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(54) Titre : COMPOSES MONOCYCLIQUES UTILES COMME MODULATEURS DE GPR120
(54) Title: MONOCYCLIC COMPOUNDS USEFUL AS GPR120 MODULATORS

(57) **Abrégé/Abstract:**

Provided herein are compounds, compositions including them, and methods of modulating GPR120 activity and treating diseases mediated by GPR120 by administering such compounds and compositions.

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(54) Title: MONOCYCLIC COMPOUNDS USEFUL AS GPR120 MODULATORS

(57) Abstract: Provided herein are compounds, compositions including them, and methods of modulating GPR120 activity and treating diseases mediated by GPR120 by administering such compounds and compositions.



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MONOCYCLIC COMPOUNDS USEFUL AS GPR120 MODULATORS

CROSS-REFERENCED TO RELATED PATENT APPLICATION

This application claims priority from Provisional U.S. Application Serial No. 62/393,616, filed September 12, 2016, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention provides compositions and methods for modulating the GPR120 receptor, and generally relates to the fields of medicinal chemistry, medicine, pharmacology, molecular biology, and biology. Compounds modulating the GPR120 receptor are useful for treating various metabolic and inflammatory diseases, including but not limited to, type 2 diabetes, obesity, hepatic steatosis, and Alzheimer's, and one or more symptoms of each thereof.

BACKGROUND OF THE INVENTION

Type 2 diabetes (T2D) is a chronic disease resulting from the body's inefficient use of the insulin it produces. The states of hyperglycemia and insulin resistance observed in T2D typically result from excess weight and lack of physical exercise. Because obesity and sedentary lifestyles are increasing worldwide, the incidence of T2D is also rapidly increasing. The World Health Organization (WHO) estimates that more than 300 million people worldwide have T2D, and that more than 1 million deaths per year can be directly attributed to T2D. WHO furthermore projects that diabetes-associated deaths will increase by 50% over the next decade. Current therapeutic strategies for T2D include treatment with agents that target the secretion or utilization of insulin. However, these strategies do not work or do not work well for all patients, and new strategies and agents are needed for treatment of the multiple aspects of T2D pathology.

GPR120, also known as free fatty acid receptor 4 (FFA4), is a 7-transmembrane-spanning G-protein coupled receptor that is activated by long-chain free fatty acids including the ω -3 fatty acids. GPR120 is expressed in a wide range of tissues and mediates multiple effects associated with energy balance and inflammation. In enteroendocrine cells, activation of GPR120 leads to secretion of the incretins glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), which in turn stimulate release of insulin from pancreatic beta cells. Activation of GPR120 in adipocytes stimulates glucose uptake and adipogenesis while

inhibiting lipolysis. Activation of GPR120 in macrophages exerts anti-inflammatory effects, inhibiting the release of cytokines including TNF- α and IL-6. In enteroendocrine cells and adipocytes, GPR120 signaling proceeds through Gq/11, but in macrophages GPR120 signaling proceeds through the β -arrestin pathway. Dysfunction in GPR120 has been associated with diabetes and obesity in both mice and humans. Accordingly, GPR120 agonists have been tested for the treatment of T2D and other metabolic diseases.(1-4)

Hepatic steatosis is a state of inflammation and cell injury associated with the accumulation of fat in the liver. In cases not related to alcohol intake, the disease is known as non-alcoholic steatohepatitis (NASH). NASH is increasingly common, can lead to liver cirrhosis or liver failure, and is often observed in people with obesity, glucose intolerance, or dyslipidemia. Recent studies utilizing wild type and GPR120 deficient mice confirm a positive role for GPR120 in controlling lipid metabolism, triglyceride and diacylglycerol levels, and inflammatory markers. Consistent with these results, a study of children with nonalcoholic fatty liver disease who were treated with the GPR120 agonist docosahexaenoic (DHA) acid resulted in reduced liver damage and inflammatory macrophages, and increased GPR120 hepatocyte expression.(5a).

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, with an estimated 47M cases worldwide at present and an expectation for more than 130M cases by 2050. Recently it has been demonstrated that activation of GPR120 exerts anti-inflammatory effects in immortalized hypothalamic neurons,(6a) and that GPR120 and another long chain free fatty acid receptor, GPR40 (FFA1), control energy homeostasis and inflammation in the mouse hypothalamus (7a). NLRP3 inflammasome activity has been shown to contribute to pathology in APP/PS1 mice (8a). Omega-3 fatty acids block activation of NLRP3 inflammasomes in macrophages, thereby inhibiting downstream activation of caspase-1 and maturation and release of interleukin-1 β (IL-1 β) (9a). Expression of NLRP1 inflammasomes is also upregulated in the brains of APP/PS1 mice, and A β induces NLRP1- and caspase-1 dependent pyroptosis in cultured cortical neurons from these animals (10a). Levels of inflammasome-activated caspase-1 are strongly enhanced in the brains of humans with mild cognitive impairment and AD, and activation of NLRP1 in cultured human neurons induces axonal degeneration (11a). Accordingly, GPR120 agonists hold promise as disease-modifying therapeutics for AD, Parkinson's disease, frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), multi-system atrophy (MSA) and other disorders associated with neuroinflammation.

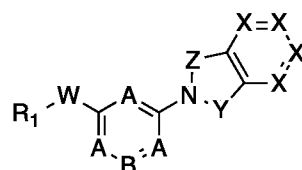
The present invention provides novel compounds, compositions of matter, particularly pharmaceutical compositions, methods for the synthesis or preparation of the compounds and compositions, and methods for using them to modulate GPR120 and treat T2D, hepatic steatosis, Alzheimer's, and other disease associated with metabolic dysfunction and inflammation.

SUMMARY OF THE INVENTION

The present invention provides, in certain aspects, compounds, compositions of matter (particularly pharmaceutical compositions), methods for the synthesis or preparation of the compounds and compositions, and methods for using them to modulate GPR120.

Provided herein are compounds, compositions including them, and methods of modulating the GPR120 receptor and treating diseases by administering such compounds and compositions.

The first aspect of the present invention provides compounds of **Formula I** that in various embodiments comprise a bicyclic core element containing a 6-membered heteroaromatic ring with 1-3 ring nitrogen atoms and up to 3 ring substituents:



Formula I

as well as tautomers, isotopomers and stereoisomers thereof, and prodrugs of any of the foregoing, and pharmaceutically acceptable salts and solvates of all of the foregoing, wherein each A is independently N or CH; B is N or CR₂, with the provision that at least one of A or B is N; W is a covalent bond or O; each X independently is CH, CR₃ or N wherein R₃ is halogen, alkyl, alkoxy, or CN; Y is SO₂, CO, CH₂, or -C(CH₃)₂-, or -CH(CH₃)-, Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -C(CH₂CH₂)- (cyclopropano), CO, -(CO)CH₂-, -CH₂CH₂-, or -CHCH-; R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, or an optionally substituted aryl or heteroaryl group; R₂ is H, halogen, CN, OCH₃, OCF₃, NHAc, an optionally substituted alkyl group, an optionally substituted amido group, an optionally substituted cycloalkyl or heterocyclyl group, or an optionally substituted aryl or heteroaryl group. As used herein, an amido includes carboxamido and a sulfonamide group.

The compounds of Formula I are contemplated to stimulate release of GLP-1, GIP and/or glucagon, inhibit release of ghrelin, stimulate glucose uptake and/or exert anti-inflammatory effects, and thereby exert therapeutic effects in T2D. In another aspect, provided herein is a method for agonizing GPR120, comprising contacting the GPR120 with a compound or the composition provided or disclosed herein.

In another aspect, provided herein is a method for modulating metabolism in a mammal, comprising contacting GPR120 in the mammal with an amount of the compound provided herein that is effective to modulate metabolism in the mammal. In another aspect, provided herein is a method for modulating metabolism in a mammal, comprising administering to the mammal an amount of the composition provided herein that is effective to modulate metabolism in the mammal.

In another aspect, provided herein is a method for reducing inflammation in a mammal, comprising contacting GPR120 in the mammal with an amount of the compound provided herein that is effective to reduce the inflammation. In another aspect, provided herein is a method for reducing inflammation in a mammal, comprising administering to the mammal an amount of the composition provided herein that is effective to reduce the inflammation.

In another aspect, provided herein is a method for reducing neuroinflammation in a mammal, comprising contacting GPR120 in the mammal with an amount of the compound provided herein that is effective to reduce the neuroinflammation. As used herein, neuroinflammation refers to inflammation of the nervous tissue. In another aspect, provided herein is a method for reducing neuroinflammation in a mammal, comprising administering to the mammal an amount of the composition provided herein that is effective to reduce neuroinflammation.

In another aspect, provided herein is a method for treating diabetes, pre-diabetes or metabolic syndrome, or one or more symptoms of each thereof in a mammal, comprising contacting GPR120 in the mammal with a therapeutically effective amount of the compound provided herein. In another aspect, provided herein is a method for treating diabetes, pre-diabetes or metabolic syndrome, or one or more symptoms of each thereof in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition provided herein.

In another aspect, provided herein is a method for treating steatohepatitis in a mammal, comprising contacting GPR120 in the mammal with a therapeutically effective amount of the compound provided herein. In another aspect, provided herein is a method for treating steatohepatitis in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition provided herein.

In another aspect, provided herein is a method for treating non-alcoholic steatohepatitis in a mammal, comprising contacting GPR120 in the mammal with a therapeutically effective amount of the compound provided herein. In another aspect, provided herein is a method for treating non-alcoholic steatohepatitis in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition provided herein.

In another aspect, provided herein is a method for treating a disorder associated with, leading to, or resulting from neuroinflammation in a mammal, comprising contacting GPR120 in the mammal with a therapeutically effective amount of the compound provided herein. In another aspect, provided herein is a method for treating a disorder associated with leading to, or resulting from neuroinflammation in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition provided herein.

In another aspect, provided herein is a method for treating Alzheimer's disease, Parkinson's disease, frontotemporal dementia, amyotrophic lateral sclerosis or multi-system atrophy, or one or more symptoms of each thereof, comprising contacting GPR120 in the patient with a therapeutically effective amount of the compound provided herein.

In another aspect, provided herein is a method for treating Alzheimer's disease, Parkinson's disease, frontotemporal dementia, amyotrophic lateral sclerosis or multi-system atrophy, or one or more symptoms of each thereof, comprising administering to the patient a therapeutically effective amount of the composition provided herein.

DETAILED DESCRIPTION OF THE INVENTION

To aid the reader in understanding the invention, how it is made and used, and the benefits thereof, the following usages and definitions are provided.

All technical and patent publications cited herein are incorporated herein by reference in their entirety.

All numerical designations, *e.g.*, pH, temperature, time, concentration, and molecular weight, including ranges, are approximations which may be varied (+) or (-) by increments of, *e.g.*, 0.1 or 1. Thus, all numerical designations may be interpreted by the reader as preceded by the term “about”. Similarly, the reagents described herein are merely exemplary; generally, the artisan of ordinary skill will appreciate that equivalents of such are known in the art. As used in the specification and claims, the singular forms “a”, “an” and “the” should be interpreted as inclusive of plural references unless the context clearly dictates otherwise.

“Acyl” refers to a group of formula --CO-R_x wherein R_x is H, or is optionally substituted alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl. Examples of acyl groups include, for example, --CHO , --CO-Me , and --CO-Ph .

“Administering” or “administration of” a compound or composition drug to a patient (and grammatical equivalents of this phrase) refers to direct administration, which may be administration to a patient by a medical professional or may be self-administration, and/or indirect administration, which may be the act of prescribing a drug. For example, a physician who instructs a patient to self-administer a drug and/or provides a patient with a prescription for a drug is administering the drug to the patient.

“Alkoxy” refers to an alkyl group covalently bonded to an oxygen atom. In other words, an alkoxy group has the general structure --O-alkyl . $\text{C}_1\text{--C}_6$ alkoxy groups include, for example, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, *tert*-butoxy, *n*-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

“Alkenyl” refers to a straight (or linear) or branched chain hydrocarbon group containing at least one carbon-carbon double bond. $\text{C}_1\text{--C}_6$ alkenyl groups include, for example, vinyl, allyl, and butenyl.

“Alkyl” refers to a straight (or linear) or branched chain hydrocarbon group. $\text{C}_1\text{--C}_6$ alkyl groups include, for example, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl.

“Amino” refers to a monovalent radical $\text{--NR}^a\text{R}^b$ wherein R^a and R^b are independently hydrogen, alkyl, aryl or heteroaryl. The term “alkylamino” refers to the group $\text{--NR}^a\text{R}^b$ where R^a is alkyl and R^b is H or alkyl. For dialkylamino groups, the alkyl portions can be the same or different and can also be combined to form a 3- to 8-membered ring with the nitrogen

atom to which each is attached. Accordingly, a group represented as $-NR^aR^b$ is meant to include heterocyclyl groups such as piperidinyl, pyrrolidinyl, morpholinyl, azetidiny and the like.

"Aryl" refers to a cyclic moiety that includes one or more monocyclic or fused ring aromatic systems containing from 6-20 ring carbon atoms. Such moieties include any moiety that has one or more monocyclic or bicyclic fused ring aromatic systems, including but not limited to phenyl and naphthyl.

" (C_m-C_n) , C_m-C_n , or C_{m-n} " refer to the number of carbon atoms in a certain group before which one of these symbols are placed. For example, C_1-C_6 alkyl refers to an alkyl group containing from 1 to 6 carbon atoms.

"Carboxamide or carboxamido" refers to a monovalent radical $-CO-NR^aR^b$, wherein NR^aR^b is an "amino" group as defined above.

"Carrier" refers to a solid or liquid substance such as a polymer, solvent, suspending agent, absorbing agent, or adsorbing agent for the pre-delivery or capture of a compound of this invention for subsequent delivery. The carrier may be liquid or solid and is selected with the planned manner of administration in mind.

"Comprising" when used to define compounds, compositions and methods means that the recited elements may be present with other materials or steps. "Consisting essentially of," when used to define compounds, compositions or methods, means that the recited elements may not be present with other elements that would materially affect the basic and novel characteristics of the claimed invention. "Consisting of," means only the recited elements. Embodiments defined by each of these transition terms are within the scope of this invention.

"Cycloalkyl" refers to, unless otherwise stated, cyclic versions of "alkyl", "alkenyl" and "alkynyl" in which all ring atoms are carbon. "Cycloalkyl" refers to a mono- or polycyclic group. "Cycloalkyl" may form a bridged ring or a spiro ring. The cycloalkyl group may have one or more double or triple bond(s). Typical cycloalkyl groups have from 3 to 8 ring atoms. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, and cycloheptyl.

"Halogen" or halo" refers to by themselves or as part of another substituent, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

"Heteroaryl" refers to a monocyclic aromatic system having 5 or 6 ring atoms, or a fused ring bicyclic aromatic system having 8-20 atoms, in which the ring atoms are C, O, S, SO, SO₂, or N, and at least one of the ring atoms is a heteroatom, i.e., O, S, SO, SO₂, or N. Heteroaryl groups include, for example, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothio-furanyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzotetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazolyl, indazolyl, indolenyl, indolyl, indolizyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, octahydroisoquinolyl, oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolyl, quinolyl, quinoxalyl, quinuclidinyl, tetrahydroisoquinolyl, tetrahydroquinolyl, tetrazolyl, thiadiazinyl, thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl and xanthenyl. Unless indicated otherwise, the arrangement of the heteroatoms within the ring may be any arrangement allowed by the bonding characteristics of the constituent ring atoms.

"Heterocyclyl" or heterocyclic refers to a monocyclic or fused ring multicyclic cycloalkyl group at least a portion of which is not aromatic and in which one or more of the carbon atoms in the ring system is replaced by a heteroatom selected from O, S, SO, SO₂, P, or N. Examples of heterocyclyl groups include but are not limited to imidazolyl, morpholyl, piperidinyl, piperidin-2-onyl, piperazinyl, pyrrolidinyl, pyrrolidine-2-onyl, tetrahydrofuranyl, tetrahydropyranyl, and tetrahydroimidazo [4,5-c] pyridinyl.

"Pharmaceutically acceptable salts" refers to salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular acidic or basic nature of the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, lithium, magnesium, potassium, sodium, and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of

primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginine and the like, and salts of organic acids like glucuronic or galactunoric acids. Certain specific compounds of the present invention may contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

"Pharmaceutically acceptable excipient, carrier, or diluent" refers to an excipient, carrier, or diluent that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient, carrier, or diluent that is acceptable for human pharmaceutical use as well as veterinary use. A "pharmaceutically acceptable excipient, carrier, or diluent" includes both one and more than one such excipient, carrier, or diluent.

"Reduction" or "inhibition" of a symptom or symptoms (and grammatical equivalents of this phrase) of a pathological condition or disease refers to decreasing the severity or frequency of the symptom(s), or elimination of the symptom(s).

"Subject," used herein interchangeably with "individual" and "patient," refers to a vertebrate, typically a mammal, and usually a human. Mammals include, but are not limited to, mice, rats, rabbits, simians, bovines, ovines, porcines, canines, felines, farm animals, sport animals, pets, equines, and primates.

"Substituted" refers to a group as defined herein in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen and non-carbon atom "substituents" include, but are not limited to, a halogen atom; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy, and acyloxy groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as nitro, -NH_2 , alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, alkoxyamino, hydroxyamino, acylamino, sulfonylamino, N-oxides, imides, and enamines; and other heteroatoms in various other groups. "Substituents" also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, acyl, amido, alkoxy carbonyl, aminocarbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. "Substituents" further include groups in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to a cycloalkyl, heterocyclyl, aryl, and heteroaryl groups. For cycloalkyl, heterocyclyl, aryl, and heteroaryl groups, "substituents" still further include, substituted and unsubstituted alkyl groups. Other substituents include ethynyl, vinyl, carboxyl and its esters and amides, hydroxymethyl, and methyl. Another "substituent" is the trifluoromethyl or other fluoroalkyl group and other groups that contain these groups. Two substituents on same or adjacent carbon atoms may together with the carbon atoms to which they are bonded form a heterocyclic or cycloalkyl group. Typically, a particular group may have 0 (unsubstituted), 1, 2 or 3 substituents. As will be apparent to the skilled artisan, substitutions with substituents will not result in polymeric moieties of greater than 1000 molecular weight.

"Sulfonamide or sulfonamido" refers to a monovalent radical $\text{-SO}_2\text{-NR}^a\text{R}^b$, wherein NR^aR^b is an "amino" group as defined above.

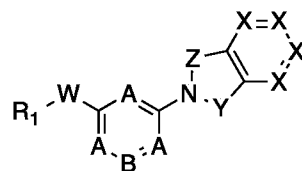
"Therapeutically effective amount" is an amount administered to a patient with a disease mediated by GPR120 that is sufficient to effect beneficial or desired results. A therapeutically effective amount can be administered in one or more administrations, applications, or dosages.

"Treating" or "treatment of" a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results such as the reduction of symptoms. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation or amelioration of one or more symptoms of diseases mediated by GPR120;

diminishment of extent of such diseases; delay or slowing of such disease progression; amelioration, palliation, or stabilization of such diseases; or other beneficial results.

“Reduction” or “inhibition” of a symptom or symptoms (and grammatical equivalents of this phrase) of a pathological condition or disease refers to decreasing the severity or frequency of the symptom(s), or elimination of the symptom(s).

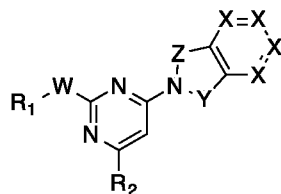
Accordingly, in a first aspect, the invention provides compounds of **Formula I**:



Formula I

as well as tautomers, isotopomers and stereoisomers thereof, and prodrugs of any of the foregoing, and pharmaceutically acceptable salts and solvates of all of the foregoing, wherein each A independently is N or CH; B is N or CR₂, with the provision that at least one of A or B is N; W is a covalent bond or O; each X independently is CH, CR₃ or N wherein R₃ is halogen, alkyl, alkoxy, or CN; Y is SO₂, CO, CH₂, -C(CH₃)₂-, or -CH(CH₃)-; Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -C(CH₂CH₂)-, CO, -(CO)CH₂-, -CH₂CH₂-, or -CHCH-; R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, or an optionally substituted aryl or heteroaryl group; R₂ is H, halogen, CN, OCH₃, OCF₃, -NH-acyl, an optionally substituted alkyl group, an optionally substituted amido group, an optionally substituted cycloalkyl, or heterocyclyl group, or an optionally substituted aryl or heteroaryl group.

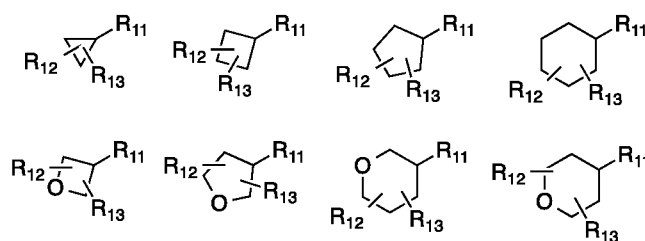
In one preferred embodiment, the central heterocycle is a di- or trisubstituted pyrimidine comprising an optionally substituted 5,6- or 6,6-bicyclic fused ring system, such as without limitation of **Formula II**:



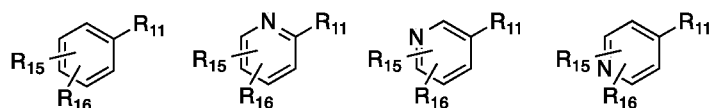
Formula II

wherein W is a covalent bond or O; each X independently is CH, CR₃ or N wherein R₃ is halogen, alkyl, alkoxy, or CN; Y is SO₂, CO, CH₂, -C(CH₃)₂-, or -CH(CH₃)-; Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -C(CH₂CH₂)-, CO, -(CO)CH₂-, -CH₂CH₂-, or -CHCH-; R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, or an optionally substituted aryl or heteroaryl group; R₂ is H, halogen, CN, OCH₃, OCF₃, NHAc, an optionally substituted alkyl group, an optionally substituted amido group, an optionally substituted cycloalkyl, or heterocyclyl group, or an optionally substituted aryl or heteroaryl group.

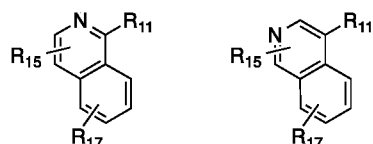
In a more preferred embodiment of **Formula II**, W is O and R₁ is an optionally substituted cycloalkyl or heterocyclyl group. Examples of specific preferred cycloalkyl and heterocyclyl groups are shown below wherein R₁₁ is attached to W. R₁₂ and R₁₃ are independently H, CH₃, CF₃, or F.



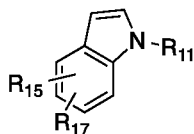
In another more preferred embodiment of **Formula II**, W is O and R₁ is an optionally substituted aryl or heteroaryl group. Examples of specific preferred aryl and heteroaryl groups are shown below wherein R₁₁ is attached to W, R₁₅ is H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN, and R₁₆ is H, halogen, alkyl, CF₃, OCH₃, OCF₃, CN, NHCOR₁₄, or N(CH₃)COR₁₄ wherein R₁₄ is alkyl, cycloalkyl, aryl or heteroaryl.



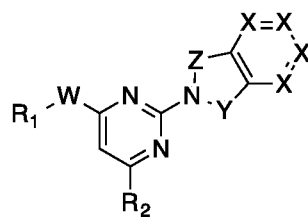
In another more preferred embodiment of **Formula II**, W is O and R₁ is an optionally substituted fused bicyclic aryl or heteroaryl group. Examples of specific preferred fused bicyclic aryl or heteroaryl groups are shown below wherein R₁₁ is attached to W, and R₁₅ and R₁₇ are independently H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN.



In another more preferred embodiment of **Formula II**, W is a covalent bond and R₁ is an optionally substituted bicyclic amine. Examples of specific preferred bicyclic amines are shown below wherein R₁₁ is attached to W, and R₁₅ and R₁₇ are independently H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN.



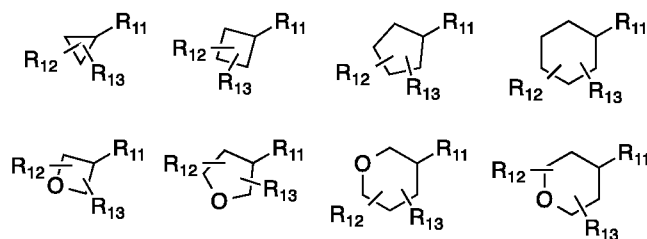
In a second preferred embodiment, the central heterocycle is a di- or trisubstituted pyrimidine comprising an optionally substituted 5,6- or 6,6-bicyclic fused ring system, such as without limitation of **Formula III**:



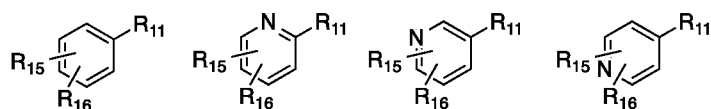
Formula III

wherein W is a covalent bond or O; each X independently is CH, CR₃ or N wherein R₃ is halogen, alkyl, alkoxy, CN; Y is SO₂, CO, CH₂, -C(CH₃)₂-, or -CH(CH₃)-; Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -C(CH₂CH₂)-, CO, -(CO)CH₂-, -CH₂CH₂-, or -CHCH-; R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, or an optionally substituted aryl or heteroaryl group; R₂ is H, halogen, CN, OCH₃, OCF₃, NHAc, an optionally substituted alkyl group, an optionally substituted amido group, an optionally substituted cycloalkyl, or heterocyclyl group, or an optionally substituted aryl or heteroaryl group.

