Title: BENZIMIDAZOLE DERIVATIVES AS ANTVIRAL AGENTS

Abstract: Provided are compounds of Formulas I, II, III, IV, V, and pharmacologically acceptable salts thereof, their pharmaceutical compositions, their methods of preparation, and their use for treating viral infections mediated by a member of the Flaviviridae family of viruses such as hepatitis C virus (HCV).
BENZIMIDAZOLE DERIVATIVES AS ANTIVIRAL AGENTS

CROSS REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

This application is a Patent Cooperation Treaty application and claims the priority benefit of U.S. Provisional Patent Application No. 61/497,113, filed June 15, 2011, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

Provided are compounds, pharmaceutical compositions, their methods of preparation, and their use for treating viral infections mediated by a member of the Flaviviridae family of viruses such as hepatitis C virus (HCV).

BACKGROUND OF THE INVENTION

Chronic infection with HCV is a major health problem associated with chronic liver disease, cirrhosis, hepatocellular carcinoma, and liver failure. HCV is a hepacivirus member of the Flaviviridae family of RNA viruses that affect animals and humans. The genome is a single ~9.6-kilobase strand of RNA, and consists of one open reading frame that encodes for a polyprotein of ~3000 amino acids flanked by untranslated regions at both 5' and 3' ends (5'- and 3'-UTR). The polyprotein serves as the precursor to at least 10 separate viral proteins critical for replication and assembly of progeny viral particles. The organization of structural and non-structural proteins in the HCV polyprotein is as follows: C-E1-E2-p7-NS2-NS3-NS4a-NS4b-NS5a-NS5b. Because the replicative cycle of HCV does not involve any DNA intermediate and the virus is not integrated into the host genome, HCV infection can theoretically be cured. While the pathology of HCV infection affects mainly the liver, the virus is found in other cell types in the body including peripheral blood lymphocytes.

HCV is major causative agent for post-transfusion and for sporadic hepatitis. Infection by HCV is insidious in a high proportion of chronically infected (and infectious) carriers who may not experience clinical symptoms for many years. An estimated 170 million chronic carriers worldwide are at risk of developing liver disease. See, for example, Szabo, et al., Pathol. Oncol. Res. 2003, 9:215-221, and Hoofnagle JH, Hepatology 1997, 26:15S-20S. In the United States alone 2.7 million are chronically infected with HCV, and the number of HCV-related deaths in 2000 was estimated between 8,000 and 10,000, a number that is expected to increase significantly over the next years.
At present, the standard treatment for chronic HCV is interferon alpha (IFN-alpha) in combination with ribavirin and this requires at least six months of treatment. IFN-alpha belongs to a family of naturally occurring small proteins with characteristic biological effects such as antiviral, immunoregulatory, and antitumoral activities that are produced and secreted by most animal nucleated cells in response to several diseases, in particular viral infections. IFN-alpha is an important regulator of growth and differentiation affecting cellular communication and immunological control. Treatment of HCV with interferon has frequently been associated with adverse side effects such as fatigue, fever, chills, headache, myalgias, arthralgias, mild alopecia, psychiatric effects and associated disorders, autoimmune phenomena and associated disorders and thyroid dysfunction. Ribavirin, an inhibitor of inosine 5’-monophosphate dehydrogenase (IMPDH), enhances the efficacy of IFN-alpha in the treatment of HCV. Despite the introduction of ribavirin, more than 50% of the patients do not eliminate the virus with the current standard therapy of interferon-alpha (IFN) and ribavirin. By now, standard therapy of chronic hepatitis C has been changed to the combination of pegylated IFN-alpha plus ribavirin. However, a number of patients still have significant side effects, primarily related to ribavirin. Ribavirin causes significant hemolysis in 10-20% of patients treated at currently recommended doses, and the drug is both teratogenic and embryotoxic. Even with recent improvements, a substantial fraction of patients do not respond with a sustained reduction in viral load and there is a clear need for more effective antiviral therapy of HCV infection.

A number of approaches are being pursued to combat the virus. These include, for example, application of antisense oligonucleotides or ribozymes for inhibiting HCV replication. Furthermore, low-molecular weight compounds that directly inhibit HCV proteins and interfere with viral replication are considered as attractive strategies to control HCV infection. Among the viral targets, the NS3/4a protease/helicase and the NS5b RNA-dependent RNA polymerase are considered the most promising viral targets for new drugs. Indeed, compounds said to be useful for treating HCV infections are disclosed, for example, in WO2005/051318 (Chunduru, et al.) and WO2009/023179 (Schmitz, et al.). These references disclose methods for preparing the compounds, compositions comprising the compounds, compositions comprising the compounds and additional compounds, and methods of treating HCV.

Besides targeting viral genes and their transcription and translation products, antiviral activity can also be achieved by targeting host cell proteins that are necessary for viral
replication. For example, antiviral activity can be achieved by inhibiting host cell cyclophilins. Alternatively, a potent TLR7 agonist has been shown to reduce HCV plasma levels in humans.

[0008] In view of the worldwide epidemic level of HCV and other members of the Flaviviridae family of viruses, and further in view of the limited treatment options, there is a strong need for new effective drugs for treating infections cause by these viruses.

SUMMARY OF THE INVENTION

[0009] In accordance with one embodiment of the present invention, there is provided a compound of any of Formulas I, II, III, IV, and V described herein or a pharmaceutically acceptable salt thereof.

[0010] In yet other embodiments of the present invention, there is provided a compound of Formula (I):

![Chemical Structure]

or a pharmaceutically acceptable salt thereof, wherein:

- Z is selected from the group consisting of a bond and a (branched or straight chain) (C₁-C₉)alkylene;
- X is selected from the group consisting of hydrogen, (CrC₆)alkoxy, nitrile, -C(0)R₁₀, -C(0)R₁₄, -S₀₂R₆, -S₀₂R₁₂, -S₀₂R₁₄(R₆)ₙ, -NHSO₂R₁₀(R₆)ₙ, -NHSO₂R₁₄(R₆)ₙ, and -NHSO₂R₁₄(R₆)ₙ;
- R¹ is selected from the group consisting of hydrogen, -R₅R₁₄, -C(0)R₉, -R₅R₁₀, -C(0)R₁₀, and -C(0)R₁₄;

- R² is selected from the group consisting of hydrogen, Q, halo, (C₁-C₉)alkyl, (C₁-C₉)alkoxy, nitrile, oxo, hydroxyl, -NHR₅R₁₄, -OR₇, -R₄R₁₄(R₆)ₙ, -R₁₀R₅R₁₄, -R₁₂, -R₁₄, -R₁₄R₆, -R₁₄(R₆)ₙ, -S₀₂R₁₀, -S₀₂R₁₂, -S₀₂R₁₄, -S₀₂R₁₄, -R₁₃R₁₄, -R₄R₁₀,
R^10R^{14},-(R^{14}R^{12}), -R^{13}R^6, -R^{14}R^6, -C_0R^7, (C_3^2-Ci_2)cycloalkyl, and (C_4-C_1)aryl,
wherein A and Q are independently chosen from -(CH_2)_wR^10 or -(CH_2)_wR^{14};
R^1 and R^2 taken together with any intervening atoms and when Z is a bond, can
optionally form a fused (C_2-C_6)heterocyclic ring having 1-3 heteroatoms selected
from S, N and O; wherein said fused heterocyclic ring can also be optionally
substituted with one to two R^6 groups;
R^3 is selected from the group consisting of hydrogen, nitrile, halo, and (Ci-C_6)alkyl;
R^4 is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-Ce)alkoxy, nitrile,
oxo, -C(0)R^{12}, -S0_2R^9, -R^9(R^{15})_m, -OR^7, -R^{12}, and halo;
R^5 is a branched or straight chain (d-Ce)alkylene;
R^6 is independently selected from the group consisting of (Cr C_6)alkyl, oxo, (C_1-
C_6)alkoxy, -OR^7, halo, nitrile, and -C0_2R^7;
R^7 is selected from the group consisting of hydrogen and (Ci-C_6)alkyl;
R^8 is independently selected from the group consisting of hydrogen, (Ci-C_7)alkyl, -R^5,
-R^{13}, -R^{14}, -R^6R^{13}, -R^5R^{10}, -R^{10}(R^{11})_m, -R^9R^{14}, and -R^6R^{10}(R^{11})_m;
R^9 is (Ci-C_7)alkyl;
R^10 is (C_4-C_14)aryl;
R^11 is selected from the group consisting of nitrile, halo, (Ci-C_6)alkyl, (Cr C_6)alkoxy, and
-R^{14}R^{12};
R^{12} is -N(R^8)_2, wherein each instance of R^8 may be independently and separately
chosen from among the possible R^8 substituents;
R^{13} is (C_3-C_12)cycloalkyl;
R^{14} is selected from (Ci-Cnjheterocycle or (CVCiOheteroaryl, each having one to three
heteroatoms selected from S, N and O;
R^{15} is halo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

[0011] Also provided is a pharmaceutical composition comprising a pharmaceutically
acceptable carrier and a therapeutically effective amount of a compound of any of Formulas I, II,
III, IV, V, or a pharmaceutically acceptable salt or solvate thereof.

[0012] Also provided are synthetic intermediates, methods for preparing the compounds
of any of Formulas I, II, III, IV, and V or a pharmaceutically acceptable salt or solvate thereof,
and compositions thereof and for their therapeutic uses. In some embodiments, provided is a
method for treating a viral infection in a patient mediated at least in part by a virus in the
*Flaviviridae* family of viruses, comprising administering to said patient a composition comprising
a compound of any of Formulas I, II, III, IV, V, or a pharmaceutically acceptable salt or solvate
thereof. In some embodiments, the viral infection is mediated by hepatitis C virus. Those and
other embodiments are further described in the text that follows.

**DETAILED DESCRIPTION OF REPRESENTATIVE EMBODIMENTS**

[001 3] Throughout this application, references are made to various embodiments
relating to compounds, compositions, and methods. The various embodiments described are
meant to provide a variety of illustrative examples and should not be construed as descriptions
of alternative species. Rather it should be noted that the descriptions of various embodiments
provided herein may be of overlapping scope. The embodiments discussed herein are merely
illustrative and are not meant to limit the scope of the present invention.

[001 4] It is to be understood that the terminology used herein is for the purpose of
describing particular embodiments only and is not intended to limit the scope of the present
invention. In this specification and in the claims that follow, reference will be made to a number
of terms that shall be defined to have the following meanings.

[001 5] "Alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1
to 14 carbon atoms and, in some embodiments, from 1 to 6 carbon atoms. "(C<sub>x</sub>–C<sub>y</sub>)alkyl" refers
to alkyl groups having from x to y carbon atoms. This term includes, by way of example, linear
and branched hydrocarbyl groups such as methyl (CH<sub>3</sub>), ethyl (CH<sub>3</sub>CH<sub>2</sub>), n-propyl
(CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>), isopropyl ((CH<sub>3</sub>)<sub>2</sub>CH), n-butyl (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), isobutyl ((CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>),
sec-butyl ((CH<sub>3</sub>)<sub>2</sub>(CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>), tert-butyl ((CH<sub>3</sub>)<sub>3</sub>C), n-pentyl (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), and
neopentyl ((CH<sub>3</sub>)<sub>4</sub>CCH<sub>2</sub>).

[001 6] "Alkylidene" or "alkylene" refers to divalent saturated aliphatic hydrocarbyl groups
having from 1 to 10 carbon atoms and, in some embodiments, from 1 to 6 carbon atoms.
"(C<sub>u</sub>–C<sub>v</sub>)alkylene" refers to alkylene groups having from u to v carbon atoms. The alkylidene and
alkylene groups include branched and straight chain hydrocarbyl groups. For example "(C<sub>6</sub>–C<sub>8</sub>)alkylene" is meant to include methylene, ethylene, propylene, 2-methylpropylene, pentylene,
and so forth.

[001 7] "Alkenyl" refers to a linear or branched hydrocarbyl group having from 2 to 10
carbon atoms and in some embodiments from 2 to 6 carbon atoms or 2 to 4 carbon atoms and
having at least 1 site of vinyl unsaturation (>C=C<). For example, (C<sub>x</sub>–C<sub>y</sub>)alkenyl refers to
alkenyl groups having from x to y carbon atoms and is meant to include for example, ethenyl, propenyl, isopropylene, 1,3-butadienyl, and the like.

[0018] "Alkynyl" refers to a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical containing at least one triple bond. The term "alkynyl" is also meant to include those hydrocarbyl groups having one triple bond and one double bond. For example, (C_2-C_6)alkynyl is meant to include ethynyl, propynyl, and the like.

[0019] "Alkoxy" refers to the group -O-alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, f-butoxy, sec-butoxy, and n-pentoxy.

[0020] "Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, alkenyl-C(O)-, alkynyl-C(O)-, cycloalkyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)-, and heterocyclic-C(O)-. Acyl includes the "acetyl" group CH_3C(O)-.

[0021] "Acylamino" refers to the groups -NR^2C(O)alkyl, -NR^2C(O)cycloalkyl, -NR^2C(O)alkenyl, -NR^2C(O)alkynyl, -NR^2C(O)aryl, -NR^2C(O)heteroaryl, and -NR^2C(O)heterocyclic, wherein R^2 is hydrogen or alkyl.

[0022] "Acyloxy" refers to the groups alkyl-C(0)O-, alkenyl-C(0)O-, alkynyl-C(0)O-, aryl-C(0)O-, cycloalkyl-C(0)O-, heteroaryl-C(0)O-, and heterocyclic-C(0)O-.

[0023] "Amino" refers to the group -NR^2R^22 where R^21 and R^22 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclic, -S0^2-alkyl, -S0^2-alkenyl, -S0^2-cycloalkyl, -S0^2-aryl, -S0^2-heteroaryl, and -S0^2-heterocyclic, and wherein R^21 and R^22 are optionally joined together with the nitrogen bound thereto to form a heterocyclic group. When R^21 is hydrogen and R^22 is alkyl, the amino group is sometimes referred to herein as alkylamino. When R^21 and R^22 are alkyl, the amino group is sometimes referred to herein as dialkylamino. When referring to a monosubstituted amino, it is meant that either R^21 or R^22 is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R^21 nor R^22 are hydrogen.

[0024] "Hydroxyamino" refers to the group -NHOH.

[0025] "Alkoxynitrogen" refers to the group -NHO-alkyl wherein alkyl is defined herein.

[0026] "Aminocarbonyl" refers to the group -C(0)NR^2R^27 where R^26 and R^27 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, alkoxy, amino, and acylamino, and where R^26 and R^27 are optionally joined together with the nitrogen bound thereto to form a heterocyclic group.

[0027] "Aryl" refers to an aromatic group of from 6 to 14 carbon atoms and no ring heteroatoms and having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g.,
naphthyl or anthryl). For multiple ring systems, including fused, bridged, and spiro ring systems having aromatic and non-aromatic rings that have no ring heteroatoms, the term "Aryl" or "Ar" applies when the point of attachment is at an aromatic carbon atom (e.g., 5,6,7,8 tetrahydronaphthalene-2-yl is an aryl group as its point of attachment is at the 2-position of the aromatic phenyl ring).

[0028] "Cyano" or "nitrile" refers to the group -CN.
[0029] "Cycloalkyi" refers to a saturated or partially saturated cyclic group of from 3 to 14 carbon atoms and no ring heteroatoms and having a single ring or multiple rings including fused, bridged, and spiro ring systems. For multiple ring systems having aromatic and non-aromatic rings that have no ring heteroatoms, the term "cycloalkyi" applies when the point of attachment is at a non-aromatic carbon atom (e.g., 5,6,7,8-tetrahydronaphthalene-5-yl and 2,3-dihydro-1H-inden-1-yl). The term "cycloalkyi" includes cycloalkenyl groups, such as cyclohexenyl. Examples of cycloalkyi groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclooctyl, cyclopentenyl, and cyclohexenyl. Examples of cycloalkyi groups that include multiple bicycloalkyi ring systems are bicyclohexyl, bicyclooctyl, bicyclooctyl, dihydroindenyl, and the like. Two such bicycloalkyi multiple ring structures are exemplified and named below:

\[
\text{bicyclohexyl, and bicyclohexyl.}
\]

[0030] "(C\textsubscript{u}C\textsubscript{v})cycloalkyi" refers to cycloalkyi groups having u to v carbon atoms.
[0031] "Spiro cycloalkyi" refers to a 3 to 10 member cyclic substituent formed by replacement of two hydrogen atoms at a common carbon atom in a cyclic ring structure or in an alkylene group having 2 to 9 carbon atoms, as exemplified by the following structure wherein the group shown here attached to bonds marked with wavy lines is substituted with a spiro cycloalkyi group:

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\text{Fused cycloalkyi} \text{ refers to a 3 to 10 member cyclic substituent formed by the replacement of two hydrogen atoms at different carbon atoms in a cycloalkyi ring structure, as exemplified by the following structure wherein the cycloalkyi group shown here contains bonds marked with wavy lines which are bonded to carbon atoms that are substituted with a fused cycloalkyi group:}
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"Halo" or "halogen" refers to fluoro, chloro, bromo, and iodo.

"Haloalkoxy" refers to substitution of alkoxy groups with 1 to 5 (e.g. when the alkoxy group has at least 2 carbon atoms) or in some embodiments 1 to 3 halo groups (e.g. trifluoromethoxy).

"Hydroxy" or "hydroxyl" refers to the group -OH.

"Heteroaryl" refers to an aromatic group of from 1 to 14 carbon atoms and 1 to 6 heteroatoms selected from oxygen, nitrogen, and sulfur and includes single ring (e.g. imidazolyl) and multiple ring systems (e.g. benzimidazol-2-yl and benzimidazol-6-yl). For multiple ring systems, including fused, bridged, and spiro ring systems having aromatic and non-aromatic rings, the term "heteroaryl" applies if there is at least one ring heteroatom and the point of attachment is at an atom of an aromatic ring (e.g. 1,2,3,4-tetrahydroquinolin-6-yl and 5,6,7,8-tetrahydroquinolin-3-yl). In some embodiments, the nitrogen and/or the sulfur ring atom(s) of the heteroaryl group are optionally oxidized to provide for the N-oxide (N→O), sulfinyl, or sulfonyl moieties. More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thienyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, imidazolinyl, isoxazolyl, pyrrolyl, pyrazolyl, pyridazinyl, pyrimidinyl, purinyl, phthalazyl, naphthypryidyl, benzofuranyl, tetrahydrobenzofuranyl, isobenzofuranyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, indolizynyl, dihydriodindolyl, indazolyl, indolinyl, benzoxazolyl, quinolyl, isoquinolyl, quinolinyl, quinoxalyl, tetrahydroquinolinyl, isoquinolyl, quinazolinonyl, benzimidazolyl, benzisoxazolyl, benzothienyl, benzoypyridazinyl, pteridinyl, carbazolyl, carbolinyl, phenanthridinyl, acridinyl, phenanthrolinyl, phenazinyl, phenoazinyl, phenothiazinyl, and phthalimidyl.

