5.31 (s, 2H), 2.99 (q, *J* = 8.0 Hz, 2H), 2.50 (s, 3H), 2.49 (s, 3H), 2.05 (s, 3H), 1.53 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).
43	536.37	^{1}H NMR (DMSO-d6, 400 MHz): δ ppm 10.72 (bs, 1H), 8.57 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.70 (m, 1H), 7.59 (m, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 6.87 (s, 2H), 5.98 (s, 1H), 4.48 (s, 2H), 3.67-2.63 (m, 1H), 2.55 (d, *J* = 7.2 Hz, 2H), 2.20 (s, 3H), 2.02-1.98 (m, 2H), 1.82-1.76 (m, 11H), 1.70-1.50 (m, 4H).
46	544.48	^{1}H NMR (400 MHz, DMSO-d_6): 10.73 (s,1H),8.03 (dd, *J* = 1.2 ,8 Hz ,1H) , 7.60-7.50 (bs ,1H) ,7.04(bs ,1H), 6.95 (bs ,1H), 5.94 (s ,2H) , 4.52 (s ,2H) ,2.50 (s,2H), 2.32 (s ,3H) , 1.82 (m ,6H), 1.64 (bs ,2H), 1.56 (m ,2H) ,1.35 (m ,2H),1.35 (m ,2H) ,0.85 (t , *J* =7.2 Hz ,3H).

Compound No	LCMS; $[M+H]^+$	^{1}H NMR data
47	522.30	^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 10.80 (bs, 1H), 6.03 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.60 (t, *J* = 6.8 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 6.98 (bs, 1H), 6.91 (s, 1H), 5.94 (s, 1H), 4.49 (s, 2H), 2.40 (d, *J* = 6.8 Hz, 2H), 2.15 (s, 3H), 1.84-1.77 (m, 6H), 1.64 (t, *J* = 14.8 Hz, 4H), 1.03-1.00 (m, 1H), 0.45-0.42 (m, 2H), 0.15 (t, *J* = 5.2 Hz, 2H).
49	522.30	^{1}H NMR (DMSO-d6, 400MHz): δ ppm 10.77 (bs, 1H), 8.05 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.67 (s, 1 H), 7.57 (s, 1H), 7.34 (d, *J* = 6.0 Hz, 1H), 6.92-6.88 (m, 2H), 5.96 (s, 1H), 4.39 (s, 2H), 3.43-3.39 (m, 1H), 2.24-2.11 (m, 7H), 1.98-1.77 (m, 11H), 1.73-1.64 (m, 2H).
55	559.33	^{1} H NMR (400 MHz, DMSO-d6): δ 10.66 (s, 1H), 8.05 (dd, *J* = 1.2, 8 Hz, 1H), 7.68 (bs, 1H), **7.57** (d, *J* = 7.2 Hz, 2H), 7.37 (d, *J* = 9.6 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 6.84 (bs, 1H), 6.05 (s, 1H), 4.81 (s, 2H), 2.18 (s, 3H), 1.68 (s, 3H), 1.32 (s, 6H).

Example 6: Synthesis of 2-(4-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-3-yl) methyl) piperidin-1-yl)-N-(4,5-dimethylisoxazol-3-yl) benzenesulfonamide (Compound 2)



Step-1: Synthesis of tert-butyl 4-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-*3yl*) methyl) piperidine-1-carboxylate (31)

[0179] To a stirred solution of 2-butyl-1,3-diazaspiro [4.4] non-1-en-4-one (0.418 g, 0.0021 mol) in DMF (5 mL), was added KOH (0.30 g, 5.35 mmol). The reaction mixture was stirred at 10 min at rt, then was added tert-butyl 4-(bromomethyl) piperidine-1-carboxylate (0.5 g, 1.79 mmol) at 0 °C. The reaction mixture was stirred at rt for 12 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material thus obtained was purified by flash chromatography (silica gel) to afford tert-butyl 4-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-*3yl*) methyl) piperidine-1-carboxylate. (0.42 g, 63%), LCMS; $[M+H]^+$: 392.28.

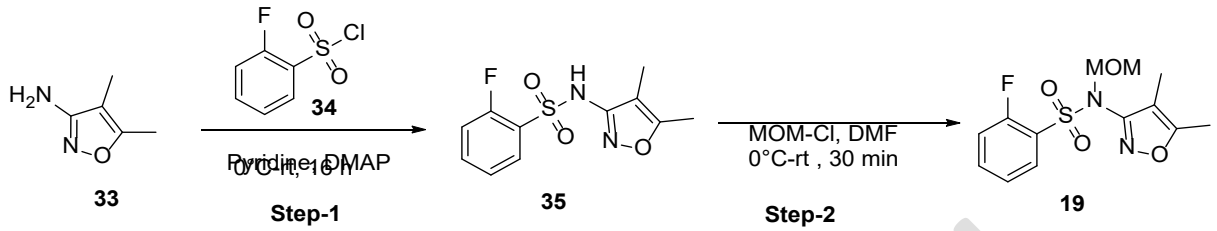
Step-2: Synthesis 2-butyl-3-(piperidin-4-ylmethyl)-1,3-diazaspiro [4.4] non-1-en-4-one (32)

[0180] tert-Butyl 4-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-3-yl) methyl) piperidine-1-carboxylate (0.42 g, 0.001072 mol) was dissolved in 4M HCl dioxane (4.2 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 2 h. After completion of the reaction, the reaction was quenched with saturated $NaHCO_3$ solution and extract compound with DCM (2 x 50 mL). The combined organic layers were washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure to afford 2-butyl-3-(piperidin-4-ylmethyl)-1,3-diazaspiro [4.4] non-1-en-4-one. (0.26 g, 83%), LCMS; $[M+H]^+$: 292.12.

Step-3: Synthesis of 2-(4-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-3-yl) methyl) piperidin-1-yl)-N-(4,5-dimethylisoxazol-3-yl) benzenesulfonamide (Compound 2)

[0181] To a stirred solution of 2-butyl-3-(piperidin-4-ylmethyl)-1,3-diazaspiro [4.4] non-1-en-4-one (0.26 g, 0.893 mmol) in DMF (2.6 mL), was added N-(4,5-dimethylisoxazol-3-yl)-2-fluoro-N-(methoxymethyl) benzenesulfonamide (0.30 g, 0.98 mmol) and K_2CO_3 (0.37 g, 2.68 mmol). The resulting reaction mixture was stirred at 130 °C for 12 h. After completion of the reaction, the reaction mixture was diluted with water (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material thus obtained was purified by Prep-HPLC using Xselect Phenyl Hexyl (250*19mm*5u) column using Mobile Phase A: 10mM ABC in water and Mobile Phase B: Acetonitrile to afford 2-(4-((2-butyl-4-oxo-1,3-diazaspiro [4.4] non-1-en-3-yl) methyl) piperidin-1-yl)-N-(4,5-dimethylisoxazol-3-yl) benzenesulfonamide (**Compound 2**). (0.006 g, 0.12%), LCMS; $[M+H]^+$:542.39.

Example 7, Intermediate 19: Synthesis of N-(4,5-dimethylisoxazol-3-yl)-2-fluoro-N-(methoxymethyl) benzenesulfonamide (19)



Step-1: Synthesis 2-butyl-3-(piperidin-4-ylmethyl)-1,3-diazaspiro [4.4] non-1-en-4-one (35)

[0182] To a solution of 4,5-dimethylisoxazol-3-amine (10 g, 89.2 mmol) and 4-(dimethylamine) pyridine (1.089 g, 8.92 mmol) in 100 mL pyridine at 0 °C, was added 2-fluro benzene sulfonyl chloride (17.35 g, 89.2 mmol) portion wise over 10 min. The reaction mixture was stirred at rt for 12 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, the residue was dissolved in 3% aqueous sodium bicarbonate. The residual solid was filtered off, the aqueous filtrate was acidified to pH 1 with 6 N aqueous HCl at 0 °C and extracted with ethyl acetate (2x250 mL). The extracts were washed with aqueous 6 N HCl, water, dried over sodium sulfate and concentrated under reduced pressure to afford N-(4,5-dimethylisoxazol-3-yl)-2-fluorobenzenesulfonamide. (21 g, 87%), LCMS; $[M+H]^+$: 271.05.