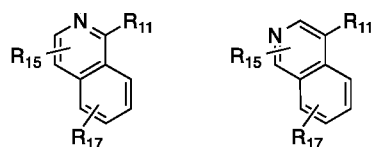
In a more preferred embodiment of **Formula III**, W is O and R₁ is an optionally substituted cycloalkyl or heterocyclyl group. Examples of specific preferred cycloalkyl and heterocyclyl groups are shown below wherein R₁₁ is attached to W. R₁₂ and R₁₃ are independently H, CH₃, CF₃, or F.



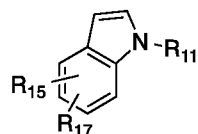
In another more preferred embodiment of **Formula III**, W is O and R₁ is an optionally substituted aryl or heteroaryl group. Examples of specific preferred aryl and heteroaryl groups are shown below wherein R₁₁ is attached to W, R₁₅ is H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN, and R₁₆ is H, halogen, alkyl, CF₃, OCH₃, OCF₃, CN, NHCOR₁₄, or N(CH₃)COR₁₄ wherein R₁₄ is alkyl, cycloalkyl, aryl or heteroaryl.



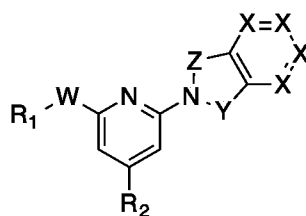
In another more preferred embodiment of **Formula III**, W is O and R₁ is an optionally substituted fused bicyclic aryl or heteroaryl group. Examples of specific preferred fused bicyclic aryl or heteroaryl groups are shown below wherein R₁₁ is attached to W, and R₁₅ and R₁₇ are independently H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN.



In another more preferred embodiment of **Formula III**, W is a covalent bond and R₁ is an optionally substituted bicyclic amine. Examples of specific preferred bicyclic amines are shown below wherein R₁₁ is attached to W, and R₁₅ and R₁₇ are independently H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN.



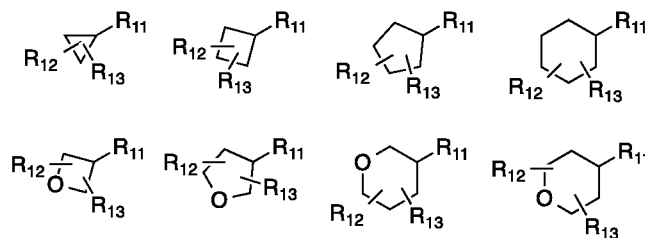
In a third preferred embodiment, the central heterocycle is a di- or trisubstituted pyridine comprising an optionally substituted 5,6- or 6,6-bicyclic fused ring system, such as without limitation of **Formula IV**:



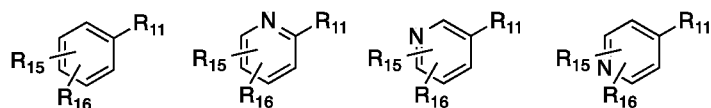
Formula IV

wherein W is a covalent bond or O; each X independently is CH, CR₃ or N wherein R₃ is halogen, alkyl, alkoxy, CN; Y is SO₂, CO, CH₂, -C(CH₃)₂-, or -CH(CH₃)-; Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -C(CH₂CH₂)-, CO, -(CO)CH₂-, -CH₂CH₂-, or -CHCH-; R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, or an optionally substituted aryl or heteroaryl group; R₂ is H, halogen, CN, OCH₃, OCF₃, NHAc, an optionally substituted alkyl group, an optionally substituted amido group, an optionally substituted cycloalkyl, or heterocyclyl group, or an optionally substituted aryl or heteroaryl group.

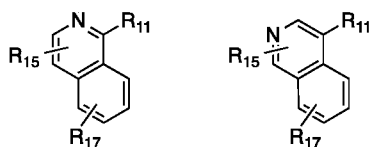
In a more preferred embodiment of **Formula IV**, W is O and R₁ is an optionally substituted cycloalkyl or heterocyclyl group. Examples of specific preferred cycloalkyl and heterocyclyl groups are shown below wherein R₁₁ is attached to W. R₁₂ and R₁₃ are independently H, CH₃, CF₃, or F.



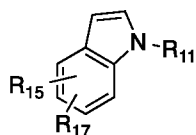
In another more preferred embodiment of **Formula IV**, W is O and R₁ is an optionally substituted aryl or heteroaryl group. Examples of specific preferred aryl and heteroaryl groups are shown below wherein R₁₁ is attached to W, R₁₅ is H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN, and R₁₆ is H, halogen, alkyl, CF₃, OCH₃, OCF₃, CN, NHCOR₁₄, N(CH₃)COR₁₄ wherein R₁₄ is alkyl, cycloalkyl, aryl or heteroaryl.



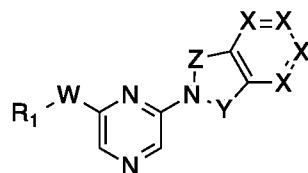
In another more preferred embodiment of **Formula IV**, W is O and R₁ is an optionally substituted fused bicyclic aryl or heteroaryl group. Examples of specific preferred fused bicyclic aryl or heteroaryl groups are shown below wherein R₁₁ is attached to W, and R₁₅ and R₁₇ are independently H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN.



In another more specific preferred embodiment of **Formula IV**, W is a covalent bond and R₁ is an optionally substituted bicyclic amine. Examples of specific preferred bicyclic amines are shown below wherein R₁₁ is attached to W, and R₁₅ and R₁₇ are independently H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN.



In a fourth preferred embodiment, the central heterocycle is a disubstituted pyrazine comprising an optionally substituted 5,6- or 6,6-bicyclic fused ring system, such as without limitation of **Formula V**:

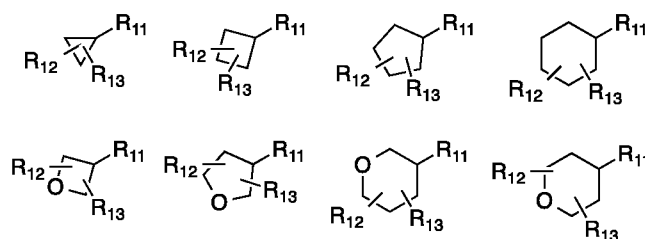


Formula V

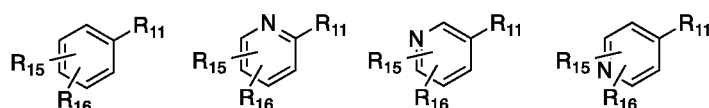
wherein W is a covalent bond or O; each X independently is CH, CR₃ or N wherein R₃ is halogen, alkyl, alkoxy, or CN; Y is SO₂, CO, CH₂, -C(CH₃)₂-, or -CH(CH₃)-; Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -C(CH₂CH₂)-, CO, -(CO)CH₂-, or -CH₂CH₂-, -CHCH-; R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, or an optionally substituted aryl or heteroaryl group.

In a more preferred embodiment of **Formula V**, W is O and R₁ is an optionally substituted cycloalkyl or heterocyclyl group. Examples of specific preferred cycloalkyl and heterocyclyl

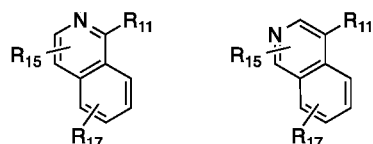
groups are shown below wherein R_{11} is attached to W. R_{12} and R_{13} are independently H, CH_3 , CF_3 , or F.



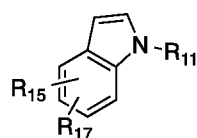
In another more preferred embodiment of **Formula V**, W is O and R_1 is an optionally substituted aryl or heteroaryl group. Examples of specific preferred aryl and heteroaryl groups are shown below wherein R_{11} is attached to W, R_{15} is H, halogen, alkyl, CF_3 , OCH_3 , OCF_3 , or CN, and R_{16} is H, halogen, alkyl, CF_3 , OCH_3 , OCF_3 , CN, $NHCOR_{14}$, or $N(CH_3)COR_{14}$ wherein R_{14} is alkyl, cycloalkyl, aryl or heteroaryl.



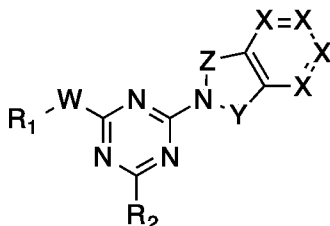
In another more preferred embodiment of **Formula V**, W is O and R_1 is an optionally substituted fused bicyclic aryl or heteroaryl group. Examples of specific preferred fused bicyclic aryl or heteroaryl groups are shown below wherein R_{11} is attached to W, and R_{15} and R_{17} are independently H, halogen, alkyl, CF_3 , OCH_3 , OCF_3 , or CN.



In another more preferred embodiment of **Formula V**, W is a covalent bond and R_1 is an optionally substituted bicyclic amine. Examples of specific preferred bicyclic amines are shown below wherein R_{11} is attached to W, and R_{15} and R_{17} are independently H, halogen, alkyl, CF_3 , OCH_3 , OCF_3 , or CN.



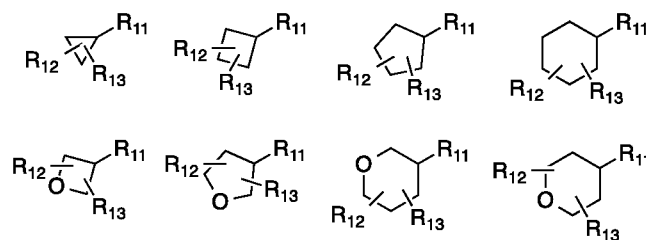
In a fifth preferred embodiment, the central heterocycle is a di- or trisubstituted triazole comprising an optionally substituted 5,6- or 6,6-bicyclic fused ring system, such as without limitation of **Formula VI**:



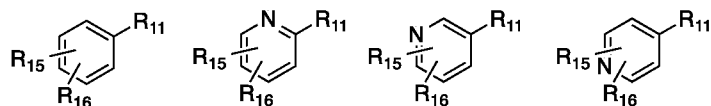
Formula VI

wherein W is a covalent bond or O; each X independently is CH, CR₃ or N wherein R₃ is halogen, alkyl, alkoxy, or CN; Y is SO₂, CO, CH₂, -C(CH₃)₂-, or -CH(CH₃)-; Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -C(CH₂CH₂)-, CO, -(CO)CH₂-, -CH₂CH₂-, or -CHCH-; R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, or an optionally substituted aryl or heteroaryl group; R₂ is H, halogen, CN, OCH₃, OCF₃, NHAc, an optionally substituted alkyl group, an optionally substituted amido group, an optionally substituted cycloalkyl, or heterocyclyl group, or an optionally substituted aryl or heteroaryl group.

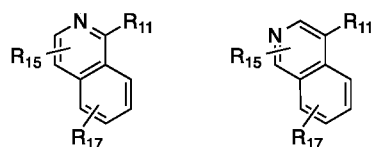
In a more preferred embodiment of **Formula VI**, W is O and R₁ is an optionally substituted cycloalkyl or heterocyclyl group. Examples of specific preferred cycloalkyl and heterocyclyl groups are shown below wherein R₁₁ is attached to W. R₁₂ and R₁₃ are independently H, CH₃, CF₃, or F.



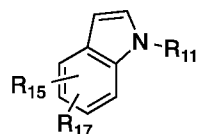
In another more preferred embodiment of **Formula VI**, W is O and R₁ is an optionally substituted aryl or heteroaryl group. Examples of specific preferred aryl and heteroaryl groups are shown below wherein R₁₁ is attached to W, R₁₅ is H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN, and R₁₆ is H, halogen, alkyl, CF₃, OCH₃, OCF₃, CN, NHCOR₁₄, or N(CH₃)COR₁₄ wherein R₁₄ is alkyl, cycloalkyl, aryl or heteroaryl.



In another more preferred embodiment of **Formula VI**, W is O and R₁ is an optionally substituted fused bicyclic aryl or heteroaryl group. Examples of specific preferred fused bicyclic aryl or heteroaryl groups are shown below wherein R₁₁ is attached to W, and R₁₅ and R₁₇ are independently H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN.

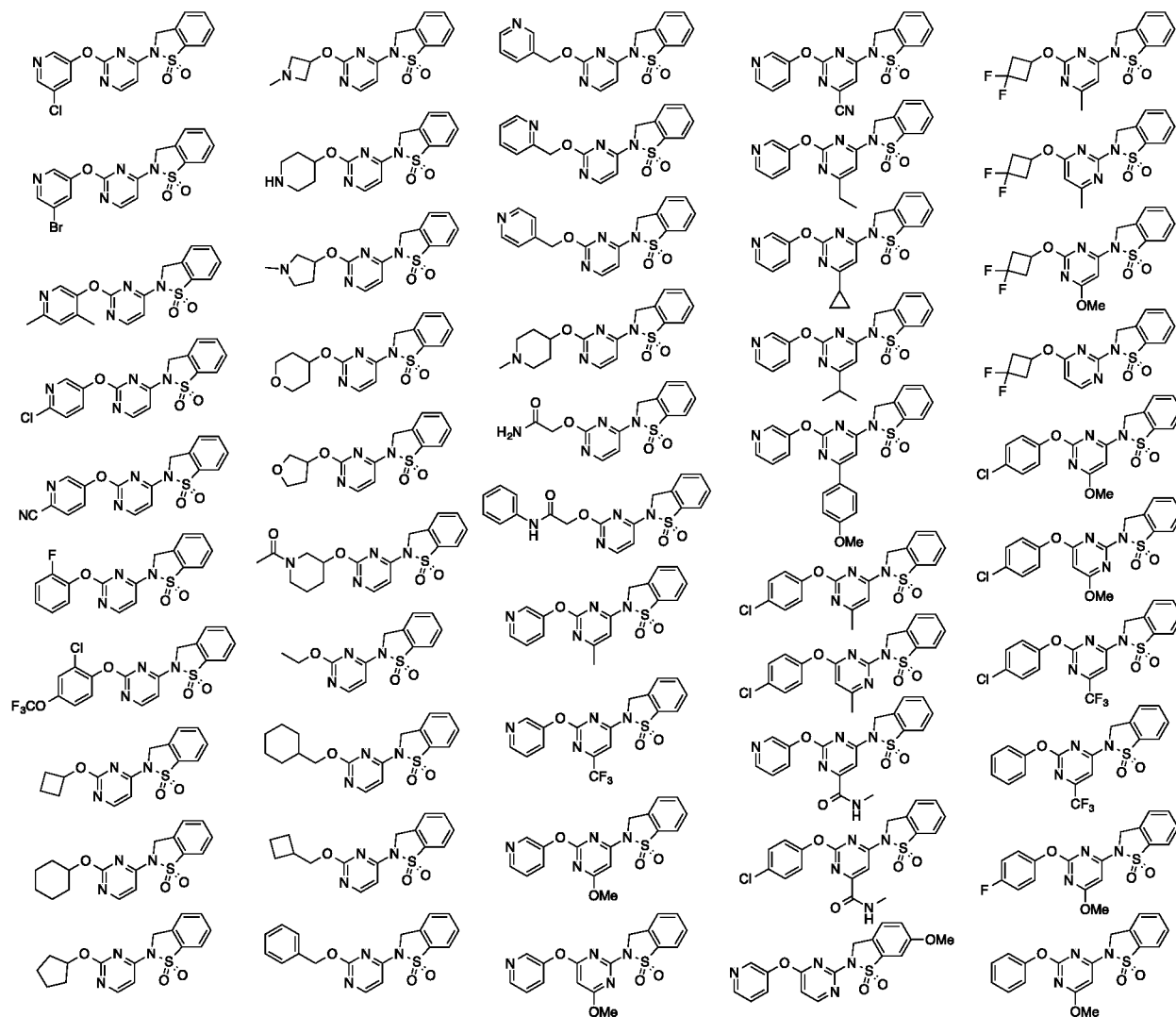


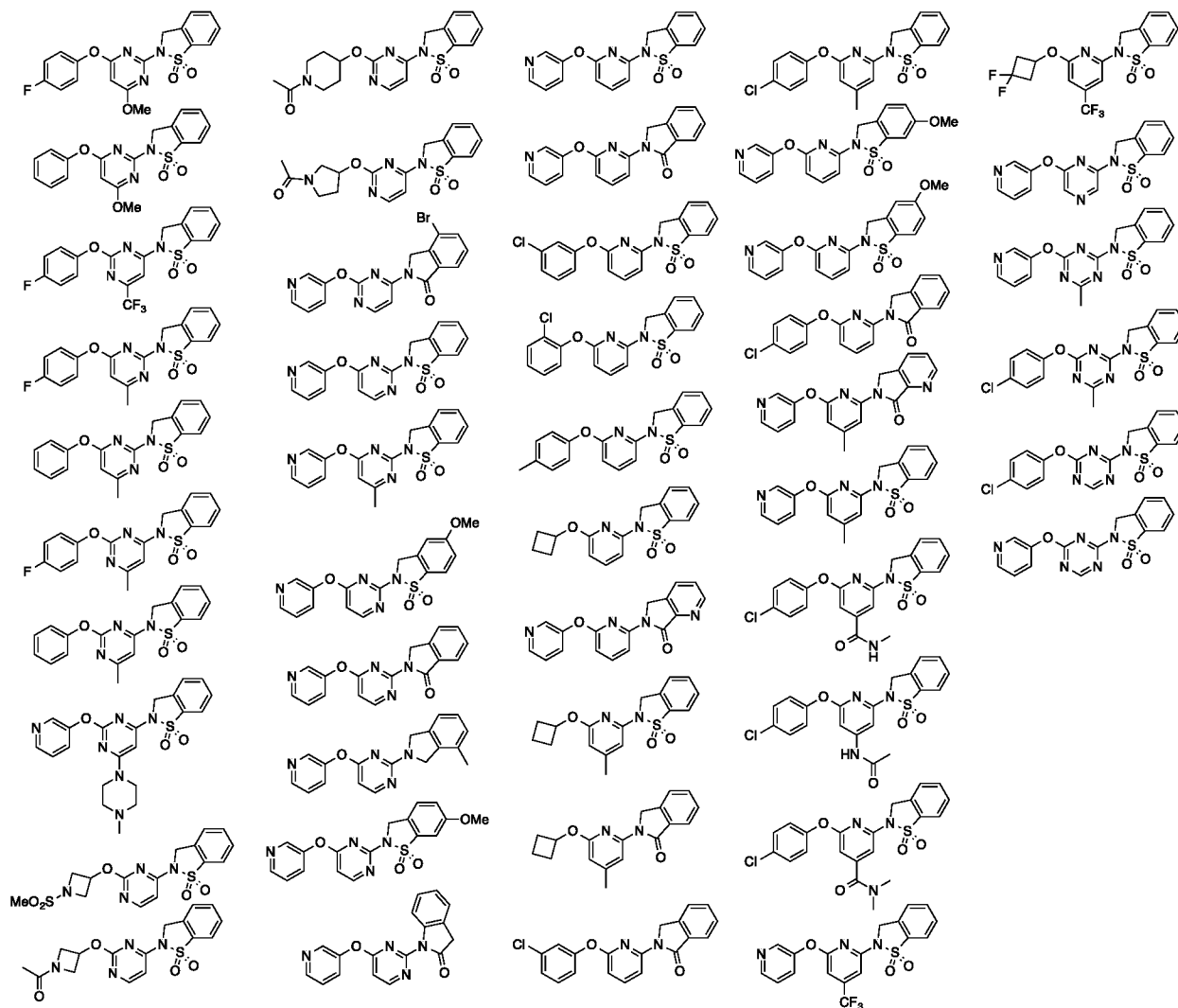
In another more preferred embodiment of **Formula VI**, W is a covalent bond and R₁ is an optionally substituted bicyclic amine. Examples of specific preferred bicyclic amines are shown below wherein R₁₁ is attached to W, and R₁₅ and R₁₇ are independently H, halogen, alkyl, CF₃, OCH₃, OCF₃, or CN.



In another aspect, a compound provided herein is selected from:







Certain compounds of the present invention are synthesized as schematically described herein below. Other compounds of the present invention can be synthesized by adapting these and other methods exemplified in the Examples section below or methods known to one of skill in the art upon appropriate substitution of starting materials, other reagents, and/or process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, and the like).

For compounds of the invention that contain one or more chiral centers, 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 the compounds provided and utilized herein 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.

In another aspect, the present invention provides compositions comprising a compound of the present invention, and at least one pharmaceutically acceptable excipient, i.e., pharmaceutical formulations. In general, the compounds of the present invention can be formulated for administration to a patient by any of the accepted modes of administration. Thus, the invention provides solid and liquid formulations of the compounds of the invention. Various formulations and drug delivery systems are available in the art. See, e.g., Gennaro, A.R., ed. (1995) *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Co..

Typically, compounds of the present invention will be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

Pharmaceutical dosage forms of a compound of the present invention may be manufactured by any of the methods well-known in the art, such as, for example, by conventional mixing, sieving, dissolving, melting, granulating, dragee-making, tableting, suspending, extruding, spray-drying, levigating, emulsifying, (nano/micro-) encapsulating, entrapping, or lyophilization processes. As noted above, the compositions of the present invention can include one or more physiologically acceptable inactive ingredients that facilitate processing of active molecules into preparations for pharmaceutical use.

Pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Patent No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability. In some embodiments, the compounds of the present invention are formulated accordingly.

The compositions are comprised of in general, a compound of the present invention in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the claimed compounds. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols. Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

The present compositions may, if desired, be presented in a pack or dispenser device containing one or more unit dosage forms containing the active ingredient. Such a pack or device may, for example, comprise metal or plastic foil, such as a blister pack, or glass, and rubber stoppers such as in vials. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01-99.99 wt % of a compound of the present invention based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Generally, the compound is present at a level of about 1-80 wt %.

In another aspect, the invention provides a method of producing a therapeutic effect of GPR120 by contacting a therapeutically effective amount of a compound or a composition of the present invention with the GPR120 in need thereof. In one embodiment, the therapeutic effect is produced in a cell. In another embodiment, the contacting is performed *in vitro* or *in vivo*.

In another aspect, provided herein is a method of treating Type 2 diabetes in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound or a composition of the present invention. In one embodiment, the subject is a human.

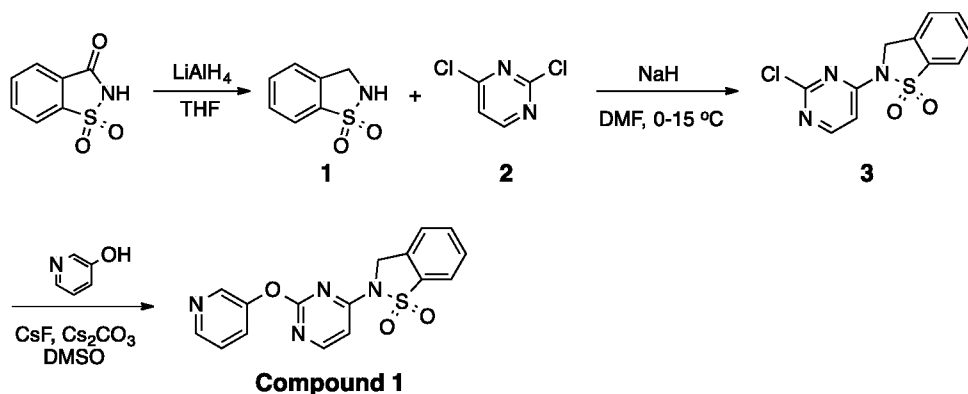
All technical and patent publications cited herein are incorporated herein by reference in their entirety.

The invention having been described in summary and in detail is illustrated and not limited by the examples below. Examples 1-146 illustrate specific compounds of the invention and methods for their synthesis. Examples 147 and 148 illustrate methods whereby the ability of compounds of the invention to activate the GPR120 receptor can be measured in biological assays.

SYNTHESIS EXAMPLES

Example 1

Synthesis of Compound 1



Step 1.

Saccharin (10.0 g, 54.6 mmol) was slowly added to solution of LiAlH₄ (2.24 g, 59.0 mmol) in 300 mL of THF at 0°C. The reaction mixture was stirred for 3h at 15°C under an inert atmosphere. Upon completion, EtOAc (100 mL) was slowly added followed by addition of 10% H₂SO₄ (100mL). The organic layer was separated and washed with 100 mL of 5% sodium carbonate solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give **1** (4.4 g, 97%).

Step 2.

To a solution of **1** (97.0 mg, 0.57 mmol) in DMF (4 mL) was added NaH (13.9 mg, 0.58 mmol) at 0°C. The mixture was stirred at 0°C for 30 minutes. Dichloropyrimidine **2** (100

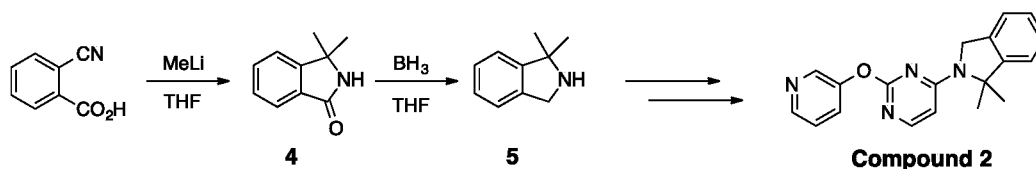
mg, 0.48 mmol, 1.0 eq) was added, the solution was allowed to warm to 15°C and stirred for 15 hours. The resulting mixture was poured into ice water (w/w = 1/1, 20 mL) and stirred for 10 minutes. The aqueous phase was extracted with EtOAc (30 mL) and the combined organic phase was washed with brine (20 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to afford **3** (120 mg, 72%).

Step 3.

A solution of **3** (200 mg, 0.71 mmol), pyridin-3-ol (81 g, 852 mmol), CsF (215 mg, 1.42 mmol) and Cs₂CO₃ (462 mg, 1.42 mmol) in DMSO (3 mL) was degassed and then heated to 80°C for 16 hours under an inert atmosphere. Upon consumption of starting material the reaction mixture was poured into water (50 mL). The mixture was extracted with EtOAc (60 mL). The organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting material was purified by preparative HPLC to afford 70 mg (29%) of **Compound 1**. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.56 (d, 1H), 8.52-8.46 (m, 2H), 8.06 (d, 1H), 7.88-7.82 (m, 1H), 7.81-7.68 (m, 3H), 7.51 (dd, 1H), 7.09 (d, 1H), 5.18 (s, 2H); LCMS (ESI⁺): m/z 341 (M+H).