"Heterocyclic" or "heterocycle" or "heterocycloalkyl" or "heterocycl" refers to a saturated or partially saturated cyclic group having from 1 to 14 carbon atoms and from 1 to 6 heteroatoms selected from nitrogen, sulfur, phosphorus or oxygen and includes single ring and multiple ring systems including fused, bridged, and spiro ring systems. For multiple ring systems having aromatic and/or non-aromatic rings, the terms "heterocyclic", "heterocycle", "heterocycloalkyl", or "heterocycl" apply when there is at least one ring heteroatom and the point of attachment is at an atom of a non-aromatic ring (e.g. 1,2,3,4-tetrahydroquinoline-3-yl, 5,6,7,8-tetrahydroquinoline-6-yl, and decahydroquinolin-6-yl). In one embodiment, the nitrogen, phosphorus and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for
the N-oxide, phosphinane oxide, sulfinyl, sulfonyl moieties. More specifically the heterocycl
includes, but is not limited to, tetrahydropyranyl, piperidinyl, piperazinyl, 3-pyrrolidinyl, 2-
pyrrolidon-1-yl, morpholinyl, and pyrrolidinyl. A prefix indicating the number of carbon atoms
(e.g. C3-C10) refers to the total number of carbon atoms in the portion of the heterocycl group
exclusive of the number of heteroatoms.

[0038] Examples of heterocycle and heteroaryl groups include, but are not limited to,
azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazidine, pyridone, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline,
phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole,
carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole,
phenoxyazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperažine, indoline,
phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole,
thiazolidine, thiophene, benzol[b]thiophene, morpholine, thiomorpholine (also referred to as
thiamorpholine), piperidine, pyrrolidine, pyrrolidone, and tetrahydrofuranyl.

[0039] "Fused heterocyclic" refers to a 3 to 10 member cyclic substituent formed by the
replacement of two hydrogen atoms at different carbon atoms in a cycloalkyi ring structure, as
exemplified by the following structure wherein the cycloalkyi group shown here contains bonds
marked with wavy lines which are bonded to carbon atoms that are substituted with a fused
heterocyclic group:

[0040] "Compound", "compounds", "chemical entity", and "chemical entities" as used
herein refers to a compound encompassed by the generic formulae disclosed herein, any
subgenus of those generic formulae, and any forms of the compounds within the generic and
subgeneric formulae, including the racemates, stereoisomers, and tautomers of the compound
or compounds.

[0041] "Oxazolidinone" refers to a 5-membered heterocyclic ring containing one nitrogen
and one oxygen as heteroatoms and also contains two carbons and is substituted at one of the
two carbons by a carbonyl group as exemplified by any of the following structures, wherein the
oxazolidinone groups shown here are bonded to a parent molecule, which is indicated by a
wavy line in the bond to the parent molecule:
"Pyrrolidione" refers to a 5-membered heterocyclic ring containing one nitrogen as a heteroatom and also contains three carbons and is substituted at one of the three carbons by a carbonyl group as exemplified by any of the following structures, wherein the pyrrolidione group exemplified here is bonded to a parent molecule, which is indicated by a wavy line in the bond to the parent molecule:

"Racemates" refers to a mixture of enantiomers. In an embodiment of the invention, the compounds of Formula I, II, III, IV or V, or pharmaceutically acceptable salts thereof, are enantiomerically enriched with one enantiomer wherein all of the chiral carbons referred to are in one configuration. In general, reference to an enantiomerically enriched compound or salt, is meant to indicate that the specified enantiomer will comprise more than 50% by weight of the total weight of all enantiomers of the compound or salt.

"Solvate" or "solvates" of a compound refer to those compounds, as defined above, which are bound to a stoichiometric or non-stoichiometric amount of a solvent. Solvates of a compound includes solvates of all forms of the compound. In certain embodiments, solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts. Suitable solvates include water.

"Stereoisomer" or "stereoisomers" refer to compounds that differ in the chirality of one or more stereocenters. Stereoisomers include enantiomers and diastereomers.

"Tautomer" refer to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- moiety and a ring =N- moiety such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

"Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, and tetraalkylammonium, and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, and
oxalate. Suitable salts include those described in P. Heinrich Stahl, Camille G. Wermuth (Eds.), Handbook of Pharmaceutical Salts Properties, Selection, and Use; 2002.

[0048] "Patient" refers to mammals and includes humans and non-human mammals.

[0049] "Treating" or "treatment" of a disease in a patient refers to 1) preventing the disease from occurring in a patient that is predisposed or does not yet display symptoms of the disease; 2) inhibiting the disease or arresting its development; or 3) ameliorating or causing regression of the disease.

[0050] Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "arylalkyloxy carbonyl" refers to the group (aryl)-(alkyl)-O-C(0)-. In a term such as "C(R\textsuperscript{X})\textsubscript{2}" it should be understood that the two R\textsuperscript{X} groups can be the same, or they can be different if R\textsuperscript{X} is defined as having more than one possible identity. In addition, certain substituents are drawn as - R\textsuperscript{X}R\textsuperscript{Y}, where the "-" indicates a bond adjacent to the parent molecule and R\textsuperscript{Y} being the terminal portion of the functionality. Similarly, it is understood that the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluoro groups). Such impermissible substitution patterns are well known to the skilled artisan.

[0051] In one embodiment of the present invention, there is provided a compound of Formula (I):

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, wherein:

- Z is selected from the group consisting of a bond and a (branched or straight chain) (C\textsubscript{1}-C\textsubscript{6})alkylene;
- X is selected from the group consisting of hydrogen, (C\textsubscript{1}-C\textsubscript{6})alkoxy, nitrile, -C(0)R\textsuperscript{12}, -C(0)R\textsuperscript{14}, -SO\textsubscript{2}R\textsuperscript{6}, -SO\textsubscript{2}R\textsuperscript{12}, -SO\textsubscript{2}R\textsuperscript{14}, -SO\textsubscript{2}R\textsuperscript{14}(R\textsuperscript{6})\textsubscript{n}, -NHSO\textsubscript{2}R\textsuperscript{10}(R\textsuperscript{6})\textsubscript{n}, -NHSO\textsubscript{2}R\textsuperscript{6}R\textsuperscript{10}(R\textsuperscript{6})\textsubscript{n}, -NHSO\textsubscript{2}R\textsuperscript{6}R\textsuperscript{10}(R\textsuperscript{6})\textsubscript{n}, -NHSO\textsubscript{2}R\textsuperscript{6}R\textsuperscript{10}(R\textsuperscript{6})\textsubscript{n}, and -NHSO\textsubscript{2}R\textsuperscript{14}(R\textsuperscript{6})\textsubscript{n};
R¹ is selected from the group consisting of hydrogen, -R⁵R¹⁴, -C(0)R⁹, -R⁵R¹⁰, -C⁰(0)R¹⁴, and -C⁰(0)R¹⁰; 
-C(0)R¹⁰, and -C(0)R¹⁴;

R² is selected from the group consisting of hydrogen, -R³R⁰(R⁶)ₙ, -R⁶Rₙ₋₅, -R¹₂, -R¹⁰(R⁶)ₙ, -S⁰₂R¹₀, -S⁰₂R¹₂, -S⁰₂R₁⁴, -R¹⁰R¹⁴, -R¹⁴, -R⁹R¹⁰, -R¹⁰R¹⁰, -(R¹⁴R¹₂), -R¹³R⁶, -R¹⁴R⁶, -C⁰₂R⁷, (C₃-C₅)cycloalkyl, and (C₄-C₆)aryl,

wherein A and Q are independently chosen from -(CH₂)ₖ₋₅R₆ or -(CH₂)₅₋₅R₁⁴;

R¹ and R² taken together with any intervening atoms and when Z is a bond, can optionally form a fused (C₂-C₆)heterocyclic ring having 1-3 heteroatoms selected from S, N and O; wherein said fused heterocyclic ring can also be optionally substituted with one to two R⁶ groups;

R³ is selected from the group consisting of hydrogen, nitrile, halo, and (C₄-C₆)alkyl;

R⁴ is selected from the group consisting of hydrogen, (d-CeJalkyl, (CVCeJalkoxy, nitrile, oxo, -C(0)R¹₂, -S⁰₂R⁹, -R⁹(R¹⁵)ₙ, -OR⁷, -R¹₂, and halo;

R⁵ is a branched or straight chain (C-C₆)alkylene;

R⁶ is independently selected from the group consisting of (C-C₆)alkyl, oxo, (C-C₆)alkoxy, -OR⁷, halo, nitrile, and -C⁰₂R⁷;

R⁷ is selected from the group consisting of hydrogen and (C-C₆)alkyl;

R⁸ is independently selected from the group consisting of hydrogen, (C-C₇)alkyl, -R⁵, -R¹₃, -R¹₄, -R⁵R¹₃, -R⁵R¹₀, -R¹₂(R¹⁴)ₙ, -R⁵R¹⁰(R¹⁴)ₙ, and -R⁵R¹⁰(R¹⁴)ₙ;

R⁹ is (C-C₇)alkyl;

R¹⁰ is (C₄-C₆)aryl;

R¹¹ is selected from the group consisting of nitrile, halo, (C-C₆)alkyl, (CrC₆)alkoxy, and -R¹₂R₁₂;

R¹² is -N(R⁸)₂, wherein each instance of R⁸ may be independently and separately chosen from among the possible R⁸ substituents;

R¹³ is (C₃-C₅)cycloalkyl;

R¹⁴ is selected from (C-C₇)heterocycle or (C-C₆)heteroaryl, each having one to three heteroatoms selected from S, N and O;

R¹⁵ is halo;

each m is independently zero or an integer from 1 to 3;

each n is independently zero or an integer from 1 to 3; and
each \( w \) is independently zero or a integer from 1 to 3.

In one embodiment of the present invention, there is provided a compound of Formula (I):

\[
\text{Formula (I)}
\]

or a pharmaceutically acceptable salt thereof, wherein:

\( Z \) is selected from the group consisting of a bond, methylene, ethylene, dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene, methylpropylene, methylecyclopropylmethylene, and isopropylmethylene;

\( X \) is selected from the group consisting of hydrogen, methoxy, nitrile, \(-C(0)R^{12}\), \(-C(0)R^{14}\), \(-S0_2R^{6}\), \(-S0_2R^{12}\), \(-S0_2R^{14}\), \(-S0_2R^{14}(R^6)_n\), \(-NHS0_2R^{10}\), \(-NHSO_2R^{16}(R^6)_n\), \(-NHS0_2R^{13}\), \(-NHS0_2R^{14}\), \(-NHS0_2R^8R^{14}\), \(-NHS0_2R^9(R^6)_n\), \(-NHS0_2R^6\), \(-NHS0_2R^{14}(R^6)_n\);

\( R^1 \) is selected from the group consisting of hydrogen, \(-R^5R^{14}\), \(-R^5R^{10}\), \(-C(0)R^{10}\), \(-C(0)R^{14}\), and \(-C(0)R^{9}\);

\( R^2 \) is selected from the group consisting of hydrogen, \(-Q\) methyl, ethyl, propyl, isopropyl, butyl, isobutyl, \( t \)-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, \(-NH_R^3R^{14}\), \(-OR^7\), \(-R^8R^{10}\), \(-R^8R^{14}\), \(-R^{12}\), \(-R^{14}\), \(-R^{14}_2\), \(-S0_2R^6\), \(-S0_2R^{12}\), \(-S0_2R^{13}\), \(-S0_2R^{14}\), \(-C0_2R^7\), \(-R^{10}R^{16}\), \(-R^{13}R^{14}\), \(-R^{13}R^{14}\), \(-R^{13}R^{6}\), \(-R^{14}R^{14}\), \(-Cyclopropyl\), \(-cyclohexyl\), \(-cyclopentyl\), \(-dihydroindanyl\), and phenyl, wherein \( A \) and \( Q \) are independently chosen from \(- CH_2\)^\( W \)R\(^ {10} \) or \(- CH_2\)^\( W \)R\(^ {14} \);

\( R^3 \) and \( R^4 \) taken together with any intervening atoms and when \( Z \) is a bond can optionally form a fused imidazole ring that can also be optionally substituted with one to two \( R^6 \) groups;

\( R^3 \) is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;

\( R^4 \) is selected from the group consisting of hydrogen, \(-C(0)R^{12}\), \(-S0_2R^{10}\), methyl, ethyl, propyl, isopropyl, butyl, \( t \)-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino,
dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;
R5 is selected from the group consisting of methylene, ethylene, and propylene;
R6 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl,
isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo,
nitrile, and -C02R7;
R7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl,
butyl, t-butyl, and pentyl;
R8 is independently selected from the group consisting of hydrogen, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, heptyl, phenyl, cyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl, -R8R10, -R8R13, -R8(R11)m, -R8R14, and -
R8R10(R11)m;
R9 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyl,
hexyl, heptyl, dimethylbutanyl, and dimethylpentanyl;
R10 is phenyl;
R11 is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy,
and -R14R12;
R12 is -N(R8)2, wherein each R8 may be independently chosen from among the R8
substituents;
R13 is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
R14 is selected from the group consisting of morpholinyl, thiomorpholinyl,
tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl,
indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidone,
piperidinyl, and pyridinyl;
R15 is selected from the group consisting of fluoro, chloro, and iodo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

[0053] In another embodiment of the present invention, there is provided a compound of
Formula (I), or a pharmaceutically acceptable salt thereof, wherein:
Z is a bond or methylene;
X is selected from the group consisting of hydrogen, (C1-C6)alkoxy, nitrile, -C(0)R 12,
-C(0)R 14, -SO2R6, -SO2R12, -SO2R14, -SO2R14(R6)n, -NHSO2R10(R6)n,
-NH2SO2R10(R6)n, -NH2SO2R13, -NH2SO2R14, -NH2SO2R14(R6)n, and
-NH2SO2R14(R6)n;
R¹ is selected from the group consisting of hydrogen, -R²R¹⁴, and -C(0)R⁹;

R² is selected from the group consisting of hydrogen, halo, (C₁₋C₆)alkyl, (C₁₋C₆)alkoxy, nitrile, oxo, hydroxyl, -NH R⁶R¹⁴, -OR R⁷, -R⁸R¹⁴(R⁶)ₙ₋₁, -R⁹R¹⁴, -R¹₀, -R¹₁, -R¹₂, -R¹₃, -R¹₄, -R¹₅, -R¹₆, -R¹₇, -R¹₈, -R¹₉, -R²₀, -R²₁, -SO₂ R¹₂, -SO₂ R¹₃, -SO₂ R¹₄, -SO₂ R¹₅, -SO₂ R¹₆, -SO₂ R¹₇, -SO₂ R¹₈, -SO₂ R¹₉, -SO₂ R²₀, -SO₂ R²₁, -R³², -R³₃, -R³₄, -R³₅, -CO₂ R⁷, (C₅₋C₆)alkyl, and (C₄₋C₁₄)aryl,

wherein A and Q are independently chosen from -(CH₂)ₙR¹⁰ or -(CH₂)ₙR¹₄;

R¹ and R² taken together with any intervening atoms and when Z is a bond, can optionally form a fused (C₂₋C₈)heterocyclic ring having 1-3 heteroatoms selected from S, N and O; wherein said fused heterocyclic ring can also be optionally substituted with one to two R⁶ groups;

R³ is selected from the group consisting of hydrogen, halo, and (C₁₋C₆)alkyl;

R⁴ is selected from the group consisting of hydrogen, (C₁₋C₆)alkyl, (CrC₆)alkoxy, nitrile, oxo, -C(0)R十二, -SO₂ R⁹, -R⁶(R₅)ₙ₋₁, -OR R⁷, -R¹₂, and halo;

R⁵ is a branched or straight chain (CrC₆)alkylene;

R⁶ is independently selected from the group consisting of (CrC₆)alkyl, oxo, (C₁₋C₆)alkoxy, -OR R⁷, halo, nitrile, and -CO₂ R⁷;

R⁷ is selected from the group consisting of hydrogen and (CrC₆)alkyl;

R⁸ is independently selected from the group consisting of hydrogen, (CrC₆)alkyl, -R⁵, -R¹₁, -R¹₄, -R²₀, -R³₀, -R¹₀(R¹₁)ₘ, and -R³₀R¹₀(R¹¹)ₘ;

R⁹ is (C₁₋C₇)alkyl;

R¹₀ is (C₄₋C₁₄)aryl;

R¹¹ is selected from the group consisting of nitrile, halo, (CrC₆)alkyl, (C₁₋C₆)alkoxy, and -R¹₄R¹₂;

R¹₂ is -(N(R⁴)₂), wherein each instance of R⁸ may be independently and separately chosen from among the possible R⁸ substituents;

R¹₃ is (C₃₋C₁₃)cycloalkyl;

R¹₄ is selected from (Cr-C₈)heterocycle or (d-di)heteroaryl, each having one to three heteroatoms selected from N and O;

R¹₅ is halo;

each m is independently zero or an integer from 1 to 3;

each n is independently zero or an integer from 1 to 3; and

each w is independently zero or an integer from 1 to 3.
In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

Z is a bond;

X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R 12, -C(0)R 14, -SO 2R 6, -SO 2R 12, -SO 2R 14, -SO 2R 14(R 6)n, -NHSO 2R 13, -NHSO 2R 14, -NHSO 2R 14(R 6)n, -NHSO 2R 15(R 6)n, -NHSO 2R 16(R 6)n;

R 1 is selected from the group consisting of hydrogen, -R 5R 14, and -C(0)R 9;