Step-2: SynthesisN-(4,5-dimethylisoxazol-3-yl)-2-fluoro-N-(methoxymethyl)benzenesulfonamide (19)

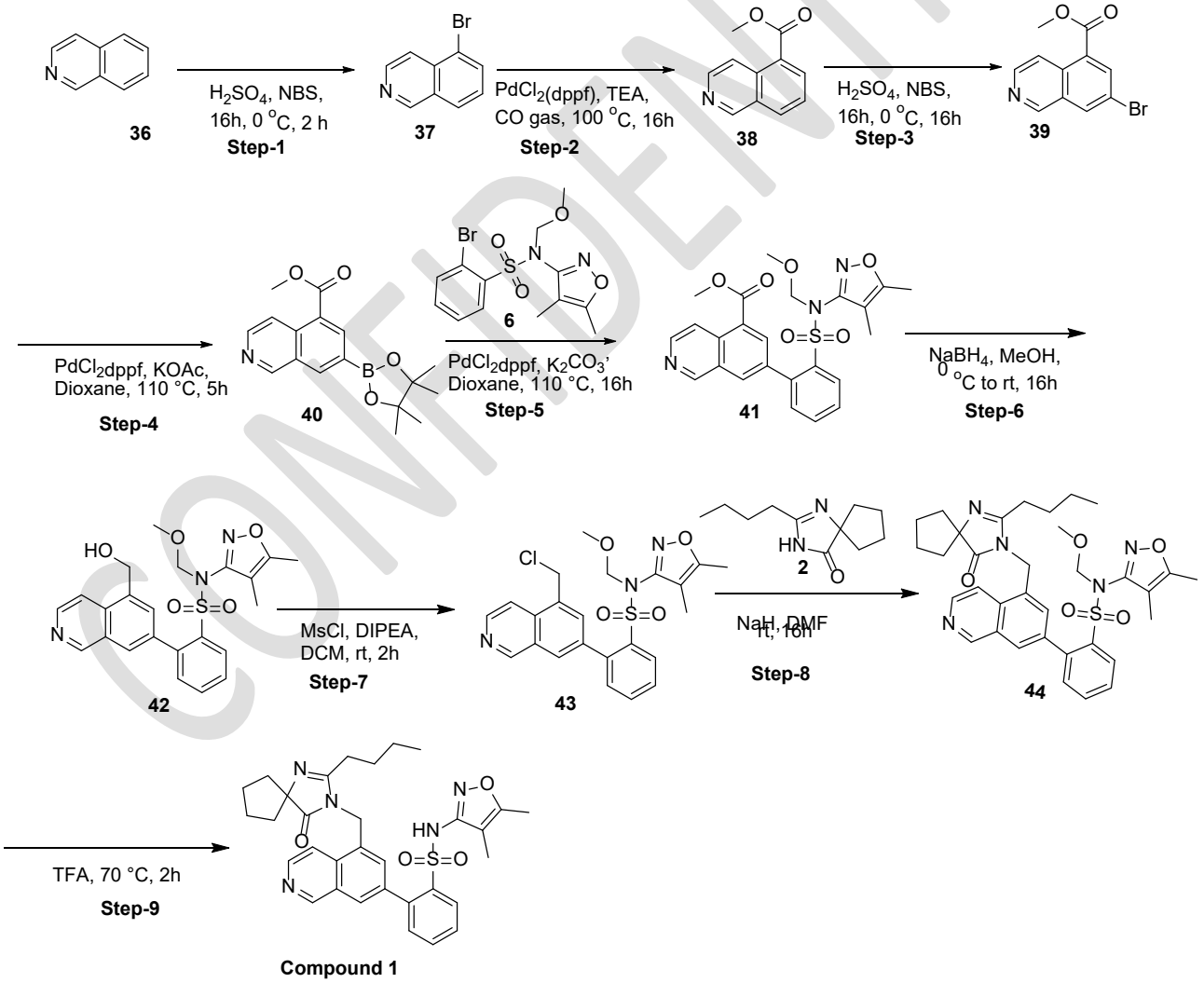
[0183] To a stirred solution of N-(3,4-dimethylisoxazol-5-yl)-2-fluorobenzenesulfonamide (20 g, 74.07 mmol) in DMF (100 mL) at 0 °C, was added K_2CO_3 (10.22 g, 74.07 mmol) and 2-methoxyethoxymethyl chloride (5.96 mL, 74.07 mmol) was added dropwise over 10 min. Then reaction mixture was stirred at same temperature for 20 min. After completion of the reaction, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (2x200 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material thus obtained was purified by flash chromatography (silica gel) to afford N-(4,5-dimethylisoxazol-3-yl)-2-fluoro-N-(methoxymethyl)benzenesulfonamide. (10.2 g, 93%), LCMS; $[M+H]^+$: 315.17.

[0184] The following compounds were synthesized using procedure demonstrated for **Compound 2**.

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
2	542.39	^{1} H NMR (400 MHz, DMSO-d6,): δ 7.84 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 3.35-3.31 (m, 2H), 3.20 (d, *J* = 10.8 Hz, 2H), 2.58-2.49 (m, 2H), 2.46 (d, *J* = 8.0 Hz, 2H), 2.12 (s, 3H), 1.84-1.75 (m, 9H), 1.66-1.57 (m, 5H), 1.45-1.36

Compound No	LCMS; $[M+H]^+$	^{1}H NMR data
		(m, 6H), 1.23 (s, 1H), 0.91 (t, *J* = 7.6 Hz, 3H).
3	523.32	^{1} H NMR (400 MHz, DMSO-d6): δ 10.14 (bs, 1H), 7.83 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.48-7.15 (m, 3H), 6.89 (s, 1H), 4.11 (d, *J* = 7.6 Hz, 2H), 3.12 (bs, 2H), 2.19 (q, *J* = 7.2 Hz, 2H), 2.55-2.48 (m, 7H), 2.19 (s, 3H), 1.98 (bs, 1H), 1.79 (s, 3H), 1.58 (t, *J* = 9.2 Hz, 2H), 1.42-1.34 (m, 5H), 1.23 (s, 1H).

Example 8: Synthesis of 2-(5-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)isoquinolin-7-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Compound 1)



Step-1: Synthesis of 5-bromoisoquinoline (37)

[0185] In a double neck round bottle flask (1L), was added H_2SO_4 (500 mL) and cooled to 0 ºC. To this was added isoquinoline (50 g, 387.1 mmol) slowly over a period of 20 min. The reaction mixture was cooled -15 ºC to -20 ºC and was added NBS (137.8 g, 774.2 mmol) portion wise over a period of 3h maintaining the same temperature. The resulting reaction mixture was allowed to warm up to rt and stirred for 2 h. After completion of the reaction, the reaction mixture was quenched with aq. ammonia (~2 L) carefully until the pH was about 10. The formed precipitate was filtered and purified by column chromatography (silica gel) to afford 5-bromoisoquinoline. (15 g, 18.6%); LCMS; $[M+H]^+$: 207.92.

Step-2: Synthesis of methyl isoquinoline-5-carboxylate (38)

[0186] The 250 mL autoclave was charged with 5-bromoisoquinoline (15 g, 72.1 mmol), TEA (30.1 mL, 216.28 mmol) and methanol (150 mL) and $PdCl_2$(dppf) (5.28 g, 7.21 mmol). The reaction mixture was degassed by bubbling argon gas for 10 min, the autoclave was filled with CO gas until 150 psi pressure. The reaction mixture was heated to 100 °C stirred for 16 h. The reaction mixture was filtered through celite and concentrated under reduce pressure to get crude material. The crude material thus obtained was purified by column chromatography (silica gel) to afford methyl isoquinoline-5-carboxylate. (4.5 g, 33%), LCMS; $[M+H]^+$: 188.12.

Step-3: Synthesis of methyl 5-bromoisoquinoline-8-carboxylate (39)

[0187] In a double neck round bottom flask (0.25 L) was added H_2SO_4 (45 mL) and cooled to 0 °C. To this was added methyl isoquinoline-5-carboxylate (4.5 g, 24.04 mmol) slowly over a period of 20 min. The reaction mixture was cooled to -20 ºC and added NBS (5.56 g, 31.25 mmol) portion wise over a period of 1h maintaining the same temperature. The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was quenched with aq. ammonia (~200 mL) carefully until the pH of the solution reached to 10. The formed ppt was filtered and purified by chromatography (silica gel) to afford methyl 5-bromoisoquinoline-8-carboxylate. (2.8 g, 43.8%), LCMS; $[M+H]^+$: 268.44.

Step-4: Synthesis of methyl 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline-5-carboxylate (40)

[0188] To a stirred solution of methyl 8-bromoisoquinoline-5-carboxylate (2.8 g, 1.88 mmol) in 1,4-Dioxane (60 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (6.68 g, 26.3 mmol), potassium acetate (3.1 g, 31.57 mmol) and $PdCl_2$(dppf) (0.77 g, 1.05 mmol) under argon atmosphere. The reaction mixture was degassed by bubbling with argon for 10 min, heated to 110 ºC and stirred for 5h. After completion of the reaction, the reaction mixture was concentrated, diluted with ice cold water (50 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure. The crude was purified by automated flash chromatography (silica gel) to afford methyl 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) isoquinoline-5-carboxylate. (1.8 g, 55%), LCMS; $[M+H]^+$: 232.57.