Example 2

Synthesis of Compound 2



Step 1.

To a solution 2-cyanobenzoic acid (1.50 g, 10.2 mmol) in THF (15 mL) was added MeLi (1M, 204 mL) drop wise at -78°C. The resulting mixture was stirred for 2h at -78°C, warmed to 30°C, and stirred for an additional 18h. Upon completion, water (300 mL) was added and the mixture was extracted with EtOAc (300 mL). The organic phase was washed with brine (100 mL), dried with Na₂SO₄, and concentrated under reduced pressure. Purification by silica gel column chromatography (petroleum ether: EtOAc = 1:1) resulted in **4** (400 mg, 22%).

Step. 2

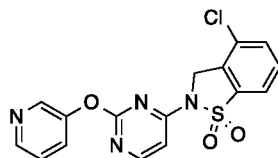
BH₃.THF (1M, 5.7 mL) was added to a solution of 3,3-dimethylphthalimidine (230 mg, 1.43 mmol) in THF (6 mL) drop wise under inert atmosphere and the resulting mixture was stirred at 80°C for 16h. Upon completion, MeOH (4 mL) was added and the reaction mixture was

allowed to stir for 5h. Concentration under reduced pressure and purification by prep-TLC (silica-gel, petroleum ether: EtOAc = 3:1) resulted in **5**.

From **5**, **Compound 2** was synthesized in a manner similar to **Compound 1**. ^1H NMR (DMSO- d_6 , 400 MHz) δ 8.79 (s, 1H), 8.67-8.66 (d, 1H), 8.27-8.25 (d, 1H), 8.08-8.06 (d, 1H), 7.77-7.74 (m, 1H), 7.30-7.28 (m, 1H), 6.60-6.58 (d, 1H), 4.85 (s, 2H), 1.34 (s, 6H); LCMS (ESI): m/z 319.1 (M+H).

Example 3

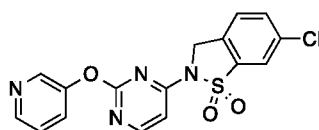
Synthesis of Compound 3



Compound 3 was synthesized in a manner similar to **Compound 1**. LCMS (ESI): m/z 375.0 (M+H).

Example 4

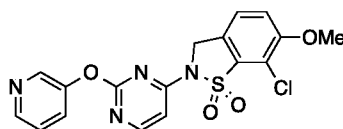
Synthesis of Compound 4



Compound 4 was synthesized in a manner similar to **Compound 1**. LCMS (ESI): m/z 375.1 (M+H).

Example 5

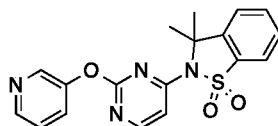
Synthesis of Compound 5



Compound 5 was synthesized in a manner similar to **Compound 1**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.55-8.50 (m, 4H), 7.79-7.77 (d, 1H), 7.67 (s, 2H), 7.53-7.51 (d, 1H), 7.08-7.07 (d, 1H), 5.7 (s, 2H), 3.98 (s, 3H); LCMS (ESI): m/z 405.0 (M+H).

Example 6

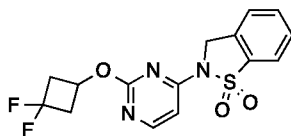
Synthesis of Compound 6



Compound 6 was synthesized in a manner similar to **Compound 1**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.87 (s, 1H), 8.70-8.69 (d, 1H), 8.59-8.57 (d, 1H), 8.18-8.16 (d, 1H), 8.05-8.03 (d, 1H), 7.88-7.82 (m, 3H), 7.72-7.71 (d, 1H), 7.41-7.40 (d, 1H), 1.64 (s, 6H); LCMS (ESI): m/z 369.1 (M+H).

Example 7

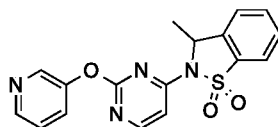
Synthesis of Compound 7



Compound 7 was synthesized in a manner similar to **Compound 1**. ^1H NMR (Methanol- d_4 , 400 MHz) δ 8.42 (d, $J=5.52$ Hz, 1H), 7.92 (d, $J=7.78$ Hz, 1H), 7.86-7.79 (m, 1H), 7.75-7.65 (m, 2H), 7.03 (d, $J=5.77$ Hz, 1H), 5.16 (s, 2H), 4.91-4.88 (m, 1H), 3.27-3.18 (m, 2H), 2.93-2.86 (m, 2H); LCMS (ESI): m/z 354.0 (M+H).

Example 8

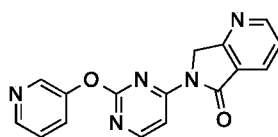
Synthesis of Compound 8



Compound 8 was synthesized in a manner similar to **Compound 1**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.93-8.92 (d, 1H), 8.71-8.70 (d, 1H), 8.57-8.56 (d, 1H), 8.30-8.29 (d, 1H), 8.06-8.04 (d, 1H), 7.89-7.85 (m, 2H), 7.80-7.78 (d, 1H), 7.72-7.70 (m, 1H), 7.22-7.20 (d, 1H), 5.68-5.64 (m, 1H), 1.57-1.55 (d, 3H); LCMS (ESI): m/z 355.0 (M+H).

Example 9

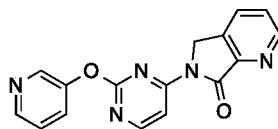
Synthesis of Compound 9



Compound 9 was synthesized in a manner similar to **Compound 1**. ^1H NMR (DMSO- d_6 , 400MHz) δ 9.09-9.08 (d, 1H), 8.90-8.89 (d, 1H), 8.80-8.79 (d, 1H), 8.63-8.62 (d, 1H), 8.48 (s, 1H), 8.30-8.28 (m, 2H), 8.08-8.06 (m, 1H), 7.64-7.62 (m, 1H), 4.97 (s, 2H); LCMS (ESI): m/z 306.1 (M+H).

Example 10

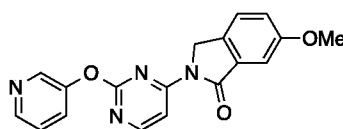
Synthesis of Compound 10



Compound 10 was synthesized in a manner similar to **Compound 1**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.82-8.81 (d, 1H), 8.60-8.57 (m, 2H), 8.53-8.52 (d, 1H), 8.30-8.29 (d, 1H), 8.21-8.19 (d, 1H), 7.82-7.81 (d, 1H), 7.72-7.69 (m, 1H), 7.58-7.56 (m, 1H), 4.98 (s, 2H); **LCMS** (ESI): m/z 306.1 (M+H).

Example 11

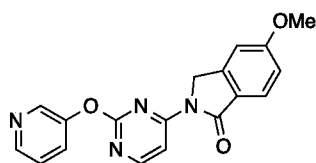
Synthesis of Compound 11



Compound 11 was synthesized in a manner similar to **Compound 1**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.78-8.65 (m, 2H), 8.53 (d, $J=4.52$ Hz, 1H), 8.07-7.99 (d, $J=7.53$ Hz, 1H), 7.65-7.49 (m, 2H), 7.32-7.23 (m, 2H), 6.96 (d, $J=5.52$ Hz, 1H), 4.87 (s, 2H), 3.85 (s, 3H); **LCMS** (ESI): m/z 335.1 (M+H).

Example 12

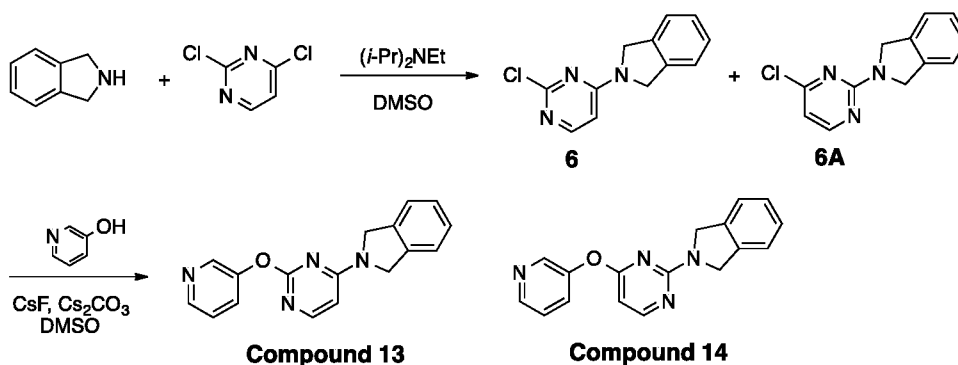
Synthesis of Compound 12



Compound 12 was synthesized in a manner similar to **Compound 1**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.75-8.63 (m, 2H), 8.58-8.42 (m, 1H), 8.07-7.92 (m, 1H), 7.70 (d, $J=8.53$ Hz, 1H), 7.55 (dd, $J=8.41, 4.64$ Hz, 1H), 7.23 (s, 1H), 7.14-7.04 (m, 1H), 6.93 (d, $J=5.77$ Hz, 1H), 4.87 (s, 2H), 3.93-3.80 (m, 3H); **LCMS** (ESI): m/z 335.0 (M+H).

Examples 13 and 14

Synthesis of Compounds 13 and 14



Step 1.

Isoindoline (175 mg, 1.47 mmol), and diisopropylethylamine (260 mg, 2.01 mmol) were dissolved in DMSO (4 mL). The resulting mixture was warmed up to 30°C, and 1,4-dichloropyrimidine (199 mg, 1.34 mmol) was added. Upon completion, water (30 mL) was added and the resulting mixture was extracted with EtOAc (60 mL). The organic phase was washed with brine, filtered, and concentrated under reduced pressure to yield a mixture of **6** and **6A** (440 mg), which was submitted to the next step without further purification.

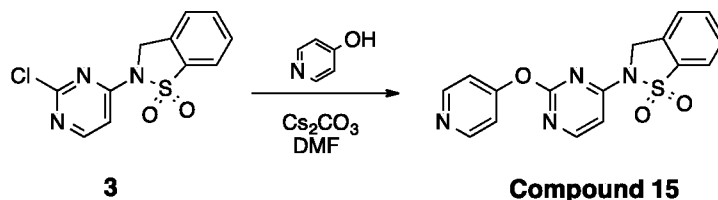
Step 2.

A mixture of **6** and **6A** (240 mg, 0.31 mmol), pyridyl-3-ol (48 mg, 0.51 mmol), Cs_2CO_3 (202 mg, 0.62 mmol), and CsF (94 mg, 0.62 mmol) in DMSO (5 mL) was stirred at 120°C for 2 hours. Upon completion, water (30 mL) was added and the resulting mixture was extracted with EtOAc (60 mL). The organic phase was washed with brine, filtered and concentrated under reduced pressure. The regioisomers were purified and separated by prep-HPLC to give **Compound 13** (20 mg, 21%) and **Compound 14** (9 mg, 9%), both as white solids.

Compound 13. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.595-8.59 (d, 1H), 8.50-8.49 (d, 1H), 8.10-8.08 (d, 1H), 7.84-7.82 (d, 1H), 7.58 (m, 1H), 7.57-7.37 (m, 2H), 7.32-7.30 (m, 2H), 6.50-6.48 (d, 1H), 4.78-4.70 (d, 4H); **LCMS** (ESI): m/z : 291.2 (M+H). **Compound 14.** ^1H NMR (DMSO- d_6 , 400MHz) δ 8.667-8.661 (d, 1H), 8.56-8.55 (d, 1H), 8.37-8.36 (d, 1H), 7.93-7.90 (d, 1H), 7.64-7.60 (m, 1H), 7.35-7.27 (m, 4H), 6.42-6.40 (d, 1H), 4.79 (s, 2H), 4.50 (s, 2H); **LCMS** (ESI): m/z : 291.2 (M+H).

Example 15

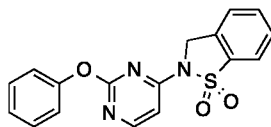
Synthesis of Compound 15



A mixture of **3** (40 mg, 0.14 mmol), pyridin-4-ol (16 mg, 0.170 mmol), and Cs_2CO_3 (92 mg, 0.28 mmol) in DMF (2 mL) was stirred at 45°C for 1.5 hours. Upon completion, the mixture was filtered and concentrated under reduced pressure. Purification by prep-HPLC (0.04% HCl/CH₃CN/H₂O system) resulted in 10 mg (21%) of **Compound 15** as white solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.85-8.83 (d, 2H), 8.75-8.74 (d, 1H), 8.08-8.06 (d, 1H), 7.89-7.85 (m, 1H), 7.77-7.70 (m, 2H), 7.23-7.19 (m, 1H), 6.37-6.35 (d, 2H), 5.33 (s, 2H); LCMS (ESI): *m/z* 341.0 (M+H).

Example 16

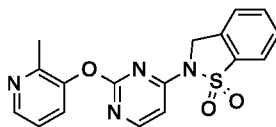
Synthesis of Compound 16



Compound 16 was synthesized in a manner similar to **Compound 15**. ¹H NMR: (DMSO-*d*₆, 400 MHz) δ 8.45-8.44 (d, 1H), 8.04-8.03 (d, 1H), 7.83-7.73 (m, 1H), 7.71-7.67 (m, 2H), 7.44-7.40 (m, 2H), 7.24-7.22 (m, 3H), 7.06-7.05 (d, 1H), 5.15 (s, 2H); LCMS (ESI): *m/z* 340.0 (M+H).

Example 17

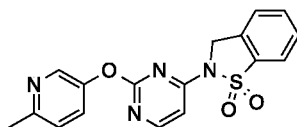
Synthesis of Compound 17



Compound 17 was synthesized in a manner similar to **Compound 15**. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.53-8.52 (d, 1H), 8.50-8.49 (d, 1H), 8.04-8.02 (d, 1H), 7.85-7.81 (t, 1H), 7.72-7.69 (m, 2H), 7.67-7.59 (t, 1H), 7.09-7.07 (d, 1H), 5.16 (s, 2H), 2.43 (s, 3H); LCMS (ESI): *m/z* 355 (M+H).

Example 18

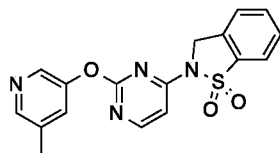
Synthesis of Compound 18



Compound 18 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 9.02 (d, 1H), 8.55-8.54 (d, 1H), 8.51 (d, 1H), 8.01-7.99 (d, 1H), 7.88-7.87 (d, 1H), 7.84-7.82 (t, 1H), 7.72-7.68 (m, 2H), 7.13-7.12 (d, 1H), 5.09 (s, 2H), 2.83 (s, 3H); **LCMS** (ESI): m/z 355 (M+H).

Example 19

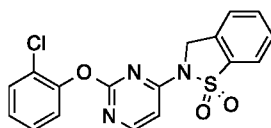
Synthesis of Compound 19



Compound 19 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.79 (s, 1H), 8.60 (s, 1H), 8.55-8.53 (d, 1H), 8.23 (s, 1H), 8.04-8.02 (d, 1H), 7.84-7.82 (t, 1H), 7.73-7.67 (m, 2H), 7.10-7.09 (d, 1H), 5.17 (s, 2H), 2.45 (s, 3H); **LCMS** (ESI): m/z 355 (M+H).

Example 20

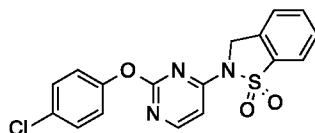
Synthesis of Compound 20



Compound 20 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.44-8.43 (d, 1H), 8.05-8.03 (d, 1H), 7.83-7.81 (t, 1H), 7.73-7.69 (m, 2H), 7.59-7.57 (d, 1H), 7.42-7.40 (m, 2H), 7.33-7.71 (m, 1H), 7.08-7.07 (d, 1H), 5.17 (s, 2H); **LCMS** (ESI): m/z 374 (M+H).

Example 21

Synthesis of Compound 21

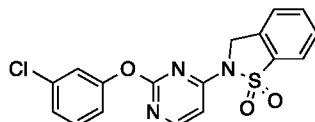


Compound 21 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.48-8.47 (d, 1H), 8.08-8.04 (d, 1H), 7.84-7.82 (t, 1H), 7.75-7.68 (m, 2H), 7.49-

7.47 (d, 2H), 7.32-7.30 (d, 1H), 7.10-7.08 (d, 1H), 5.16 (s, 2H); **LCMS** (ESI): m/z 374 (M+H).

Example 22

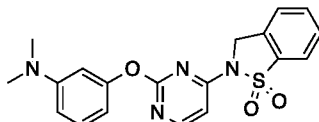
Synthesis of Compound 22



Compound 22 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.49-8.48 (d, 1H), 8.07-8.05 (d, 1H), 7.85-7.75 (m, 1H), 7.73-7.70 (m, 2H), 7.47-7.43 (m, 2H), 7.35 (d, 1H), 7.27 (d, 1H), 7.09-7.08 (d, 1H), 5.18 (s, 2H); **LCMS** (ESI): m/z 374.0 (M+H).

Example 23

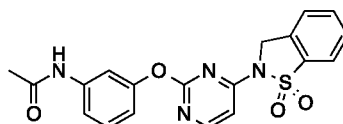
Synthesis of Compound 23



Compound 23 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.49-8.48 (d, 1H), 8.06-8.04 (d, 1H), 7.84-7.82 (m, 1H), 7.75-7.68 (m, 2H), 7.41-7.39 (m, 1H), 7.14-7.06 (m, 3H), 6.93 (bs, 1H), 5.17 (s, 2H), 3.01 (s, 6H); **LCMS** (ESI): m/z 383.0 (M+H).

Example 24

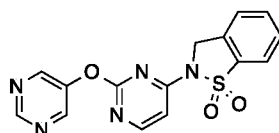
Synthesis of Compound 24



Compound 24 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 10.06 (s, 1H), 8.47-8.46 (d, 1H), 8.07-8.05 (d, 1H), 7.87-7.83 (m, 1H), 7.75-7.71 (m, 2H), 7.55 (s, 1H), 7.37-7.33 (m, 2H), 7.09-7.08 (d, 1H), 6.91-6.90 (d, 1H), 5.19 (s, 2H), 2.04 (s, 3H); **LCMS** (ESI): m/z 397.0 (M+H).

Example 25

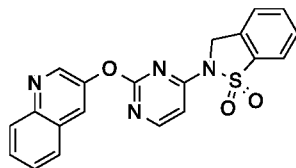
Synthesis of Compound 25



Compound 25 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 9.10 (s, 1H), 8.91 (s, 2H), 8.54-8.52 (d, 1H), 8.06-8.04 (d, 1H), 7.86-7.82 (m, 1H), 7.74-7.68 (m, 2H), 7.12-7.10 (d, 1H), 5.17 (s, 2H); LCMS (ESI): m/z 342.0 (M+H).

Example 26

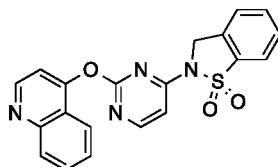
Synthesis of Compound 26



Compound 26 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.91-8.90 (d, 1H), 8.52-8.50 (d, 1H), 8.34-8.33 (d, 1H), 8.09-7.99 (m, 3H), 7.84-7.65 (m, 4H), 7.12-7.11 (d, 1H), 5.19 (s, 2H); LCMS (ESI): m/z 391.0 (M+H).

Example 27

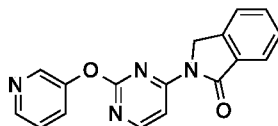
Synthesis of Compound 27



Compound 27 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.89-8.87 (d, 1H), 8.57-8.55 (d, 1H), 8.28-8.26 (d, 1H), 8.23-8.21 (d, 1H), 8.11-8.09 (d, 1H), 7.87 (m, 1H), 7.79 (m, 1H), 7.73-7.68 (m, 2H), 7.47 (m, 1H), 7.42-7.40 (d, 1H), 6.31-6.29 (d, 1H), 5.32 (s, 2H); LCMS (ESI): m/z 391.0 (M+H).

Example 28

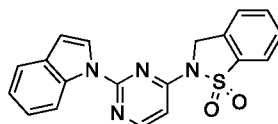
Synthesis of Compound 28



Compound 28 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.71 (s, 1H), 8.59-8.55 (m, 2H), 8.27-8.27 (d, 1H), 7.87-7.85 (m, 1H), 7.76-7.71 (m, 2H), 7.64 (d, 1H), 4.99 (s, 2H); LCMS (ESI): m/z 305.0 (M+H).

Example 29

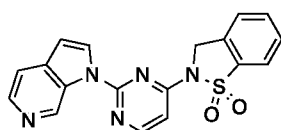
Synthesis of Compound 29



Compound 29 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.91-8.89 (d, 1H), 8.71-8.69 (d, 1H), 8.27 (d, 1H), 8.05-8.03 (d, 1H), 7.85-7.83 (d, 1H), 7.78-7.72 (m, 2H), 7.64-7.62 (d, 1H), 7.32 (m, 1H), 7.24-7.22 (d, 1H), 7.00-6.99 (d, 1H), 6.80-6.79 (d, 1H), 5.28 (s, 2H); **LCMS** (ESI): m/z 363.0 (M+H).

Example 30

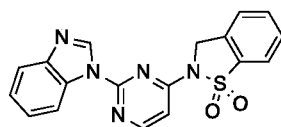
Synthesis of Compound 30



Compound 30 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 9.32 (s, 1H), 9.23-9.21 (d, 1H), 8.83-8.81 (d, 2H), 8.06-8.04 (d, 1H), 7.75-7.68 (m, 2H), 7.25-7.17 (m, 3H); **LCMS** (ESI): m/z 364.0 (M+H).

Example 31

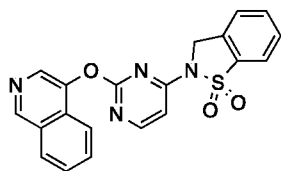
Synthesis of Compound 31



Compound 31 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 9.14 (s, 1H), 8.77-8.72 (m, 2H), 8.09-8.07 (d, 1H), 7.83-7.81 (d, 1H), 7.73-7.68 (m, 3H), 7.35-7.13 (d, 1H), 5.33 (s, 2H); **LCMS** (ESI): m/z 364.0 (M+H).

Example 32

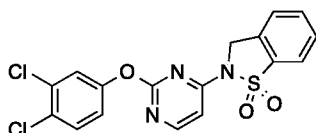
Synthesis of Compound 32



Compound 32 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 9.42 (s, 1H), 8.62 (s, 1H), 8.44-8.42 (d, 1H), 8.35-8.33 (d, 1H), 8.04 (s, 1H), 7.90-7.83 (m, 4H), 7.75-7.71 (m, 2H), 7.11-7.10 (d, 1H), 7.47 (m, 1H), 5.20 (s, 2H); **LCMS** (ESI): m/z 391.0 (M+H).

Example 33

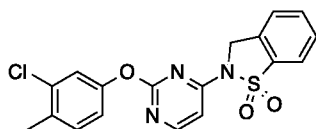
Synthesis of Compound 33



Compound 33 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.44-8.42 (d, 1H), 7.90-7.88 (d, 1H), 7.79-7.77 (m, 1H), 7.67-7.66 (m, 2H), 7.59-7.57 (d, 1H), 7.51-7.50 (d, 1H), 7.24-7.21 (m, 2H), 5.03 (s, 2H); LCMS (ESI): m/z 407.9 (M+H).

Example 34

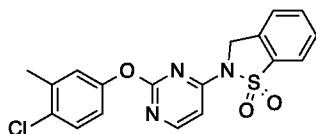
Synthesis of Compound 34



Compound 34 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.46-8.44 (d, 1H), 8.05-8.03 (d, 1H), 7.83-7.81 (m, 1H), 7.73-7.69 (m, 2H), 7.40-7.37 (d, 2H), 7.16-7.13 (m, 1H), 7.06-7.05 (d, 1H), 5.16 (s, 2H), 2.32 (s, 3H); LCMS (ESI): m/z 388.0 (M+H).

Example 35

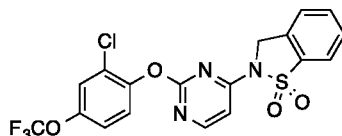
Synthesis of Compound 35



Compound 35 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.46-8.45 (d, 1H), 8.05-8.03 (d, 1H), 7.83-7.81 (m, 1H), 7.74-7.68 (m, 2H), 7.45-7.42 (d, 1H), 7.28 (s, 1H), 7.13-7.04 (d, 2H), 5.15 (s, 2H), 2.32 (s, 3H); LCMS (ESI): m/z 388.0 (M+H).

Example 36

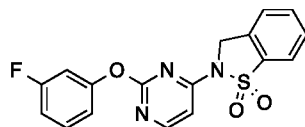
Synthesis of Compound 36



Compound 36 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400 MHz) δ 8.51 (d, $J=5.77$ Hz, 1H), 8.09 (d, $J=7.78$ Hz, 1H), 7.92-7.84 (m, 1H), 7.79-7.66 (m, 4H), 7.41 (d, $J=8.53$ Hz, 1H), 7.12 (d, $J=5.77$ Hz, 1H), 5.20 (s, 2H); LCMS (ESI): m/z 458.0 (M+H).

Example 37

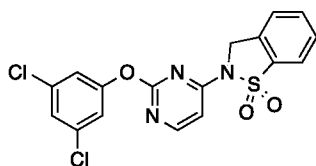
Synthesis of Compound 37



Compound 37 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.51-8.49 (d, 1H), 8.08-8.06 (d, 1H), 7.88-7.86 (d, 1H), 7.76-7.71 (m, 2H), 7.49-7.47 (d, 1H) 7.27-7.24 (d, 1H), 7.14-7.09 (m, 3H), 5.18 (s, 2H); **LCMS** (ESI): m/z : 358.0 (M+H).