R 2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR 5R 14, -OR 7, -R 9R 10, -R 10R 5R 14, -R 12, -R 14, -(R 14) 2, -SO 2R 10, -SO 2R 12, -SO 2R 13, -SO 2R 14, -C0 2R 7, -R 10R 6, -R 10R 16R 14, -R 10R 14, -R 10R 16, -R 14R 6, -(R 14R 12), cyclopentyl, dihydroindenyl, and phenyl, wherein A and Q are independently chosen from -(CH 2) 1R 10 or -(CH 2) nR 14;

R 1 and R 2 taken together with any intervening atoms and when Z is a bond can optionally form a fused imidazole ring that can also be optionally substituted with one to two R 6 groups;

R 3 is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;

R 4 is selected from the group consisting of hydrogen, -C(0)R 12, -SO 2R 9, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;

R 5 is selected from the group consisting of methylene, ethylene, and propylene;

R 6 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and -C0 2R 7;

R 7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl;

R 8 is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, heptyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -R 5R 10, -R 5R 13, -R 10R 13, -R 10R 11, and -R 8R 10(R 11)n; 

R 9 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, hexyl, heptyl, neopentyl, dimethylbutanyl, and dimethylpentanyl.
R_{10} is phenyl;
R_{11} is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and -R_{14}R_{12};
R_{12} is -N(R_{5})_{2}, wherein each R_{8} may be independently chosen from among the R_{8} substituents;
R_{13} is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
R_{14} is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidone, piperidinyl, and pyridinyl;
R_{15} is selected from the group consisting of fluoro, chloro, and iodo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:
Z is a bond or methylene;
X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R_{12},
-C(0)R_{14}, -SO_{2}R_{6}, -SO_{2}R_{12}, -SO_{2}R_{14}, -SO_{2}R_{14}(R_{6})_{n}, -NHSO_{2}R_{14}, -NHSO_{2}R_{14}(R_{6})_{n},
-NHSO_{2}R_{13}, -NHSO_{2}R_{14}, -NHSO_{2}R_{14}(R_{6})_{n}, -NHSO_{2}R_{14}(R_{6})_{n},
-R_{14}(R_{6})_{n},
R_{1} is hydrogen;
R_{2} is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl,
butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy,
hydroxyl, -NHR_{3}R_{14}, -OR_{7}, -R_{9}R_{10}, -R_{10}R_{10}, -R_{10}R_{14}, -R_{12}, -R_{14}, -(R_{14})_{2}, -S0_{2}R_{12},
-SO_{2}R_{13}, -SO_{2}R_{14}, -CO_{2}R_{7}, -R_{10}R_{6}, -R_{13}R_{14}, -R_{10}R_{14}, -R_{13}R_{6}, -R_{14}R_{6},
(R_{14}R_{12}), cyclopentyl, dihydroindenyly, and phenyl;
R_{3} is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;
R_{4} is selected from the group consisting of hydrogen, -C(0)R_{12}, -SO_{2}R_{6}, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino,
dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;
R_{5} is selected from the group consisting of methylene, ethylene, and propylene;
R_{6} is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl,
isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo,
nitrile, and -CO₂R²;
R¹ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl;
R⁸ is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, heptyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -R⁸R¹⁰, -R⁸R¹³, -R¹⁰(R¹¹)ₘ, and -R⁸R¹⁰(R¹¹)ₘ;
R⁹ is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyl, hexyl, heptyl, dimethylbutanyl, and dimethylpentanyl;
R¹⁰ is phenyl;
R¹¹ is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, and methoxy;
R¹² is -N(R⁸)₂, wherein each R⁸ may be independently chosen from among the R⁸ substituents;
R¹³ is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
R¹⁴ is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepiny, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperaziny, pyrrolidinyl, pyrrolidinone, piperidinyl, and pyridinyl;
R¹⁵ is selected from the group consisting of fluoro, chloro, and iodo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

Z is a bond;
X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R¹²,
-C(0)R¹⁴, -SO₂R⁶, -SO₂R¹², -SO₂R¹⁴, -SO₂R¹⁴(R⁶)ₙ, -NHSO₂R¹⁰,
-NHSO₂R¹⁰(R⁶)ₙ, -NHSO₂R¹³, -NHSO₂R¹⁴, -NHSO₂R⁵R¹⁴, -NHSO₂R⁵(R⁶)ₙ, -NHSO₂R⁸, and
-NHSO₂R¹⁴(R⁶)ₙ;
R¹ is hydrogen;
R² is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR⁵R¹⁴, -OR⁷, -R⁶R¹⁰, -R¹⁰R⁶R¹⁴, -R¹², -R¹⁴, -(R¹⁴)₂, -SO₂R¹⁰,
-SO₂R¹², -SO₂R¹³, -SO₂R¹⁴, -CO₂R⁷, -R¹⁰R⁸, -R¹³R¹⁴, -R¹⁰R¹⁴, -R¹³R⁸, -R¹⁴R⁸,-
(R^{14}R^{15}), cyclopentyl, dihydroindenyl, and phenyl;

R^{3} is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;

R^{4} is selected from the group consisting of hydrogen, -C(0)R^{12}, -S0_{2}R^{9}, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methlamino, dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;

R^{5} is selected from the group consisting of methylene, ethylene, and propylene;

R^{6} is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and -C0_{2}R^{7};

R^{7} is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl;

R^{8} is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, heptyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -R^{5}R^{10}, -R^{5}R^{13}, -R^{10}(R^{11})_{M}, and -R^{5}R^{10}(R^{11})_{M};

R^{9} is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyl, hexyl, heptyl, dimethylbutanyl, and dimethylpentanyl;

R^{10} is phenyl;

R^{11} is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, and methoxy;

R^{12} is -N(R^{8})_{2}, wherein each R^{8} may be independently chosen from among the R^{8} substituents;

R^{13} is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;

R^{14} is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidione, piperidinyl, and pyridinyl;

R^{15} is selected from the group consisting of fluoro, chloro, and iodo;

each m is independently zero or an integer from 1 to 3;

each n is independently zero or an integer from 1 to 3; and

each w is independently zero or an integer from 1 to 3.

[0057] In another embodiment of the present invention, there is provided a compound of Formula (IA):

(IA)
or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from the group consisting of a bond and a (branched or straight chain) (C<sub>1</sub>-
C<sub>6</sub>)alkylene;

X is selected from the group consisting of hydrogen, (d-C<sub>6</sub>)alkoxy, nitrile, -C(0)R<sup>12</sup>,
- C(0)R<sup>14</sup>, -SO<sub>2</sub>R<sup>6</sup>, -SO<sub>2</sub>R<sup>12</sup>, -SO<sub>2</sub>R<sup>14</sup>(R<sup>5</sup>)<sub>n</sub>, -NHSO<sub>2</sub>R<sup>10</sup>(R<sup>6</sup>)<sub>n</sub>,
-NHSO<sub>2</sub>R<sup>5</sup>R<sup>10</sup>(R<sup>5</sup>)<sub>n</sub>, -NHSO<sub>2</sub>R<sup>13</sup>, -NHSO<sub>2</sub>R<sup>14</sup>, -NHSO<sub>2</sub>R<sup>5</sup>(R<sup>6</sup>)<sub>n</sub>, and
-NHSO<sub>2</sub>R<sup>14</sup>(R<sup>5</sup>)<sub>n</sub>;

R'<sup>1</sup> is selected from the group consisting of hydrogen, -R<sup>5</sup>R<sup>14</sup>, and -C(0)R<sup>9</sup>;

R<sup>2</sup> is selected from the group consisting of hydrogen,
-alkoxy, halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-
C<sub>6</sub>)alkoxy, nitrile, oxo, hydroxyl, -NHR<sup>5</sup>R<sup>14</sup>, -OR<sup>7</sup>, -R<sup>5</sup>R<sup>14</sup>(R<sup>6</sup>)<sub>n</sub>, -R<sup>10</sup>R<sup>5</sup>R<sup>14</sup>, -R<sup>12</sup>, -
R<sup>14</sup>, -R<sup>10</sup>R<sup>6</sup>, -R<sup>10</sup>(R<sup>6</sup>)<sub>n</sub>, -SO<sub>2</sub>R<sup>6</sup>, -SO<sub>2</sub>R<sup>12</sup>, -SO<sub>2</sub>R<sup>14</sup>, -SO<sub>2</sub>R<sup>13</sup>, -SO<sub>2</sub>R<sup>14</sup>, -R<sup>15</sup>R<sup>14</sup>, -R<sup>15</sup>R<sup>13</sup>, -
R<sup>10</sup> R<sup>14</sup>, -(R<sup>14</sup>R<sup>12</sup>)<sub>n</sub>, -(R<sup>14</sup>R<sup>6</sup>)<sub>n</sub>, -C<sub>6</sub>O<sub>2</sub>R<sup>7</sup>, (C<sub>5</sub>=C<sub>12</sub>)<sub>1</sub>cycloalkyl, and (C<sub>4</sub>=C<sub>14</sub>)<sub>1</sub>aryll,
wherein A and Q are independently chosen from -(CH<sub>2</sub>)<sub>n</sub>R<sup>10</sup> or-(CH<sub>2</sub>)<sub>n</sub>W<sup>14</sup>;

R<sup>1</sup> and R<sup>2</sup> taken together with any intervening atoms and when Z is a bond, can
optionally form a fused (C<sub>2</sub>-C<sub>6</sub>)heterocyclic ring having 1-3 heteroatoms selected
from S, N and O; wherein said fused heterocyclic ring can also be optionally
substituted with one to two R<sup>6</sup> groups;

R<sup>4</sup> is selected from the group consisting of hydrogen, (d-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, nitrile,
oxo, -C(0)R<sup>12</sup>, -SO<sub>2</sub>R<sup>9</sup>, -R<sup>3</sup>(R<sup>15</sup>)<sub>n</sub>, -OR<sup>7</sup>, -R<sup>12</sup>, and halo;

R<sup>5</sup> is a branched or straight chain (CrC<sub>6</sub>)alkylene;

R<sup>6</sup> is independently selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkyl, oxo, (d-
C<sub>6</sub>)alkoxy, -OR<sup>7</sup>, halo, nitrile, and -CO<sub>2</sub>R<sup>7</sup>;

R<sup>7</sup> is selected from the group consisting of hydrogen and (C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>8</sup> is independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>7</sub>)alkyl, -R<sup>10</sup>,
-R<sup>13</sup>, -R<sup>14</sup>, -R<sup>5</sup>R<sup>13</sup>, -R<sup>9</sup>R<sup>10</sup>, -R<sup>10</sup>(R<sup>11</sup>)<sub>M</sub>, and -R<sup>6</sup>R<sup>10</sup>(R<sup>11</sup>)<sub>M</sub>;

R<sup>9</sup> is (d-d)alkyl;

R<sup>10</sup> is (d-C<sub>1</sub>-aryl);
R^{11} is selected from the group consisting of nitrile, halo, (Ci-C\textsubscript{6})alkyl, (CrC\textsubscript{6})alkoxy, and -R^{14}R^{12};

R^{12} is -N(R^{8})\textsubscript{2}, wherein each instance of R^{8} may be independently and separately chosen from among the possible R^{8} substituents;

R^{13} is (C\textsubscript{3}-C\textsubscript{12})cycloalkyl;

R^{14} is selected from (CrC\textsubscript{n})heterocycle or (d-CuJheteroaryl, each having one to three heteroatoms selected from N and O;

R^{15} is halo;

each m is independently zero or an integer from 1 to 3;

each n is independently zero or an integer from 1 to 3; and

each w is independently zero or an integer from 1 to 3.

[0058] In another embodiment of the present invention, there is provided a compound of Formula (IA), or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from the group consisting of a bond, methylene, ethylene, dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene, methylpropylene, methylcyclopropylmethyl, and isopropylmethylene;

X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R^{12}, -C(0)R^{14}, -S0\textsubscript{2}R^{6}, -SO\textsubscript{2}R^{12}, -SO\textsubscript{2}R^{14}, -SO\textsubscript{2}R^{14}(R^{6})\textsubscript{n}, -NHS0\textsubscript{2}R^{14}, -NHS0\textsubscript{2}R^{10}(R^{6})\textsubscript{n}, -NHS0\textsubscript{2}R^{13}, -NHS0\textsubscript{2}R^{14}, -NHS0\textsubscript{2}R^{10}(R^{6})\textsubscript{n}, -NHS0\textsubscript{2}R^{10}(R^{6})\textsubscript{n},

R^{1} is selected from the group consisting of hydrogen, -R^{8}R^{14}, and -C(0)R^{9};

R^{2} is selected from the group consisting of hydrogen, Q, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR\textsubscript{3}R\textsubscript{14}, -OR\textsubscript{7}, -R^{9}R\textsubscript{10}, -R\textsubscript{10}R\textsubscript{5}R\textsubscript{14}, -R\textsubscript{12}, -R\textsubscript{14}, -(R^{14})\textsubscript{2}, -S0\textsubscript{2}R\textsubscript{14}, -SO\textsubscript{2}R\textsubscript{12}, -SO\textsubscript{2}R\textsubscript{13}, -SO\textsubscript{2}R\textsubscript{14}, -C0\textsubscript{2}R\textsubscript{7}, -R\textsubscript{10}R\textsubscript{6}, -R\textsubscript{13}R\textsubscript{14}, -R\textsubscript{10}R\textsubscript{14}, -R\textsubscript{15}R\textsubscript{6}, -R\textsubscript{14}R\textsubscript{6}, -(R^{14}R\textsubscript{13}), cyclopropyl, dihydroiridenyl, and phenyl, wherein A and Q are independently chosen from -(CH\textsubscript{2})\textsubscript{w}R\textsubscript{10} or -(CH\textsubscript{2})\textsubscript{w}R\textsubscript{14};

R\textsuperscript{1} and R\textsuperscript{2} taken together with any intervening atoms and when Z is a bond can optionally form a fused imidazole ring that can also be optionally substituted with one to two R\textsuperscript{6} groups;

R\textsuperscript{4} is selected from the group consisting of hydrogen, -C(0)R\textsubscript{12}, -SO\textsubscript{2}R\textsubscript{9}, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino,
dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;
R^5 is selected from the group consisting of methylene, ethylene, and propylene;
R^6 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl,
isobutyl, t-butyl, oxp, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo,
nitrile, and -CO_2R^7;
R^7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl,
butyl, t-butyl, and pentyl;
R^8 is independently selected from the group consisting of hydrogen, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, penty1, hexyl, hepty1, phenyl, cyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl, -R^5R^{10}, -R^5R^{13}, -R^{10}(R^{11})_M, and -R^9R^{10}(R^{11})_M;
R^9 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, penty1, t-pentyl, neopenty1,
hexyl, hepty1, dimethylbutanyl, and dimethylpentanyl;
R^{10} is phenyl;
R^{11} is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy,
and -R^{14}R^{12};
R^{12} is -N(R^8)_2, wherein each R^8 may be independently chosen from among the R^8
substituents;
R^{13} is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
R^{14} is selected from the group consisting of morpholinyl, thiomorpholinyl,
tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl,
indolyl, thiophenyl, tetrahydrofuranyl, piperezinyl, pyrrolidinyl, pyrrolidione,
piperidinyl, and pyridinyl;
R^{15} is selected from the group consisting of fluoro, chloro, and iodo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

[0059] In another embodiment of the present invention, there is provided a compound of
Formula (IB):
or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from the group consisting of a bond and a (branched or straight chain) (C₁-
C₆)alkylene;

X is selected from the group consisting of hydrogen, (C₁-C₆)alkoxy, nitrile, -C(0)R₁²;
- C(0)R₁⁴, -SO₂R₆, -SO₂R₁₂, -SO₂R₁⁴, -SO₂R₁⁴(R₆)ₙ, -NHSO₂R₁⁴(R₆)ₙ, and
-NHSO₂R₁⁴(R₆)ₙ;

R¹ is selected from the group consisting of hydrogen, -R⁵R¹⁴, and -C(0)R₉;

R² is selected from the group consisting of hydrogen, -C₁-C₆)alkyl, (C₁-
C₆)alkoxy, nitrile, oxo, hydroxyl, -NHR₅R₁⁴, -OR₇, -R⁵R₁⁴(R₆)ₙ, -R₁⁰R₁⁴, -R₁², -
R₁⁴, -R₁⁰R₁⁶, -R₁⁰(R₆)ₙ, -S0₂R₁⁰, -SO₂R₁₂, -SO₂R₁⁴, -SO₂R₁⁴, -R₁⁴, -R₁⁰R₁⁴, -(C₃-C₆)cycloalkyl, and (C₄-C₆)aryl,
wherein A and Q are independently chosen from -(CH₂)ₕR₁⁰ or -(CH₂)ₕR₁⁴;

R¹ and R² taken together with any intervening atoms and when Z is a bond, can
optionally form a fused (C₂-C₆)heterocyclic ring having 1-3 heteroatoms selected
from S, N and O; wherein said fused heterocyclic ring can also be optionally
substituted with one to two R⁶ groups;

R³ is selected from the group consisting of hydrogen, halo, and (C₁-C₆)alkyl;

R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-
C₆)alkoxy, nitrile, oxo, -C(0)R₁², -SO₂R₆, -R⁵(R₁⁴)ₙ, -OR₇, and -R₁²;

R⁵ is a branched or straight chain (C₁-C₆)alkylene;

R⁶ is independently selected from the group consisting of (C₁-C₆)alkyl, oxo, (C₁-
C₆)alkoxy, -OR₇, halo, nitrile, and -C₀₂R⁷;

R⁷ is selected from the group consisting of hydrogen and (C₆-C₆)alkyl;

R⁸ is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, -R₉;
- R₁³, - R₁⁴, - R₅R₁³, - R₅R₅(R₁⁴)ₙ, and - R₅R₁⁴(R₁⁴)ₙ.
R⁰ is (C₁−C₇)alkyl;  
R¹⁰ is (C₄−C₁₄)aryl;  
R¹¹ is selected from the group consisting of nitriie, halo, (d-C₈alkyl, (C₁−C₆)alkoxy, and -R¹⁴R¹²;  
R¹² is -N(R³)₂, wherein each instance of R³ may be independently and separately chosen from among the possible R³ substituents;  
R¹³ is (C₃−C₁₂)cycloalkyl;  
R¹⁴ is selected from (d-CuJheterocycle or (C₁−C₆)heteroaryl, each having one to three heteroatoms selected from N and O;  
R¹⁵ is halo;  
each m is independently zero or an integer from 1 to 3;  
each n is independently zero or an integer from 1 to 3; and  
each w is independently zero or an integer from 1 to 3.  