Step-5: Synthesis of methyl 8-(2-(N-(4,5-dimethylisoxazol-3-yl)-N (methoxymethyl)sulfamoyl)phenyl)isoquinoline-5-carboxylate (41)

[0189] To a stirred solution of 2-bromo-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide(1.8 g, 4.8 mmol) and methyl 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline-5-carboxylate (1.5 g, 0.762 mmol) in 1,4-Dioxane (25 mL), was added potassium carbonate (1.99 g, 14.39 mmol) in water (3 mL) and $PdCl_2$(dppf) (0.35 g, 0.48 mmol). The resulting reaction mixture was degassed by bubbling with argon for 10 min, was heated to 110 ºC and stirred for 16 h. After completion of the reaction, the reaction mixture was concentrated, diluted with ice cold water (50 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material thus obtained was purified by flash chromatography (silica gel) to afford methyl 8-(2-(N-(4,5-dimethylisoxazol-3-yl)-N (methoxymethyl)sulfamoyl)phenyl)isoquinoline-5-carboxylate. (1.8 g, 78%), LCMS; $[M+H]^+$: 482.64.

Step-6: Synthesis of N-(4,5-dimethylisoxazol-3-yl)-2-(5-(hydroxymethyl)isoquinolin-8-yl)-N-(methoxymethyl)benzenesulfonamide (42)

[0190] To a stirred solution of methyl 8-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)sulfamoyl)phenyl)isoquinoline-5-carboxylate (1.7 g, 3.53 mmol) in methanol (35 mL) at 0 °C, was added sodiumborohydride (1.35 g, 35.3 mmol). The resulting reaction mixture was allowed to warm to rt and stirred for 16 h. After completion of the reaction, the reaction mixture was concentrated, diluted with ice cold water (50 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with water, dried over sodium sulfate and concentrated under reduced pressure. The crude material thus obtained was purified by column chromatography (silica gel) to afford N-(4,5-dimethylisoxazol-3-yl)-2-(5-(hydroxymethyl)isoquinolin-8-yl)-N-(methoxymethyl)benzenesulfonamide. (0.22 g, 14%), LCMS; $[M+H]^+$: 453.86.

Step-7: Synthesis of 2-(8-(chloromethyl)isoquinolin-6-yl)-N-(3,4-dimethylisoxazol-5-yl)-N-(methoxymethyl)benzenesulfonamide (43)

[0191] To a solution of N-(3,4-dimethylisoxazol-5-yl)-2-(8-(hydroxymethyl)isoquinolin-6-yl)-N-(methoxymethyl)benzenesulfonamide (0.22 g, 0.48 mmol) in DCM (3 mL), was added methanesulfonyl chloride (0.061 mL, 0.79 mmol) and DIPEA (0.28, 1.56 mmol) . The resulting reaction mixture was allowed to stir at rt for 8 h. After completion of the reaction (monitored by TLC), the solvents were evaporated and the crude mixture thus obtained was purified by column chromatography to afford 2-(8-(chloromethyl)isoquinolin-6-yl)-N-(3,4-dimethylisoxazol-5-yl)-N-(methoxymethyl)benzenesulfonamide. (0.2 g, 87%), LCMS; $[M+H]^+$: 471.99.

Step-8: Synthesis of 2-(8-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)isoquinolin-6-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide (44)

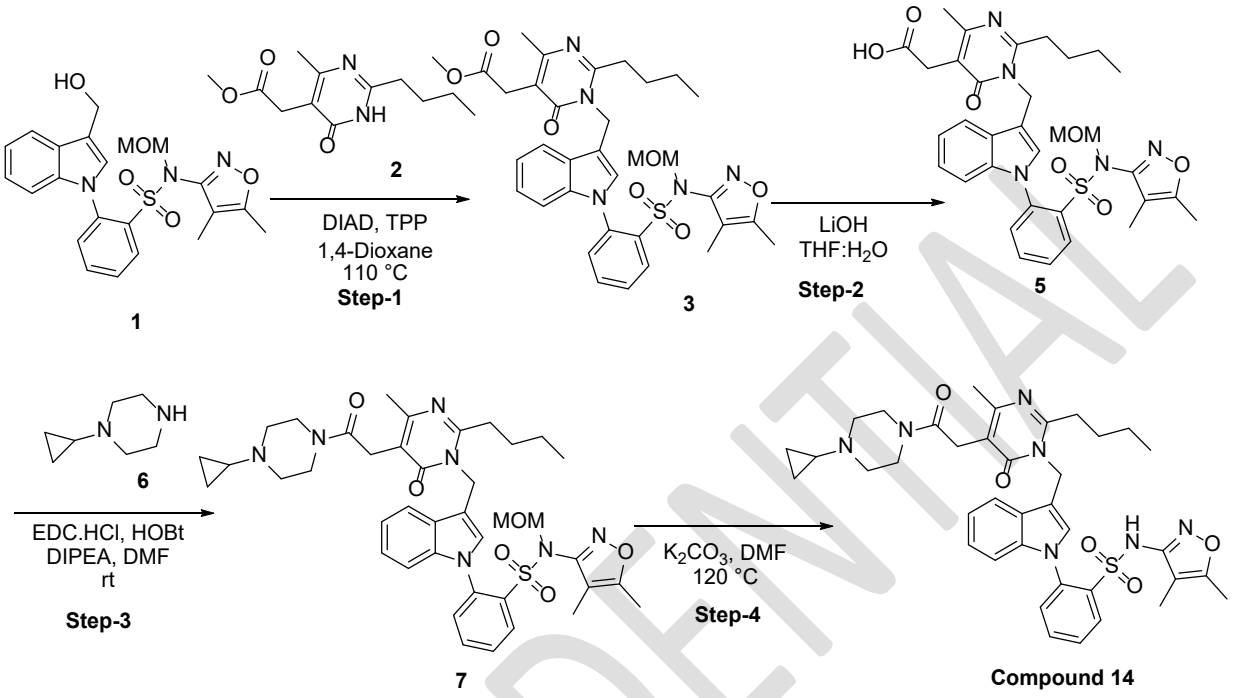
[0192] To a solution of benzyl 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (0.1 g, 0.51 mmol) in DMF (5 mL) at 0 °C, was added sodium hydride (0.037 g, 1.53 mmol) and the resulting mixture was stirred for 30 min. To this reaction mixture was added 2-(8-(chloromethyl)isoquinolin-6-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide (0.2 g, 0.424 mmol) and stirred for 6 h. After completion of the reaction (monitored by TLC), the solvents were evaporated and the crude material was dissolved in ethyl acetate, then washed with water and brine. The combined organic layer was dried over sodium sulfate and concentrated. The crude material thus obtained was purified by column chromatography to afford 2-(8-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)isoquinolin-6-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide. (0.1 g, 41%), LCMS; $[M+H]^+$: 630.20.

Step-9: Synthesis of 2-(5-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)isoquinolin-7-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide(Compound 1)

[0193] 2-(5-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)isoquinolin-7-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide (0.11 g, 0.17 mmol), was dissolved in TFA (8 mL) and stirred at 60 °C for 1 hour. After completion of the reaction (monitored by TLC), the solvents were evaporated and the crude material was dissolved in ethyl acetate, then washed with water and brine. The combined organic layer was dried over sodium sulfate and concentrated. The crude material thus obtained was purified by column chromatography to afford2-(5-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)isoquinolin-7-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (**Compound 1**). (3.5 mg, 3%), LCMS; $[M+H]^+$: 586.37

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
1		^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 10.60 (s, 1H), 9.3 (s, 1H), 8.57 (d, *J* = 6.0 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 6.0 Hz, 1H), 7.91 (s, 1H), 7.68-7.31 (m, 4H), 5.14 (s, 2H), 2.34-2.32 (m, 2H), 2.12 (bs, 2H), 1.83-1.79 (m, 6H), 1.62-1.40 (m, 4H), 1.33-1.20 (m, 6H), 0.72 (t, *J* = 7.2 Hz, 3H).

Example 9: Synthesis of 2-(3-((2-butyl-5-(2-(4-cyclopropylpiperazin-1-yl)-2-oxoethyl)-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Compound 14)



Step-1: Synthesis of methyl 2-(2-butyl-1-((1-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)sulfamoyl)phenyl)-1H-indol-3-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)acetate

[0194] To a stirred solution of N-(4,5-dimethylisoxazol-3-yl)-2-(3-(hydroxymethyl)-1H-indol-1-yl)-N-(methoxymethyl)benzenesulfonamide (0.9 g, 2.03 mmol) in 1,4-Dioxane (9 mL) at 0 °C, was added triphenylphosphine (0.841g, 2.45mmol) and diisopropylazodicarboxylate (0.618 g, 3.05 mmol). The resulting reaction mixture was stirred at 110 °C for 2 h. The completion of the reaction was monitored by the TLC. After completion of the reaction, the reaction mixture was diluted with ice cold water (30 mL) extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over sodium sulphate, concentrated under reduced pressure. The crude material thus obtained was purified by the combi-flash chromatography (silica gel 100-200 mesh) eluted with 30 % ethyl acetate / petroleum ether to afford methyl 2-(2-butyl-1-((1-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)sulfamoyl)phenyl)-1H-indol-3-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)acetate. (0.4 g, 29 %), LCMS; $[M+H]^+$: 662.