Example 38

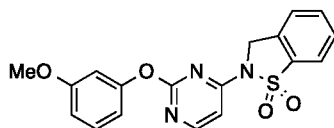
Synthesis of Compound 38



Compound 38 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 5.19 (s, 2H), 7.10 (d, 1H), 7.45-7.58 (m, 3H), 7.67-7.79 (m, 2H), 7.81-7.90 (m, 1H), 8.07 (d, 1H), 8.52 (d, 1H); **LCMS** (ESI): m/z 409.9 (M+H).

Example 39

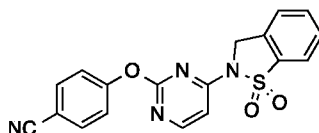
Synthesis of Compound 39



Compound 39 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.49 (d, 1H), 8.09 (d, 1H), 7.91-7.83 (m, 1H), 7.80-7.68 (m, 2H), 7.35 (t, 1H), 7.09 (d, 1H), 6.91-6.80 (m, 3H), 5.20 (s, 2H), 3.78 (s, 3H); **LCMS** (ESI): m/z 370.0 (M+H).

Example 40

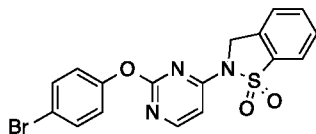
Synthesis of Compound 40



Compound 40 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.53 (d, 1H), 8.08 (d, 1H), 7.96 (d, 2H), 7.90-7.83 (m, 1H), 7.80-7.68 (m, 2H), 7.14 (d, 1H), 5.19 (s, 2H); **LCMS** (ESI): m/z 365.0 (M+H).

Example 41

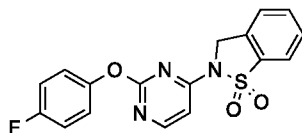
Synthesis of Compound 41



Compound 41 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.50 (d, 1H), 8.09 (d, 1H), 7.82-7.91 (m, 1H), 7.69-7.80 (m, 2H), 7.64 (d, 2H), 7.28 (d, 2H), 7.10 (d, 1H), 5.19 (s, 2H); **LCMS** (ESI): m/z 419.9 (M+H).

Example 42

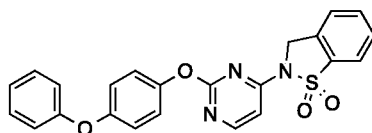
Synthesis of Compound 42



Compound 42 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.49 (d, 1H), 8.08 (d, 1H), 7.90-7.82 (m, 1H), 7.79-7.67 (m, 2H), 7.38-7.23 (m, 4H), 7.09 (d, 1H), 5.19 (s, 2H); **LCMS** (ESI): m/z 358.0 (M+H).

Example 43

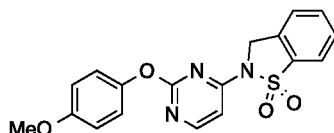
Synthesis of Compound 43



Compound 43 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.50 (d, $J=5.27$ Hz, 1H), 8.08 (d, $J=7.78$ Hz, 1H), 7.91-7.82 (m, 1H), 7.79-7.63 (m, 2H), 7.43 (t, $J=7.53$ Hz, 2H), 7.30 (d, $J=8.53$ Hz, 2H), 7.16 (t, $J=7.28$ Hz, 1H), 7.12-7.01 (m, 5H), 5.20 (s, 2H); **LCMS** (ESI): m/z 432.0 (M+H).

Example 44

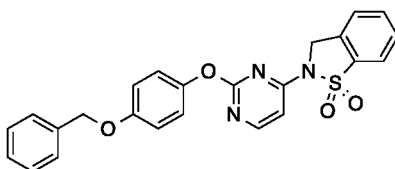
Synthesis of Compound 44



Compound 44 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.46 (d, $J=5.27$ Hz, 1H), 8.08 (d, $J=7.78$ Hz, 1H), 7.91-7.82 (m, 1H), 7.80-7.60 (m, 2H), 7.19 (d, $J=8.53$ Hz, 2H), 7.07 (d, $J=5.52$ Hz, 1H), 6.99 (d, $J=8.53$ Hz, 2H), 5.19 (s, 2H), 3.79 (s, 3H); LCMS (ESI): m/z 370.0 (M+H).

Example 45

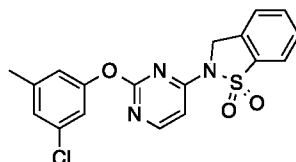
Synthesis of Compound 45



Compound 45 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.45-8.44 (d, 1H), 8.08-8.06 (d, 1H), 7.84 (m, 1H), 7.76-7.71 (m, 2H), 7.49-7.47 (m, 2H), 7.43 (m, 2H), 7.41-7.39 (m, 1H), 7.19-7.17 (m, 2H), 7.07-7.05 (m, 3H), 5.18 (s, 2H), 5.13 (s, 2H); LCMS (ESI): m/z 446.1 (M+H).

Example 46

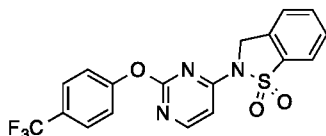
Synthesis of Compound 46



Compound 46 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.51 (d, $J=5.52$ Hz, 1H), 8.09 (d, $J=7.78$ Hz, 1H), 7.93-7.83 (m, 1H), 7.80-7.61 (m, 2H), 7.22 (d, $J=12.80$ Hz, 2H), 7.13-6.95 (m, 2H), 5.21 (s, 2H), 2.35 (s, 3H); LCMS (ESI): m/z 388.0 (M+H).

Example 47

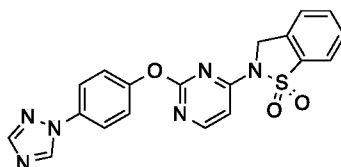
Synthesis of Compound 47



Compound 47 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.50 (d, $J=5.73$ Hz, 1H), 8.06 (d, $J=7.94$ Hz, 1H), 7.91-7.79 (m, 3H), 7.76-7.67 (m, 2H), 7.51 (d, $J=8.82$ Hz, 2H), 7.11 (d, $J=5.73$ Hz, 1H), 5.19 (s, 2H); **LCMS** (ESI): m/z 408.0 (M+H).

Example 48

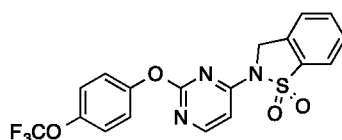
Synthesis of Compound 48



Compound 48 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 9.30 (s, 1H), 8.50 (d, $J=5.73$ Hz, 1H), 8.25 (s, 1H), 8.06 (d, $J=7.50$ Hz, 1H), 7.92 (d, $J=8.82$ Hz, 2H), 7.87-7.81 (m, 1H), 7.76-7.63 (m, 2H), 7.47 (d, $J=9.26$ Hz, 2H), 7.09 (d, $J=5.73$ Hz, 1H), 5.18 (s, 2H); **LCMS** (ESI): m/z 407.0 (M+H).

Example 49

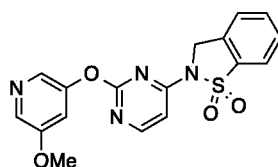
Synthesis of Compound 49



Compound 49 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.50-8.48 (d, 1H), 8.09-8.07 (d, 1H), 7.86-7.84 (d, 1H), 7.76 - 7.70 (m, 2H), 7.47-7.40 (m, 4H), 7.10-7.09 (m, 1H), 5.19 (s, 2H); **LCMS** (ESI): m/z 424.0 (M+H).

Example 50

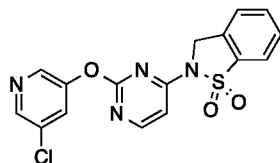
Synthesis of Compound 50



Compound 50 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.55-8.53 (d, 1H), 8.37 (m, 2H), 8.08-8.06 (d, 1H), 7.88-7.84 (t, 1H), 7.76-7.69 (m, 3H), 7.11-7.09 (m, 1H), 5.19 (s, 2H), 3.89 (s, 3H); **LCMS** (ESI): m/z 371.0 (M+H).

Example 51

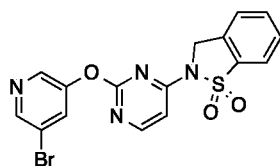
Synthesis of Compound 51



Compound 51 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.59-8.57 (m, 2H), 8.54-8.52 (m, 1H), 8.12 (s, 1H), 8.08-8.06 (d, 1H), 7.86-7.84 (m, 1H), 7.76-7.71 (m, 2H), 7.12-7.10 (d, 1H), 5.19 (s, 2H); **LCMS** (ESI): m/z 375.0 (M+H).

Example 52

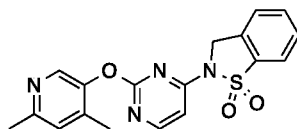
Synthesis of Compound 52



Compound 52 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.65-8.62 (m, 2H), 8.54-8.52 (d, 1H), 8.23 (s, 1H), 8.08-8.06 (d, 1H), 7.86-7.84 (m, 1H), 7.76-7.71 (m, 2H), 7.11-7.10 (d, 1H), 5.19 (s, 2H); **LCMS** (ESI): m/z 419.0 (M+H).

Example 53

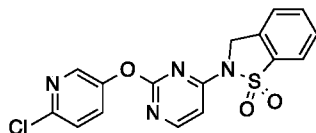
Synthesis of Compound 53



Compound 53 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.72 (s, 1H); 8.50 (d, 1H), 8.03 (d, 1H), 7.87-7.80 (m, 1H), 7.77-7.66 (m, 3H), 7.10 (d, 1H), 5.18 (s, 2H), 2.66 (s, 3H), 2.28 (s, 3H); **LCMS** (ESI): m/z 369.1 (M+H).

Example 54

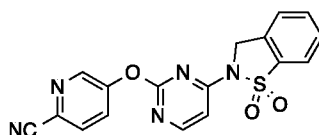
Synthesis of Compound 54



Compound 54 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.53-8.51 (d, 1H), 8.46-8.45 (d, 1H), 8.08-8.06 (d, 1H), 7.91-7.90 (d, 1H), 7.86 (m, 1H), 7.76-7.71 (m, 2H), 7.64-7.62 (d, 1H), 7.12-7.10 (d, 1H), 5.18 (s, 2H); LCMS (ESI): m/z 375.0 (M+H).

Example 55

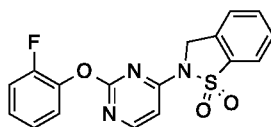
Synthesis of Compound 55



Compound 55 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.83 (d, 1H), 8.56 (d, 1H), 8.23-8.17 (m, 1H), 8.14-8.05 (m, 2H), 7.91-7.83 (m, 1H), 7.79-7.68 (m, 2H), 7.15 (d, 1H), 5.19 (s, 2H); LCMS (ESI): m/z 366.0 (M+H).

Example 56

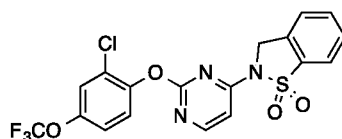
Synthesis of Compound 56



Compound 56 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.48 (d, 1H), 8.07 (d, 1H), 7.90-7.81 (m, 1H), 7.79-7.67 (m, 2H), 7.48-7.22 (m, 4H), 7.10 (d, 1H), 5.20 (bs, 2H); LCMS (ESI): m/z 358.0 (M+H).

Example 57

Synthesis of Compound 57

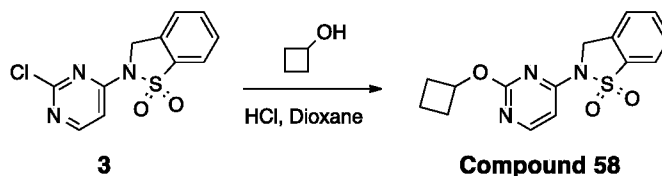


Compound 57 was synthesized in a manner similar to **Compound 15**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.48 (d, $J=5.73$ Hz, 1H), 8.06 (d, $J=7.94$ Hz, 1H), 7.91-7.81 (m, 1H), 7.80-7.67

(m, 3H), 7.60 (d, $J=9.26$ Hz, 1H), 7.52-7.43 (m, 1H), 7.15-7.06 (m, 1H), 5.27-5.14 (m, 2H); **LCMS** (ESI): m/z 458.0 (M+H).

Example 58

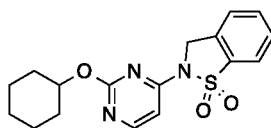
Synthesis of Compound 58



A mixture of **3** (30 mg, 0.11 mmol) and cyclobutanol (230 mg, 3.2 mmol) in HCl/dioxane (4M, 1.5 mL) was heated to 100°C for 16 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. Purification by prep-HPLC (0.04% HCl/CH₃CN/H₂O system) resulted in **Compound 58** (1.6 mg, 5%) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ ppm 8.45 (d, $J=5.73$ Hz, 1H), 8.02 (d, $J=7.94$ Hz, 1H), 7.86-7.79 (m, 1H), 7.76-7.65 (m, 2H), 6.89 (d, $J=5.73$ Hz, 1H), 5.16 (s, 2H), 5.14-5.05 (m, 1H), 2.15-2.01 (m, 2H), 1.78 (q, $J=10.14$ Hz, 1H), 1.70-1.55 (m, 1H); **LCMS** (ESI): m/z 318 (M+H).

Example 59

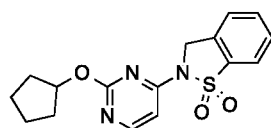
Synthesis of Compound 59



Compound 59 was synthesized in a manner similar to **Compound 58**. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.47-8.46 (d, 1H), 8.05-8.03 (d, 1H), 7.86-7.82 (m, 1H), 7.75-7.68 (m, 2H), 6.88-6.87 (d, 1H), 5.17 (s, 2H), 4.99-4.95 (m, 1H), 2.01-1.90 (m, 2H), 1.75-1.73 (m, 2H), 1.54-1.29 (m, 6H); **LCMS** (ESI): m/z 346 (M+H).

Example 60

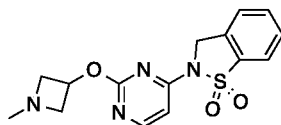
Synthesis of Compound 60



Compound 60 was synthesized in a manner similar to **Compound 58**. ¹H NMR (Methanol-*d*₄, 400 MHz) δ 8.27 (d, $J=5.73$ Hz, 1H), 7.87 (d, $J=7.94$ Hz, 1H), 7.82-7.74 (m, 1H), 7.72-7.62 (m, 2H), 6.47 (d, $J=6.17$ Hz, 1H), 5.62-5.50 (m, 1H), 5.19-5.05 (m, 2H), 2.20-2.05 (m, 2H), 1.90-1.74 (m, 4H), 1.73-1.57 (m, 2H); **LCMS** (ESI): m/z 332.0 (M+H).

Example 61

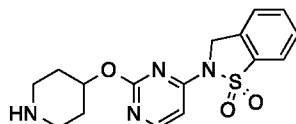
Synthesis of Compound 61



Compound 61 was synthesized in a manner similar to **Compound 58**. ^1H NMR (Methanol- d_4 , 400MHz) δ 8.17-8.15 (d, 1H), 7.96-7.94 (d, 1H), 7.88-7.84 (m, 1H), 7.74-7.71 (m, 2H), 6.97 (bs, 1H), 5.27 (s, 2H), 4.47-4.48 (m, 1H), 4.32-4.29 (d, 1H), 4.21-4.16 (m, 1H), 3.89-3.86 (d, 1H), 3.56-3.53 (d, 1H), 3.40 (s, 3H); **LCMS** (ESI): m/z 333.0 (M+H).

Example 62

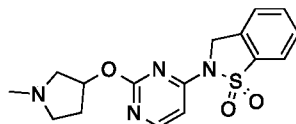
Synthesis of Compound 62



Compound 62 was synthesized in a manner similar to **Compound 58**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.28-8.26 (d, 1H), 8.04-8.02 (d, 1H), 7.86-7.82 (t, 1H), 7.74-7.68 (m, 2H), 6.63-6.61 (d, 1H), 5.22 (s, 2H), 4.20-4.17 (m, 2H), 3.81-3.77 (m, 1H), 3.51-3.46 (t, 2H), 1.83-1.80 (m, 2H), 1.45-1.39 (m, 2H); **LCMS** (ESI): m/z 347.0 (M+H).

Example 63

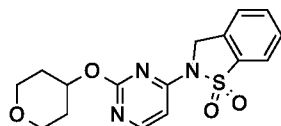
Synthesis of Compound 63



Compound 63 was synthesized in a manner similar to **Compound 58**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.51-8.50 (d, 1H), 8.00-7.98 (d, 1H), 7.86-7.81 (m, 1H), 7.75-7.69 (m, 2H), 7.00-6.99 (d, 1H), 5.61-5.55 (m, 1H), 5.19 (s, 2H), 4.08 (m, 1H), 3.67-3.53 (m, 2H), 3.28-3.18 (m, 1H), 2.86 (s, 3H), 2.70-2.66 (m, 1H), 2.31-2.22 (m, 1H); **LCMS** (ESI): m/z 347.1 (M+H).

Example 64

Synthesis of Compound 64

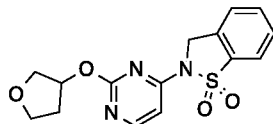


Compound 64 was synthesized in a manner similar to **Compound 58**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.47-8.45 (d, 1H), 8.03-8.01 (d, 1H), 7.82-7.80 (d, 1H), 7.72-7.66 (m, 2H), 6.88-

6.87 (d, 1H), 5.16 (s, 1H), 5.14-5.10 (m, 1H), 5.0 (s, 2H), 3.88-3.84 (m, 2H), 3.50-3.44 (m, 2H), 2.07-2.05 (m, 2H), 1.70-1.64 (m, 2H); **LCMS** (ESI): m/z 348.0 (M+H).

Example 65

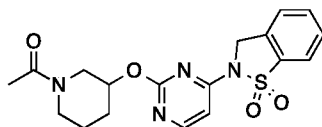
Synthesis of Compound 65



Compound 65 was synthesized in a manner similar to **Compound 58**. ^1H NMR (Methanol- d_4 , 400MHz) δ 7.94-7.92 (d, 1H), 7.86-7.82 (t, 1H), 7.73-7.69 (m, 2H), 7.10-7.09 (d, 1H), 5.69 (s, 1H), 5.19 (s, 1H), 4.14-4.10 (m, 1H), 4.02-3.99 (m, 2H), 3.92-3.91 (m, 1H), 2.45-2.35 (m, 2H), 2.26-2.22 (m, 1H); **LCMS** (ESI): m/z 334.0 (M+H).

Example 66

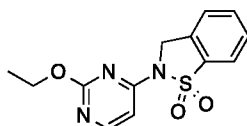
Synthesis of Compound 66



Compound 66 was synthesized in a manner similar to **Compound 58**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.26-8.22 (d, 1H), 7.99-7.97 (d, 1H), 7.82-7.80 (d, 1H), 7.73-7.66 (m, 2H), 6.48-6.46 (d, 1H), 5.11 (s, 1H), 4.75 (s, 1H), 3.97-3.92 (m, 1H), 3.88-3.85 (m, 2H), 3.70-3.66 (m, 1H), 1.89 (m, 1H), 1.72 (m, 2H), 1.52 (m, 1H); **LCMS** (ESI): m/z 389.1 (M+H).

Example 67

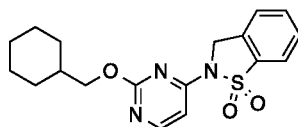
Synthesis of Compound 67



Compound 67 was synthesized in a manner similar to **Compound 58**. ^1H NMR (Methanol- d_4 , 400MHz) δ 8.42 (bs, 1 H), 7.93 (d, $J=7.94$ Hz, 1H), 7.86-7.79 (m, 1H), 7.75-7.61 (m, 2H), 7.09 (d, $J=6.17$ Hz, 1H) 5.28-5.12 (m, 2H), 4.56 (q, $J=7.06$ Hz, 2H), 1.52-1.41 (m, 3H); **LCMS** (ESI): m/z 292.0 (M+H).

Example 68

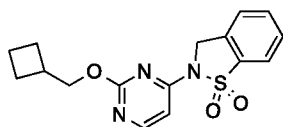
Synthesis of Compound 68



Compound 68 was synthesized in a manner similar to **Compound 58**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.49 (d, J =5.77 Hz, 1H), 8.06 (d, J =7.78 Hz, 1H), 7.91-7.81 (m, 1H), 7.78-7.66 (m, 2H), 6.95 (d, J =5.77 Hz, 1H), 5.21 (s, 2H), 4.33 (d, J =7.03 Hz, 2H), 2.78 (q, J =7.40 Hz, 1H), 2.15-2.01 (m, 2 H), 1.96-1.76 (m, 4 H); LCMS (ESI): m/z 360.1 (M+H).

Example 69

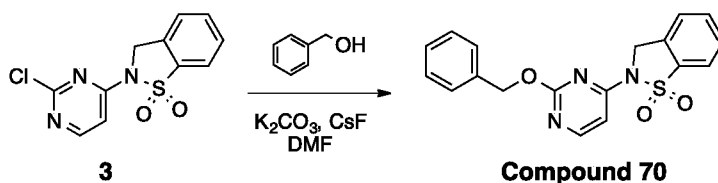
Synthesis of Compound 69



Compound 69 was synthesized in a manner similar to **Compound 58**. ^1H NMR (Methanol- d_4 , 400MHz) δ 8.40 (d, J =6.17 Hz, 1H), 7.93 (d, J =7.94 Hz, 1H), 7.78-7.86 (m, 1H), 7.74-7.65 (m, 2H), 7.13-7.02 (m, 1H), 5.20 (s, 2H), 4.36-4.27 (m, 2 H), 1.96-1.64 (m, 6H), 1.40-1.05 (m, 5H); LCMS (ESI): m/z 332.1 (M+H).

Example 70

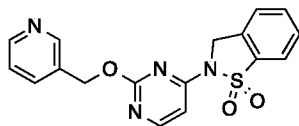
Synthesis of Compound 70



A mixture of **3** (30 mg, 0.11 mmol), benzyl alcohol (17 mg, 0.16 mmol), potassium carbonate (29 mg, 0.21 mmol), and cesium fluoride (33 mg, 0.21 mmol) in DMF (2 mL) was stirred at 65°C for 10 hours under an inert atmosphere. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure. Purification by prep-HPLC (0.04% HCl/CH₃CN/H₂O system) resulted in **Compound 70** (2 mg, 5%). ^1H NMR (DMSO- d_6 , 400MHz) δ 8.51-8.49 (d, 1H), 7.84-7.83 (d, 1H), 7.75-7.70 (m, 2H), 7.50-7.49 (d, 2H), 7.39-7.35 (m, 2H), 7.33-6.98 (m, 1H), 5.43 (s, 2H), 5.20 (s, 2H); LCMS (ESI): m/z 354.0 (M+H).

Example 71

Synthesis of Compound 71

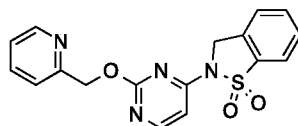


Compound 71 was synthesized in a manner similar to **Compound 70**. ^1H NMR (DMSO- d_6 , 400MHz) δ 9.94-9.91 (d, 2H), 9.08-9.04 (d, 1H), 8.88-8.06 (d, 1H), 8.40-8.38 (d, 1H), 8.17-

8.15 (d, 1H), 7.93-7.91 (d, 1H), 7.82-7.70 (d, 1H), 7.76-7.64 (d, 1H), 6.16-6.13 (t, 1H), 5.48 (s, 2H), 4.90-4.89 (d, 2H); **LCMS** (ESI): m/z 355.0 (M+H).

Example 72

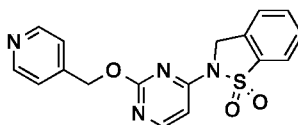
Synthesis of Compound 72



Compound 72 was synthesized in a manner similar to **Compound 70**. **¹H NMR** (Methanol-*d*₄, 400MHz) δ 8.85-8.83 (d, 2H), 8.63-8.60 (d, 1H), 8.61-8.50 (d, 1H), 8.24-8.03 (m, 1H), 7.89-7.87 (d, 1H), 7.71-7.69 (m, 1H), 7.03-7.01 (d, 1H), 5.87 (s, 2H), 5.17-5.11 (d, 2H); **LCMS** (ESI): m/z 355.0 (M+H).

Example 73

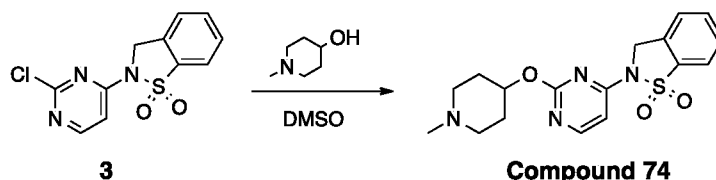
Synthesis of Compound 73



Compound 73 was synthesized in a manner similar to **Compound 70**. **¹H NMR** (DMSO-*d*₆, 400MHz) δ 8.83-8.82 (d, 2H), 8.48-8.47 (d, 1H), 8.18-8.16 (d, 2H), 7.88-7.79 (m, 2H), 7.70-7.68 (d, 2H), 7.00-6.99 (d, 1H), 5.82 (s, 2H), 5.09 (s, 2H); **LCMS** (ESI): m/z 355.0 (M+H).