[0060] In another embodiment of the present invention, there is provided a compound of Formula (IB), or a pharmaceutically acceptable salt thereof, wherein:  
Z is selected from the group consisting of a bond, methylene, ethylene,  
dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene,  
methylpropylene, methylvicyclopentymethyl, and isopropylmethylene;  
X is selected from the group consisting of hydrogen, methoxy, nitriie, -C(0)R¹²,  
-C(0)R¹⁴, -S0₂R⁶, -SO₂R¹², -SO₂R¹⁴, -SO₂R¹⁴(Rⁿ)ₙ, -NHSO₂R¹⁰, -NHSO₂R¹⁰(Rⁿ)ₙ,  
-NHSO₂R¹³, -NHSO₂R¹⁴, -NHSO₂R¹⁴(Rⁿ)ₙ, -NHSO₂R¹⁹, -NHSO₂R¹⁹(Rⁿ)ₙ,  
-NHSO₂R¹⁴(Rⁿ)ₙ.  
R¹ is selected from the group consisting of hydrogen, -R⁵R¹⁴, and -C(0)R⁹;  

R² is selected from the group consisting of hydrogen,  
methyl, ethyl, propyl,  
isopropyl, butyl, isobutyl, t-butyl, nitriie, fluoro, chloro, iodo, methoxy, ethoxy,  
propoxy, hydroxyl, -NHR⁸R¹⁴, -OR⁷, -R⁸R¹⁰, -R¹⁰R³R¹⁴, -R¹², -R¹⁴, -(R¹⁴)₂, -  
SO₂R¹⁰, -SO₂R¹², -SO₂R¹⁴, -C₀₂R⁷, -R¹⁰R³, -R¹³R¹⁴, -R¹⁹R¹⁴, -R¹³R⁶, -  
R¹⁴R⁶, -(R¹⁴R¹²), cyclopentyl, dihydroindenyl, and phenyl, wherein A and Q are independently chosen from -CH₂ₙR¹⁰ or -(CH₂)ₙR¹⁴;  
R¹ and R² taken together with any intervening atoms and when Z is a bond can  
optionally form a fused imidazole ring that can also be optionally substituted with  
one to two R⁶ groups;
R³ is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;
R⁴ is selected from the group consisting of hydrogen, -C(0)R¹², -SO₂R⁹, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, and trifluoromethyl;
R⁵ is selected from the group consisting of methylene, ethylene, and propylene;
R⁶ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and CO₂R⁷;
R⁷ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl;
R⁸ is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, heptyl, neopentyl, isopropyl, pentyl, t-pentyl, neopentyl, hexyl, heptyl, dimethylbutanyl, and dimethylpentanyl;
R⁹ is phenyl;
R¹ is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and CO₂R¹;
R¹² is -NR¹⁰₂, wherein each R⁸ may be independently chosen from among the R⁸ substituents;
R¹³ is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
R¹⁴ is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidione, piperidinyl, and pyridinyl;
R¹⁵ is selected from the group consisting of fluoro, chloro, and iodo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

In another embodiment of the present invention, there is provided a compound of
Formula (II):

(II)
or a pharmaceutically acceptable salt thereof, wherein:

\[ \text{Z is selected from the group consisting of a bond and a (branched or straight chain) (C}_1-\text{C}_6\text{alkylene;} } \]

\[ \text{X is selected from the group consisting of -R}^{10}, -R^{10}(R^6)_{n1}, -R^{13}, -R^{14}, -R^5R^{14}, -R^9(R^6)_{n2}, -R^9, \text{and } -R^{14}(R^6)_{n3}; \]

\[ \text{R}^1 \text{ is selected from the group consisting of hydrogen, } -R^5R^{14}, \text{ and } -C(0)R^9; \]

\[ \text{R}^2 \text{ is selected from the group consisting of hydrogen, } -\text{Q, halo, (C}_1-\text{C}_6\text{alkyl, (C}_1-\text{C}_6) \text{alkoxy, nitrile, oxo, hydroxyl, } -\text{NHR}^5R^{14}, -\text{OR}^7, -R^5R^{14}(R^6)_{n3}, -R^{10}R^5R^{14}, -R^{12}R^4, -R^{14}, -R^{10}R^6, -R^{10}(R^6)_{n3}, -S0^2R^{13}, -S0^2R^{14}, -R^{10}R^{14}, -R^9R^{10}R^{14}, -R^{10}R^{14}, -R^{14}R^6, -R^13R^6, -R^14R^6, -C0^2R^7, (\text{C}_3\text{C}_12) \text{cycloalkyl, and (C}_4\text{C}_1\text{aryl, } \]

\[ \text{wherein A and Q are independently chosen from } -(\text{CH}_2)_nR^{10} \text{ or } -(\text{CH}_2)_nR^{14}; \]

\[ \text{R}^3 \text{ is selected from the group consisting of hydrogen, halo, and (C}_1\text{C}_6\text{alkyl;} \]

\[ \text{R}^4 \text{ is selected from the group consisting of hydrogen, (CrC}_6\text{alkyl, (CrC}_6\text{alkoxy, nitrile, oxo, } -\text{C}(0)R^{12}, -S0^2R^9, -R^9(R^{15})_n, -\text{OR}^7, -R^{12}, \text{ and halo;} \]

\[ \text{R}^5 \text{ is a branched or straight chain (C}_1\text{C}_6\text{)alkylene;} \]

\[ \text{R}^6 \text{ is independently selected from the group consisting of (C}_1\text{C}_6\text{)alkyl, oxo, (C}_1-\text{C}_6\text{alkoxy, } -\text{OR}^7, \text{ halo, nitrile, and } -\text{C}0^2R^7; \]

\[ \text{R}^7 \text{ is selected from the group consisting of hydrogen and (C}_1\text{C}_6\text{)alkyl;} \]

\[ \text{R}^8 \text{ is independently selected from the group consisting of hydrogen, (C}_1\text{C}_7\text{)alkyl, } -R^{10}, -R^{13}, -R^{14}, -R^5R^{13}, -R^5R^{10}, -R^9(R^{11})_n, \text{ and } -R^5R^5(R^1)_n; \]

\[ \text{R}^9 \text{ is } (\text{d-Cy}) \text{alkyl;} \]

\[ \text{R}^{10} \text{ is (C}_4\text{C}_1\text{aryl;} \]

\[ \text{R}^{11} \text{ is selected from the group consisting of nitrile, halo, (CrC}_6\text{)alkyl, (Cr-C}_6\text{alkoxy, and } -R^{14}R^{12;} \]
R^{12} is -N(R^8)_2, wherein each instance of R^8 may be independently and separately chosen from among the possible R^8 substituents;
R^{13} is (C_9-C_{12})cycloalkyl;
R^{14} is selected from (C_1-C_{11})heterocycle or (CrCn)heteroaryl, each having one to three heteroatoms selected from N and O;
R^{15} is halo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

[0062] In another embodiment of the present invention, there is provided a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from the group consisting of a bond, methylene, ethylene, dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene, methylpropylene, methylocyclopropylmethyl, and isopropylmethylene;
X is selected from the group consisting of X is selected from the group consisting of -R^{16}, -R^10(R^8)_n, -R^{13}, -R^{14}, -R^5R^{14}, -R^9(R^6)_n, -R^9, and -R^{14}(R^6)_n;
R^1 is selected from the group consisting of hydrogen, -R^5R^{14}, and -C(0)R^9;
R^2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR^5R^{14}, -OR^7, -R^5R^{10}, -R^10R^5R^{14}, -R^{12}, -R^{13}, -(R^{14})^2, -SO_2R^{16}, -SO_2R^{12}, -SO_2R^{13}, -SO_2R^{14}, -CO_2R^7, -R^{10}R^6, -R^{13}R^{14}, -R^{10}R^{14}, -R^{13}R^6, -R^{14}R^6, -(R^{14}R^{12}), cyclopentyl, and phenyl, wherein A and Q are independently chosen from -(CH_2)_W^R^{10} or -(CH_2)_W^R^{14}.
R^3 is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;
R^4 is selected from the group consisting of hydrogen, -C(0)R^{12}, -SO_2R^9, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;
R^5 is selected from the group consisting of methylene, ethylene, and propylene;
R^6 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and -CO_2R^7;
R^7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl,
butyl, t-butyl, and pentyl;
R\textsuperscript{8} is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, heptyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, - R\textsuperscript{5}R\textsuperscript{10}, - R\textsuperscript{5}R\textsuperscript{13}, - R\textsuperscript{10}(R\textsuperscript{11})\textsubscript{M}, and - R\textsuperscript{5}R\textsuperscript{10}(R\textsuperscript{11})\textsubscript{M};
R\textsuperscript{9} is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, penty1, t-pentyl, neopentyl, hexyl, heptyl, dimethylbutanyl, and dimethylpentanyl;
R\textsuperscript{10} is phenyl;
R\textsuperscript{11} is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and - R\textsuperscript{14}R\textsuperscript{12};
R\textsuperscript{12} is - N(R\textsuperscript{8})\textsubscript{2}, wherein each R\textsuperscript{8} may be independently chosen from among the R\textsuperscript{8} substituents;
R\textsuperscript{13} is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
R\textsuperscript{14} is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidone, piperidinyl, and pyridinyl;
R\textsuperscript{15} is selected from the group consisting of fluoro, chloro, and iodo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.
[0063] In another embodiment of the present invention, there is provided a compound of Formula (III):

\begin{align*}
\text{(III)}
\end{align*}

or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from the group consisting of a bond and a (branched or straight chain) (d-C\textsubscript{6})alkylene;
X is selected from the group consisting of \(-R^6\), \(-R^{12}\), \(-R^4\), and \(-R^{14}(R^6)\);  
R\(^1\) is selected from the group consisting of hydrogen, \(-R^5 R^{14}\), and \(-C(0)R^9\);  
R\(^2\) is selected from the group consisting of hydrogen, halo, \((C_1-C_6)\)alkoxyl, \((C_1-C_6)\)alkoxy, nitrile, oxo, hydroxyl, \(-\text{NHR}^5 R^{14}\), \(-\text{OR}^7\), \(-R^5 R^{14}(R^6)\), \(-R^{10} R^9 R^{14}\), \(-R^{12}\), \(-R^{14}\), \(-R^{16}(R^6)\), \(-S0_2 R^{10}\), \(-S0_2 R^{12}\), \(-S0_1 R^{14}\), \(-S0_2 R^{15}\), \(-R^{13} R^{14}\), \(-R^9 R^{10}\), \(-R^{10} R^{14}\), \(-R^{11} R^{12}\), \(-R^{13} R^{6}\), \(-R^{14} R^{6}\), \(-C0_2 R^7\), \((C_3\text{-}C_{12})\)cycloalkyl, and \((C_4\text{-}C_4)\)aryl,  
wherein A and Q are independently chosen from \(-(\text{CH}_2\)\)\(_n\)R\(^{10}\) or \(-(\text{CH}_2\)\)\(_2\)R\(^{14}\);  
R\(^3\) is selected from the group consisting of hydrogen, halo, and \((C_1-C_6)\)alkyl;  
R\(^4\) is selected from the group consisting of hydrogen, \((C_1-CeJ)\)alkyl, \((d\text{-}C_eJ)\)alkoxy, \((d\text{-}C_eJ)\)alkoxyl, \(-\text{NHR}^5 R^{12}\), \(-\text{OR}^9\), \(-R^9 R^{15}\), \(-\text{OR}^7\), \(-R^{12}\), and halo;  
R\(^5\) is a branched or straight chain \((C_1-C_6)\)alkylene;  
R\(^6\) is independently selected from the group consisting of \((C_1-C_6)\)alkyl, oxo, \((d\text{-}C_e)\)alkoxy, \(-\text{OR}^7\), halo, nitrile, and \(-C0_2 R^7\);  
R\(^7\) is selected from the group consisting of hydrogen and \((C_1-C_6)\)alkyl;  
R\(^8\) is independently selected from the group consisting of hydrogen, \((C_1-C_6)\)alkyl, \(-R^{10}\), \(-R^{13}\), \(-R^9 R^{13}\), \(-R^{10} R^{10}(R^{11})_M\), and \(-R^{10} R^{10}(R^{11})_M\);  
R\(^9\) is \((d\text{-}C_{1})\)alkyl;  
R\(^{10}\) is \((C_4\text{-}C_{14})\)aryl;  
R\(^{11}\) is selected from the group consisting of nitrile, halo, \((C_1-C_6)\)alkyl, \((C_1-C_6)\)alkoxy, and \(-R^{14} R^{12}\);  
R\(^{12}\) is \(-N(R^6)\)\(_2\), wherein each instance of R\(^8\) may be independently and separately chosen from among the possible R\(^8\) substituents;  
R\(^{13}\) is \((C_3\text{-}C_{12})\)cycloalkyl;  
R\(^{14}\) is selected from \((d\text{-}d\text{i})\)heterocycle or \((d\text{-}d\text{i})\)heteroaryl, each having one to three heteroatoms selected from N and O;  
R\(^{15}\) is halo;  
each m is independently zero or an integer from 1 to 3;  
each n is independently zero or an integer from 1 to 3; and  
each w is independently zero or an integer from 1 to 3.  
[0064] In another embodiment of the present invention, there is provided a compound of Formula (III), or a pharmaceutically acceptable salt thereof, wherein:  
Z is selected from the group consisting of a bond, methylene, ethylene,
dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene, methylpropylene, methylcyclopropylmethyl, and isopropylmethylene;

X is selected from the group consisting of -R^6, -R^12, -R^14, and -R^{14}(R^8)_m, -C(0)R^6, and -C(0)R^14;

R^1 is selected from the group consisting of hydrogen, -R^5R^14, and -C(0)R^9;

R^2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR^9R^14, -OR^7, -R^9R^10, -R^{10}R^8R^14, -R^12, -R^14, -(R^14)_2, -S0_2R^{10}, -S0_2R^{12}, -S0_2R^{13}, -S0_2R^{14}, -C0_2R^7, -R^{16}R^8, -R^{14}R^14, -R^{10}R^{14}, -R^{13}R^6, -R^{14}R^6, -(R^{14}R^{12}), cyclopentyl, dihydroidenyl, and phenyl, wherein A and Q are independently chosen from -(CH_2)_wR^10 or -(CH_2)_wR^14;

R^3 is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;

R^4 is selected from the group consisting of hydrogen, -C(0)R^6, -S0_2R^9, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;

R^5 is selected from the group consisting of methylene, ethylene, and propylene;

R^6 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and -C0_2R^7;

R^7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl;

R^8 is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, heptyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -R^9R^{10}, -R^9R^{13}, -R^{10}(R^{11})_m, and -R^{12}R^{10}(R^{11})_m;

R^9 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyl, hexyl, heptyl, dimethylbutanyl, and dimethylpentanyl;

R^{10} is phenyl;

R^{11} is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and -R^{14}R^{12};

R^{12} is -N(R^8)_2, wherein each R^8 may be independently chosen from among the R^8 substituents;

R^{13} is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
$R^4$ is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidone, piperidinyl, and pyridinyl;

$R^5$ is selected from the group consisting of fluoro, chloro, and iodo;

each $m$ is independently zero or an integer from 1 to 3;

each $n$ is independently zero or an integer from 1 to 3; and

each $w$ is independently zero or an integer from 1 to 3.