Step-2: Synthesis of 2-(2-butyl-1-((1-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)sulfamoyl)phenyl)-1H-indol-3-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)acetic acid

[0195] To a stirred solution of methyl 2-(2-butyl-1-((1-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)sulfamoyl)phenyl)-1H-indol-3-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)acetate (0.9 g, 1.48 mmol) in THF:H_2O (20 mL) at rt, was added LiOH.H_20 (0.16 g, 7.39 mmol). The resulting reaction mixture was stirred at rt for 12 h. After completion of the reaction (monitored by TLC), the volatiles were evaporated under reduced pressure. The crude solid was dissolved in water and extracted with DCM (2x 20mL). The combined organic layers were dried over sodium sulphate and concentrated under reduced pressure to get 2-(2-butyl-1-((1-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)sulfamoyl)phenyl)-1H-indol-3-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)acetic acid.(0.35 g, 40 %), LCMS; $[M+H]^{+:}$ 648.

Step-3: Synthesis of 2-(3-((2-butyl-5-(2-(4-cyclopropylpiperazin-1-yl)-2-oxoethyl)-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide

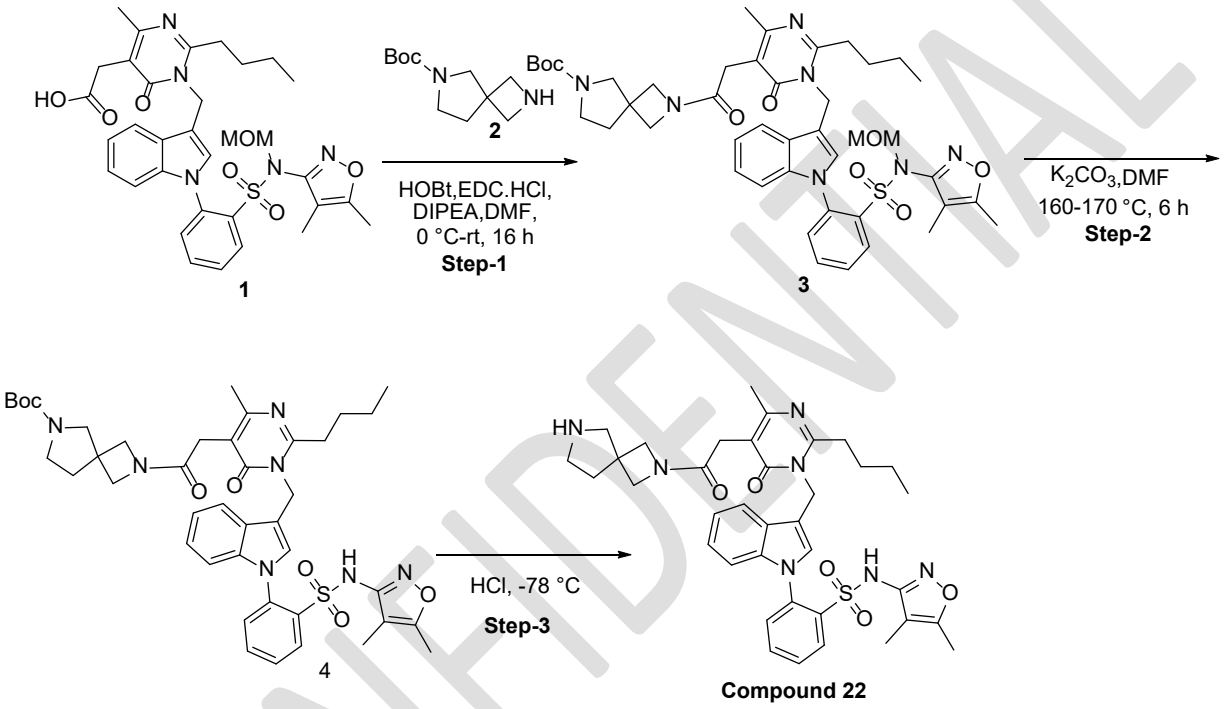
[0196] To a stirred solution of 2-(2-butyl-1-((1-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)sulfamoyl)phenyl)-1H-indol-3-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)acetic acid (0.2 g, 0.309 mmol) in DMF (2 mL) at rt, was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.089 g, 0.463 mmol), hydroxybenzotriazole (0.063 g , 0.463 mmol), DIPEA (0.171 mL , d = 0.7 g/mL, 0.926 mmol) and 1-cyclopropylpiperazine (0.078 g, 0.618 mmol). The resulting reaction mixture was stirred for 6h at rt. After completion of the reaction (monitored by the TLC), the reaction mixture was concentrated under reduced pressure and diluted with water (25 mL) and extracted with DCM (2X 50 mL). The combined organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude material thus obtained was purified on Combi-flash chromatography system (silica gel 100-200 mesh) by eluting with 30% ethyl acetate / petroleum ether to afford 2-(3-((2-butyl-5-(2-(4-cyclopropylpiperazin-1-yl)-2-oxoethyl)-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide. (0.1 g, 43 %), LCMS; $[M+H]^{+:}$ 756.

Step-4: Synthesis of 2-(3-((2-butyl-5-(2-(4-cyclopropylpiperazin-1-yl)-2-oxoethyl)-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (Compound 14)

[0197] To a stirred solution of 2-(3-((2-butyl-5-(2-(4-cyclopropylpiperazin-1-yl)-2-oxoethyl)-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)benzenesulfonamide (0.12 g, 0.16 mmol) in DMF (2 mL) at rt, was added K_2CO_3 (0.07 g, 0.48 mmol). The resulting reaction mixture was stirred at 140 °C for 12 h. After completion of the reaction (monitored by LCMS), the reaction mixture was quenched by addition of water (10 mL) and extracted with DCM (3X 20 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude material thus obtained was purified by Prep. HPLC on Hi chrome c18 (250*22*5u) column, using 10mM ABC in water and acetonitrile as eluents. The pure fractions were collected and

evaporated under reduced pressure and lyophilized to afford 2-(3-((2-butyl-5-(2-(4-cyclopropylpiperazin-1-yl)-2-oxoethyl)-4-methyl-6-oxopyrimidin-1(6H)-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (**Compound 14**). (0.05 g, 45 %), LCMS; $[M+H]^{+:}$ 711.88.

Example 10: Synthesis of 2-(3-((2-butyl-4-methyl-6-oxo-5-(2-oxo-2-(2,6-diazaspiro [3.4] octan-2-yl) ethyl) pyrimidin-1(6H)-yl) methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3-yl) benzenesulfonamide (Compound 22)



Step-1: Synthesis of tert-butyl 2-(2-(2-butyl-1-((1-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl) sulfamoyl) phenyl)-1H-indol-3-yl) methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl) acetyl)-2,6-diazaspiro [3.4] octane-6-carboxylate

[0198] To a stirred solution of 2-(2-butyl-1-((2'-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)sulfamoyl)-2-(ethoxymethyl)-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)acetic acid (0.40 g, 0.618 mmol) in DMF (10 mL) at rt, was added HOBt (0.125 g, 0.926 mmol), EDC.HCl (0.177 g, 0.926 mmol) and DIPEA (0.327 mL, 1.853 mmol). The resulting reaction mixture was stirred for 30 min, was added tert-butyl 2,6-diazaspiro[3.4]octane-6-carboxylate (0.157 g, 0.741 mmol) and stirred for 16 h at rt. After completion of the reaction, the reaction mixture was diluted with DCM (50 mL), washed with water (2x50 mL), brine (50 mL), dried over sodium sulphate and concentrated under reduced pressure. The crude material thus obtained was purified by column chromatography (silica gel

100-200 mesh) by using a mixtue of 0-100%ethyl acetate in petroleum ether to get afford the title compound (0.22 g, 42%), LCMS; $[M+H]^+$: 842.77.

Step-2: Synthesis of tert-butyl 2-(2-(2-butyl-1-((1-(2-(N-(4,5-dimethylisoxazol-3-yl)sulfamoyl)phenyl)-1H-indol-3-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)acetyl)-2,6-diazaspiro[3.4]octane-6-carboxylate

[0199] To a stirred solution of tert-butyl 2-(2-(2-butyl-1-((1-(2-(N-(4,5-dimethylisoxazol-3-yl)-N-(methoxymethyl)sulfamoyl)phenyl)-1H-indol-3-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)acetyl)-2,6-diazaspiro[3.4]octane-6-carboxylate (120 mg, 0.143 mmol) in DMF (5 mL) at rt, was added K_2CO_3 (59 mg, 0.428 mmol). The resulting reaction mixture was heated to 160 °C and stirred for 6 h. After completion of reaction, reaction mixture was diluted with ice cold water and extracted with DCM (2 x 25 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4, filtered and concentrated. The crude material thus obtained was triturated with ether and dried to afford the title compound. (0.075 g, 66%), LCMS; $[M+H]^+$: 798.83.