Example 74

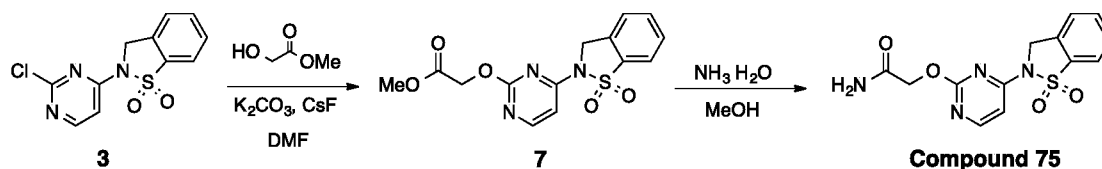
Synthesis of Compound 74



A mixture of **3** (30 mg, 0.11 mmol) and 1-methylpiperidin-4-ol (182 mg, 1.59 mmol) in DMSO (1.0 mL) was stirred at 50°C for 2 hours. Purification by prep-HPLC (0.04% HCl/CH₃CN/H₂O system) resulted in **Compound 74** (12 mg, 32%) as a white solid. **¹H NMR** (DMSO-*d*₆, 400MHz) δ 8.51-8.50 (d, 1H), 7.95-7.92 (m, 1H), 7.86-7.84 (m, 1H), 7.75-7.66 (m, 2H), 7.11-7.06 (m, 1H), 5.22 (s, 2H), 4.77-4.74 (m, 1H), 3.69-3.66 (d, 1H), 3.51-3.48 (d, 1H), 3.38-3.34 (m, 2H), 2.95 (s, 3H), 2.65-2.63 (d, 1H), 2.50-2.46 (d, 1H), 2.28-2.21 (m, 1H), 2.11-2.04 (m, 1H); **LCMS** (ESI): m/z 361.0 (M+H).

Example 75

Synthesis of Compound 75



Step 1.

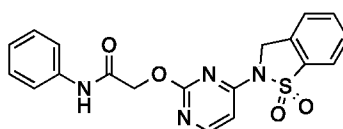
A mixture of **3** (200 mg, 0.71 mmol), methyl-2-hydroxyacetate (192 mg, 2.13 mmol), CsF (216 mg, 1.42 mmol) and potassium carbonate (196 mg, 1.42 mmol) in DMF (3 mL) was stirred at 120°C for 4 hours under an inert atmosphere. The resulting mixture was filtered and purification with pre-HPLC (0.075% TFA/CH₃CN/H₂O system) resulted in **7** (60 mg, 25%).

Step 2.

To a solution of **7** (30 mg, 0.09 mmol) in MeOH (2 mL) was added NH₃·H₂O (9.4 mg, 0.27 mmol). The mixture was stirred at 60°C for 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure and purification by prep-HPLC (0.04% HCl/CH₃CN/H₂O system) resulted in **Compound 75** (2.5 mg, 8.5%) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.48 (d, 1H), 8.05 (d, 1H), 7.85 (d, 1H), 7.76-7.72 (t, 2H), 7.51 (s, 1H), 7.20 (d, 1H), 6.99 (d, 1H), 5.19 (s, 2H), 4.75 (s, 2H); LCMS (ESI): *m/z* 321.0 (M+H).

Example 76

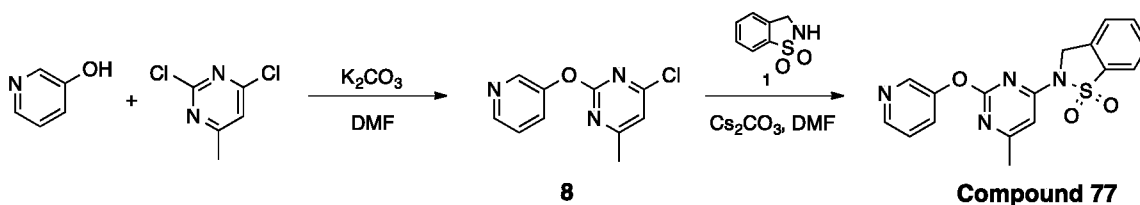
Synthesis of Compound 76



Compound 76 was synthesized in a manner similar to **Compound 75**. ¹H NMR (DMSO-*d*₆, 400MHz) δ 10.23 (s, 1H), 8.50-8.48 (d, 1H), 8.06-8.04 (d, 1H), 7.84-7.82 (t, 1H), 7.70-7.65 (dd, 2H), 7.62-7.60 (d, 2H), 7.33-7.29 (t, 2H), 7.07-7.05 (t, 1H), 7.05-6.99 (d, 1H), 5.16 (s, 2H), 4.98 (s, 2H); LCMS (ESI): *m/z* 397 (M+H).

Example 77

Synthesis of Compound 77



Step 1.

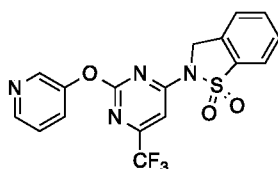
To a solution of 6-methyl-2,4-dichloropyrimidine (120 mg, 0.74 mmol) and pyridin-3-ol (70 mg, 0.74 mmol) in anhydrous DMF (4 mL) was added potassium carbonate (204 mg, 1.47 mmol) and the resulting mixture heated to 50°C for 2 hours. Upon completion, the reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (60 mL). The combined organic layer was washed with water (150 mL), saturated brine (80 mL), and dried over anhydrous sodium sulfate. Filtration and concentration under reduced pressure resulted in **8** (150 mg), which was submitted to the next step without further purification.

Step 2.

To a solution of **8** (150 mg, 0.54 mmol) and **1** (92 mg, 0.54 mmol) in anhydrous DMF (4 mL) was added cesium carbonate (353 mg, 1.08 mmol), and the resulting mixture was stirred at 40°C for 2 hours. Upon completion, the reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (60 mL). The combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by prep-HPLC (0.04% HCl/CH₃CN/H₂O system) resulted in **Compound 77** (3.9 mg, 9.0%) as a white solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.78 (d, 1H), 8.61 (d, 1H), 8.10-8.03 (m, 2H), 7.84 (d, 1H), 7.76-7.71 (m, 3H), 6.99 (s, 1H), 5.14 (s, 2H), 2.40 (s, 3H); LCMS (ESI): m/z 355.0 (M+H).

Example 78

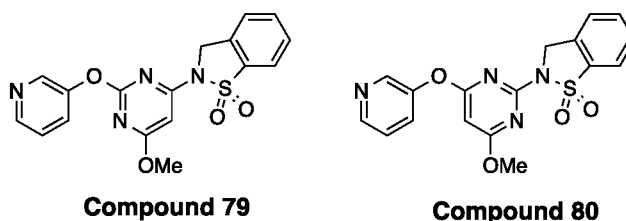
Synthesis of Compound 78



Compound 78 was synthesized in a manner similar to **Compound 77**. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.14 (s, 1H), 8.80 (s, 1H), 8.63-8.61 (d, 1H), 8.17-8.15 (m, 1H), 7.89-7.80 (m, 2H), 7.70-7.67 (m, 2H), 7.43 (s, 1H), 5.15 (s, 2H); LCMS (ESI): m/z 409.0 (M+H).

Examples 79 and 80

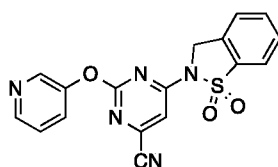
Synthesis of Compounds 79 and 80



Compound 79 and **Compound 80** were synthesized in a manner similar to **Compound 77**. Separation of isomers (~1:1 ratio) was achieved by prep-HPLC (0.04% HCl/CH₃CN/H₂O system). **Compound 79**. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.19 (s, 1H), 8.76-8.75 (d, 1H), 8.63-8.61 (d, 1H), 8.15-8.13 (m, 1H), 7.85-7.78 (m, 2H), 7.69-7.65 (m, 2H), 6.35 (s, 1H), 5.01 (s, 2H), 4.01 (s, 3H); **LCMS** (ESI): *m/z* 371.0 (M+H). **Compound 80**. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.20-9.19 (d, 1H), 8.75-8.73 (d, 1H), 8.58-8.57 (d, 1H), 8.14-8.11 (m, 1H), 7.83-7.77 (m, 2H), 7.68-7.64 (m, 2H), 6.28 (s, 1H), 5.11 (s, 2H), 4.10 (s, 3H); **LCMS** (ESI): *m/z* 371.0 (M+H).

Example 81

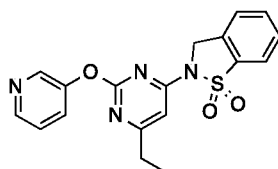
Synthesis of Compound 81



Compound 81 was synthesized in a manner similar to **Compound 77**. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.61 (s, 2H), 8.10-8.08 (d, 1H), 7.95-7.93 (d, 1H), 7.87-7.85 (d, 1H), 7.75-7.71 (m, 2H), 7.65 (m, 2H), 5.24 (s, 2H); **LCMS** (ESI): *m/z* 366 (M+H).

Example 82

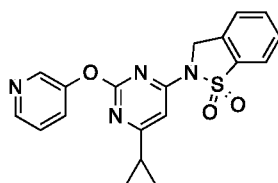
Synthesis of Compound 82



Compound 82 was synthesized in a manner similar to **Compound 77**. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.74 (bs, 1H); 8.58 (d, 1H), 8.09-7.98 (m, 2H), 7.89-7.82 (m, 1H), 7.72 (dd, 3H), 6.97 (s, 1H), 5.16 (s, 2H), 2.68 (q, 2H), 1.18 (t, 3H); **LCMS** (ESI): *m/z* 369.0 (M+H).

Example 83

Synthesis of Compound 83

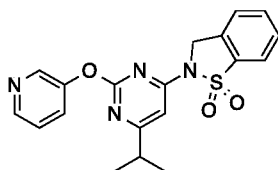


Compound 83 was synthesized in a manner similar to **Compound 77**. ¹H NMR (Methanol-*d*₄, 400 MHz) δ 9.19 (d, *J*=1.76 Hz, 1H), 8.78 (d, *J*=5.73 Hz, 1H), 8.67 (dd, *J*=8.60, 1.54 Hz,

1H), 8.20 (dd, $J=8.82, 5.73$ Hz, 1H), 7.91-7.78 (m, 2H), 7.68 (dt, $J=7.61, 3.47$ Hz, 2H), 7.00 (s, 1H), 5.16-5.04 (m, 2H), 2.21-2.12 (m, 1H), 1.18-1.11 (m, 4H); **LCMS** (ESI): m/z 381.0 (M+H).

Example 84

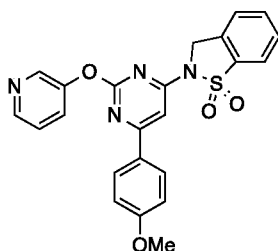
Synthesis of Compound 84



Compound 84 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.92 (bs, 1H); 8.69 (d, 1H), 8.28 (d, 1H), 8.04 (d, 1H), 7.85 (t, 2H), 7.76-7.66 (m, 2H), 6.96 (s, 1H), 5.18 (s, 2H), 2.96 (m, 1H), 1.20 (d, 6H); **LCMS** (ESI): m/z 383.1 (M+H).

Example 85

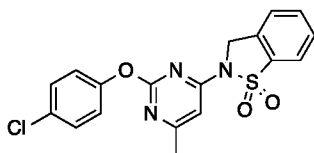
Synthesis of Compound 85



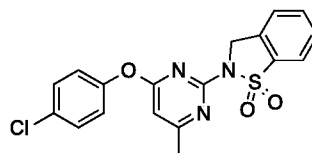
Compound 85 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.96 (s, 1H), 8.72-8.71 (d, 1H), 8.31 (s, 1H), 8.06-8.02 (m, 3H), 7.88-7.84 (t, 2H), 7.75-7.72 (m, 2H), 7.42 (s, 1H), 7.10-7.08 (d, 2H), 5.29 (s, 2H), 3.84 (s, 3H); **LCMS** (ESI): m/z 447.1 (M+H).

Examples 86 and 87

Synthesis of Compounds 86 and 87



Compounds 86



Compounds 87

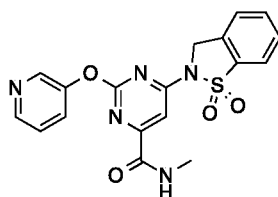
Compound 86 and Compound 87 were synthesized in a manner similar to **Compound 77**. Separation of isomers was achieved by prep-HPLC (0.04% HCl/CH₃CN/H₂O system).

Compound 86. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.07-8.05 (d, 1H), 7.84-7.82 (d, 1H), 7.74-7.70 (m, 2H), 7.50-7.48 (d, 2H), 7.32-7.30 (d, 2H), 6.96 (s, 1H), 5.14 (s, 2H), 3.37 (s, 3H); **LCMS** (ESI): m/z 388.0 (M+H). **Compound 87**. ^1H NMR (DMSO- d_6 , 400MHz) δ 7.97-

7.95 (d, 1H), 7.79-7.77 (d, 1H), 7.73-7.71 (d, 1H), 7.67-7.65 (d, 1H), 7.53-7.51 (d, 2H), 7.39-7.37 (d, 2H), 6.63 (s, 1H), 5.04 (s, 2H), 2.42 (s, 3H); **LCMS** (ESI): m/z 388.0 (M+H).

Example 88

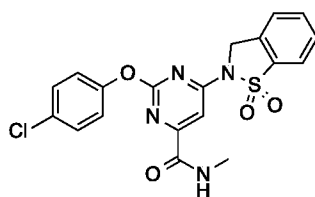
Synthesis of Compound 88



Compound 88 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.98-8.97 (d, 1H), 8.74-8.72 (t, 2H), 8.35-8.33 (d, 1H), 8.09-8.07 (d, 2H), 7.91-7.84 (m, 2H), 7.75-7.71 (t, 2H), 7.60 (s, 1H), 5.21 (s, 1H), 2.82-2.80 (d, 3H); **LCMS** (ESI): m/z 398.0 (M+H).

Example 89

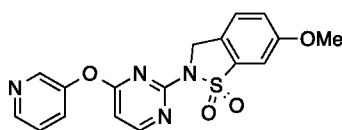
Synthesis of Compound 89



Compound 89 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.63 (s, 1H), 8.09-8.07 (d, 1H), 7.85-7.83 (d, 1H), 7.76-7.71 (m, 2H), 7.58 (s, 1H), 7.52-7.50 (d, 2H), 7.41-7.39 (d, 2H), 5.16 (s, 1H), 2.82-2.81 (d, 3H); **LCMS** (ESI): m/z 431.0 (M+H).

Example 90

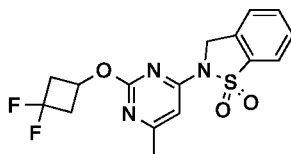
Synthesis of Compound 90



Compound 90 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.56 (s, 1H), 8.50-8.48 (d, 2H), 7.80-7.78 (d, 1H), 7.64-7.62 (m, 2H), 7.52-7.51 (d, 1H), 7.41-7.39 (d, 1H), 7.08-7.07 (d, 1H), 5.07 (s, 2H), 3.88 (s, 3H); **LCMS** (ESI): m/z 371.0 (M+H).

Example 91

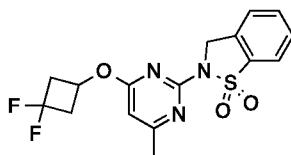
Synthesis of Compound 91



Compound 91 was synthesized in a manner similar to **Compound 77**. ^1H NMR (Methanol- d_4 , 400MHz) δ 7.98 (d, 1H), 7.93-7.85 (m, 1H), 7.79-7.71 (m, 2H), 7.13 (s, 1H), 5.40 (s, 1H), 5.28 (s, 2H), 3.42-3.33 (m, 2H), 3.03-2.91 (m, 2H), 2.62 (s, 3H); LCMS (ESI): m/z 368.1 (M+H).

Example 92

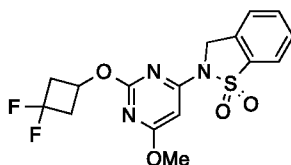
Synthesis of Compound 92



Compound 92 was synthesized in a manner similar to **Compound 77**. ^1H NMR (Methanol- d_4 , 400MHz) δ 7.89 (d, 1H), 7.81-7.75 (m, 1H), 7.71-7.64 (m, 2H), 6.46 (s, 1H), 5.26-5.16 (m, 1H), 5.12 (s, 2H), 3.29-3.21 (m, 2H), 2.81-2.68 (m, 2H), 2.42 (s, 3H); LCMS (ESI): m/z 368.0 (M+H).

Example 93

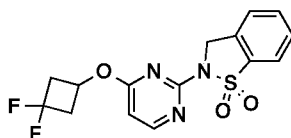
Synthesis of Compound 93



Compound 93 was synthesized in a manner similar to **Compound 77**. ^1H NMR (Methanol- d_4 , 400MHz) δ 7.89 (d, 1H), 7.82-7.76 (m, 1H), 7.72-7.64 (m, 2H), 6.26 (s, 1H), 5.14 (s, 1H), 5.06 (s, 2H), 4.01-3.90 (m, 3H), 3.27-3.17 (m, 2H), 2.83-2.70 (m, 2H); LCMS (ESI): m/z 384.0 (M+H).

Example 94

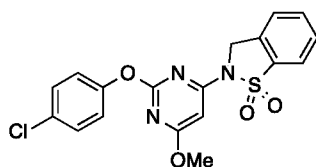
Synthesis of Compound 94



Compound 94 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.39-8.38 (d, 1H), 7.92-7.90 (d, 1H), 7.83-7.79 (t, 1H), 7.72-7.69 (m, 2H), 6.62-6.61 (d, 1H), 6.41-6.20 (m, 1H), 5.15 (s, 2H), 3.28-3.21 (m, 2H), 2.84-2.77 (m, 2H); **LCMS** (ESI): m/z 354.0 (M+H).

Example 95

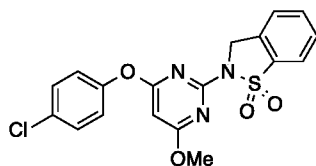
Synthesis of Compound 95



Compound 95 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400 MHz) δ 8.03 (d, $J=7.78$ Hz, 1H), 7.90-7.80 (m, 1H), 7.77-7.66 (m, 2H), 7.50 (d, $J=8.78$ Hz, 2H), 7.41-7.30 (m, 2H), 6.41-6.20 (m, 1H), 5.10 (s, 2H), 3.84 (s, 3H); **LCMS** (ESI): m/z 404.0 (M+H).

Example 96

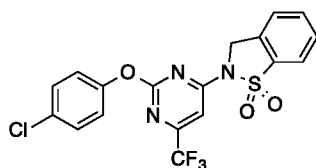
Synthesis of Compound 96



Compound 96 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400 MHz) δ 7.97 (d, $J=7.78$ Hz, 1H), 7.87-7.78 (m, 1H), 7.76-7.71 (m, 1H), 3.99 (s, 3H), 7.70-7.62 (m, 1H), 7.52 (d, $J=8.78$ Hz, 2H), 7.36 (d, $J=8.78$ Hz, 2H), 6.04 (s, 1H), 5.05 (s, 2H); **LCMS** (ESI): m/z 404.0 (M+H).

Example 97

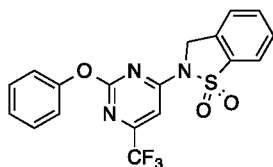
Synthesis of Compound 97



Compound 97 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.10 (d, 1H), 7.90-7.84 (m, 1H), 7.77-7.69 (m, 2H), 7.53 (d, 2H), 7.40 (d, 2H), 7.34 (s, 1H), 5.26 (s, 2H); **LCMS** (ESI): m/z 442.1 (M+H).

Example 98

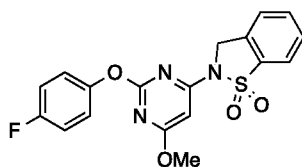
Synthesis of Compound 98



Compound 98 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.09 (d, 1H), 7.89-7.84 (m, 1H), 7.76-7.71 (m, 2H), 7.50-7.45 (m, 2H), 7.35-7.30 (m, 4H), 5.26 (s, 2 H); LCMS (ESI): m/z 408.0 (M+H).

Example 99

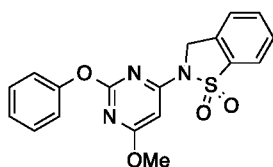
Synthesis of Compound 99



Compound 99 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.03 (d, $J=7.78$ Hz, 1H), 7.89-7.80 (m, 1H), 7.75-7.57 (m, 2H), 7.37 (dd, $J=8.91$, 4.64 Hz, 2H), 7.32-7.21 (m, 2H), 5.09 (s, 2H), 6.31 (s, 1H), 3.90-3.73 (m, 3H); LCMS (ESI): m/z 388.0 (M+H).

Example 100

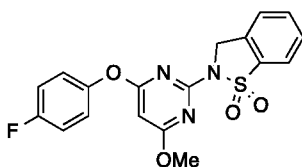
Synthesis of Compound 100



Compound 100 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.02 (d, 1H), 7.85-7.80 (m, 1H), 7.70 (d, 2H), 7.47-7.42 (m, 2H), 7.33-7.25 (m, 3H), 6.30 (s, 1H), 5.08 (s, 2H), 3.81 (s, 3H); LCMS (ESI): m/z 370.0 (M+H).

Example 101

Synthesis of Compound 101

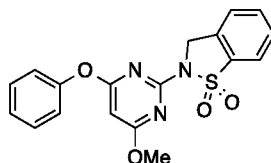


Compound 101 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400 MHz) δ 7.97 (d, $J=7.78$ Hz, 1H), 7.86-7.77 (m, 1H), 7.75-7.71 (m, 1H), 7.70-7.62 (m,

1H), 7.40-7.25 (m, 4H), 5.95 (s, 1H), 5.11-4.97 (m, 2H), 3.98 (s, 3H); **LCMS** (ESI): m/z 388.0 (M+H).

Example 102

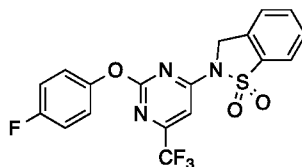
Synthesis of Compound 102



Compound 102 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 7.96 (d, 1H), 7.82-7.76 (m, 1H), 7.73-7.64 (m, 2H), 7.50-7.45 (m, 2H), 7.33-7.28 (m, 3H), 5.86 (s, 1H), 5.05 (s, 2H), 3.96 (s, 3H); **LCMS** (ESI): m/z 370.1 (M+H).

Example 103

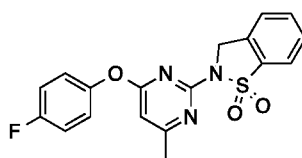
Synthesis of Compound 103



Compound 103 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.09 (d, 1H), 7.89-7.84 (m, 1H), 7.76-7.70 (m, 2H), 7.41-7.37 (m, 2H), 7.34-7.31 (m, 2H), 7.30-7.27 (m, 1H), 5.25 (s, 2H); **LCMS** (ESI): m/z 426.0 (M+H).

Example 104

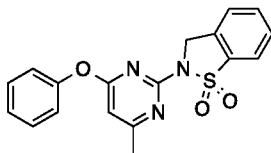
Synthesis of Compound 104



Compound 104 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 7.95 (d, 1H), 7.81-7.76 (m, 1H), 7.73-7.74 (m, 1H), 7.68-7.63 (m, 1H), 7.40-7.35 (m, 2H), 7.33-7.27 (m, 2H), 6.58 (s, 1H), 5.04 (s, 2H), 2.42 (s, 3H); **LCMS** (ESI): m/z 372.1 (M+H).

Example 105

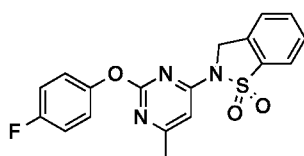
Synthesis of Compound 105



Compound 105 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 7.95 (d, 1H), 7.82-7.76 (m, 1H), 7.73-7.64 (m, 2H), 7.51-7.46 (m, 2H), 7.35-7.30 (m, 3H), 6.51 (s, 1H), 5.05 (s, 2H), 2.41 (s, 3H); **LCMS** (ESI): m/z 354.0 (M+H).

Example 106

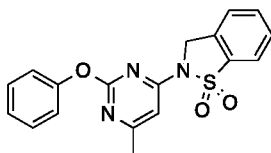
Synthesis of Compound 106



Compound 106 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.05 (d, 1H), 7.87-7.81 (m, 1H), 7.75-7.68 (m, 2H), 7.33-7.21 (m, 4H), 6.94 (s, 1H), 5.13 (s, 2H), 2.36 (s, 3H); **LCMS** (ESI): m/z 372.1 (M+H).

Example 107

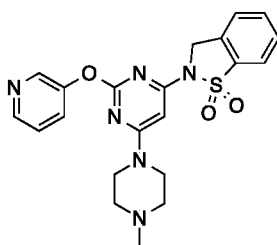
Synthesis of Compound 107



Compound 107 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.05 (d, 1H), 7.87-7.81 (m, 1H), 7.75-7.67 (m, 2H), 7.47-7.41 (m, 2H), 7.28-7.23 (m, 3H), 6.95 (s, 1H), 5.14 (s, 2H), 2.36 (s, 3H); **LCMS** (ESI): m/z 354.0 (M+H).

Example 108

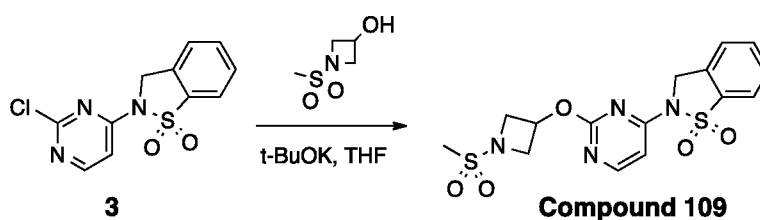
Synthesis of Compound 108



Compound 108 was synthesized in a manner similar to **Compound 77**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.53 (s, 1H), 8.45 (d, 1H), 7.89 (d, 1H), 7.76 (t, 2H), 7.70-7.59 (m, 2H), 7.47 (dd, 1H), 6.12 (s, 1H), 4.92 (s, 2H), 3.67 (s, 4H), 2.33 (s, 4H), 2.26 (s, 3H); LCMS (ESI): m/z 439.1 (M+H).