[0065] In another embodiment of the present invention, there is provided a compound of Formula (I):

\[ \text{(I)} \]

or a pharmaceutically acceptable salt thereof, wherein:

$Z$ is selected from the group consisting of a bond and a (branched or straight chain) (C$_1$-C$_6$)alkylene;

$X$ is selected from the group consisting of hydrogen, (d-C$_2$)alkoxy, nitrile, -C(0)R$_1^2$, and -C(0)R$_{14}$;

$R^1$ is selected from the group consisting of hydrogen, -R$_5^4$R$_{14}$, -C(0)R$_9^9$,

$R^2$ is selected from the group consisting of hydrogen, -NRH$_5^5$R$_{14}$, -OR$_7^7$, -R$_5^5$R$_{14}$R$_{14}$, -R$_{12}^5$, -R$_{14}^5$, -R$_{10}^5$R$_6^6$, R$_{10}^5$, -SO$_2$R$_{10}^1$, -SO$_2$R$_{12}^2$, -SO$_2$R$_{13}^3$, -SO$_2$R$_{14}^4$, -R$_{14}^2$, -R$_{14}^9$, -R$_{14}^2$R$_{12}^2$, -R$_{14}^2$R$_{6}^6$, -R$_{14}^2$R$_{12}^6$, -C$_2$O$_2$R$_7^7$, (C$_5$C$_6$)$_2$), cycloalkyl, and (C$_4$C$_4$)$_2$)aryl,

wherein A and $Q$ are independently chosen from -(CH$_2$)$_n$R$_{10}^1$ or -(CH$_2$)$_n$R$_{14}^4$;

$R^3$ is selected from the group consisting of hydrogen, halo, and (C$_2$C$_6$)alkyl;

$R^4$ is selected from the group consisting of hydrogen, (C$_2$C$_6$)alkyl, (C$_2$C$_6$)alkoxy, nitrile, oxo, -C(0)R$_{14}$, -SO$_2$R$_9^9$, -OR$_7^7$, -R$_{12}^5$, and halo;

$R^5$ is a branched or straight chain (C$_1$-C$_6$)alkylene;

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R⁶ is independently selected from the group consisting of (C₁₋C₆)alkyl, oxo, (C₁₋C₆)alkoxy, -OR⁷, halo, nitrile, and -CO₂R⁷;
R⁷ is selected from the group consisting of hydrogen and (C₁₋C₆)alkyl;
R⁸ is independently selected from the group consisting of hydrogen, (C₁₋C₆)alkyl, -R¹⁸, -R¹⁹, -R²⁰, -R²¹(R¹²)₄, and -R²₂R¹⁰(R¹₁)₆;
R⁹ is (C₁₋C₆)alkyl;
R¹⁰ is (C₄₋C₆)aryl;
R¹¹ is selected from the group consisting of nitrile, halo, (C₁₋C₆)alkyl, (C₁₋C₆)alkoxy, and -R¹⁴R¹²;
R¹² is -N(R³)₂, wherein each instance of R⁶ may be independently and separately chosen from among the possible R⁶ substituents;
R¹³ is (C₃₋C₁₂)cycloalkyl;
R¹⁴ is selected from (C₁₋C₆)heterocycle or (C₆₋C₆)heteroaryl, each having one to three heteroatoms selected from N and O;
R¹⁵ is halo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:
Z is selected from the group consisting of a bond, methylene, ethylene, dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene, methylpropylene, methylcyclopropylmethyl, and isopropylmethylene;
X is selected from the group consisting of hydrogen, (C₁₋C₆)alkoxy, nitrile, -C(0)R¹², and -C(0)R¹⁴;
R¹ is selected from the group consisting of hydrogen, -R⁵R¹⁴, and -C(0)R⁹;
R² is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR⁶R¹⁴, -OR⁷, -R⁹R¹⁰, -R¹⁰R¹⁵R¹⁴, -R¹², -R¹⁴, -(R¹⁴)₂, -S₀₂R¹⁰, -SO₂R¹², -SO₂R¹³, -SO₂R¹⁴, -C₀₂R⁷, -R¹⁰R⁶, -R¹³R¹⁴, -R¹⁰R¹⁴, -R¹³R⁶, -R¹⁴R⁶, -(R¹⁴R¹²), cyclopentyl, and phenyl, wherein A and Q are independently chosen from -(CH₂)₆R¹⁰ or -(CH₂)₆R¹⁴;

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R³ is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;
R⁴ is selected from the group consisting of hydrogen, -C(0)R̵¹², -SO₂R⁹, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;
R⁵ is selected from the group consisting of methylene, ethylene, and propylene;
R⁶ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and -C(0)₂R⁷;
R⁷ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl;
R⁸ is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, hexyl, heptyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -R⁸R¹⁰, -R⁸R¹³, -R¹⁰(R¹¹)ₗ, and -R⁹R₁⁰(R¹¹)ₗ;
R⁹ is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyi, hexyl, heptyl, dimethylbutanyl, and dimethylpentanyl;
R¹⁰ is phenyl;
R¹¹ is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and -R¹⁴R¹²;
R¹² is -N(R⁸)₂, wherein each R⁸ may be independently chosen from among the R⁸ substituents;
R¹³ is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
R¹⁴ is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, piperidinyl, and pyridinyl;
R¹⁵ is selected from the group consisting of fluoro, chloro, and iodo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

[0067] In another embodiment of the present invention, there is provided a compound of
Formula (IV):
or a pharmaceutically acceptable salt thereof, wherein:

- **Z** is selected from the group consisting of a bond and a (branched or straight chain) (C₁-C₆)alkylene;

- **X** is selected from the group consisting of hydrogen, (CrC₆)alkoxy, nitrile, -C(0)R₁², -C(0)R₁⁴, -SO₂R₆, -SO₂R₁², -SO₂R₁³, -SO₂R₁⁴, -SO₂R₂R₆(R₈)ₙ, -NHSO₂R₁⁴, -(R₈)n, and -NHSO₂R₆(R₈)ₙ;

- **R¹** is selected from the group consisting of hydrogen, -R⁵R₁⁴, and -C(0)R₉;

- **R²** is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, nitrile, oxo, hydroxyl, -NHR₈R₁⁴, -OR₇, -R₅R₁⁴, -R₁⁵R₁⁴, -R₁², -R₁⁴, -R₁⁵R₆, -R₁⁵(R₈)n, -SO₂R₁⁰, -SO₂R₁², -SO₂R₁³, -SO₂R₁⁴, -R₁⁵R₁⁴, -R₅R₁⁰, -(R₈)n, -(R₁⁴R₁²)₂, -(R₁⁴R₆)₂, -R¹⁴R₆, -CO₂R₇, (C₃-C₁₂)cycloalkyl, and (C₄-C₁₄)aryl, wherein **A** and **Q** are independently chosen from -(CH₂)nR₁⁴ or -(CH₂)ₙR₁⁴;

- **R¹** and **R²** taken together with any intervening atoms and when **Z** is a bond, can optionally form a fused (C₆-C₆)heterocyclic ring having 1-3 heteroatoms selected from S, N and O; wherein said fused heterocyclic ring can also be optionally substituted with one to two R₆ groups;

- **R³** is selected from the group consisting of hydrogen, halo, and (C₁-C₆)alkyl;

- **R⁴** is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, nitrile, oxo, -C(0)R₁², -SO₂R₉, -R₉(R₁⁵)ₙ, -OR₇, -R₁², and halo;

- **R⁵** is a branched or straight chain (d-CeJalkylene);

- **R⁶** is independently selected from the group consisting of (d-CeJalkyl, oxo, (C₁-C₆)alkoxy, -OR₇, halo, nitrile, and -CO₂R₇;

- **R⁷** is selected from the group consisting of hydrogen and (C₁-C₆)alkyl;

- **R⁸** is independently selected from the group consisting of hydrogen, (CrC₇)alkyl, -R₁⁵, -R₁³, -R₅R₁³, -R₅R₁⁴, -R₅(R₁³)ₙ, and -R₅R₁⁴(R₁³)ₙ.
R^9 is (C_1-C_7)alkyl;
R^10 is (C_4-C_14)aryl;
R^{11} is selected from the group consisting of nitrile, halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, and -R^{14}R^{12};
R^{12} is -N(R^9)^2, wherein each instance of R^9 may be independently and separately chosen from among the possible R^9 substituents;
R^{13} is (C_3-C_14)cycloalkyl;
R^{14} is selected from (d-C_nJheterocycle or (C=CuJheteroaryl, each having one to three heteroatoms selected from N and O;
R^{15} is halo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

[0068] In another embodiment of the present invention, there is provided a compound of Formula (IV), or a pharmaceutically acceptable salt thereof, wherein:
Z is selected from the group consisting of a bond, methylene, ethylene, dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene, methylpropylene, methylcyclopropylmethyl, and isopropylmethylene;
X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R^{12}, -C(0)R^{14}, -SO_2R^9, -SO_2R^{12}, -SO_2R^{14}, -SO_2R^{14}(R^9)_n, -NHSO_2R^{13}, -NHSO_2R^{14}, -NHSO_2R^9R^{14}, -NHSO_2R^{10}(R^9)_n, -NHSO_2R^{14}(R^9)_n;
R^1 is selected from the group consisting of hydrogen, -R^5R^{14}, and -C(0)R^9;
R^2 is selected from the group consisting of hydrogen, -N(H)R^{14}, -OR^{14}, -R^{10}R^{14}, -R^{12}, -R^{14}, -(R^{14})_2, -SO_2R^{10}, -SO_2R^{12}, -SO_2R^{14}, -SO_2R^{14}, -C(0)R^{10}, -R^{10}R^{14}, -R^{12}, -R^{14}, -(R^{14})_2, -R^{14}R^{14}, -(R^{14}R^{12}), cyclopentyl, dihydroyindenyl, and phenyl, wherein A and Q are independently chosen from -(CH_2)_wR^{10} or -(CH_2)_wR^{14};
R^1 and R^2 taken together with any intervening atoms and when Z is a bond can optionally form a fused imidazole ring that can also be optionally substituted with one to two R^9 groups;
R₃ is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;
R₄ is selected from the group consisting of hydrogen, -C(0)R₁₂, -SO₂R⁹, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;
R₅ is selected from the group consisting of methylene, ethylene, and propylene;
R₆ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and -C₀₂R₇;
R₇ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl;
R₈ is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, heptyl, hexyl, heptyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -R₉R₁₀, -R⁹R₁³, -R¹⁰(R¹¹)ₐ and -R⁹R¹⁰(R¹¹)ₐ;
R₉ is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, penty, t-pentyl, neopentyl, hexyl, heptyl, dimethylbutanyl, and dimethylpentanyl;
R₁₀ is phenyl;
R₁¹ is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and -R¹⁴R₁₂;
R₁² is -N(R⁸)₂, wherein each R⁸ may be independently chosen from among the R⁸ substituents;
R₁³ is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
R₁⁴ is selected from the group consisting of morpholyl, thiomorpholyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, piperidinyl, and pyridinyl;
R₁⁵ is selected from the group consisting of fluoro, chloro, and iodo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

[0069] In another embodiment of the present invention, there is provided a compound of Formula (V):
or a pharmaceutically acceptable salt thereof, wherein:

X is selected from -NHSO₂R₀(R₆)₀ or -SO₂R₁;
R¹ is selected from the group consisting of hydrogen, -C₀₂R₇, -C(O)R₁₀, and -C(O)R₉;
R² is selected from the group consisting of hydrogen, -R¹₀R₁₂, -R¹₀R₁₄, -R¹₀, -R¹₆, and -R¹₀R₆;
R⁴ is selected from hydrogen or (C₁-C₆)alkoxy;
R⁶ is independently selected from the group consisting of (C₁-C₆)alkyl, oxo, (C₁-C₆)alkoxy, -OR₇, halo, nitrile, and -C₀₂R₇;
R⁷ is selected from hydrogen or (C₆-C₆)alkyl;
R⁸ is selected from hydrogen or (C₁-C₆)alkyl;
R⁹ is (C₁-C₇)alkyl;
R¹₀ is (C₄-C₄₅)aryl;
R¹₂ is -N(R₈)₂, wherein each instance of R₈ may be independently and separately chosen from among the possible R₈ substituents;
R¹₄ is selected from (C₁-C₄₅)heterocycle or (d-CuJheteroaryl, each having one to three heteroatoms selected from N and O;
R¹₅ is halo; and
each n is independently zero or an integer from 1 to 3.

In another embodiment of the present invention, there is provided a compound of Formula (V), or a pharmaceutically acceptable salt thereof, wherein:

X is selected from -NHSO₂R¹₀(R₆)₀ or -SO₂R₁;
R¹ is selected from the group consisting of hydrogen, -C₀₂R₇, -C(O)R₁₀, and -C(O)R₉;
R² is selected from the group consisting of hydrogen, -R¹₀R₁₂, -R¹₀R₁₄, -R¹₀, -R¹₆, and -R¹₀R₆;
R⁴ is selected from hydrogen or methoxy;
R⁶ is independently selected from the group consisting of methyl, oxo, methoxy, fluoro, bromo, nitrile, and -C₀₂R₇;
R⁷ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, and butyl;
R⁸ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, heptyl,
hexyl, and heptyl;
R^9 is selected from the group consisting of methyl, ethyl, propyl, butyl heptyl, hexyl, and heptyl;
R^{10} is phenyl;
R^{12} is -N(R^8)_2, wherein each instance of R^8 may be independently and separately
chosen from among the possible R^8 substituents;
R^{14} is morpholinyl; and
R^{15} is selected from fluoro or bmeno.

[0071] In another embodiment of the present invention, there is provided a compound of
Formula (I), or a pharmaceutically acceptable salt thereof, wherein:
[0072] In another embodiment of the present invention, there is provided a compound of
Formula (I), or a pharmaceutically acceptable salt thereof, wherein Z is selected from the group
consisting of a bond, methylene, ethylene, dimethylmethylene, methylethylene, ethylmethylene, propylimethylene, methylpropylene, methylcyclopropylmethylene, and
isopropylmethylene.

[0073] In another embodiment of the present invention, there is provided a compound of
Formula (I), or a pharmaceutically acceptable salt thereof, wherein Z is selected from the group
consisting of a bond, methylene, and ethylene.

[0074] In another embodiment of the present invention, there is provided a compound of
Formula (I), or a pharmaceutically acceptable salt thereof, wherein Z is selected from a bond or
methylene.

[0075] In another embodiment of the present invention, there is provided a compound of
Formula (I), or a pharmaceutically acceptable salt thereof, wherein Z is a bond.

[0076] In another embodiment of the present invention, there is provided a compound of
Formula (I), or a pharmaceutically acceptable salt thereof, wherein Z is methylene.

[0077] In another embodiment of the present invention, there is provided a compound of
Formula (I), or a pharmaceutically acceptable salt thereof, wherein X is selected from the group
consisting of -SO_2R^6, -SO_2R^{12}, -SO_2R^{14}, -SO_2R^{14}(R^6)_n, -NHSO_2R^{10}, -NHSO_2R^{10}(R^6)_n,
-NHSO_2R^{13}, -NHSO_2R^{14}, -NHSO_2R^{14}(R^6)_n, -NHSO_2R^{14}, and, -NHSO_2R^{14}(R^6)_n.

[0078] In another embodiment of the present invention, there is provided a compound of
Formula (I), or a pharmaceutically acceptable salt thereof, wherein X is selected from the group
consisting of -SO_2R^6, -SO_2R^{12}, -SO_2R^{14}, and -SO_2R^{14}(R^6)_n.

[0079] In another embodiment of the present invention, there is provided a compound of
Formula (I), or a pharmaceutically acceptable salt thereof, wherein X is selected from the group
consisting of -NHSO₂R¹⁰, -NHSO₂R¹⁰(R⁶)ₙ, -NHSO₂R¹³, -NHSO₂R¹⁴, -NHSO₂R⁶R¹⁴, -NHSO₂R⁶(R⁶)ₙ, -NHSO₂R⁹, and, -NHSO₂R¹⁴(R⁶)ₙ.

[0080] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein X is selected from -NHSO₂R¹⁰(R⁶)ₙ or -S₀₂R¹₂.

[0081] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein X is -NHSO₂R¹⁰(R⁶)ₙ.

[0082] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from the group consisting of hydrogen, -R⁵R¹⁴, and -C(0)R⁹;

[0083] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen.

[0084] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR³R¹⁴, -OR⁷, -R⁶R¹⁰, -R¹⁰R⁶R¹⁴, -R¹₂, -R¹⁴, -(R¹⁴)₂, -SO₂R¹⁰, -S₀₂R¹², -S₀₂R¹³, -S₀₂R¹⁴, -C₀₂R⁷, -R¹⁰R⁶, -R¹³R¹⁴, -R¹³R¹⁶, -R¹⁴R⁶, -(R¹⁴)₂, (C₅₋₇-C₁₃)cycloalkyl, and phenyl.

[0085] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR³R¹⁴, -OR⁷, -R⁶R¹⁰, -R¹⁰R⁶R¹⁴, -R¹₂, -R¹⁴, -(R¹⁴)₂, -SO₂R¹⁰, -S₀₂R¹², -S₀₂R¹³, -S₀₂R¹⁴, -C₀₂R⁷, -R¹⁰R⁶, -R¹³R¹⁴, -R¹³R¹⁶, -R¹⁴R⁶, -(R¹⁴)₂, cyclopentyl, dihydroindenyl, and phenyl.

[0086] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² is -R¹⁰R¹⁴.

[0087] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² is selected from the group consisting of morpholinylphenyl.

[0088] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen.

[0089] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁴ is selected from the group consisting of hydrogen, -C(0)R¹², -S₀₂R⁹, methyl, ethyl, propyl, isopropyl, butyl, t-butyl,
methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, trifluoromethyl, fluoro, and iodo.

[0090] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^4$ is methoxy.

[0091] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^5$ is methylene.

[0092] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^6$ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and $-C_0_2R^7$.

[0093] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^7$ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and t-butyl.

[0094] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^8$ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl.

[0095] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^9$ is selected from the group of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, t-isobutyl, hydroxy, fluoro, chloro, iodo, methylamino, dimethylamino, trifluoromethyl, fluoro, and iodo.

[0096] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^10$ is independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, t-isobutyl, hydroxy, fluoro, chloro, iodo, neopentyl, hexyl, and heptyl.

[0097] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^10$ is independently selected from the group of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, t-isobutyl, hydroxy, fluoro, chloro, iodo, methylamino, dimethylamino, trifluoromethyl, fluoro, and iodo.

[0098] In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^{11}$ is independently selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, and methoxy.
In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein \( R^{13} \) is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl.

In another embodiment of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein \( R^{14} \) is morpholinyl.

In another embodiment of the present invention, there is provided a compound of Formula (I), wherein \( Z \) is selected from the group consisting of a bond, methylene, and ethylene.

In another embodiment of the present invention, there is provided a compound of Formula (I), wherein \( Z \) is a bond.

In another embodiment of the present invention, there is provided a compound of Formula (I), wherein \( Z \) is methylene.

In another embodiment of the present invention, there is provided a compound of Formula (I), wherein each \( m \) is independently an integer ranging from 1 to 3.

In another embodiment of the present invention, there is provided a compound of Formula (I), wherein each \( n \) is independently an integer from 1 to 3.

In another embodiment of the present invention, there is provided a compound of Formula (I), wherein each \( w \) is independently an integer from 1 to 6.

In another embodiment of the present invention, there is provided a compound of Formula (I), wherein \( m \) is 3.

In another embodiment of the present invention, there is provided a compound of Formula (I), wherein \( n \) is 2.

In another embodiment of the present invention, there is provided a compound of Formula (I), wherein \( w \) is 1.

In another embodiment of the invention, there is provided a compound of any of Formulas I, II, III, IV, and V, wherein the compound or salt of the compound is used in the manufacture of a medicament for use in the treatment of a viral infection in a human.

In another embodiment of the invention, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable diluent and a therapeutically effective amount of a compound as defined in any of Formulas I, II, III, IV, and V.
In another embodiment of the invention, there is provided a method for treating a viral infection in a mammal mediated at least in part by a virus in the Flaviviridae family of viruses which method comprises administering to a mammal, that has been diagnosed with said viral infection or is at risk of developing said viral infection, a compound of any of Formulas 1, II, III, IV, and V.

In another embodiment of the invention, there is provided a method for treating a viral infection in a mammal mediated at least in part by a virus in the Flaviviridae family of viruses which method comprises administering to a mammal, that has been diagnosed with said viral infection or is at risk of developing said viral infection, a compound of any of Formulas 1, II, III, IV, V, and VI, wherein said virus is hepatitis C virus.