Step-3: Synthesis of 2-(3-((2-butyl-4-methyl-6-oxo-5-(2-oxo-2-(2,6-diazaspiro[3.4]octan-2-yl)ethyl)pyrimidin-1(6H)-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3 yl)benzenesulfonamide

[0200] To a stirred solution of tert-butyl 2-(2-(2-butyl-1-((1-(2-(N-(4,5-dimethylisoxazol-3-yl)sulfamoyl)phenyl)-1H-indol-3-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)acetyl)-2,6-diazaspiro[3.4]octane-6-carboxylate (0.13 g, 0.163 mmol) in 4N HCl in dioxane (1.0 mL) at -78 °C, was added Conc HCl solution (0.5 mL). The resulting reaction mixture was stirred at same temp for 3-4 h. After completion of reaction, reaction mixture was concentrated under reduced pressure, diluted with ice cold water (20 mL), basified with sat. $NaHCO_3$ solution and extract with 20% MeOH in DCM (3 x 25 mL). The combined organic layers were washed with water, brine, dried over sodium sulphate, and concentrated under reduced pressure. The crude material thus obtained was purified by Prep HPLC on hichrome 21.2*150 mm, using 10 mm ABC in water and acetonitrile as eluents. The pure fractions were evaporated and lyophilized to afford to 2-(3-((2-butyl-4-methyl-6-oxo-5-(2-oxo-2-(2,6-diazaspiro[3.4]octan-2-yl)ethyl)pyrimidin-1(6H)-yl)methyl)-1H-indol-1-yl)-N-(4,5-dimethylisoxazol-3 yl)benzenesulfonamide (**Compound 22**). (0.016 g, 14%); LCMS; [M+H]+: 698.42.

[0201] The following compounds were prepared using the methods described above.

Compound No	**LCMS; $[M+H]^+$**	**^{1}H NMR data**
14	711.88	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.12 (m, 1H), 7.67 (s, 1H), 7.59 (m, 1H), 7.45 (m, 2H), 7.17 (m, 1H), 6.95 (m, 2H), 6.82 (m, 1H), 5.44 (s, 2H), 3.57 (m, 4H), 3.41 (s, 2H), 2.96 (m, 2H), 2.50 (m, 4H), 2.11 (s, 3H), 1.93 (s, 3H),

Compound No	LCMS; $[M+H]^+$	^{1}H NMR data
		1.61 (m, 3H), 1.34 (m, 3H), 1.23 (s, 3H), 0.84 (t, *J* = 7.2 Hz, 3H), 0.42 (m, 2H), 0.38 (m, 2H).
22	698.42	^{1}H NMR (400 MHz, DMSO-d_6 at 90 °C): δ ppm 8.13-8.11 (m, 1H), 7.64 (d, *J* =8.4 Hz, 1H), 7.58 (s, 1H), 7.45-7.38 (m, 2H), 7.15 (dd, *J* =2, 7.6 Hz, 1H), 7.0-6.94 (m, 2H), 6.88 (d, *J* =6.4 Hz, 1H), 5.43 (s, 2H), 3.99 (bs, 2H), 3.78 (bs, 2H), 3.33 (s, 2H), 2.95-2.87 (m, 6H), 2.18 (s, 3H), 1.98 (s, 5H), 1.65-1.62 (m, 2H), 1.35-1.29 (m, 5H), 0.81 (t, *J* = 7.2 Hz, 3H)
23	512.31	^{1}H NMR (400 MHz, DMSO-d_6): 10.81 (s, 1H), 8.16 (m, 1H) ,7.75 (d, *J* = 8.0 Hz, 1H), 7.66 (bs, 2H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 6.8 Hz, 2H), 7.19 (m, 1H), 7.11 (m ,1H) ,6.97 (m, 2H), 6.78 (d, *J* = 7.6 Hz, 1H), 5.59 (s, 2H), 2.51 (s, 3H) , 2.07 (s, 3H), 1.43 (s, 3H).
53	597.35	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.14-8.12 (m, 1H), 7.71 (s, 1H), 7.52-7.45 (m, 3H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.16-7.14 (m, 1H), 6.95-6.82 (m, 4H), 6.75 (dd, *J* = 2.0 Hz, *J* = 8.8 Hz, 1H), 5.47 (s, 2H), 2.96-2.91 (m, 3H), 2.84 (s, 6H), 1.98 (s, 3H), 1.75-1.69 (m, 3H), 1.40-1.29 (m, 6H), 1.23-1.22 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 4H). The compound is in the form of DEA salt
57	597.35	^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.5 (br s, 1H), 8.16 (dd, *J* = 1.6 Hz, *J* = 7.6 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.46 (s, 1H), 7.32 (d, *J* = 6.8 Hz, 2H), 7.00-6.95 (m, 2H), 6.85 (s, 1H), 6.82-6.78 (m, 2H), 5.56 (s, 2H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.87 (s, 6H), 2.10 (s, 3H), 1.73-1.67 (m, 2H), 1.46 (s, 3H), 1.39-1.33 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H).

BIOLOGICAL EXAMPLES

Dual ET_A and AT_1 Receptor Antagonist: Invitro Assay

[0202] Intracellular Calcium Flux Assessment - FLIPR Assay Protocol

CHOK1 cells stably expressing Angiotensin-II receptor type 1 (AGTR1) and Endothelin-1 receptor type-A (EDNRA) from different species (human, mouse and rat) were generated using the lipofectamine 3000 transfection reagent. Fluorescence Imaging plate reader (FLIPR, Molecular Devices) was employed to evaluate the dual inhibition and to determine IC50 values of compounds screened against AGTR1 and EDNRA receptors. FLIPR assay detects the G-protein coupled receptors (GPCRs) activation through changes in the intracellular Ca^{2+} concentration. Addition of AGTR1 and EDNRA receptors agonists, Angiotensin II

and Endothelin-1, respectively, stimulates the cells and the change in intracellular calcium flux is measured using calcium sensitive dyes (FLIPR Calcium 6 assay, Molecular Devices). Briefly, 50,000 cells seeded per well in a 96 well black, flat clear bottom plate coated with poly-d-lysine. Calcium sensitive dyes incubation performed for 60 minutes followed by 30 minutes' compound treatment. Compounds were treated at eight different concentrations (10μM through 3nM) and the cells were then stimulated with respective agonists. Basal fluorescence read out was read for 30 seconds and following agonist addition the calcium response was assessed for 90 seconds. Table 2 below shows results from this assay.

[0203] Activity of the tested compounds in the assays above is provided in Table 3 as follows: +++ =IC50 ≤ 100 nM;++ = IC50 >100 nm to ≤ 500 nM;+ =IC50 >500 nM to ≤ 5000 nM; * = IC50 >5000 μM.

TABLE 2

Compound No	**hAT1_IC50_ nM**	**hETA_IC50_nM**
1	*	*
2	*	*
3	*	*
4	+++	+
5	+++	*
6	+++	*
7	*	*
8	+++	*
9	+++	*
10	+++	*
11	++	*
12	+++	*
13	+++	*
14	++	++
15	+	++
16	+	++
17	++	+++
18	+	+
19	+++	+

Compound No	hAT1_IC50_ nM	hETA_IC50_nM
20	+++	*
21	+++	*
22	+++	+
23	+	++
24	+++	+++
25	+++	++
26	+++	++
27	+++	+++
28	+++	+++
29	*	++
30	*	+
31	*	+
32	*	+++
33	*	*
34	+	++
35	*	++
36	+	+
37	++	++
38	*	++
39	+	++
40	++	+
41	++	++
42	+	++
43	++	++
44	+	+
45	++	++
46	*	+
47	+	+++

Compound No	hAT1_IC50_ nM	hETA_IC50_nM
48	+	++
49	+	++
50	++	++
51	+++	+++
52	++	++
53	+	++
54	++	++
55	+	++
56	+	+
57	*	+++

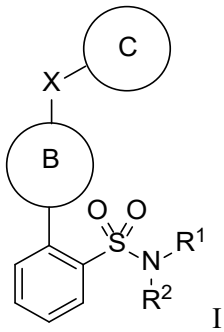
[0204] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0205] The inventions illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including," "containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

[0206] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

What is Claimed is:

1. A compound of Formula I:



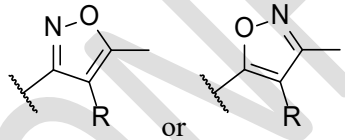
I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

X is $-CH_2-$;

Ring B is C_{5-10} cycloalkyl, 4- to 9-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein each cycloalkyl, heterocyclyl, or heteroaryl is independently optionally substituted with one to six Z^1;

Ring C is 4- to 9-membered heterocyclyl or 5- to 10-membered heteroaryl; wherein the 4- to 9-membered heterocyclyl or 5- to 10-membered heteroaryl is independently optionally substituted with one to six Z^1;

R^1 is  or ;

R is C_{1-6} alkyl or halo;