Example 109

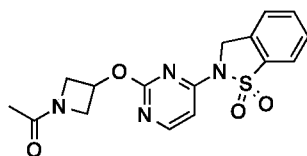
Synthesis of Compound 109



To a solution of **3** (120 mg, 0.43 mmol) and 1-methylsulfonylazetidin-3-ol (77 mg, 0.51 mmol) in THF (2 mL) was added t-BuOK (96 mg, 0.85 mmol) at 0°C. The resulting mixture was stirred at 0°C for 2 hours. Upon completion, the reaction mixture was quenched by addition NH_4Cl (5 mL) at 0°C and then extracted with EtOAc (10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification by HPLC (0.04% $\text{HCl}/\text{CH}_3\text{CN}/\text{H}_2\text{O}$ system) resulted in **Compound 109** (13 mg, 7%) as a white solid. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.53-8.46 (m, 1H), 8.05 (d, $J=7.94$ Hz, 1H), 7.91-7.82 (m, 1H), 7.77- 7.52 (m, 2H), 7.03-6.86 (m, 1H), 5.40-5.25 (m, 1H), 5.23 - 5.13 (m, 2 H), 4.32 (dd, $J=9.48$, 6.84 Hz, 2H), 4.09-3.96 (m, 2H), 3.06 (s, 3H); LCMS (ESI): m/z 397.0 (M+H).

Example 110

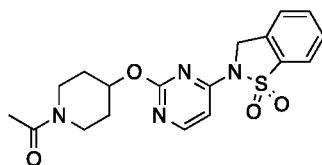
Synthesis of Compound 110



Compound 110 was synthesized in a manner similar to **Compound 109**. ^1H NMR (Methanol- d_4 , 400MHz) δ 8.45 (d, $J=5.77$ Hz, 1H), 7.94 (d, $J=7.78$ Hz, 1H), 7.88-7.81 (m, 1H), 7.75-7.66 (m, 2H), 7.06 (d, $J=5.77$ Hz, 1H), 5.47 (bs, 1H), 5.17 (s, 2H), 4.75 (t, $J=8.28$ Hz, 1H), 4.55-4.45 (m, 1H), 4.33 (d, $J=7.53$ Hz, 1H), 4.07 (d, $J=10.54$ Hz, 1H), 1.94 (s, 3H); LCMS (ESI): m/z 361.0 (M+H).

Example 111

Synthesis of Compound 111

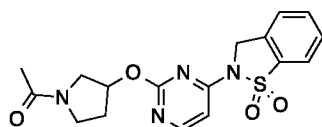


Compound 111 was synthesized in a manner similar to **Compound 109**. ¹H NMR:

(Methanol-*d*₄, 400MHz) δ 8.33 (d, *J*=5.73 Hz, 1H), 7.87 (d, *J*=7.94 Hz, 1H), 7.82-7.75 (m, 1H), 7.71-7.62 (m, 2H), 6.54 (d, *J*=5.73 Hz, 1H), 5.43 (dt, *J*=8.05, 4.13 Hz, 1H), 5.13 (s, 2H), 4.08-3.97 (m, 1H), 3.83 (d, *J*=13.67 Hz, 1H), 3.58-3.39 (m, 2H), 2.30-2.05 (m, 5H), 1.95-1.62 (m, 1H); LCMS (ESI): *m/z* 389.1 (M+H).

Example 112

Synthesis of Compound 112

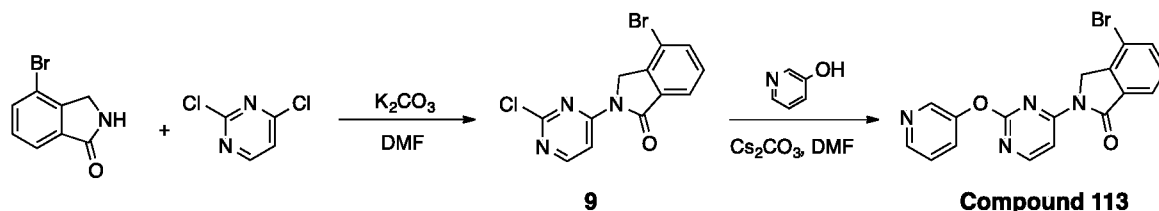


Compound 112 was synthesized in a manner similar to **Compound 109**. ¹H NMR:

(Methanol-*d*₄, 400MHz) δ 8.42 (t, *J*=5.29 Hz, 1H), 8.02-7.79 (m, 2H), 7.74-7.63 (m, 2H), 7.04 (dd, *J*=16.32, 5.73 Hz, 1H), 5.67 (bs, 1H), 5.24-5.11 (m, 2H), 4.02 (dd, *J*=12.35, 4.41 Hz, 1H), 3.84-3.44 (m, 4H), 2.47- 2.25 (m, 2H), 2.14-2.01 (m, 3H); LCMS (ESI): *m/z* 375.1 (M+H).

Example 113

Synthesis of Compound 113



Step 1.

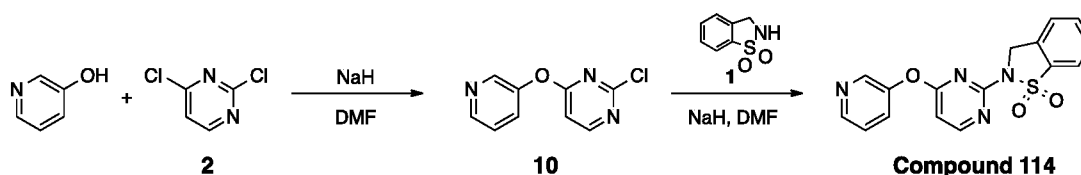
A mixture of 2,4-dichloropyrimidine (116 mg, 0.78 mmol), 4-bromoisoindolin-1-one (150 mg, 0.71 mmol), K₂CO₃ (196 mg, 1.41 mmol) in DMF (3 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 80°C for 14 hours under an inert atmosphere. The resulting mixture was filtered and concentrated under reduced pressure. Purification by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 3:1) provided **9** (80 mg) as a light yellow solid which was used directly in the next step without further purification.

Step 2.

A mixture of **9** (80 mg, 0.13 mmol), pyridin-3-ol (14.6 mg, 0.15 mmol) and Cs₂CO₃ (83 mg, 0.26 mmol) in DMF (3 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 50°C for 1 hour under an inert atmosphere. The reaction mixture was filtered, and then diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (3 x 15 mL) and saturated brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (HCl, 0.05% HCl-ACN) to afford (13.9 mg, 28%) of **Compound 113** as an orange solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.89 (s, 1H), 8.69-8.68 (d, 1H), 8.60-8.58 (d, 1H), 8.26-8.24 (m, 2H), 8.00-7.98 (d, 1H), 7.90-7.85 (m, 2H), 7.58-7.54 (m, 1H), 4.88 (s, 2H); LCMS (ESI): *m/z* 383.0 (M+H).

Example 114

Synthesis of Compound 114



Step 1.

A solution of 3-hydroxypyridine (3.06 g, 32.2 mmol) in DMF (100 mL) was cooled to 0°C, and NaH (773 mg, 32.22 mmol) was added. The mixture was stirred at 0°C for 30 minutes, warmed to 15°C, and then **2** (4.0 g, 26.9 mmol) was added. The reaction mixture was allowed to stir for another 3 hours. Upon completion, water (100 mL) was added and the resulting mixture was extracted with EtOAc (90 mL). The organic layer was dried over sodium sulfate, filtered, concentrated to give a residue. Purification by silica-gel chromatography (petroleum ether: EtOAc = 50:1 to 20:1) resulted in **10** (2.2 g, 37%).

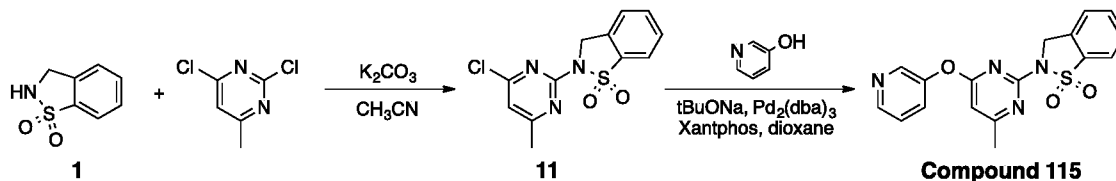
Step 2.

Solution of **1** (97 mg, 0.053 mmol) in DMF (4 mL) was cooled to 0°C and NaH (13.9 mg, 0.058 mmol) was added. The mixture was stirred at 0°C for 30 minutes followed by addition of **10** (100 mg, 0.48 mmol). The solution was allowed to stir 15 hours at 0°C. The resulting mixture was poured into water (20 mL) and stirred for 10 minutes. The aqueous phase was extracted with ethyl acetate (30 mL). The combined organic layer was washed with brine (20 mL), dried with anhydrous sodium sulfate, filtered, and concentrated. Purification with prep-HPLC (0.04% NH₃.H₂O/ ACN/ H₂O system) resulted in **Compound 114** (20 mg) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.56 (d, 1H), 8.51-8.46 (m, 2H), 8.06 (d, 1H), 7.88-

7.82 (m, 1H), 7.81-7.67 (m, 3H), 7.50 (dd, 8.2 Hz, 1H), 7.09 (d, 1H), 5.17 (s, 2H); LCMS (ESI+): m/z 341 (M+H).

Example 115

Synthesis of Compound 115



Step 1.

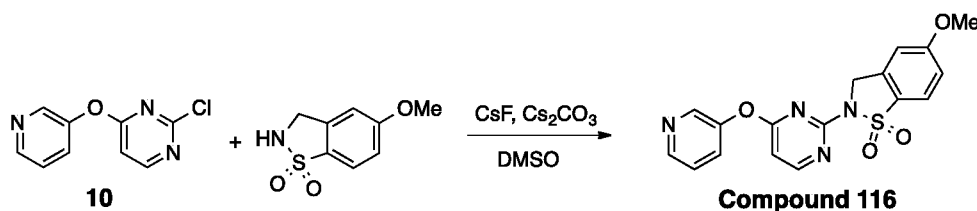
To a mixture of 6-methyl-2,4-dichloropyrimidine (162 mg, 0.994 mmol) and **1** (185 mg, 1.1 mmol) in anhydrous CH_3CN (4 mL) was added K_2CO_3 (274 mg, 2 mmol), the mixture was stirred at $80^\circ C$ for 3 hrs. Concentration under reduced pressure resulted in **11** (130 mg), which was submitted to the next step without further purification.

Step 2.

To a solution of **11** (130 mg crude material), pyridin-3-ol (26 mg, 0.28 mmol), $t-BuONa$ (45 mg, 0.47 mmol) and Xantphos (13.5 mg, 0.023 mmol) in anhydrous dioxane (3 mL) was added $Pd_2(dba)_3$ (21 mg, 0.023 mmol). The mixture was stirred at $100^\circ C$ for 12 hours under inert atmosphere, filtered, and then concentrated under reduced pressure. Purification with prep-HPLC (0.04% HCl/ CH_3CN/H_2O system) resulted in **Compound 115** (3.6 mg, 2.1%) as an HCl salt. 1H NMR (DMSO- d_6 , 400MHz) δ 8.74 (s, 1H), 8.60 (d, 1H), 7.93 (d, 1H), 7.77 (d, 1H), 7.71-7.65 (m, 4H), 6.79 (m, 1H), 5.03 (s, 2H), 2.46 (s, 3H); LCMS (ESI): m/z 355.0 (M+H).

Example 116

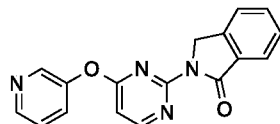
Synthesis of Compound 116



To a mixture of **10** (123 mg, 0.59 mmol), 2,3-dihydro-5-methoxy-1,1-dioxo-1,2-benzisothiazole (96 mg, 0.48 mmol), and CsF (146 mg, 0.96 mmol) in anhydrous DMSO (2 mL) was added cesium carbonate (314 mg, 0.96 mmol). The resulting mixture was degassed and stirred at $80^\circ C$ for 3 hours under inert atmosphere. Upon completion, the mixture was filtered. Purification by prep-HPLC (0.04% HCl/ CH_3CN/H_2O system) resulted in **Compound 116** (3.5 mg, 1.4%) as the HCl salt. 1H NMR (Methanol- d_4 , 400MHz) δ 9.08 (s,

Example 117

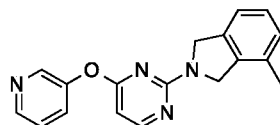
Synthesis of Compound 117



Compound 117 was synthesized in a manner similar to **Compound 116**. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.81 (s, 1H), 8.65-8.63 (d, 1H), 8.57-8.56 (d, 1H), 8.29-8.28 (d, 1H), 8.14-8.13 (d, 1H), 7.87-7.85 (d, 1H), 7.78-7.72 (m, 3H), 7.60-7.58 (m, 1H), 4.98 (s, 2H); **LCMS** (ESI): *m/z* 305.1 (M+H).

Example 118

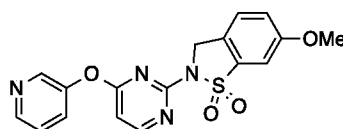
Synthesis of Compound 118



Compound 118 was synthesized in a manner similar to **Compound 116**. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.86 (s, 1H), 8.68-8.67 (d, 1H), 8.43-8.41 (d, 1H), 8.20-8.18 (t, 1H), 7.83-7.81 (t, 1H), 7.18-7.07 (m, 3H), 6.58-6.55 (m, 1H), 4.85-4.80 (d, 2H), 4.54 (s, 1H), 2.25-2.16 (d, 3H); **LCMS** (ESI): *m/z* 305.1 (M+H).

Example 119

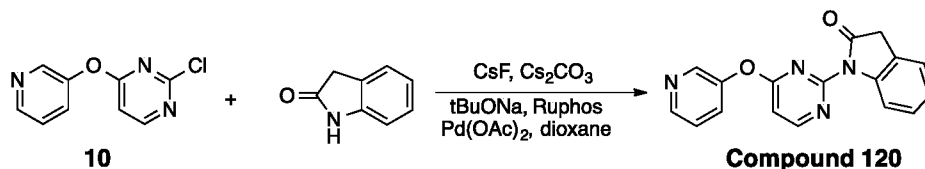
Synthesis of Compound 119



Compound 119 was synthesized in a manner similar to **Compound 116**. ¹H NMR (Methanol-*d*₄, 400MHz) δ 9.08 (s, 1H), 8.74 (d, 1H), 8.53 (d, 1H), 8.10-8.07 (q, 1H), 7.77 (d, 1H), 7.23-7.14 (m, 3H), 5.03 (s, 2H), 3.93 (s, 3H); **LCMS** (ESD): *m/z* 371.0 (M+H).

Example 120

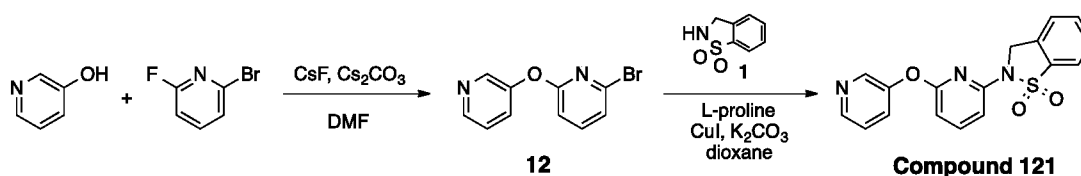
Synthesis of Compound 120



A mixture of **10** (150 mg, 0.72 mmol), 2-oxindole (125 mg, 0.94 mmol), tBuONa (139 mg, 1.44 mmol), Ruphos (67 mg, 0.144 mmol) and Pd(OAc)₂ (32 mg, 0.144 mmol) in dioxane (2 mL) was degassed and stirred at 100°C for 12 hours under an inert atmosphere. Upon completion, the mixture was filtered and concentrated under reduced pressure. Purification by prep-HPLC (0.04% HCl/CH₃CN/H₂O system) resulted in **Compound 120** (1 mg) as a yellow oil. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.68 (s, 2H), 8.25 (d, 1H), 7.93 (d, 1H), 7.69-7.66 (m, 1H), 6.79-6.75 (m, 2H), 6.64 (d, 1H), 6.53 (d, 1H), 6.51 (d, 1H), 6.45 (d, 1H), 3.50 (s, 2H); LCMS (ESI): m/z 305.1 (M+H).

Example 121

Synthesis of Compound 121



Step 1.

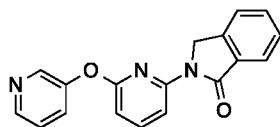
A mixture of 2-bromo-6-fluoropyridine (500 mg, 2.84 mmol), pyridin-3-ol (297 mg, 3.13 mmol), cesium carbonate (1.85 g, 5.68 mmol) and CsF (22 mg, 142 mmol) in DMF (5 mL) was stirred at 120°C for 2 hours. Upon completion, water (40 mL) was added and the reaction mixture was extracted with EtOAc (90 mL). The organic phase was washed with brine (50 mL), dried with anhydrous MgSO₄, filtered, and concentrated under reduced pressure to give **12** (700 mg).

Step 2.

A mixture of **12** (100 mg, 0.40 mmol), **1** (67 mg, 0.40 mmol), potassium carbonate (55 mg, 0.40 mmol), CuI (3.8 mg, 0.019 mmol), and L-proline (2.3 mg, 0.019 mmol) in dioxane (4 mL) was stirred at 110°C for 16 hours under an inert atmosphere. Upon completion, water (40 mL) was added and the reaction mixture was extracted with EtOAc (90 mL). The organic phase was washed with brine (50 mL) and concentrated under reduced pressure. Purification with prep-HPLC (0.075% TFA/CH₃CN/H₂O system) resulted in **Compound 121** (40 mg, 29%) as yellow solid and TFA salt. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.69-8.68 (d, 1H), 8.53-8.52 (d, 1H), 7.99-7.94 (m, 3H), 7.77 (m, 1H), 7.67-7.62 (m, 3H), 7.07-7.05 (d, 1H), 6.83-6.81 (d, 1H), 4.95 (s, 2H); LCMS (ESI): m/z 340.1 (M+H).

Example 122

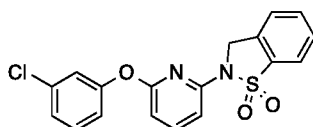
Synthesis of Compound 122



Compound 122 was synthesized in a manner similar to **Compound 121**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.84 (s, 1H), 8.33-8.31 (d, 1H), 8.04-8.00 (t, 1H), 7.82-7.80 (m, 1H), 7.68-7.64 (m, 1H), 7.56-7.54 (d, 2H), 6.94-6.93 (d, 1H), 4.80 (s, 2H); **LCMS** (ESI): m/z 304.0 (M+H).

Example 123

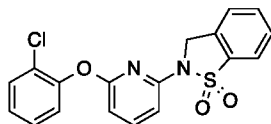
Synthesis of Compound 123



Compound 123 was synthesized in a manner similar to **Compound 121**. ^1H NMR (Methanol- d_4 , 400MHz) δ 8.20 (s, 1H), 7.90-7.88 (d, 1H), 7.79-7.77 (t, 1H), 7.71-7.67 (m, 2H), 7.58-7.55 (m, 2H), 7.38-7.35 (t, 1H), 7.16-7.15 (d, 1H), 7.04 (s, 1H), 5.15 (s, 2H); **LCMS** (ESI): m/z 373.0 (M+H).

Example 124

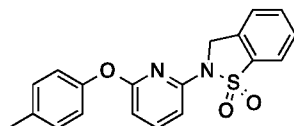
Synthesis of Compound 124



Compound 124 was synthesized in a manner similar to **Compound 121**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.26-8.25 (d, 1H), 8.02-8.00 (d, 1H), 7.83-7.71 (m, 1H), 7.69-7.61 (m, 4H), 7.43-7.40 (m, 2H), 7.42-7.38 (d, 1H), 7.13-7.11 (d, 1H), 5.17 (s, 2H); **LCMS** (ESI): m/z 373.0 (M+H).

Example 125

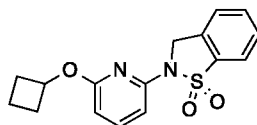
Synthesis of Compound 125



Compound 125 was synthesized in a manner similar to **Compound 121**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.30 (d, 1H), 7.90 (d, 1H), 7.74 (d, 1H), 7.71-7.69 (m, 3H), 7.45-7.43 (m, 3H), 7.09-7.06 (m, 2H), 5.17 (s, 2H); **LCMS** (ESI): m/z 373.0 (M+H).

Example 126

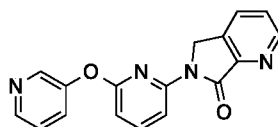
Synthesis of Compound 126



Compound 126 was synthesized in a manner similar to **Compound 121**. ^1H NMR (Methanol- d_4 , 400MHz) δ 7.99-7.98 (d, 1H), 7.87-7.85 (d, 1H), 7.77-7.75 (d, 1H), 7.68-7.65 (m, 2H), 7.42 (m, 1H), 7.38-7.37 (m, 1H), 5.08 (s, 2H), 4.76-4.69 (m, 1H), 2.49-2.47 (m, 2H), 2.17-2.12 (m, 2H), 1.75-1.88 (m, 2H); **LCMS** (ESI): m/z 317.0 (M+H).

Example 127

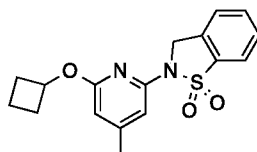
Synthesis of Compound 127



Compound 127 was synthesized in a manner similar to **Compound 121**. ^1H NMR (Methanol- d_4 , 400 MHz) δ 9.06 (bs, 1H), 8.90 (d, $J=7.94$ Hz, 1H), 8.83 (d, $J=2.65$ Hz, 1H), 8.75 (d, $J=9.26$ Hz, 1H), 8.69 (d, $J=5.29$ Hz, 1H), 8.51 (d, $J=2.65$ Hz, 1H), 8.36 (dd, $J=8.82$, 1.76 Hz, 1H), 5.44 (s, 2H), 8.27 (dd, $J=7.94$, 5.73 Hz, 1H), 8.13 (dd, $J=8.82$, 5.29 Hz, 1H), 7.92 (dd, $J=9.04$, 2.87 Hz, 1H); **LCMS** (ESI): m/z 305.0 (M+H).

Example 128

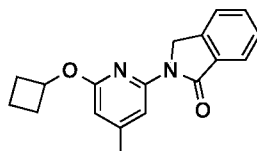
Synthesis of Compound 128



Compound 128 was synthesized in a manner similar to **Compound 121**. ^1H NMR (Methanol- d_4 , 400MHz) δ 7.86-7.84 (d, 1H), 7.78-7.74 (m, 1H), 7.69-7.63 (m, 2H), 6.73 (s, 1H), 6.29 (s, 1H), 5.22-5.15 (m, 1H), 5.05 (s, 2H), 2.54-2.52 (m, 2H), 2.32 (s, 3H), 2.14-2.09 (m, 2H), 1.85-1.71 (m, 2H); **LCMS** (ESI): m/z 331.1 (M+H).

Example 129

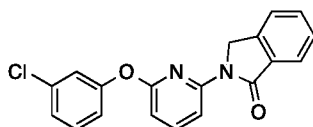
Synthesis of Compound 129



Compound 129 was synthesized in a manner similar to **Compound 121**. ^1H NMR (Methanol- d_4 , 400MHz) δ 8.41-8.39 (d, 1H), 8.02-8.01 (d, 1H), 7.87-7.85 (d, 1H), 7.69-7.65 (m, 2H), 7.55-7.53 (m, 1H), 7.43-7.40 (m, 1H), 5.10 (s, 2H), 4.79-4.75 (m, 1H), 2.52-2.49 (m, 2H), 2.19-2.14 (m, 2H), 1.90-1.72 (m, 2H); **LCMS** (ESI): m/z 281.1 (M+H).

Example 130

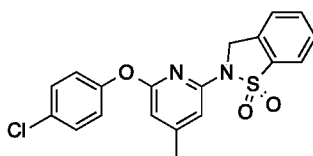
Synthesis of Compound 130



Compound 130 was synthesized in a manner similar to **Compound 121**. ^1H NMR (Methanol- d_4 , 400MHz) δ 8.64-8.61 (d, 1H), 8.23-8.22 (d, 1H), 7.88-7.86 (d, 1H), 7.70-7.68 (m, 2H), 7.61-7.57 (m, 2H), 7.36-7.34 (m, 1H), 7.17-7.15 (m, 1H), 7.06 (s, 1H), 6.98-6.96 (d, 1H), 5.16 (s, 2H); **LCMS** (ESI): m/z 337.0 (M+H).

Example 131

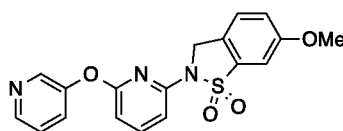
Synthesis of Compound 131



Compound 131 was synthesized in a manner similar to **Compound 121**. ^1H NMR (Methanol- d_4 , 400MHz) δ 7.86-7.84 (d, 1H), 7.75-7.73 (m, 1H), 7.64-7.60 (m, 2H), 7.41-7.38 (m, 2H), 7.20-7.17 (m, 2H), 7.04 (s, 1H), 6.54 (s, 1H), 4.87 (s, 2H), 2.40 (s, 3H); **LCMS** (ESI): m/z 387.0 (M+H).

Example 132

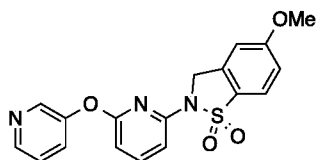
Synthesis of Compound 132



Compound 132 was synthesized in a manner similar to **Compound 121**. ^1H NMR (DMSO- d_6 , 400MHz) 8.70 (s, 1H), 8.58 (d, $J=4.85$ Hz, 1H), 8.37 (d, $J=2.65$ Hz, 1H), 8.20-8.12 (m, 1H), 7.98 (dd, $J=8.82, 5.29$ Hz, 1H), 7.78 (dd, $J=9.04, 2.87$ Hz, 1H), 7.63-7.53 (m, 2 =H), 7.41 (d, $J=2.65$ Hz, 1H), 7.36 (dd, $J=8.60, 2.43$ Hz, 1H), 5.08 (s, 2H). 3.92 (s, 1H); **LCMS** (ESI): m/z 370.0 (M+H).