In another embodiment of the invention, there is provided a method for treating a viral infection in a mammal mediated at least in part by a virus in the Flaviviridae family of viruses which method comprises administering to a mammal, that has been diagnosed with said viral infection or is at risk of developing said viral infection, a compound of any of Formulas 1, II, III, IV, and V, further comprising administration of a therapeutically effective amount of one or more agents active against hepatitis C virus.

In another embodiment of the invention, there is provided a method for treating a viral infection in a mammal mediated at least in part by a virus in the Flaviviridae family of viruses which method comprises administering to a mammal, that has been diagnosed with said viral infection or is at risk of developing said viral infection, a compound of any of Formulas 1, II, III, IV, and V, further comprising administration of a therapeutically effective amount of one or more agents active against hepatitis C virus, wherein said agent active against hepatitis C virus is an inhibitor of HCV protease, HCV polymerase, HCV helicase, HCV entry, HCV assembly, HCV egress, HCV replicase, HCV NS5A protein, or inosine 5’-monophosphate dehydrogenase.

In another embodiment of the invention, there is provided a method for treating a viral infection in a mammal mediated at least in part by a virus in the Flaviviridae family of viruses which method comprises administering to a mammal, that has been diagnosed with said viral infection or is at risk of developing said viral infection, a compound of any of Formulas 1, II, III, IV, and V, further comprising administration of a therapeutically effective amount of one or more agents active against hepatitis C virus, wherein said agent active against hepatitis C virus is interferon.

In another embodiment of the invention, there is provided a method for treating a viral infection in a mammal mediated at least in part by a virus in the Flaviviridae family of viruses which method comprises administering to a mammal, that has been diagnosed with said
viral infection or is at risk of developing said viral infection, a compound of any of Formulas I, II, III, IV, and V, further comprising administration of a therapeutically effective amount of one or more agents active against hepatitis C virus, wherein said agent active against hepatitis C virus is ribavirin.

[00120] In another embodiment of the invention, there is provided a method for treating a viral infection in a mammal mediated at least in part by a virus in the Flaviviridae family of viruses which method comprises administering to a mammal, that has been diagnosed with said viral infection or is at risk of developing said viral infection, a compound of any of Formulas I, II, III, IV, and V, further comprising administration of a therapeutically effective amount of one or more agents active against hepatitis C virus, wherein said agent active against hepatitis C virus is interferon in combination with ribavirin.

[00121] In yet further embodiments, the compound of the present invention, or a pharmaceutically acceptable salt thereof, is chosen from the compounds set forth in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Compound No. and Example No.</th>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-benzyl-2-methoxy-N-methylpyridine-3-sulfonamide</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-cyclohexyl-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6-(6-methoxy-5-(morpholinosulfonyl)pyridin-3-yl)-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-isopropyl-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6-(6-methoxy-5-(piperidin-1-ylsulfonyl)pyridin-3-yl)-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-cyclopropyl-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(2,4-dimethylpentan-3-yl)-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td></td>
<td>Molecule Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>---</td>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Molecule 8" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-(tert-pentyl)pyridine-3-sulfonamide</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Molecule 9" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-methylpyridine-3-sulfonamide</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Molecule 10" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-ethyl-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Molecule 11" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-neopentylpyridine-3-sulfonamide</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="Molecule 12" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(3,3-dimethylbutan-2-yl)-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td>13</td>
<td><img src="image" alt="Molecule 13" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-cyclobutyl-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>---</td>
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<td>-----------------</td>
</tr>
<tr>
<td>14</td>
<td><img src="structure14.png" alt="Structure" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(cyclopentylmethyl)-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td>15</td>
<td><img src="structure15.png" alt="Structure" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-(tetrahydro-2H-pyran-4-yl)pyridine-3-sulfonamide</td>
</tr>
<tr>
<td>16</td>
<td><img src="structure16.png" alt="Structure" /></td>
<td>2-amino-5-(2-amino-1-cyclopentyl-1H-benzimidazol-6-yl)-N-cyclopropyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>17</td>
<td><img src="structure17.png" alt="Structure" /></td>
<td>2-amino-5-(2-amino-1-phenyl-1H-benzimidazol-6-yl)-N-cyclopropyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>18</td>
<td><img src="structure18.png" alt="Structure" /></td>
<td>2-amino-5-(2-amino-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-6-yl)-N-cyclopropyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>19</td>
<td><img src="structure19.png" alt="Structure" /></td>
<td>2-amino-5-(2-amino-1-cyclopentyl-1H-benzimidazol-6-yl)-N-phenyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2-amino-5-{2-amino-1-[3-(4-morpholiny1)propyl]-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>---</td>
<td>----</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>2-amino-5-{2-amino-1-phenyl-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>2-amino-5-{2-amino-1-[(1S)-1-phenylethyl]-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>2-amino-5-{2-amino-1-[(1S)-1-phenylethyl]-1H-benzimidazol-6-yl]-N-cyclopropyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>5-{2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl]-N,N-dimethyl-2-(methyloxy)-3-pyridinesulfonamide</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>2-amino-5-{2-amino-1-[2-(4-morpholiny1)cyclopropyl]-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide formic acid salt</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>26</td>
<td><img src="image" alt="Structure 26" /></td>
<td>2-amino-5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-N-cyclopropyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>27</td>
<td><img src="image" alt="Structure 27" /></td>
<td>2-amino-5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-N,N-dimethyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>28</td>
<td><img src="image" alt="Structure 28" /></td>
<td>2-amino-5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>29</td>
<td><img src="image" alt="Structure 29" /></td>
<td>5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-N,N-dimethyl-2-(methylxy)-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>30</td>
<td><img src="image" alt="Structure 30" /></td>
<td>5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-N-(2,4-difluorophenyl)-2-(methylxy)-3-pyridinesulfonamide</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>31</td>
<td><img src="image1" alt="Molecule Image" /></td>
<td>5-[2-amino-1-{1,1-dimethylethyl}-1H-benzimidazol-6-yl]-2-(m ethyloxy)-N-phenyl-3-pyridinesulfonamide formic acid salt</td>
</tr>
<tr>
<td>32</td>
<td><img src="image2" alt="Molecule Image" /></td>
<td>2-amino-5-[2-amino-1-(phenylsulfonyl)-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>33</td>
<td><img src="image3" alt="Molecule Image" /></td>
<td>5-[2-amino-1-{4-(4-morpholinyl)phenyl}-1H-benzimidazol-6-yl]-N-(2,4-difluorophenyl)-2-(m ethyloxy)-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>34</td>
<td><img src="image4" alt="Molecule Image" /></td>
<td>5-[2-amino-1-(phenylsulfonyl)-1H-benzimidazol-6-yl]-N,N-dimethyl-2-(m ethyloxy)-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>35</td>
<td><img src="image5" alt="Molecule Image" /></td>
<td>5-[2-amino-1-{2-(4-morpholinyl)cyclopentyl}-1H-benzimidazol-6-yl]-2-(m ethyloxy)-N-phenyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>36</td>
<td><img src="image6" alt="Molecule Image" /></td>
<td>5-[2-amino-1-{4-(4-morpholinyl)phenyl}-1H-benzimidazol-6-yl]-2-(m ethyloxy)-N-phenyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Description</td>
</tr>
<tr>
<td>---</td>
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<td>-------------</td>
</tr>
<tr>
<td>37</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-[[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl]-1H-benzimidazol-6-yl)-2-(methyloxy)-N-phenyl-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>38</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-[[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl]-1H-benzimidazol-6-yl)-N-(4-fluorophenyl)-2-(methyloxy)-3-pyridinesulfonamide</td>
</tr>
<tr>
<td>39</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-(tert-butyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td>40</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-phenyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td>41</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-((4-(dimethylamino)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-phenylpyridine-3-sulfonamide, Formic acid salt</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Description</td>
</tr>
<tr>
<td>---</td>
<td>--------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>42</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-methyl-N-phenylpyridine-3-sulfonamide, Formic acid salt</td>
</tr>
<tr>
<td>43</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-((4-dimethylamino)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td>44</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-isobutyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide, Formic acid salt</td>
</tr>
<tr>
<td>45</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-cyclopentyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide, Formic acid salt</td>
</tr>
<tr>
<td>46</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-(pyridin-3-ylmethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide, Formic acid salt</td>
</tr>
<tr>
<td>47</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-((1r,4r)-4-hydroxycyclohexyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Description</td>
</tr>
<tr>
<td>---</td>
<td>------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>48</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxy-N-methylpyridine-3-sulfonamide, Formic acid salt</td>
</tr>
<tr>
<td>49</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>tert-butyl 3-(2-amino-6-(5-(N-(tert-butyl)sulfamoyl)-6-methoxyimidazol-3-yl)-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate, Formic acid salt</td>
</tr>
<tr>
<td>50</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-(pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide, Trifluoroacetate</td>
</tr>
<tr>
<td>51</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-(2-phenylpropan-2-yl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide, Formic acid salt</td>
</tr>
<tr>
<td>52</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>(S)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide, Formic acid salt</td>
</tr>
<tr>
<td>53</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>5-(2-amino-1-(2,3-dihydro-1H-inden-1-yl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide, Formic acid salt</td>
</tr>
<tr>
<td>54</td>
<td>5-(2-amino-1-((4-(dimethylamino)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-N-(3-fluorophenyl)-2-methoxypyridine-3-sulfonamide, Formic acid salt</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>5-(2-amino-1-(4-morpholino-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-(1-phenylethyl)pyridine-3-sulfonamide formic acid salt</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>5-(2-amino-1-(4-morpholino-1H-benzo[d]imidazol-6-yl)-N-benzyl-2-methoxypyridine-3-sulfonamide formic acid salt</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>5-(2-amino-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt</td>
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<tr>
<td>58</td>
<td>5-(2-amino-1-(2-morpholinoethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxy pyridine-3-sulfonamide formic acid salt</td>
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<td>59</td>
<td>(R)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxy-N-methylpyridine-3-sulfonamide formic acid salt</td>
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<td>(R)-5-[(2-amino-1-(1-phenylethyl))-1H-benzo[d]imidazol-6-yl]-N-benzyl-2-methoxypyridine-3-sulfonamide, Formic acid salt</td>
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<td>61</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(R)-5-[(2-amino-1-(1-phenylethyl))-1H-benzo[d]imidazol-6-yl]-N-(3-fluorophenyl)-2-methoxypyridine-3-sulfonamide formic acid salt</td>
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<td>(R)-5-[(2-amino-1-(1-phenylethyl))-1H-benzo[d]imidazol-6-yl]-N-benzyl-2-methoxy-N-methylpyridine-3-sulfonamide formic acid salt</td>
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<td>63</td>
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<td>5-[(2-amino-1-(4-morpholinophenyl))-1H-benzo[d]imidazol-6-yl]-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt</td>
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<td><img src="image65" alt="Structure 65" /></td>
<td>5-(2-amino-1-(3-(oxazol-5-yl)phenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
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<td>66</td>
<td><img src="image66" alt="Structure 66" /></td>
<td>5-(2-amino-1-(3-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
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<td><img src="image67" alt="Structure 67" /></td>
<td>(R)-5-(2-amino-5-fluoro-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
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<td>68</td>
<td><img src="image68" alt="Structure 68" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(3-chlorophenyl)-2-methoxypyridine-3-sulfonamide, Formic acid salt</td>
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<td>69</td>
<td><img src="image69" alt="Structure 69" /></td>
<td>(R)-5-(2-amino-1-(1-phenylpropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide, Formic acid salt</td>
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<td>70</td>
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<td>(R)-5-(2-amino-1-(2-methyl-1-phenylpropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide, Formic acid salt</td>
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<td>71</td>
<td><img src="image" alt="Molecular Structure 1" /></td>
<td>5-(2-amino-1-benzyl-5-methyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide, Trifluoroacetic acid salt</td>
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<td>76</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>6-{6-amino-5-(1-piperidinylsulfonyl)-3-pyridinyl}-1-[4-(4-morpholinyl)phenyl]-1 H-benzimidazol-2-amine</td>
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<td>6-{6-amino-5-[[1,1-dioxido-4-thiomorpholinyl]sulfonyl]-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1 H-benzimidazol-2-amine</td>
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<td><img src="image3" alt="Chemical Structure" /></td>
<td>2-amino-5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1 H-benzimidazol-6-yl}-N-(4-cyanophenyl)-3-pyridinesulfonamide</td>
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<td>2-amino-5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1 H-benzimidazol-6-yl}-N-(tetrahydro-2H-pyran-4-yl)-3-pyridinesulfonamide</td>
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<td>80</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>2-amino-5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1 H-benzimidazol-6-yl}-N-(2,4-difluorophenyl)-3-pyridinesulfonamide</td>
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<td><img src="image1" alt="Molecule 1" /></td>
<td>2-amino-5-{2-amino-1-[4-{4-morpholinyl}phenyl]-1H-benzimidazol-6-yl]-N-3-pyridinyl-3-pyridinesulfonamide</td>
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<td>82</td>
<td><img src="image2" alt="Molecule 2" /></td>
<td>5-{2-amino-1-[4-{4-morpholinyl}phenyl]-1H-benzimidazol-6-yl]-N-cyclopropyl-3-pyridinesulfonamide</td>
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<td>83</td>
<td><img src="image3" alt="Molecule 3" /></td>
<td>5-{2-amino-1-[4-{4-morpholinyl}phenyl]-1H-benzimidazol-6-yl]-N,N-dimethyl-3-pyridinesulfonamide</td>
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<td>84</td>
<td><img src="image4" alt="Molecule 4" /></td>
<td>5-{2-amino-1-[4-{4-morpholinyl}phenyl]-1H-benzimidazol-6-yl]-N-(2,4-difluorophenyl)-3-pyridinesulfonamide</td>
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<td>85</td>
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<td>5-{2-amino-1-[4-{4-morpholinyl}phenyl]-1H-benzimidazol-6-yl]-N-ethyl-3-pyridinesulfonamide</td>
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<td>86</td>
<td><img src="image6" alt="Molecule 6" /></td>
<td>5-{2-amino-1-[4-{4-morpholinyl}phenyl]-1H-benzimidazol-6-yl]-N,N-diethyl-3-pyridinesulfonamide</td>
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87  

2-amino-5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-methyl-N-phenyl-3-pyridinesulfonamide

88  

2-amino-6-{6-amino-5-[(phenylamino)sulfonyl]-3-pyridinyl]-N,N-dimethyl-1H-benzimidazole-1-sulfonamide

89  

2-amino-5-{2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide

90  

2-amino-6-{5-[(dimethylamino)sulfonyl]-6-(methyl oxy)-3-pyridinyl]-N,N-dimethyl-1H-benzimidazole-1-sulfonamide

91  

5-{2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N,N-dimethyl-2-(methyl oxy)-3-pyridinesulfonamide

92  

2-amino-6-{6-amino-5-{(tetrahydro-2H-pyran-4-ylamino)sulfonyl]-3-pyridinyl]-N,N-dimethyl-1H-benzimidazole-1-sulfonamide
<p>| <strong>93</strong> | 2-amino-5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N-cyclopropyl-3-pyridinesulfonamide |
| <strong>94</strong> | 2-amino-6-[6-amino-5-[(cyclopropylamino)sulfonyl]-3-pyridiny]-N,N-dimethyl-1H-benzimidazole-1-sulfonamide |
| <strong>95</strong> | 2-amino-5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N-(tetrahydro-2H-pyran-4-yl)-3-pyridinesulfonamide |
| <strong>96</strong> | 2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(phenylmethyl)-3-pyridinesulfonamide |
| <strong>97</strong> | 5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-methyl-3-pyridinesulfonamide |
| <strong>98</strong> | 2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-methyl-3-pyridinesulfonamide |</p>
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<td>99</td>
<td><img src="image99" alt="Image" /></td>
<td>5-{2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl]-2-(ethyloxy)-N,N-dimethyl-3-pyridinesulfonamide</td>
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<td>100</td>
<td><img src="image100" alt="Image" /></td>
<td>5-{2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl]-N-(cyclopropylmethyl)-2-(methyloxy)-3-pyridinesulfonamide</td>
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<td>101</td>
<td><img src="image101" alt="Image" /></td>
<td>5-{2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl]-2-(dimethylamino)-N,N-dimethyl-3-pyridinesulfonamide</td>
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<td>102</td>
<td><img src="image102" alt="Image" /></td>
<td>5-{2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl]-N,N-dimethyl-2-(methylamino)-3-pyridinesulfonamide</td>
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<td>103</td>
<td><img src="image103" alt="Image" /></td>
<td>5-{2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl]-N-(1,1-dimethylethyl)-2-(methyloxy)-3-pyridinesulfonamide</td>
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<td><img src="image" alt="104" /></td>
<td>5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-(4-fluorophenyl)-2-(methyloxy)-3-pyridinesulfonamide</td>
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<td><img src="image" alt="105" /></td>
<td>6-{6-(methyloxy)-5-(1-pyrrolidinylsulfonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine</td>
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<td><img src="image" alt="106" /></td>
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<td>107</td>
<td><img src="image" alt="107" /></td>
<td>5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-(2-hydroxyethyl)-2-(methyloxy)-3-pyridinesulfonamide</td>
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<td>108</td>
<td><img src="image" alt="108" /></td>
<td>5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-cyclopentyl-2-(methyloxy)-3-pyridinesulfonamide</td>
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<td>109</td>
<td>5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-[3-(methyloxy)phenyl]-3-pyridinesulfonamide</td>
<td><img src="image1.png" alt="Structure 109" /></td>
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<tr>
<td>110</td>
<td>5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-(4-methylphenyl)-3-pyridinesulfonamide</td>
<td><img src="image2.png" alt="Structure 110" /></td>
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<td>111</td>
<td>5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-(2-methylphenyl)-3-pyridinesulfonamide</td>
<td><img src="image3.png" alt="Structure 111" /></td>
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<td>112</td>
<td>5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-(3-methylphenyl)-3-pyridinesulfonamide</td>
<td><img src="image4.png" alt="Structure 112" /></td>
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<tr>
<td>113</td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-4-methoxy-N-(4-methoxyphenyl)pyridine-3-sulfonamide</td>
<td><img src="image5.png" alt="Structure 113" /></td>
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<td>115</td>
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<td>116</td>
<td><img src="image3.png" alt="Structure" /></td>
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<td>117</td>
<td><img src="image4.png" alt="Structure" /></td>
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<td>118</td>
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<td>119</td>
<td><img src="image6.png" alt="Structure" /></td>
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**Description:**