R^2 is hydrogen or alkoxyalkyl;

each Z^1 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxyalkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-C(O)N(R^{10})_2$, $-NR^{10}C(O)R^{10}$, $-OC(O)N(R^{10})_2$, $-NR^{10}C(O)OR^{10}$, $-S(O)_{0-2}R^{10}$, $-NR^{10}S(O)_{1-2}R^{10}$, $-NR^{10}C(O)N(R^{10})_2$, or $-NR^{10}S(O)_{1-2}N(R^{10})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{10} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each Z^{1a} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10a}$, $-N(R^{10a})_2$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-OC(O)R^{10a}$, $-C(O)N(R^{10a})_2$, $-NR^{10}C(O)R^{10a}$, $-OC(O)N(R^{10a})_2$, $-NR^{10a}C(O)OR^{10a}$, $-S(O)_{0-2}R^{10a}$, $-NR^{10a}S(O)_{1-2}R^{10a}$, $-NR^{10a}C(O)N(R^{10a})_2$, or $-NR^{10a}S(O)_{1-2}N(R^{10a})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R^{10a} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

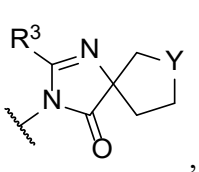
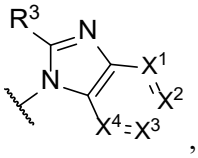
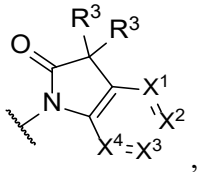
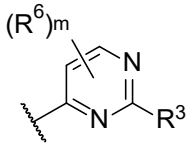
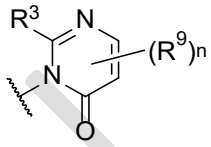
each Z^{1b} is independently halo, cyano, -OH, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C_{1-6} alkyl, -L-C_{2-6} alkenyl, -L-C_{2-6} alkynyl, -L-C_{1-6} haloalkyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, $-S(O)_2$-, -N(C_{1-6} alkyl)-, -N(C_{2-6} alkenyl)-, -N(C_{2-6} alkynyl)-, -N(C_{1-6} haloalkyl)-, -N(C_{3-10} cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C_{1-6} alkyl)-, -C(O)N(C_{2-6} alkenyl)-, -C(O)N(C_{2-6} alkynyl)-, -C(O)N(C_{1-6} haloalkyl)-, -C(O)N(C_{3-10} cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -OC(O)NH-, -OC(O)N(C_{1-6} alkyl)-, -OC(O)N(C_{2-6} alkenyl)-, -OC(O)N(C_{2-6} alkynyl)-, -OC(O)N(C_{1-6} haloalkyl)-, -OC(O)N(C_{3-10} cycloalkyl)-, -OC(O)N(heterocyclyl)-, -OC(O)N(aryl)-, -OC(O)N(heteroaryl)-, -NHC(O)-, -N(C_{1-6} alkyl)C(O)-, -N(C_{2-6} alkenyl)C(O)-, -N(C_{2-6} alkynyl)C(O)-, -N(C_{1-6} haloalkyl)C(O)-, -N(C_{3-10} cycloalkyl)C(O)-, -N(heterocyclyl)C(O)-, -N(aryl)C(O)-, -N(heteroaryl)C(O)-, -NHC(O)O-, -N(C_{1-6} alkyl)C(O)O-, -N(C_{2-6} alkenyl)C(O)O-, -N(C_{2-6} alkynyl)C(O)O-, -N(C_{1-6} haloalkyl)C(O)O-, -N(C_{3-10} cycloalkyl)C(O)O-, -N(heterocyclyl)C(O)O-, -N(aryl)C(O)O-, -N(heteroaryl)C(O)O-, -NHC(O)NH-, -NHS(O)-, $-NHS(O)_2NH$, $-S(O)NH$-, $-S(O)_2NH$, -NHS(O)NH-, or $-NHS(O)_2NH$-;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five halo,

cyano, hydroxy, -SH, -NH_2, -NO_2, -SF_5, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl.

2. The compound of claim 1, wherein Ring C is:


, 
, 
, 
, or 
;

where

Y is -CH_2- or -$S(O)_2$-;

X^1, X^2, X^3, and X^4 are independently chosen from CR^4 and N, provided that at least three of X^1, X^2, X^3, and X^4 are CR^4;

R^3 is C_{1-6} alkyl, C_{3-7} cycloalkyl, or (C_{3-7} cycloalkyl)alkyl;

each R^4 is independently hydrogen, halo, C_{1-6} alkyl optionally substituted with 1 to 3 halo, C_{1-6} alkoxy optionally substituted with 1 to 3 halo, cyano, -$N(R^5)_2$, -NH-$S(O)_2$-R^5, -$C(O)OR^5$, or -$C(O)NR^5{}_2$;

each R^5 is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^{1a};

each R^6 is independently C_{1-6} alkyl optionally substituted with -$C(O)NR^7{}_2$;

each R^7 is independently hydrogen, C_{1-6} alkyl, 4- to 11-membered heterocyclyl, C_{3-7} cycloalkyl, 5- to 9-membered heteroaryl, or C_{6-10} aryl, wherein each heterocyclyl contains from 1 to 3 heteroatoms selected from O, N, NR^8, and S, and wherein each heteroaryl contain from 1 to 3 heteroatoms selected from O, N, and NR^8;;

or two R^7, together with the nitrogen to which they attach, form a 4- to 9-membered heterocyclyl optionally containing 1 to 2 additional heteroatoms selected from O, NR^8, and S;

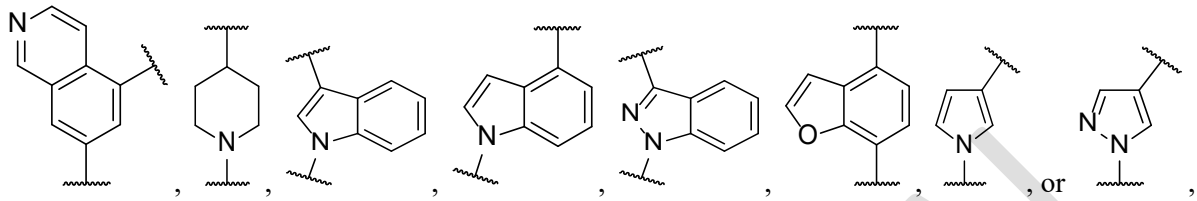
each R^8 is independently hydrogen, C_{1-6} alkyl, or C_{3-7} cycloalkyl;

each R^9 is independently -$C(O)NR^7{}_2$ or C_{1-6} alkyl optionally substituted with -$C(O)NR^7{}_2$;

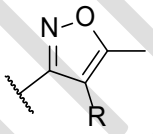
m is 0, 1, or 2; and

n is 0, 1, or 2.

3. The compound of claim 1 or 2, wherein Ring B is:

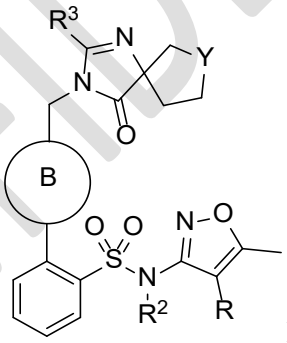


, , , , , , , or , each optionally substituted with C_{1-6} alkyl or C_{1-6} alkoxyalkyl,.

4. The compound of any of the preceding claims wherein R^1 is 

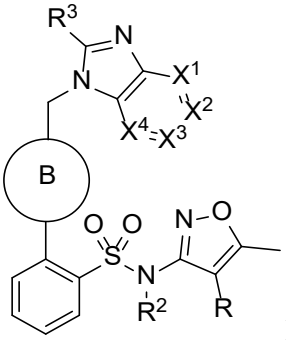
.

5. The compound of claim 1, wherein the compound is represented by Formula II:



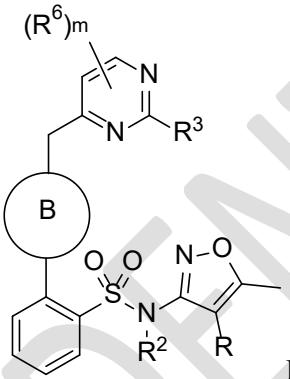
II.

6. The compound of claim 1, wherein the compound is represented by Formula III:



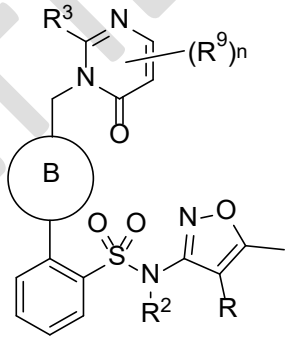
III.

7. The compound of claim 1, wherein the compound is represented by Formula IV:



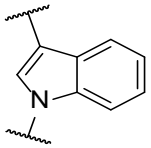
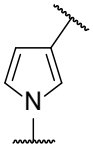
IV.