Example 133

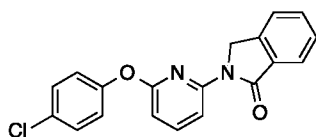
Synthesis of Compound 133



Compound 133 was synthesized in a manner similar to **Compound 121**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.45-8.33 (m, 3H), 7.94-7.92 (d, 1H), 7.77-7.74 (dd, 1H), 7.49-7.45 (m, 3H), 7.42 (s, 2H), 7.28-7.22 (dd, 1H), 5.11 (s, 1H), 3.90 (s, 3H); **LCMS** (ESI): m/z 370.0 (M+H).

Example 134

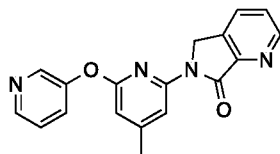
Synthesis of Compound 134



Compound 134 was synthesized in a manner similar to **Compound 121**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.59-8.57 (d, 1H), 8.29 (s, 1H), 7.83-7.81 (d, 1H), 7.68-7.60 (m, 3H), 7.56-7.55 (d, 1H), 7.46-7.44 (d, 2H), 7.09-7.07 (d, 2H), 5.10 (s, 1H); **LCMS** (ESI): m/z 337.0 (M+H).

Example 135

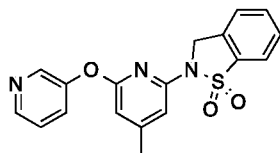
Synthesis of Compound 135



Compound 135 was synthesized in a manner similar to **Compound 121**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.91 (s, 1H), 8.78-8.77 (d, 1H), 8.69-8.68 (d, 1H), 8.23 (s, 2H), 8.13-8.11 (d, 1H), 7.89-7.86 (m, 1H), 7.66-7.63 (m, 1H), 6.86 (s, 1H), 4.80 (s, 2H), 2.45 (s, 3H); **LCMS** (ESI): m/z 319.1 (M+H).

Example 136

Synthesis of Compound 136

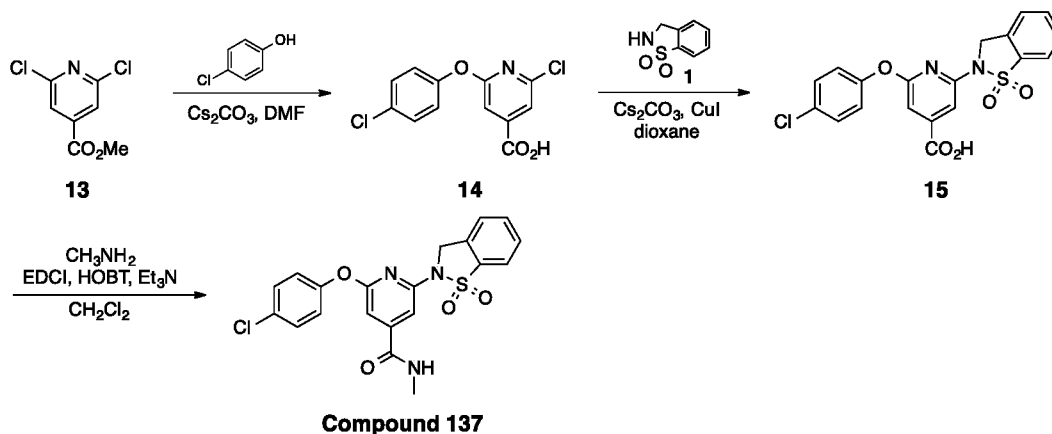


Compound 136 was synthesized in a manner similar to **Compound 121**. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.87 (s, 1H), 8.65 (s, 1H), 8.20-8.19 (d, 1H), 7.97-7.95 (d, 1H), 7.81-7.78 (m,

2H), 7.68-7.65 (m, 2H), 6.92 (s, 1H), 6.75 (s, 1H), 4.97 (s, 2H), 2.41 (s, 3H); LCMS (ESI): m/z 354.0 (M+H).

Example 137

Synthesis of Compound 137



Step 1.

A mixture of **13** (500 mg, 2.43 mmol), 4-chlorophenol (312 mg, 2.43 mmol), Cs_2CO_3 (1.58 g, 4.85 mmol) and CsF (369 mg, 2.43 mmol) in DMF (30 mL) was degassed and purged with N_2 (3X). The mixture was stirred at 100°C for 12 h, then cooled and poured into water (100 mL). The solution was extracted with ethyl acetate (3 x 40 mL) and the organic layer was washed with saturated brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by prep-TLC (petroleum ether: ethyl acetate = 1:1) to provide **14** (380 mg) as a light yellow solid.

Step 2.

A mixture of **14** (200 mg, 0.70 mmol), **1** (143 mg, 0.84 mmol), Cs_2CO_3 (459 mg, 1.41 mmol), CuI (40 mg, 0.21 mmol) and 2-(dimethylamino)acetic acid hydrochloride (30 mg, 0.21 mmol) in dioxane (2 mL) was degassed and purged with N_2 (3X). The mixture was stirred at 100°C for 12 h under N_2 atmosphere. The reaction mixture was diluted with ethyl acetate (50 mL), adjusted to pH=7 with 2N HCl, and separated. The aqueous layer was extracted with ethyl acetate (2 x 40 mL) and the combined organic layer was washed with saturated brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give **15** (230 mg) as a light yellow solid.

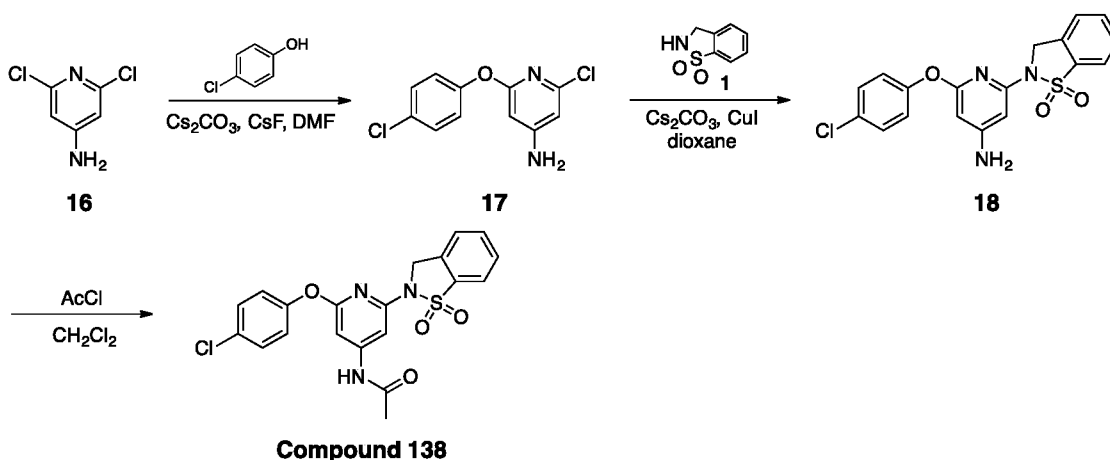
Step 3.

A mixture of compound **15** (210 mg, 0.50 mmol), methylamine hydrochloride (41 mg, 0.60 mmol), EDCI (126 mg, 0.65 mmol), HOBT (89 mg, 0.65 mmol) and Et_3N (102 mg, 1.01 mmol) in CH_2Cl_2 (30 mL) was degassed and purged with N_2 (3X). The mixture was stirred at

15°C for 12 h. The solution was extracted with water (30 mL) and saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified by prep-HPLC to give **Compound 137** (1045 mg, 44%) as a white solid. ^1H NMR (DMSO- d_6 , 400MHz) δ 8.81 (d, 1H), 8.01 (d, 1H), 7.83-7.77 (m, 1H), 7.74-7.65 (m, 2H), 7.49 (d, 2H), 7.42 (s, 1H), 7.33 (d, 2H), 7.06 (s, 1H), 5.04 (s, 2H), 2.81 (d, 3H); LCMS (ESI): m/z 430.0 (M+H).

Example 138

Synthesis of Compound 138



Step1.

A mixture of compound **16** (500 mg, 3.07 mmol), 4-chlorophenol (394 mg, 3.07 mmol), Cs_2CO_3 (2.00 g, 6.14 mmol) and CsF (466 mg, 3.07 mmol) in DMF (8 mL) was degassed and purged with N_2 (3X). The mixture was stirred at 100°C for 12 h and then poured into water (80 mL). The solution was extracted with ethyl acetate (3 x 40 mL) and the organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to give **17** (650 mg) as a dark brown oil.

Step2.

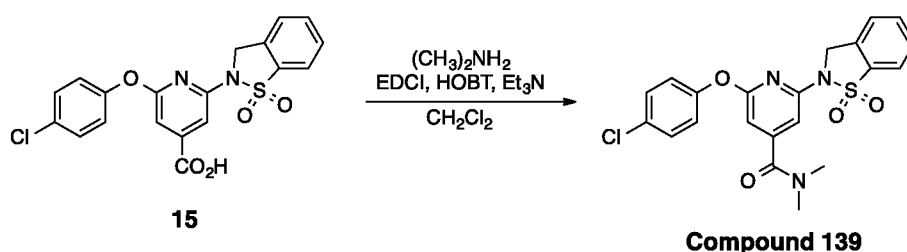
A mixture of compound **17** (300 mg, 1.18 mmol), **1** (240 mg, 1.42 mmol), Cs_2CO_3 (769 mg, 2.36 mmol), CuI (67 mg, 0.35 mmol) and 2-(dimethylamino)acetic acid hydrochloride (49 mg, 0.354 mmol) in dioxane (20 mL) was degassed and purged with N_2 for (3X). The mixture was stirred at 100°C for 12 hrs, filtered, and then diluted with ethyl acetate (50 mL). The solution was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give **18** as a dark brown oil which was used without further purification.

Step3.

To a solution of **18** (520 mg, 1.34 mmol) and Et₃N (271 mg, 2.68 mmol) in CH₂Cl₂ (30 mL) at 0°C was added dropwise acetyl chloride (116 mg, 1.47 mmol). The mixture was stirred at 15°C for 2 h and then quenched with saturated brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by prep-HPLC to give **Compound 138** (73 mg, 12.14%) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 10.58 (s, 1H), 8.06-7.97 (m, 1 H), 7.83-7.77 (m, 1H), 7.74-7.64 (m, 2H), 7.49 (d, 2H), 7.41 (s, 1H), 7.28 (d, 2H), 6.98 (s, 1H), 4.98 (s, 2H), 2.08 (s, 3H); LCMS (ESI): *m/z* 430.0 (M+H).

Example 139

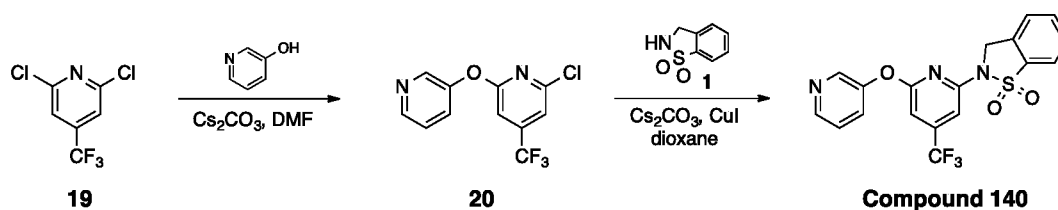
Synthesis of Compound 139



A mixture of **15** (210.00 mg), dimethylamine hydrochloride (49 mg, 0.60 mmol), EDCI (125 mg, 0.65 mmol), HOBT (88 mg, 0.65 μmol) and Et₃N (102 mg, 1.01 mmol) in CH₂Cl₂ (20 mL) was degassed and purged with N₂ (3X). The mixture was stirred at 15°C for 12 h and then washed with water (30 mL), saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude material was purified by prep-HPLC to give **Compound 139** (13 mg, 6%) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.09 (d, 1H), 7.89-7.84 (m, 1H), 7.77-7.69 (m, 2H), 7.51 (d, 2H), 7.36 (d, 2H), 7.13 (s, 1H), 5.22 (s, 2H), 2.95 (s, 3H), 2.89 (s, 3H); LCMS (ESI): *m/z* 445.0 (M+H).

Example 140

Synthesis of Compound 140



Step 1.

A mixture of **19** (120 mg, 0.56 mmol), pyridin-3-ol (53 mg, 0.56 mmol), Cs₂CO₃ (0.36 mg, 1.11 mmol) and CsF (84 mg, 0.56 μmol) in DMF (2 mL) was degassed and purged with N₂ (3X). The mixture was stirred at 100°C for 12 h and then poured into water (80 mL). The

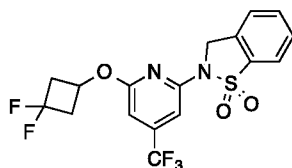
reaction mixture was extracted with ethyl acetate (3 x 40 mL) and the organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated to give **20** (160 mg) as a light yellow oil.

Step 2.

A mixture of **20** (160 mg, 0.58 mmol), **1** (99 mg, 0.58 mmol), Cs₂CO₃ (380 mg, 1.17 mmol), CuI (33 mg, 0.17 mmol) and 2-(dimethylamino)acetic acid hydrochloride (24 mg, 0.17 mmol) in dioxane (2 mL) was degassed and purged with N₂ (3X). The mixture was stirred at 100°C for 12 h and then filtered and concentrated. The crude material was purified by prep-HPLC to give **Compound 140** (27 mg, 10%) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.98 (s, 1H), 8.74 (d, 1H), 8.34 (d, 1H), 7.99 (d, 1H), 7.92 (dd, 1H), 7.85-7.79 (m, 1H), 7.71-7.66 (m, 2H), 7.34 (s, 1H), 7.21 (s, 1H), 5.10 (s, 2H); LCMS (ESI): m/z 408.0 (M+H).

Example 141

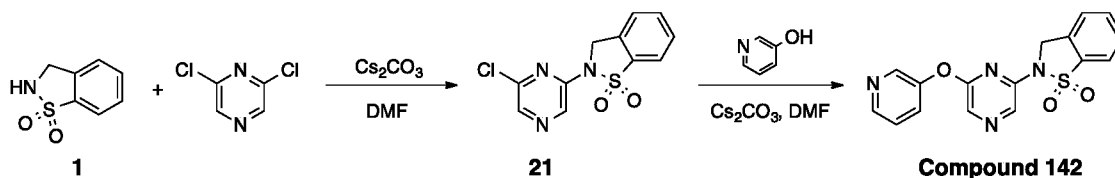
Synthesis of Compound 141



Compound 141 was synthesized in a manner similar to **Compound 140**. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.05 (d, 1H), 7.88-7.82 (m, 1H), 7.77-7.68 (m, 2H), 6.99 (d, 2H), 5.22 (br. s., 2H), 5.14 (br. s., 1H), 2.80 (d, 4H); LCMS (ESI): m/z 421.0 (M+H).

Example 142

Synthesis of Compound 142



Step 1.

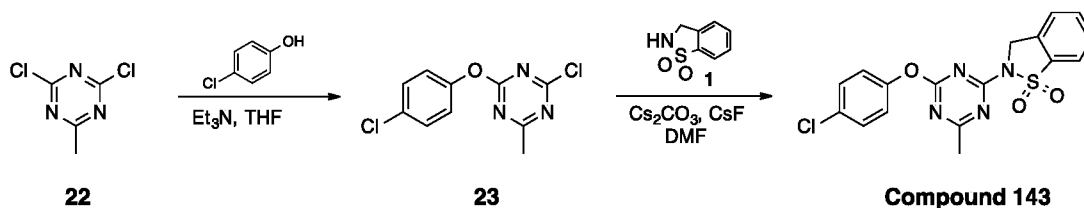
To a mixture of 2,6-dichloropyrazine (193 mg, 1.30 mmol) and **1** (200 mg, 1.18 mmol) in DMF (5 mL), was added Cs₂CO₃ (770 mg, 2.36 mmol). The resulting mixture was stirred at 100°C for 5 hours. The mixture was cooled to 25°C and poured into ice water. The aqueous phase was extracted with ethyl acetate (20 mL). The combined organic phase was washed with saturated brine (20 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by TLC (petroleum ether/ethyl acetate = 2:1) to afford **21** (220 mg, 60%) as yellow solid.

Step. 2

To a mixture of **21** (220 mg, 0.78 mmol) and pyridine-3-ol (74 mg, 0.78 mmol) in DMF (3 mL), was added Cs₂CO₃ (509 mg, 1.56 mmol) in one portion. The mixture was stirred at 50°C for 1 hour, cooled to 25°C, and then poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (20 mL). The combined organic phase was washed with saturated brine (20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford **Compound 142** (22 mg, 13%) as yellow solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.95 (s, 1H); 8.71-8.70 (d, 1H), 8.40-8.37 (d, 2H), 8.32-8.30 (d, 1H), 8.01-8.00 (d, 1H), 7.89-7.82 (m, 2H), 7.72-7.70 (m, 2H), 5.25-5.15 (m, 2 H); LCMS (ESI⁺): m/z 341 (M+1).

Example 143

Synthesis of Compound 143



Step 1.

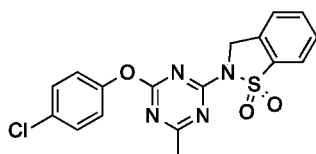
To a solution of compound **22** (100 mg, 0.61 mmol) and Et₃N (123 mg, 1.22 mmol) in anhydrous THF (15 mL) at 0°C was added 4-chlorophenol (78 mg, 0.61 mmol). The mixture was stirred at 15°C for 1 h and then concentrated to give **23** (180 mg) as a light yellow solid.

Step 2.

A mixture of **23** (180 mg, 0.70 mmol), **1** (60 mg, 0.35 mmol), CsF (107 mg, 0.70 mmol), Cs₂CO₃ (458 mg, 1.41 mmol) in DMF (3 mL) was degassed and purged with N₂ (3X). The mixture was stirred at 80°C for 1 h, filtered, and then purified by prep-HPLC to give **Compound 143** (15 mg, 5%) as a light yellow solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 7.97 (d, 1H), 7.81 (s, 1H), 7.72 (d, 1H), 7.43 (s, 1H), 7.31 (s, 2H), 7.18 (s, 2H), 5.09 (s, 2H), 2.33 (s, 3H); LCMS (ESI): m/z 356.0 (M+H).

Example 144

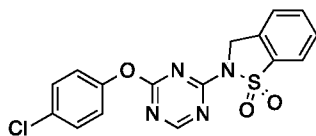
Synthesis of Compound 144



Compound 144 was synthesized in a manner similar to **Compound 143**. **¹H NMR** (DMSO-*d*₆, 400MHz) δ 8.02 (d, 1H), 7.86-7.81 (m, 1H), 7.75 (d, 1H), 7.72-7.65 (m, 1H), 7.53 (d, 2H), 7.38 (d, 2H), 5.15 (br. s., 2H), 2.45 (s, 3H); LCMS (ESI): m/z 389.0 (M+H).

Example 145

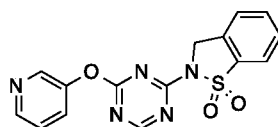
Synthesis of Compound 145



Compound 145 was synthesized in a manner similar to **Compound 143**. **¹H NMR** (DMSO-*d*₆, 400MHz) δ 8.86 (s, 1 H), 8.04 (d, 1 H), 7.88-7.81 (m, 1 H), 7.79-7.67 (m, 2 H), 7.54 (d, 2 H), 7.40 (d, 2 H), 5.17 (br. s., 2 H); LCMS (ESI): m/z 375.0 (M+H).

Example 146

Synthesis of Compound 146



Compound 146 was synthesized in a manner similar to **Compound 143**. **¹H NMR** (DMSO-*d*₆, 400MHz) δ 8.91 (s, 1 H), 8.80 (d, 1 H), 8.65 (d, 1 H), 8.10 (d, 1 H), 8.04 (d, 1 H), 7.88-7.82 (m, 1 H), 7.77-7.68 (m, 3 H), 5.18 (s, 2 H); LCMS (ESI): m/z 342.0 (M+H).

BIOLOGICAL EXAMPLES

Example 147

GPR120 β-Arrestin Recruitment Assay

This in vitro assay tests compounds' ability to activate intracellular signaling via β-Arrestin recruitment to heterologously expressed human GPR120. This functional cellular assay utilizes enzyme fragment complementation with β-galactosidase (β-gal) as a functional reporter (DiscoverX PathHunter® β-Arrestin assay platform). The human GPR120 receptor (GenBank accession Number NM_181745) was fused in frame with the small enzyme fragment ProLink™ and co-expressed in CHO-K1 cells with a fusion protein of β-Arrestin 2 and the larger, N-terminal deletion mutant of β-gal. Activation by a GPR120 agonist stimulates binding of β-arrestin to the ProLink-tagged GPCR and forces complementation of the two enzyme fragments, resulting in the formation of an active β-gal enzyme. This

interaction leads to an increase in enzyme activity that can be measured using chemiluminescent PathHunter® Detection Reagents.

One day prior to the assay, cells were seeded in a total volume of 20µl of growth medium into white walled 384-well microplates and incubated at 37°C / 5% CO₂ overnight. On the day of the assay, growth medium was removed and 20µl assay buffer (HBSS + 10mM HEPES + 0.1% heat-inactivated BSA) were added to each well.

Test compounds were dissolved in 100% DMSO to a concentration of 10 mM to provide stock solutions. Serial dilutions were performed from stock solutions into assay buffer to obtain intermediate concentrations of 5-fold higher than the concentrations to be tested. 5µl of the 5x compound solutions were added to the cells and the assay plates were incubated at 37°C for 90 minutes. The final concentration of compounds tested in the assay ranged from 1.5nM to 100µM. Following incubation, 12.5µl of PathHunter® detection reagent were added to each well, and plates were incubated at room temperature for 60 minutes. Chemiluminescence was read using an EnVision plate reader (PerkinElmer), raw data were expressed as relative light units (RLU).

To determine agonist potencies (EC₅₀ values), non-linear least-squares curve fits of the raw data (RLU) were performed in the GraphPad Prism software package, using the 4-parameter model with variable Hill Slope:

$$Y = Bottom + \frac{Top - Bottom}{1 + 10^{((\log EC_{50} - x) * Hill Slope)}}$$

Reported below in **Table 1** are pEC₅₀ values (pEC₅₀ = -log(EC₅₀) from curve fit) for compounds of Formula I in this assay, β-Arr pEC₅₀. Alternatively, percent activation at a single concentration is reported.

Example 148

Human GPR120 Calcium-Release Assay

This in vitro assay tests compounds' ability to activate heterologously expressed human GPR120 via G-protein coupling leading to generation of inositol 1,4,5-triphosphate and mobilization of intracellular calcium. This functional cellular assay is based on the luminescence of mitochondrial aequorin following intracellular Ca²⁺ release. Aequorin is a photoprotein isolated from the jellyfish *Aequorea victoria*. The active protein is formed in the

presence of molecular oxygen from apoaeguorin and its cofactor coelenterazine. Binding of Ca^{2+} to the active protein induces a conformational change, resulting in oxidation of coelenterazine and subsequent blue luminescence.

The short variant of the human GPR120 receptor (GenBank accession Number AAI01176) was stably expressed in a CHO-K1 cell line coexpressing Gα16 and mitochondrial apoaeguorin.

Cells were grown to mid-log phase in culture media without antibiotics, were detached with PBS/EDTA, centrifuged and resuspended in assay buffer (DMEM-F12 medium with 15mM HEPES pH 7.0 and 0.1% protease free BSA) at a concentration of 10^6 cells/mL. Cells were incubated at room temperature for at least 4 hours with 5μM coelenterazine h.

Test compounds were dissolved in 100% DMSO to a concentration of 20 mM to provide stock solutions. Serial dilutions were performed from stock solutions in 100% DMSO to obtain intermediate concentrations 200-fold higher than the concentrations to be tested. Each sample was diluted 100-fold into assay buffer. 50μl of these compound solutions were dispensed into each well of 96-well assay plates. The final concentration of compounds tested in the assay ranged from 5nM to 100μM. α-Linolenic acid was used as a reference compound. Each test was performed in duplicate.

To start the assay, 50μl of cell suspension were added to each well of the assay plate. The resulting luminescence was recorded using a Hamamatsu Functional Drug Screening System 6000 (FDSS 6000), and raw data were expressed as relative light units (RLU).

To determine agonist potencies (EC_{50} values), non-linear least-squares curve fits of the raw data (RLU) were performed in the GraphPad Prism software package, using the 4-parameter model with variable Hill Slope:

$$Y = \text{Bottom} + \frac{\text{Top} - \text{Bottom}}{1 + 10^{((\log \text{EC}_{50} - x) * \text{Hill Slope})}}$$

Reported below in **Table 1** are pEC_{50} values ($\text{pEC}_{50} = -\log(\text{EC}_{50})$ from curve fit) for representative compounds of Formula I in this assay, Ca^{2+} pEC_{50} .