1. Compound 114: 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-(2-methoxyphenyl)pyridine-3-sulfonamide
2. Compound 115: 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(3-fluorophenyl)-2-methoxypyridine-3-sulfonamide
3. Compound 116: 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(2-fluorophenyl)-2-methoxypyridine-3-sulfonamide
4. Compound 117: 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(2-fluoro-3-methylphenyl)-2-methoxypyridine-3-sulfonamide
5. Compound 118: 5-(2-amino-1-isopropyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide
6. Compound 119: 5-(2-amino-1-(3-morpholinopropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide
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<td><img src="image" alt="Chemical Structure 120" /></td>
<td>5-(2-amino-1-methyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
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<td>121</td>
<td><img src="image" alt="Chemical Structure 121" /></td>
<td>5-(2-amino-1-(2-hydroxyethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
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<td>122</td>
<td><img src="image" alt="Chemical Structure 122" /></td>
<td>5-(2-amino-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
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<td>123</td>
<td><img src="image" alt="Chemical Structure 123" /></td>
<td>5-(2-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
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<td>124</td>
<td><img src="image" alt="Chemical Structure 124" /></td>
<td>5-(2-amino-1-phenethyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
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<td>125</td>
<td><img src="image" alt="Chemical Structure 125" /></td>
<td>5-(2-amino-1-(3-phenylpropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide</td>
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<td>126</td>
<td><img src="image1.png" alt="Image 1" /></td>
<td>2-amino-6-(5-((N-(tert-butyl)sulfamoyl)-6-methoxypyrindin-3-yl)-N,N-dimethyl-1H-benzo[d]imidazole-1-sulfonamide</td>
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<td>127</td>
<td><img src="image2.png" alt="Image 2" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-(methylamino)pyridine-3-sulfonamide</td>
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<td>128</td>
<td><img src="image3.png" alt="Image 3" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-(dimethylamino)pyridine-3-sulfonamide</td>
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<tr>
<td>129</td>
<td><img src="image4.png" alt="Image 4" /></td>
<td>5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-ethoxypyridine-3-sulfonamide, Formate salt</td>
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<tr>
<td>130</td>
<td><img src="image5.png" alt="Image 5" /></td>
<td>N-[5-[2-amino-1-(2-methylpropyl)-1H-benzimidazol-6-yl]-2-(methylxoy)-3-pyridinyl]-2,4-diflorobenzenesulfonamide</td>
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<tr>
<td>131</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>N-[5-(2-amino-1-methyl-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-(2-amino-1-cyclopentyl-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>133</td>
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<td>N-[5-[2-amino-1-(1-methylethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>134</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>2,4-difluoro-N-[2-(methyloxy)-5-(2-[[2-(4-morpholinyl)ethyl]amino]-1H-benzimidazol-5-yl)-3-pyridinyl]benzenesulfonamide</td>
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<td>135</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>2,4-difluoro-N-[2-(methyloxy)-5-(2-[[2-(1-pyrrolidinyl)ethyl]amino]-1H-benzimidazol-5-yl)-3-pyridinyl]benzenesulfonamide</td>
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N-[5-{2-amino-1-[3-{2-oxo-1-pyrrolidinyl}propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

N-[5-{2-amino-1-{2-(methyloxy)phenyl}-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

N-[5-{2-amino-1-[3-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

N-[5-{2-amino-1-(phenylmethyl)-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide hydrobromide

N-[5-{2-amino-1-[4-(methyloxy)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

N-[5-{2-amino-1-[(1R)-1-phenylethyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide
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<td>142</td>
<td><img src="image1.png" alt="Image" /></td>
<td>N-[5-{2-amino-1-(3-pyridinylmethyl)-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>143</td>
<td><img src="image2.png" alt="Image" /></td>
<td>N-[5-{2-amino-1-[3-(3-oxo-4-morpholiny]propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>144</td>
<td><img src="image3.png" alt="Image" /></td>
<td>N-[5-{2-amino-1-(trans-4-hydroxycyclohexyl)-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>145</td>
<td><img src="image4.png" alt="Image" /></td>
<td>N-[5-{2-amino-1-[(1S)-1-phenylethyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>146</td>
<td><img src="image5.png" alt="Image" /></td>
<td>N-[5-{2-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>147</td>
<td><img src="image6.png" alt="Image" /></td>
<td>N-[5-{2-amino-1-[3-(4-morpholiny]methyl]phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<tr>
<td>148</td>
<td><img src="image1.png" alt="Image" /></td>
<td>N-[5-{2-amino-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-3-pyridinesulfonamide</td>
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<td>149</td>
<td><img src="image2.png" alt="Image" /></td>
<td>N-[5-(2-amino-1-[4-(dimethylamino)tetrahydro-2H-pyran-4-yl][methyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-3-pyridinesulfonamide</td>
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<td><img src="image4.png" alt="Image" /></td>
<td>N-[5-{2-amino-1-[2-(4-morpholinyl)cyclopentyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-{2-amino-1-[1,1-dimethylethyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-3-pyridinesulfonamide</td>
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<td><img src="image6.png" alt="Image" /></td>
<td>N-[5-{2-amino-1-[phenylsulfonyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-3-pyridinesulfonamide</td>
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<td>154</td>
<td><img src="image1.jpg" alt="Molecule 154" /></td>
<td>N-[5-[2-amino-1-(phenylsulfonyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>155</td>
<td><img src="image2.jpg" alt="Molecule 155" /></td>
<td>N-[5-[2-amino-1-(2-phenylethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>156</td>
<td><img src="image3.jpg" alt="Molecule 156" /></td>
<td>N-[5-[2-amino-1-(3-phenylpropyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>157</td>
<td><img src="image4.jpg" alt="Molecule 157" /></td>
<td>N-(5-(2-amino-1-(2,3-dihydro-1H-inden-1-yl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide</td>
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<td>158</td>
<td><img src="image5.jpg" alt="Molecule 158" /></td>
<td>5-(2-amino-1-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-N-(2,4-difluorophenyl)-2-methoxypyridine-3-sulfonamide formic acid salt</td>
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<td>159</td>
<td><img src="image1.png" alt="Image" /></td>
<td>N-(5-(2-amino-1-(morpholinosulfonyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide</td>
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<td>160</td>
<td><img src="image2.png" alt="Image" /></td>
<td>N-(6-(5-(2,4-difluorophenylsulfonamido)-6-methoxypyridin-3-yl)-1H-benzo[d]imidazol-2-yl)acetamide</td>
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<td>161</td>
<td><img src="image3.png" alt="Image" /></td>
<td>N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide, Formic acid salt</td>
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<td>162</td>
<td><img src="image4.png" alt="Image" /></td>
<td>N-[5-(2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzo[d]imidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td><img src="image5.png" alt="Image" /></td>
<td>N-[5-(2-amino-1-[3-(4-morpholinyl)propyl]-1H-benzo[d]imidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>164</td>
<td><img src="image6.png" alt="Image" /></td>
<td>N-[5-(2-amino-1-[[4-(4-morpholinyl)phenyl]methyl]-1H-benzo[d]imidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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72
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<td>N-[5-{2-amino-1-(2-hydroxyethyl)-1H-benzimidazol-6-yl}-2-(methylene)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-{2-amino-1-[2-(dimethylamino)ethyl]-1H-benzimidazol-6-yl}-2-(methylene)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-{2-amino-1-[2-(1-pyrrolidinyl)ethyl]-1H-benzimidazol-6-yl}-2-(methylene)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-{2-amino-1-[2-(4-methyl-1-piperazinyl)ethyl]-1H-benzimidazol-6-yl}-2-(methylene)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td><strong>1,1-dimethylethyl 3-{2-amino-6-[5-([(2,4-difluorophenyl)sulfonyl]amino)-6-(methyloxy)-3-pyridinyl]-1 H-benzimidazol-1-yl}-1-pyrrolidinecarboxylate</strong></td>
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<td>172</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td><strong>N-[5-[2-amino-1-(4-methylphenyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</strong></td>
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<td><strong>N-[5-[2-amino-1-(3-methylphenyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</strong></td>
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<td><strong>N-[5-[2-amino-1-(3-pyrrolidinyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</strong></td>
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<td><strong>N-[5-[2-amino-1-{3-(1,3-oxazol-5-yl)phenyl]-1 H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</strong></td>
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<td>176</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td><strong>1,1-dimethylethyl (2S)-2-{2-amino-6-[5-][(2,4-difluorophenyl)sulfonyl]amino)-6-(methyloxy)-3-pyridinyl]-1 H-benzimidazol-1-yl}-3-methylbutanoate</strong></td>
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<td>1,1-dimethyl-2-{2-amino-6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl}propanoate</td>
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<td>178</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(2S)-2-{2-amino-6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl]-3-methylbutanoic acid</td>
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<td>179</td>
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<td>N-[6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1-methyl-1H-benzimidazol-2-yl]acetamide</td>
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<td>180</td>
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<td>2,4-difluoro-N-[5-[[3S]-3-(1-methylethyl)-2-oxo-2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]benzenesulfonamide</td>
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<td><img src="image5" alt="Chemical Structure" /></td>
<td>N-[5-(2-amino-1-[[2-(4-morpholinyl)cyclohexyl]methyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td><img src="image6" alt="Chemical Structure" /></td>
<td>(R)-tert-butyl 2-(2-amino-6-(5-(2,4-difluorophenyl)sulfonylamido)-6-methoxypyridin-3-yl)-1H-benzo[d]imidazol-1-yl]-3-methylbutanoate</td>
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<td>N-[5-{2-amino-1-[4-(4-morpholino)phenyl]-1H-benzimidazol-6-yl}-2-(methylxy)-3-pyridinyl]-8-quinoinesulfonamide</td>
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<td>N-[5-{2-amino-1-[4-(4-morpholino)phenyl]-1H-benzimidazol-6-yl}-2-(methylxy)-3-pyridinyl]-1-phenylmethanesulfonamide</td>
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<td>N-[5-{2-amino-1-[4-(4-morpholino)phenyl]-1H-benzimidazol-6-yl}-2-(methylxy)-3-pyridinyl]-3,4-bis(methylxy)benzenesulfonamide</td>
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<td>N-[5-{2-amino-1-[4-(4-morpholino)phenyl]-1H-benzimidazol-6-yl}-2-methyl-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>189</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>N-{5-{2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl}-2-[(1-methylethyl)oxy]-3-pyridinyl}benzenesulfonamide</td>
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<td>190</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>N-{5-{2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-4-cyanobenzenesulfonamide</td>
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<td><img src="image3.png" alt="Structure 3" /></td>
<td>N-{5-{2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2-methyl-1-propanesulfonamide</td>
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<td><img src="image4.png" alt="Structure 4" /></td>
<td>N-{5-{2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl}benzenesulfonamide</td>
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<td>193</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>N-{5-{2-amino-1-[3-(4-thiomorpholiny1)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl}-2,4-difluorobenzenesulfonamide</td>
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<td><img src="image6.png" alt="Structure 6" /></td>
<td>N-{5-{2-amino-1-[3-(tetrahydro-1,4-oxazepin-4(5H)-yl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl}-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-{2-aminob-1-{3-[4-hydroxy-1-piperidinyl]propyl}-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-{2-amino-1-[3-(1,1-dioxido-4-thiomorpholinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-{2-amino-1-[3-(4-fluoro-1-piperidinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-{2-amino-1-[3-[(tetrahydro-2-furanyl)methyl]amino]propyl}-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-{2-amino-1-[3-(2,6-dimethyl-4-morpholinypropyl)-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>2-amino-6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-N,N-dimethyl-1H-benzimidazole-1-sulfonamide</td>
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<td>202</td>
<td>N-[5-[2-amino-1-(cyclopropylsulfonyl)]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-[2-amino-1-[[1-(4-morpholinylmethyl)cyclopropyl]methyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-[5-[2-amino-1-[[3-(4-morpholinyl)butyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
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<td>N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)thiophene-2-sulfonamide</td>
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<td>N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-1-methyl-1H-indole-7-sulfonamide</td>
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<td>N-(5-(2-amino-1-(2-thiomorpholinoethyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide</td>
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<td>213</td>
<td><img src="image" alt="Structure 213" /></td>
<td>N-(5-(2-amino-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide</td>
</tr>
<tr>
<td>214</td>
<td><img src="image" alt="Structure 214" /></td>
<td>N-(5-(2-amino-1-((tetrahydro-2H-pyran-4-yl)ethyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide</td>
</tr>
<tr>
<td>215</td>
<td><img src="image" alt="Structure 215" /></td>
<td>N-(5-(2-amino-1-((pyridin-2-yl)methyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide</td>
</tr>
<tr>
<td>216</td>
<td><img src="image" alt="Structure 216" /></td>
<td>N-(5-(2-amino-1-((2-morpholino-1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide</td>
</tr>
<tr>
<td>217</td>
<td><img src="image" alt="Structure 217" /></td>
<td>N-(5-(2-amino-1-((2-morpholino-2-phenylethyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide</td>
</tr>
<tr>
<td>218</td>
<td><img src="image" alt="Structure 218" /></td>
<td>1-cyclopentyl-6-[5-(methylsulfanyl)-3-pyridinyl]-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td></td>
<td>Image</td>
<td>Chemical Structure</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>219</td>
<td><img src="image1.png" alt="Image" /></td>
<td>6-[5-(methylsulfonyl)-3-pyridinyl]-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>220</td>
<td><img src="image2.png" alt="Image" /></td>
<td>6-[5-(methylsulfonyl)-3-pyridinyl]-1-[(1S)-1-phenylethyl]-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>221</td>
<td><img src="image3.png" alt="Image" /></td>
<td>1-(1,1-dimethylethyl)-6-[5-(methylsulfonyl)-3-pyridinyl]-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>222</td>
<td><img src="image4.png" alt="Image" /></td>
<td>6-[5-(methylsulfonyl)-3-pyridinyl]-1-(phenylsulfonyl)-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>223</td>
<td><img src="image5.png" alt="Image" /></td>
<td>6-[6-(methyloxy)-5-(methylsulfonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>224</td>
<td><img src="image6.png" alt="Image" /></td>
<td>N-(5-(2-amino-1-(4-morpholinophenyl)-1 H-benzo[d]imidazol-6-yl)pyridin-2-yl)benzenesulfonamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structural Formula</td>
<td>Chemical Structure</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>225</td>
<td><img src="image1.png" alt="Image" /></td>
<td>6-{5-(methylsulfonyl)-3-pyridinyl}-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>226</td>
<td><img src="image2.png" alt="Image" /></td>
<td>5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-(1,1-dimethylethyl)-3-pyridinecarboxamide</td>
</tr>
<tr>
<td>227</td>
<td><img src="image3.png" alt="Image" /></td>
<td>5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-methyl-2-pyridinecarboxamide</td>
</tr>
<tr>
<td>228</td>
<td><img src="image4.png" alt="Image" /></td>
<td>5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-3-pyridinecarbonitrile</td>
</tr>
<tr>
<td>229</td>
<td><img src="image5.png" alt="Image" /></td>
<td>6-{5-(methyloxy)-3-pyridinyl}-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>230</td>
<td><img src="image6.png" alt="Image" /></td>
<td>5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-3-pyridinecarboxamide</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>---</td>
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<td>------------------</td>
</tr>
<tr>
<td>231</td>
<td><img src="image1.png" alt="Image" /></td>
<td>6-{5-(4-morpholinylcarbonyl)-3-pyridinyl}-1-{4-(4-morpholinyl)phenyl}-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>232</td>
<td><img src="image2.png" alt="Image" /></td>
<td>6-{6-(methylsulfonyl)-3-pyridinyl}-1-{4-(4-morpholinyl)phenyl}-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>233</td>
<td><img src="image3.png" alt="Image" /></td>
<td>6-{5,6-bis(methoxy)-3-pyridinyl}-1-{4-(4-morpholinyl)phenyl}-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>234</td>
<td><img src="image4.png" alt="Image" /></td>
<td>1-{4-(4-morpholinyl)phenyl}-6-{2-(trifluoromethyl)-3-pyridinyl}-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>235</td>
<td><img src="image5.png" alt="Image" /></td>
<td>6-{2-(methoxy)-3-pyridinyl}-1-{4-(4-morpholinyl)phenyl}-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>236</td>
<td><img src="image6.png" alt="Image" /></td>
<td>6-{4-(methoxy)-3-pyridinyl}-1-{4-(4-morpholinyl)phenyl}-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>237</td>
<td><img src="image1" alt="Chemical Structure 1" /></td>
<td>1-(cyclopropylsulfonyl)-6-[5-(methylsulfonyl)-3-pyridinyl]-1H-benzimidazol-2-amine</td>
</tr>
<tr>
<td>238</td>
<td><img src="image2" alt="Chemical Structure 2" /></td>
<td>2-amino-N,N-dimethyl-6-[5-(methylsulfonyl)-3-pyridinyl]-1H-benzimidazole-1-sulfonamide</td>
</tr>
<tr>
<td>239</td>
<td><img src="image3" alt="Chemical Structure 3" /></td>
<td>N-[5-{2-amino-3-[4-(4-morpholinyl)phenyl]imidazo[1,2-a]pyridin-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
</tr>
<tr>
<td>240</td>
<td><img src="image4" alt="Chemical Structure 4" /></td>
<td>1,1-dimethylethyl [3-bromo-6-[5-{{(2,4-difluorophenyl)sulfonyl}amino}-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]carbamate</td>
</tr>
<tr>
<td>241</td>
<td><img src="image5" alt="Chemical Structure 5" /></td>
<td>1,1-dimethylethyl [6-{5-{{(2,4-difluorophenyl)sulfonyl}amino}-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]carbamate</td>
</tr>
<tr>
<td>242</td>
<td><img src="image6" alt="Chemical Structure 6" /></td>
<td>N-[5-{2-amino-3-[3-(4-morpholinyl)phenyl]imidazo[1,2-a]pyridin-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
</tr>
<tr>
<td>Compound</td>
<td>Structural Formula</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>243</td>
<td><img src="image" alt="Structure 243" /></td>
<td>(N{6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl}acetamide</td>
</tr>
<tr>
<td>244</td>
<td><img src="image" alt="Structure 244" /></td>
<td>(N[5-(2-aminimidazo[1,2-a]pyridin-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide</td>
</tr>
<tr>
<td>245</td>
<td><img src="image" alt="Structure 245" /></td>
<td>(N{6-[[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-methoxypyridin-3-yl]pyridin-2,4-difluorobenzenesulfonamide</td>
</tr>
<tr>
<td>246</td>
<td><img src="image" alt="Structure 246" /></td>
<td>(5-(2-aminimidazo[1,2-a]pyridin-6-yl)-N-(tert-butyl)}-2-methoxypyridine-3-sulfonamide</td>
</tr>
<tr>
<td>247</td>
<td><img src="image" alt="Structure 247" /></td>
<td>(N{6-[5-(N-(tert-butyl)sulfonyl)amino]-6-methoxypyridin-3-yl]imidazo[1,2-a]pyridin-2-yl}acetamide</td>
</tr>
<tr>
<td>248</td>
<td><img src="image" alt="Structure 248" /></td>
<td>(N{5-(2-amino-3-(4-cyanophenyl)imidazo[1,2-a]pyridin-6-yl)-2-(methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide</td>
</tr>
</tbody>
</table>

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The compounds of Table 1 can be synthesized according to the Synthetic Methods, General Schemes, and the Examples described below.