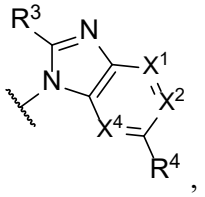
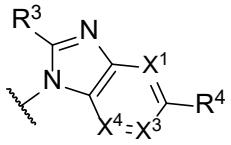
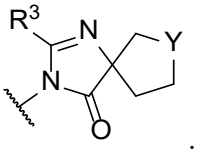
8. The compound of claim 1, wherein the compound is represented by Formula V:



V.

9. The compound of claim 1, wherein

ring B is selected from  and  ; and

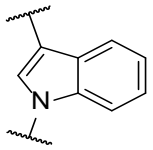
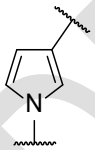
ring C is selected from  ,  , and  .

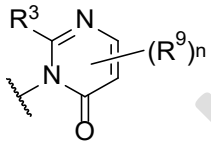
10. The compound of any one of claims 1-5 and 9, wherein Y is CH_2.

11. The compound of any one of claims 1-4, 6, and 9, wherein R^4 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, cyano, $-OR^{10}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})_2$, and $-NR^{10}S(O)_{1-2}R^{10}$.

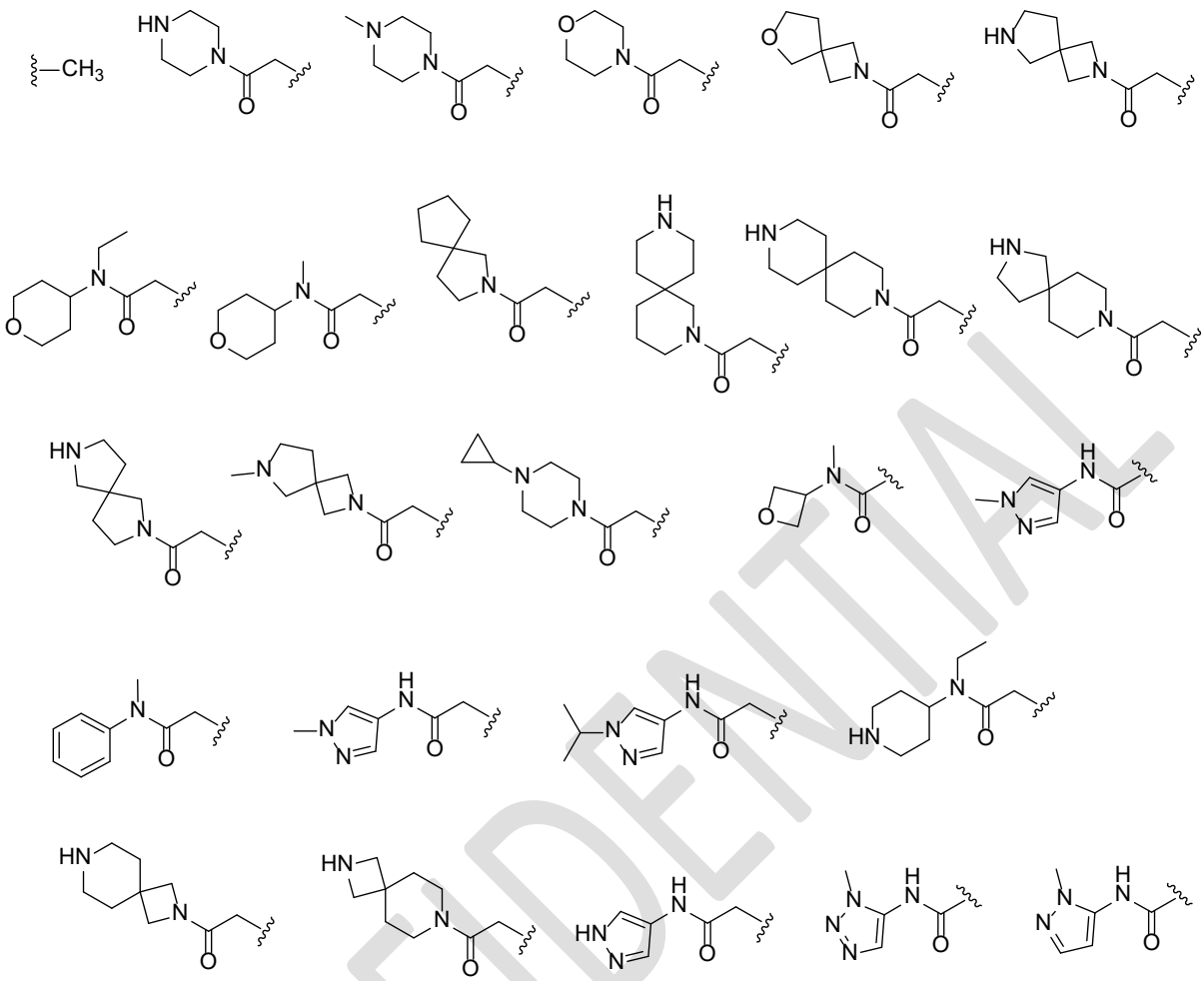
12. The compound of any one of claims 1-4, 6, and 9, wherein R^4 is selected from $-CH_3$, $-CH_2CH_3$, $-CF_3$, -CN, halo, $-OCH_3$, $-OCF_3$, -C(O)OH, and $-C(O)NH_2$.