Table 1. Activity of compounds of Formula I in in vitro assays.**Table 1**

Compound #	β -Arr pEC50	Ca2+ pEC50
1	5.1	5.1
2	18% @ 10uM	
3	< 4.5	
4	< 4.5	
5	< 5.0	
6	< 5.0	
7	4.9	
8	4.9	
9	< 4.5	
10	< 4.5	
11	< 5.0	
12	< 4.5	
13	9% @ 10uM	
14	8% @ 10uM	
15	3% @ 10uM	
16	5.2	5.9
17	4% @ 10uM	
18	<5	
19	5.3	6.1
20	5.2	5.4
21	<5.1	6.3
22	5.8	< 4.0
23	5.5	
24	1% @ 10uM	
25	16% @ 10uM	
26	4.9	
27	9% @ 10uM	
28	4.9	
29	4.8	
30	17% @ 10uM	
31	11% @ 10uM	
32	4.6	
33	5.1	<4
34	5.8	6.7
35	5.8	< 4.0
36	6.2	5.1
37	6	6.7
38	4.8	
39	< 5.0	
40	< 5.0	

41	5.6	6.1
42	6	6.5
43	< 4.5	
44	< 5.0	5.8
45	5.8	< 4.0
46	5.3	
47	5.2	
48	< 5.0	
49	5.6	
50	5.3	5.2
51	5	6
52	4.9	
53	< 5.0	
54	< 5.0	
55	< 5.0	
56	< 5.0	6.1
57	6	
58	5.6	6.2
59	5.2	4.9
60	5.8	6.3
61	< 4.5	< 4.0
62	< 5.0	
63	6.3	< 4.0
64	< 5.0	
65	< 5.0	
66	< 5.0	
67	< 5.0	5.2
68	5.6	
69	5.4	
70	4.8	
71	1% @ 10uM	
72	< 5.0	< 4.0
73	< 5.0	
74	< 4.5	
75	< 4.5	
76	< 4.5	
77	5.6	6
78	5.8	5.4
79	5.8	6.3
80	6.3	5.6
81	5.2	
82	5.6	5.9
83	5.6	6.1
84	< 5.0	

85	< 4.5	
86	6.6	6.4
87	6.1	5.8
88	< 5.0	
89	5.6	4.7
90	4.9	
91	5.4	
92	5.5	
93	5.1	6.2
94	< 5.0	
95	6.4	
96	6	< 5.0
97	6.2	6
98	6.1	5.6
99	6.3	6.8
100	6.8	
101	6.4	< 7.0
102	6.1	
103	5.7	
104	5.4	
105	5.6	
106	6	6.7
107	6.1	
108	< 4.5	
109	< 4.5	
110	< 4.5	
111	< 5.0	
112	< 4.5	
113	4.9	
114	4.9	4.8
115	5.2	
116	4.4	
117	<5	
118	6	
119	4.5	
120	< 4.5	
121	5.8	6.7
122	<5	6.3
123	< 4.5	< 4.0
124	< 4.5	
125	< 4.5	< 5.0
126	< 4.5	
127	< 4.5	
128	7.4	7.1

129	< 4.5	
130	< 4.5	
131	6.8	6.5
132	< 4.5	
133	< 4.5	
134	5	
135	< 5.0	
136	6.2	
137	5.6	
138	5.5	
139	< 5.0	
140	6	
141	5.2	
142	4.4	5.9
143	< 4.5	
144	5.7	
145	5.1	
146	4.8	

The results above show that the compounds of the invention, as illustrated in the examples above and generally as defined by Formula 1, are potent GRP120 agonists that will find application in the treatment of T2D. While, as disclosed in the detailed description above, these compounds can be administered via any route of administration and at various frequencies, in one preferred embodiment, they are administered once a day to T2D patients for treatment and control of that condition in the form of a tablet or capsule, taken orally.

Example 149

GRP120 C57BL/6J Mouse Oral Glucose Tolerance Test

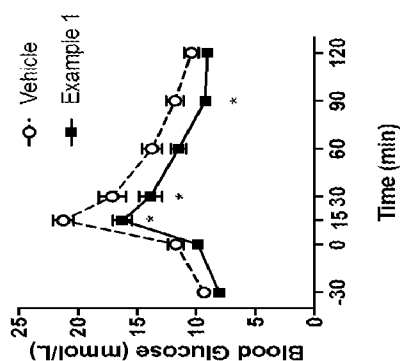
An oral glucose tolerance test (OGTT) was performed with certain compounds to determine their acute effect on glucose excursions.

Male C57BL/6J mice aged 8-10 weeks and kept on a regular chow diet were used for the study. 10 Mice were used per treatment group, with individual mice weighing in the range of 24-30 grams on study day, and a mean weight of 27.2 – 27.3 grams for each treatment group.

Test articles were prepared as suspensions in dosing vehicle (0.5% hydroxypropyl methylcellulose and 2% Tween-20 in water) at a concentration of 10 mg/mL by mixing and sonication.

The mice were fasted for 6 hours prior to dosing of vehicle or test articles at 100 mg/kg (10 mL/kg) by oral gavage. Glucose was dosed (PO) at 3g/kg 30 min after dosing of test articles. Animals were bled via tail snip to determine basal glucose levels 30 min prior to the glucose challenge, and again at 0, 15, 30, 60, 90 and 120 minutes following the glucose challenge. A Johnson & Johnson OneTouch Glucometer was used to determine glucose levels in all blood samples.

Glucose values were entered into an Excel sheet, and mean values \pm standard error of the mean were graphed in GraphPad Prism. Significance of difference between groups was analyzed by performing two-way RM ANOVA for the time course study. P values less than 0.05 were considered statistically significant.



Example 150

Anti-Inflammatory Activity In LPS-Stimulated Human Peripheral Blood Mononuclear Cells

The ability of compounds of this invention to inhibit TNF α production was assessed by using human peripheral blood mononuclear cells (hPBMC) which synthesize and secrete TNF α when stimulated with lipopolysaccharide (LPS).

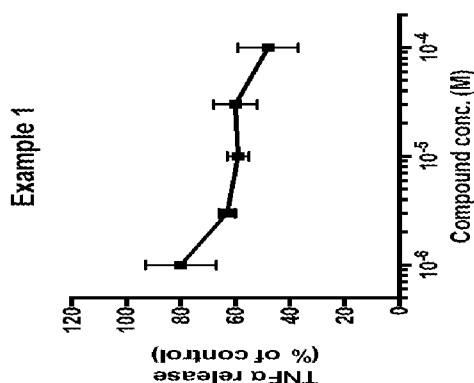
Mononuclear Cell packs collected by and purchased from Key Biologics were used for the preparation of hPBMC. Briefly, cell product was sterilely removed from the phoresis bag, carefully layered onto pre-warmed Ficoll (Histopaque 1077) and centrifuged at 1,800 \times g for 15 minutes at room temperature with the brake off. Following centrifugation, the interface was removed and added to sterile Dulbecco's Phosphate Buffered Saline (DPBS).

The cells were then pelleted at 300 x g for ten minutes at room temperature. The cells were resuspended in fresh DPBS then repelleted to minimize platelet contamination. The subsequent pellet was resuspended in DPBS and the cells counted. Cells were repelleted and then cryopreserved at 1×10^8 cells per ml in DMEM / 30% FBS / 10% DMSO. For all hPBMC preparations, individual donors were kept separate throughout the entire process. For the assay, hPBMC were seeded into flat-bottom 96-well plates at 500,000 cells/well in 80 μ l assay medium (DMEM, 0.1% FBS, 1% penicillin / streptomycin) and allowed to recover in a 37°C incubator for one hour before the addition of compounds.

Compounds were solubilized from powder as 20mM stocks with 100% DMSO and then serially diluted into assay medium to prepare 10x stocks to achieve five concentrations (100 μ M, 30 μ M, 10 μ M, 3 μ M and 1 μ M) in the assay. All compound dilutions were added to the plates containing hPBMC (10 μ l in final assay volume of 100 μ l) and incubated at 37°C for an hour before the addition of stimulus. Control wells received 10 μ l vehicle (media containing 5% DMSO).

For the LPS challenge, a 1mg/ml stock solution of lipopolysaccharide (LPS) was diluted 1000-fold into assay medium (10 μ l LPS + 10ml media). All wells except the "Unstimulated" control wells received 10 μ l of LPS. The "Unstimulated" control wells received 10 μ l media. The plates were incubated for 4 hours at 37°C. After 4 hours, the plates were centrifuged at 1,200 rpm for 5 minutes and culture media supernatants were collected into fresh 96-well plates.

TNF α levels in culture supernatants were determined by immunoassay using the Meso Scale Diagnostics electrochemiluminescent immunoassay system. Meso Scale V-plex 96-well plates (Meso Scale Diagnostics, Rockville, MD) were used for detection of TNF α as directed by the manufacturer (overnight incubation protocol). Samples were diluted 100-fold. TNF α concentrations were determined by interpolating against a standard curve and then multiplying by 100 to arrive at "pg/ml" values. TNF α release was reported as % of vehicle treated LPS stimulated cells.



While certain embodiments have been illustrated and described, it will be understood that changes and modifications can be made therein in accordance with ordinary skill in the art without departing from the present invention in its broader aspects as defined in the following claims.

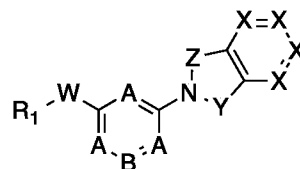
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CLAIMS

1. A compound of formula:



Formula I

or a tautomer thereof, or an isotopomer thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of each thereof, or a prodrug thereof, or a pharmaceutically acceptable solvate of each of the foregoing, wherein

each A independently is N or CH;

B is N or CR₂ wherein R₂ is H, halogen, CN, OCH₃, OCF₃, -NH-acyl, an optionally substituted alkyl group, an optionally substituted carboxamido or a sulfonamido group, an optionally substituted cycloalkyl or heterocyclyl group, or an optionally substituted aryl or heteroaryl group;

with the provision that at least one of A or B is N;

W is a covalent bond or O;

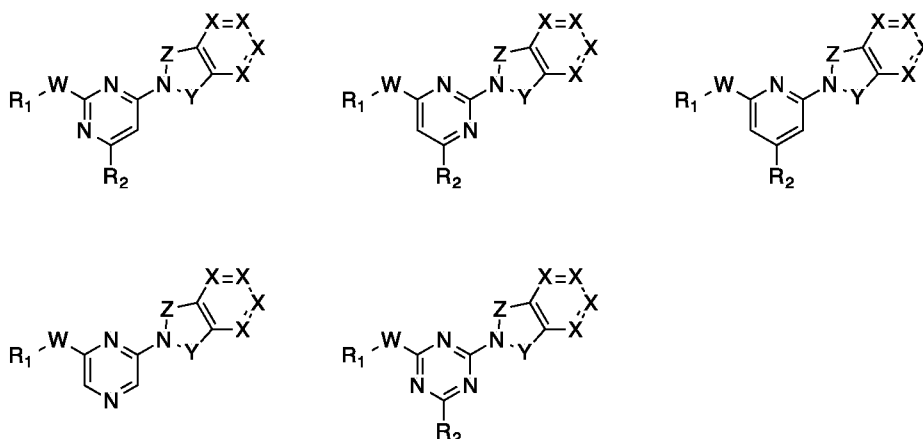
each X independently is CH, CR₃ or N wherein R₃ is halogen, alkyl, alkoxy, or CN;

Y is SO₂, CO, CH₂, -C(CH₃)₂-, or -CH(CH₃)-;

Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -C(CH₂CH₂)-, CO, -(CO)CH₂-, -CH₂CH₂-, or -CHCH-;

R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, or an optionally substituted aryl or heteroaryl group.

2. The compound of claim 1 of formula selected from:



wherein

W is a covalent bond or O;

each X independently is CH, CR₃ or N wherein R₃ is halogen, alkyl, alkoxy, or CN;

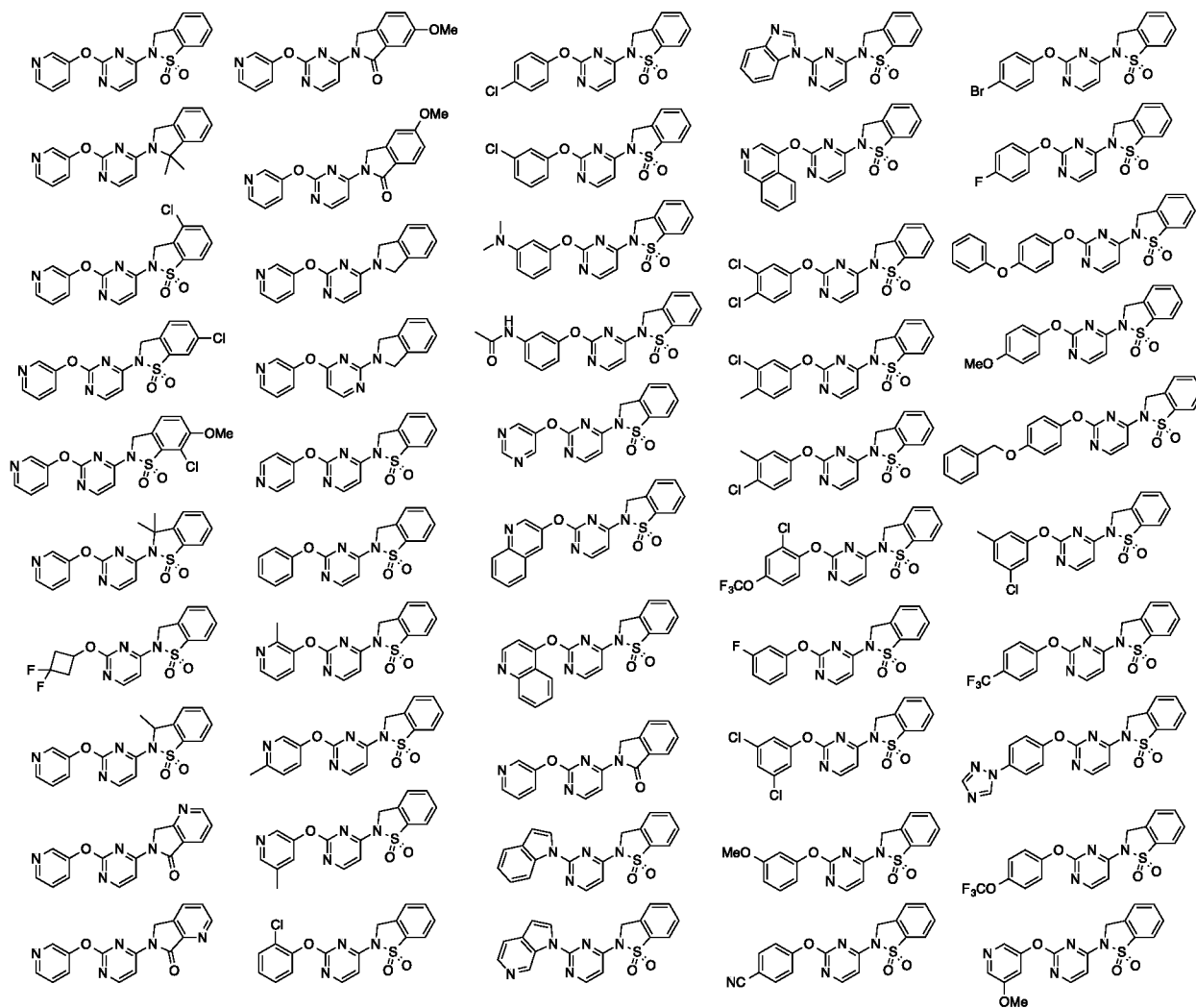
Y is SO₂, CO, CH₂, -C(CH₃)₂-, or -CH(CH₃)-;

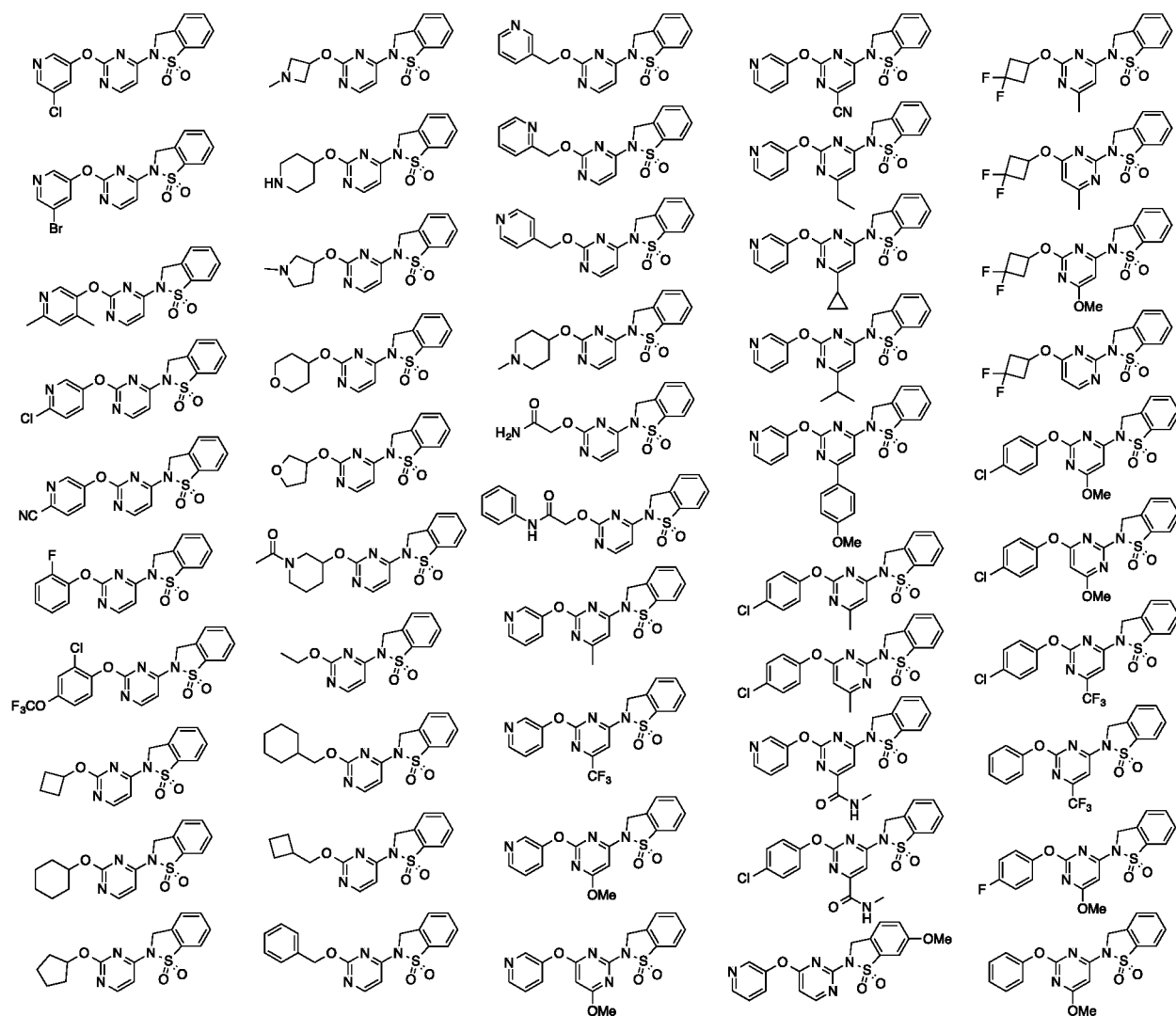
Z is -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -C(CH₂CH₂)-, CO, -(CO)CH₂-, -CH₂CH₂-, or -CHCH-;

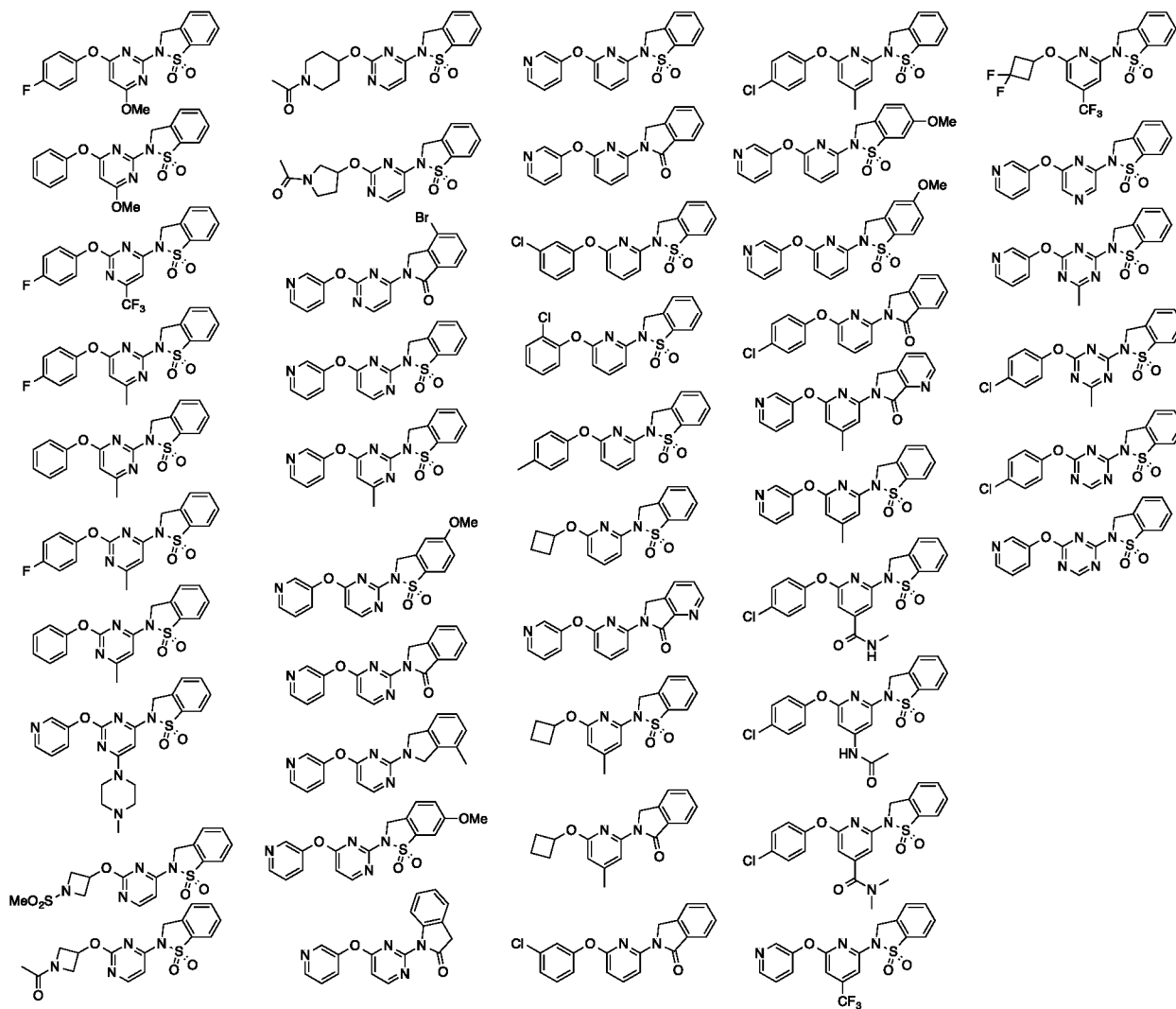
R₁ is an optionally substituted alkyl group, an optionally substituted 3-7 membered cycloalkyl or heterocyclyl group, or an optionally substituted aryl or heteroaryl group; and

R₂ is H, halogen, CN, OCH₃, OCF₃, NH-acyl, an optionally substituted alkyl group, an optionally substituted carboxamide or sulfonamido group, an optionally substituted cycloalkyl, or heterocyclyl group, an optionally substituted aryl or heteroaryl group.

3. A compound of the structure







or a tautomer thereof, or an isotopomer thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of each thereof, or a prodrug thereof, or a pharmaceutically acceptable solvate of each of the foregoing.

4. A pharmaceutical composition comprising a compound of any one of claims 1-3 and a pharmaceutically acceptable excipient.
5. A method for agonizing GPR120, comprising contacting the GPR120 with a compound of any one of claims 1-3 or the composition of claim 4.
6. A method for modulating metabolism in a mammal, comprising contacting GPR120 in the mammal with an amount of the compound of any one of the claims 1-3 effective to modulate metabolism in the mammal.

7. A method for modulating metabolism in a mammal, comprising administering to the mammal an amount of the composition of claim 4 effective to modulate metabolism in the mammal.
8. A method for reducing inflammation in a mammal, comprising contacting GPR120 in the mammal with an amount of the compound of any one of the claims 1-3 effective to reduce the inflammation.
9. A method for reducing inflammation in a mammal, comprising administering to the mammal an amount of the composition of claim 4 effective to reduce the inflammation.
10. A method for reducing neuroinflammation in a mammal, comprising contacting GPR120 in the mammal with an amount of the compound of any one of the claims 1-3 effective to reduce the neuroinflammation.
11. A method for reducing neuroinflammation in a mammal, comprising administering to the mammal an amount of the composition of claim 4 effective to reduce neuroinflammation.
12. A method for treating diabetes, pre-diabetes or metabolic syndrome, or one or more symptoms of each thereof in a mammal, comprising contacting GPR120 in the mammal with a therapeutically effective amount of the compound of any one of the claims 1-3.
13. A method for treating diabetes, pre-diabetes or metabolic syndrome, or one or more symptoms of each thereof in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition of claim 4.
14. A method for treating steatohepatitis in a mammal, comprising contacting GPR120 in the mammal with a therapeutically effective amount of the compound of any one of the claims 1-3.
15. A method for treating steatohepatitis in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition of claim 4.
16. A method for treating non-alcoholic steatohepatitis in a mammal, comprising contacting GPR120 in the mammal with a therapeutically effective amount of the compound of any one of the claims 1-3.
17. A method for treating non-alcoholic steatohepatitis in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition of claim 4.

18. A method for treating a disorder associated with, leading to, or resulting from neuroinflammation in a mammal, comprising contacting GPR120 in the mammal with a therapeutically effective amount of the compound of any one of the claims 1-3.
19. A method for treating a disorder associated with, leading to, or resulting from neuroinflammation in a mammal, comprising administering to the mammal a therapeutically effective amount of the composition of claim 4.
20. A method for treating Alzheimer's disease, Parkinson's disease, frontotemporal dementia, amyotrophic lateral sclerosis or multi-system atrophy, or one or more symptoms of each thereof, comprising contacting GPR120 in the patient with a therapeutically effective amount of the compound of any one of the claims 1-3.
21. A method for treating Alzheimer's disease, Parkinson's disease, frontotemporal dementia, amyotrophic lateral sclerosis or multi-system atrophy, or one or more symptoms of each thereof, comprising administering to the patient a therapeutically effective amount of the composition of claim 4.