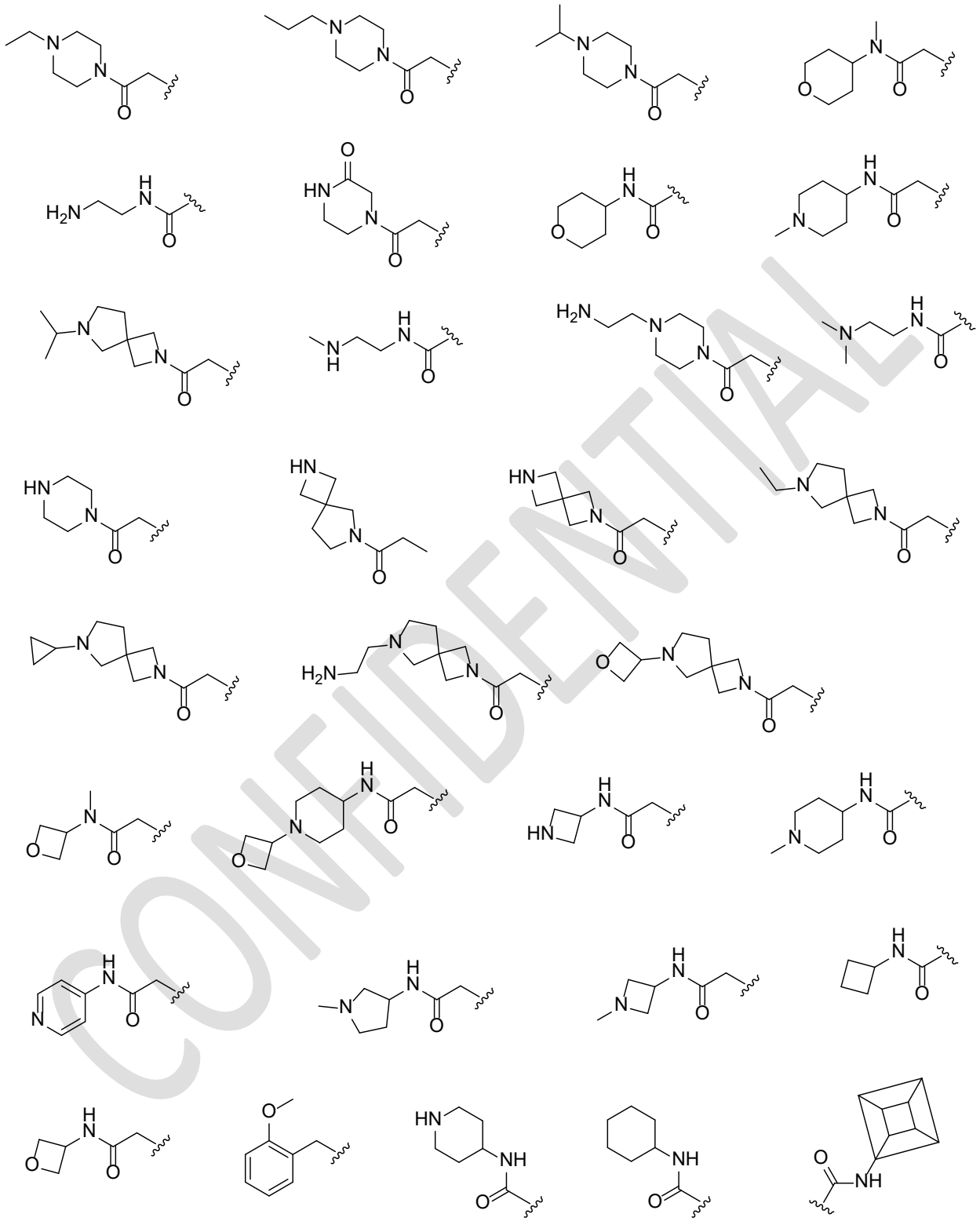
13. The compound of claim 1, wherein

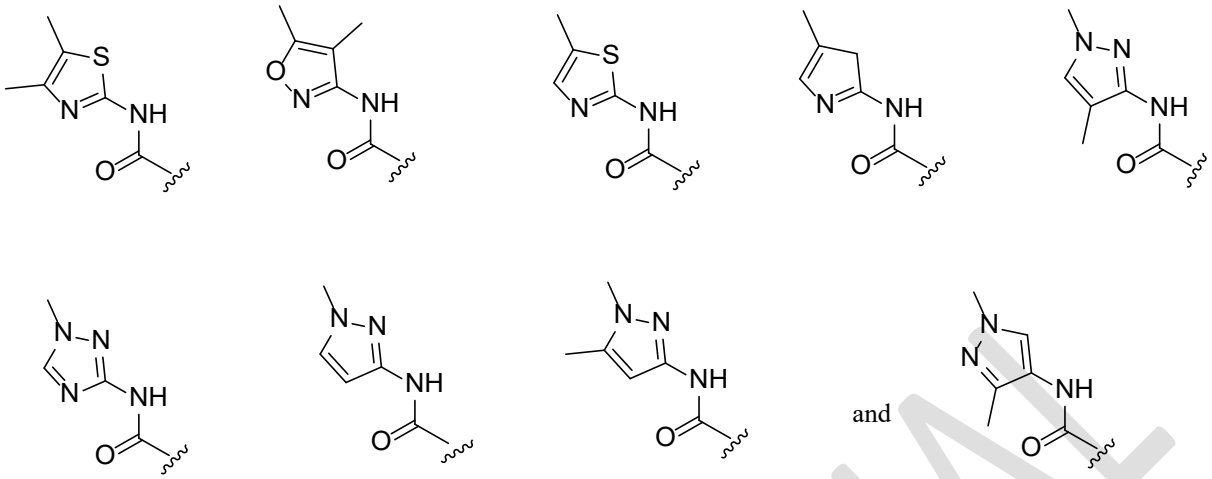
ring B is selected from  and  ; and

ring C is  .

14. The compound of claim 13, wherein R^9 is selected from







15. The compound of any of the preceding claims, wherein R^3 is selected from

16. The compound of any of the preceding claims R^2 is hydrogen.

17. The compound of any of the preceding claims, wherein n is 1 or 2.

18. A compound selected from Table 1, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

19. A pharmaceutical composition comprising a compound of any of the preceding claims, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable carrier.

20. A method for treating idiopathic pulmonary fibrosis (IPF), comprising administering a therapeutically effective amount of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, to a patient in need thereof.

21. A method for treating idiopathic pulmonary fibrosis, comprising administering a composition, comprising a therapeutically effective amount of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable carrier, to a patient in need thereof.

22. The method of any one of claims 20-21, wherein said administration of a therapeutically effective amount of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, treats idiopathic pulmonary fibrosis in a patient in need thereof while reducing the occurrence of at least one known side effect of currently known IPF therapies, including, but not limited to, diarrhea, gastrointestinal distress, nausea, disinterest in eating, and photosensitivity.

23. The method of any one of claims 20-21, wherein said administration of a therapeutically effective amount of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, treats idiopathic pulmonary fibrosis in a patient in need thereof by suppressing lung epithelial inflammation and fibrosis.

24. The method of any one of claims 20-21, wherein said administration of a therapeutically effective amount of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, treats idiopathic pulmonary fibrosis in a patient in need thereof by suppressing lung myofibroblast phenotypic transition.

25. A method for treating hypertension, portal hypertension, hypertension secondary to treatment with erythropoietin and low renin hypertension, pulmonary arterial hypertension (PAH), disorders related to renal, glomerular and mesangial cell function, acute (ischemic, nephrotoxic, or glomerulonephritis) and chronic (diabetic, hypertensive or immune-mediated) renal failure, diabetic nephropathy, glomerular injury, renal damage secondary to old age or related to dialysis, nephrosclerosis (hypertensive nephrosclerosis), nephrotoxicity (including nephrotoxicity related to imaging and contrast agents and to cyclosporine), renal ischemia, primary vesicoureteral reflux, proteinuric glomerular diseases, glomerulosclerosis, focal segmental glomerulosclerosis (FSGS),kidney disease such as chronic kidney disease (CKD), disorders related to paracrine and endocrine function, diabetic nephropathy, hypertension-

induced nephropathy, IGA-induced nephropathy, endotoxemia or endotoxin shock, hemorrhagic shock, in alleviation of pain associated cancer, such as the pain associated with prostate cancer, and bone pain associated with bone cancer, in the prevention and/or reduction of end-organ damage associated with the cell-proliferative effects of endothelin, hypoxic and ischemic disease, for example, cardiac, renal and cerebral ischemia and reperfusion (such as that occurring following cardiopulmonary bypass surgery), coronary and cerebral vasospasm, myocardial infarction; therapy for peripheral vascular disease (e.g., Raynaud's disease, intermittent claudication and Takayasu's disease); treatment of cardiac hypertrophy (e.g., hypertrophic cardiomyopathy); treatment of primary pulmonary hypertension (e.g., plexogenic, embolic) in adults and in the newborn and pulmonary hypertension secondary to heart failure, radiation and chemotherapeutic injury, or other trauma; treatment of central nervous system vascular disorders, such as stroke, migraine and subarachnoid hemorrhage; treatment of central nervous system behavioral disorders; treatment of gastrointestinal diseases such as ulcerative colitis, Crohn's disease, gastric mucosal damage, ulcer, inflammatory bowel disease and ischemic bowel disease; treatment of gall bladder or bile duct-based diseases such as cholangitis; pancreatitis; cell growth; benign prostatic hypertrophy; restenosis following angioplasty or following any procedure including transplantation and stenting; congestive heart failure including inhibition of fibrosis; inhibition of left ventricular dilatation, remodeling and dysfunction; treatment of hepatotoxicity and sudden death; sickle cell disease including the initiation and/or evolution of the pain crises of this disease; hypertension resulting from hemangiopericytoma; early and advanced liver disease and injury including attendant complications (e.g., hepatotoxicity, fibrosis and cirrhosis); treatment of spastic diseases of the urinary tract and/or bladder; hepatorenal syndrome; immunological diseases involving vasculitis such as lupus, systemic sclerosis, mixed cryoglobulinemia; fibrosis associated with renal dysfunction and hepatotoxicity, metabolic and neurological disorders; cancer; insulin-dependent and non-insulin-dependent diabetes mellitus; neuropathy; retinopathy; epilepsy; hemorrhagic and ischemic stroke; bone remodeling; psoriasis; and chronic inflammatory diseases such as arthritis, rheumatoid arthritis, osteoarthritis, sarcoidosis and eczematous dermatitis (all types of dermatitis); disorders involving bronchoconstriction and disorders of chronic or acute pulmonary inflammation such as chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS); sexual dysfunction; Alzheimer's dementia, senile dementia and vascular dementia; comprising administering a therapeutically effective amount of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or a composition of claim 19, to a patient in need thereof.

26. The method of any one of claims 20-25, wherein said patient has a genetic mutation in the MUC5B, TERT, TERC, RTEL1, PARN, SFTPC, or SFTPA2 genes.

27. The method of any one of claims 20-25, wherein the patient has a genetic mutation in the MUC5B gene.

28. The method of any one of claims 20-25, wherein the patient has a genetic mutation in the TERT gene.

29. The method of any one of claims 20-25, wherein the patient has a genetic mutation in the TERC gene.

30. The method of any one of claims 20-25, wherein the patient has a genetic mutation in the RTEL1 gene.

31. The method of any one of claims 20-25, wherein the patient has a genetic mutation in the PARN gene.

32. The method of any one of claims 20-25, wherein the patient has a genetic mutation in the SFTPC gene.

33. The method of any one of claims 20-25, wherein the patient has a genetic mutation in the SFTPA2 gene.

34. The method of any one of claims 20-25, wherein said patient is 50 years of age or older.

35. The method of any one of claims 20-25, wherein said patient is a smoker.

36. The method of any one of claims 20-25, wherein said patient also suffers from gastroesophageal reflux disease.

37. The method of any one of the preceding claims, further comprising administering one or more of an additional therapeutic agent.

38. The method of any one of claims 20-37, wherein the therapeutically effective amount of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, is formulated for oral administration to a patient in need thereof.

39. The method of any one of claims 20-37, wherein the therapeutically effective amount of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, is in tablet form or capsule form.

40. The method of any one of claims 20-37, wherein the therapeutically effective amount of a compound of any one of claims 1-18ers, or prodrug thereof, is formulated for parenteral administration to a patient in need thereof.

41. The method of any one of claims 20-37, wherein the therapeutically effective amount of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, is administered once daily to a patient in need thereof.

ABSTRACT

The present disclosure relates generally to dual-acting angiotensin and endothelin receptor antagonists, or pharmaceutically acceptable salts, stereoisomers, mixtures of stereoisomers, or prodrugs thereof, and methods of making and using the same.