In certain embodiments, the compound(s) of the present invention, or a pharmaceutically acceptable salt thereof, is chosen from the compounds set forth in Table 1.

**Synthetic Methods**

The methods of synthesis for the provided chemical entities employ readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given; other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, the methods of this invention may employ protecting groups which prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and

Furthermore, the provided chemical entities may contain one or more chiral centers and such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this specification, 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.

The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Ernka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplemental (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from -78 °C to 200 °C. Further, except as employed in the Examples or as otherwise specified, reaction times and conditions are intended to be approximate, e.g., taking place at about atmospheric pressure within a temperature range of about -78 °C to about 110 °C over a period of about 1 to about 24 hours; reactions left to run overnight average a period of about 16 hours.

The terms "solvent," "organic solvent," and "inert solvent" each mean a solvent inert under the conditions of the reaction being described in conjunction therewith, including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, N-methylpyrrolidone ("NMP"), pyridine and the like.
Isolation and purification of the chemical entities and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples herein below. However, other equivalent separation or isolation procedures can also be used.

When desired, the (R)- and (S)-isomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. Alternatively, a specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

**EXAMPLES**

The following examples serve to more fully describe the manner of making and using the above-described invention. It is understood that these examples in no way serve to limit the true scope of the invention, but rather are presented for illustrative purposes. In the examples below and the synthetic schemes above, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

- aq. = aqueous
- µL = microliters
- µM = micromolar
- NMR = nuclear magnetic resonance
- boc = tert-butoxycarbonyl
- br = broad
- Cbz = benzyloxycarbonyl
- d = doublet
\( \delta \) = chemical shift
\( ^\circ \text{C} \) = degrees celcius
DCM = dichloromethane
dd = doublet of doublets
DMEM = Dulbecco's Modified Eagle's Medium
DMF = N,N-dimethylformamide
DMSO = dimethylsulfoxide
EtOAc = ethyl acetate
g = gram
h or hr = hours
HCV = hepatitus C virus
HPLC = high performance liquid chromatography
Hz = hertz
IU = International Units
IC\textsubscript{50} = inhibitory concentration at 50\% inhibition
J = coupling constant (given in Hz unless otherwise indicated)
m = multiplet
M = molar
M+H\textsuperscript{+} = parent mass spectrum peak plus H\textsuperscript{+}
mg = milligram
min = minutes
mL = milliliter
mM = millimolar
mmol = millimole
MS = mass spectrum
nm = nanomolar
ppm = parts per million
q.s. = sufficient amount
s = singlet
RT = room temperature
sat. = saturated
t = triplet
TFA = trifluoroacetic acid
EXAMPLES

General Scheme 1

Example 1

5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-methyl-2-(methyloxy)-N-(phenylmethyl)-3-pyridinesulfonamide

Step A
5-bromo-2-chloro-3-pyridinesulfonyl chloride

Step (1) Thionyl chloride (60.1 ml, 823 mmol) was added dropwise over 60 min to water (361 ml), cooled to 0 °C, maintaining the temperature of the mixture 0-7 °C. The solution was allowed to warm to 18 °C over 17 hr. Copper(I) chloride (218 mg, 2.2 mmol) was added to the mixture, and the resultant yellow-green solution was cooled to -3 °C using an acetone/ice bath.

Step (2) HCl (195 ml, 6.418 mol) (37% w/w) was added, with agitation, to 5-bromo-2-chloro-3-pyridineamine (25 g, 121 mmol), maintaining the temperature of the mixture below 30 °C with ice cooling. The reaction mixture was cooled to -5 °C using an ice/acetone bath and a solution of sodium nitrite (14.72 g, 213 mmol) in water (58 ml) was added dropwise over 45 min, maintaining the temperature of the reaction mixture between -5 to 0 °C, the resultant slurry was cooled to -2 °C and stirred for 10 min.

Step (3) The slurry from step (2) was cooled to -5 °C and added to the solution obtained from step (1) over 30 min, maintaining the temperature of the reaction mixture between -3 to 0 °C (the slurry from step (2) was maintained at -5 °C throughout the addition). As the reaction proceeded, a solid began to precipitate. When the addition was complete, the reaction mixture was agitated at 0 °C for 75 min. The suspended solid was collected by vacuum filtration, washed with water, and dried under vacuum to give 5-bromo-2-chloro-3-pyridinesulfonyl chloride. ES-LCMS: m/z 271.9, 269.9 (M-1).

Step B

5-bromo-N-methyl-2-(methyloxy)-(phenylmethyl)-3-pyridinesulphonamide

To a cold (0 °C) suspension of 2-chloro-5-bromo-3-pyridinesulfonyl chloride (1 g, 3.3 mmol) in dry 1,4-dioxane (25 mL) was added pyridine (1.1 mL, 13 mmol) followed by a N-methyl-1-phenylmethanamine (1 mL, 10 mmol). The reaction mixture was allowed to warm to RT for 2 hrs, heated to 50 °C for 1 hr, then cooled to RT. Sodium methoxide (25% in methanol) (2 mL) was added and the mixture was sealed and heated by microwave at 95 °C for 30 min. After cooled to RT, the mixture was dissolved in 60 mL EtOAc and washed with H₂O (50 mL),
brine (50 ml), dried by Mg$_2$SO$_4$. The solid was filtrated and the filtration was evaporated to afford yellow solid 850 mg, yield 67%. ES-LCMS: m/z 371.1, 373.1 (M+1).

[00137] The following intermediates in Table 2 were prepared using the procedure described above for Example 1.

**Table 2**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>ES-LCMS: m/z (M+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>4-[[5-bromo-2-(methyloxy)-3-pyridinyl]sulfonyl]morpholine</td>
<td>337.0, 339.0</td>
</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>5-bromo-N-cyclohexyl-2-(methyloxy)-3-pyridinesulfonamide</td>
<td>349.0, 351.0</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>5-bromo-N-isopropyl-2-methoxy-3-sulfonamide</td>
<td>309.1, 311.1</td>
</tr>
<tr>
<td><img src="image4" alt="Structure 4" /></td>
<td>5-bromo-2-methoxy-3-(piperidin-1-ylsulfonyl)pyridine</td>
<td>335.0, 337.0</td>
</tr>
<tr>
<td><img src="image5" alt="Structure 5" /></td>
<td>5-bromo-N-cyclopropyl-2-methoxy-3-sulfonamide</td>
<td>307.0, 309.0</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Description</td>
<td>Molecular Weight</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td><img src="image1" alt="Chemical Structure 1" /></td>
<td>5-bromo-N-(2,4-dimethylpentan-3-yl)-2-methoxypyridine-3-sulfonamide</td>
<td>365.0, 367.0</td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure 2" /></td>
<td>5-bromo-N-(1,1-dimethylpropyl)-2-(methyloxy)-3-pyridinesulfonamide</td>
<td>337.1, 339.1</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure 3" /></td>
<td>5-bromo-N-methyl-2-(methyloxy)-3-pyridinesulfonamide</td>
<td>280.9, 282.9</td>
</tr>
<tr>
<td><img src="image4" alt="Chemical Structure 4" /></td>
<td>5-bromo-N-ethyl-2-methoxypyridine-3-sulfonamide</td>
<td>295.1, 297.1</td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure 5" /></td>
<td>5-bromo-2-methoxy-N-neopentylpyridine-3-sulfonamide</td>
<td>337.3, 339.3</td>
</tr>
<tr>
<td><img src="image6" alt="Chemical Structure 6" /></td>
<td>5-bromo-N-(3,3-dimethylbutan-2-yl)-2-methoxypyridine-3-sulfonamide</td>
<td>351.1, 353.1</td>
</tr>
<tr>
<td><img src="image7" alt="Chemical Structure 7" /></td>
<td>5-bromo-N-cyclobutyl-2-(methyloxy)-3-pyridinesulfonamide</td>
<td>321.0, 323.0</td>
</tr>
</tbody>
</table>
Step C

\[ \text{(N-methyl-2-(methyloxy)-N-(phenylmethyl)-5-(4, 4', 5, 5'-tetramethyl-1,3, 2-dioxaborolan-2-yl)-3-pyridinesulfonamide)} \]

To a solution of 5-bromo-N-methyl-2-(methyloxy)-N-(phenylmethyl)-3-pyridinesulfonamide (1.1g, 3.0 mmol) in 1,4-dioxane (15 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolan (1.1 g, 4.5 mmol), potassium acetate (0.87 g, 8.9 mmol) and Pd(PPh\(_3\))\(_2\)Cl\(_2\) (242 mg, 0.3 mmol). The reaction mixture was stirred at 100 °C overnight. The reaction was concentrated in vacuo, purified on silica using 60% ethyl acetate/ hexane to yield the title compound as a white solid 870 mg (65 %). ES-LCMS: m/z 337.1 (M+1).

The following intermediates in Table 3 were prepared using the procedure described above in Example 1, Step C.
<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>ES-LCMS: m/z (M+1)</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>N-cyclohexyl-2-(methoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide</td>
<td>397.3</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>1-4-[[2-(methoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]sulfonyl]morpholine</td>
<td>385.2</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>N-(1-methylethyl)-2-(methoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide</td>
<td>357.2</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure" /></td>
<td>2-(methoxy)-3-(1-piperidinylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine</td>
<td>383.3</td>
</tr>
<tr>
<td><img src="image5.png" alt="Structure" /></td>
<td>N-cyclopropyl-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide</td>
<td>355.2</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
<td>MW</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>N-[2-methyl-1-(1-methylethyl)propyl]-2-(methoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide</td>
<td>413.2</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>2-methoxy-N-(tert-pentyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide</td>
<td>385.2</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>2-methoxy-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide</td>
<td>329.1</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>N-ethyl-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide</td>
<td>343.1</td>
</tr>
<tr>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>N-(3-chlorophenyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide</td>
<td>383.2</td>
</tr>
<tr>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>N-(3,3-dimethylbutan-2-yl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide</td>
<td>399.2</td>
</tr>
</tbody>
</table>
Step D

5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-methyl-2-(methyloxy)-N-(phenylmethyl)-3-pyridinesulfonamide

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Chemical Formula</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>N-cyclobuty1-2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide</td>
<td>369.2</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>N-(cyclopentylmethyl)-2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide</td>
<td>397.3</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>2-methoxy-N-(tetrahydro-2H-pyran-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide</td>
<td>399.2</td>
</tr>
</tbody>
</table>

Mixed 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (50 mg, 0.13 mmol), N-benzyl-2-methoxy-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-
pyridine-3-sulfonamide (62 mg, 0.15 mol), PdCl₂(dppf)-CH₂Cl₂ adduct (11 mg, 0.01 mmol) and KOAc (39 mg, 0.4 mmol) in a schlenk flask and purged with N₂ (3 times) before heated to 130 °C under microwave condition for 15 min. The crude product was cooled down and loaded to the column and was eluted with 10% methanol/EtOAc. Collected the resulting fractions and then evaporation afforded a white solid (40 mg, 50%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.61 (d, J=2.34 Hz, 1 H) 8.18 (d, J=2.34 Hz, 1 H) 7.25 - 7.41 (m, 10 H) 7.15 (d, J=8.98 Hz, 2 H) 6.99 (s, 1 H) 6.29 (s, 2 H) 4.35 (s, 2 H) 4.02 (s, 3 H) 3.71 - 3.82 (m, 4 H) 3.19 - 3.26 (m, 4 H) 2.71 (s, 3 H); ES-LCMS: 585.3 (M+1).

[00141] Additional benzimidazoles, shown in Example 2 through Example 15, were prepared using similar procedures in Example 1 and by varying the boronic ester accordingly.

**Example 2**

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-cyclohexyl-2-(methyloxy)-3-pyridinesulfonamide

![Chemical structure]

[00142] (38 mg, 48%). ¹H NMR (400 MHz, DMSO-cf) δ ppm 8.58 (d, J=2.54 Hz, 1 H) 8.12 (d, J=2.54 Hz, 1 H) 7.61 (d, J=7.80 Hz, 1 H) 7.27 - 7.37 (m, 5 H) 7.15 (d, J=8.98 Hz, 2 H) 6.95 (s, 1 H) 6.28 (s, 2 H) 4.00 (s, 3 H) 3.75 - 3.79 (m, 4 H) 3.18 - 3.26 (m, 4 H) 1.56 (br. s., 4 H) 1.17 (t, 4 H); ES-LCMS: 563.3 (M+1).

**Example 3**

6-{6-(methyloxy)-5-(4-morpholinylsulfonyl)-3-pyridinyl}-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

99
(28 mg, 38%). \( ^1H \) NMR (400 MHz, DMSO-d6) \( \delta \) ppm 8.63 (s, 1 H) 8.13 (s, 1 H) 7.24 - 7.41 (m, 5 H) 7.14 (d, \( J=8.39 \) Hz, 2 H) 6.98 (s, 1 H) 6.68 (br. s., 1 H) 6.34 (br. s., 2 H) 4.00 (s, 3 H) 3.77 (br. s., 4 H) 3.58 (br. s., 4 H) 3.39 (br. s., 3 H) 3.22 (br. s., 5 H) 3.15 (br. s., 4 H) 1.75 (s, 4 H); ES-LCMS: 551.4 (M+1).

**Example 4**

5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(1-methyl)-2-(methyloxy)-3-pyridinesulfonamide

(40 mg, 39%). \( ^1H \) NMR (400 MHz, DMSO-d6) \( \delta \) ppm 8.58 (d, \( J=2.54 \) Hz, 1 H) 8.12 (d, 1 H) 7.55 (d, 1 H) 7.35 (d, 2 H) 7.28 - 7.31 (m, 2 H) 7.15 (d, 2 H) 6.96 (s, 1 H) 6.28 (s, 2 H) 4.00 (s, 3 H) 3.72 - 3.81 (m, 4 H) 3.20 - 3.26 (m, 4 H) 0.97 (d, 6 H); ES-LCMS: 523.2 (M+1).

**Example 5**

6-[6-(methyloxy)-5-(1-piperidinesulfonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine
Example 6

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-cyclopropyl-2-(methyloxy)-3-pyridinesulfonamide

Example 7

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-[2-methyl-1-(1-methylethyl)propyl]-2-(methyloxy)-3-pyridinesulfonamide
[00147] (40 mg, 35%). $^1$H NMR (400 MHz, DMSO-cfc) $\delta$ ppm 8.55 (d, $J$=2.34 Hz, 1 H) 8.09 (d, $J$=2.34 Hz, 1 H) 7.35 (d, $J$=8.78 Hz, 3 H) 7.29 (s, 2 H) 7.15 (d, $J$=8.78 Hz, 2 H) 6.93 (s, 1 H) 6.28 (s, 2 H) 4.00 (s, 3 H) 3.75 - 3.80 (m, 4 H) 3.20 - 3.26 (m, 4 H) 2.76 - 2.90 (m, 1 H) 1.62 - 1.80 (m, 2 H) 0.62 - 0.79 (m, 12 H); ES-LCMS: 579.5 (M+1).

Example 8

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-(1, 1-dimethylpropyl)-2-(methylthioxy)-3-pyridinesulfonamide

[00148] (37 mg, 34%). $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 8.57 (d, 1 H) 8.13 (d, 1 H) 7.36 (d, 2 H) 7.28 - 7.32 (m, 3 H) 7.15 (d, 2 H) 6.96 (s, 1 H) 6.32 (br. s., 2 H) 4.00 (s, 3 H) 3.74 - 3.81 (m, 5 H) 3.20 - 3.26 (m, 5 H) 1.42 (d, $J$=7.41 Hz, 2 H) 1.01 (s, 6 H) 0.74 (t, $J$=7.41 Hz, 3 H); ES-LCMS: 551.3 (M+1).

Example 9

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-methyl-2-(methylthioxy)-3-pyridinesulfonamide
Example 10

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-ethyl-2-(methyloxy)-3-pyridinesulfonamide

Example 11

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-ethyl-2-(methyloxy)-3-pyridinesulfonamide
[00151] (17.4 mg.16%). $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 8.58 (d, $J$=2.34 Hz, 1 H) 8.11 (d, $J$=2.34 Hz, 1 H) 7.52 (s, 1 H) 7.35 (d, $J$=8.98 Hz, 2 H) 7.30 (s, 2 H) 7.15 (d, $J$=8.98 Hz, 2 H) 6.95 (s, 1 H) 6.29 (s, 2 H) 3.99 (s, 3 H) 3.75 - 3.80 (m, 4 H) 3.20 - 3.25 (m, 4 H) 2.63 (d, $J$=6.44 Hz, 2 H) 0.81 (s, 9 H); ES-LCMS: 551.5 (M+1).

Examples 12

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinesulfonamide

[00152] (39 mg.35%). $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 8.58 (d, $J$=2.34 Hz, 1 H) 8.14 (d, $J$=2.34 Hz, 1 H) 7.27 - 7.37 (m, 5 H) 7.15 (d, $J$=8.98 Hz, 2 H) 6.95 (d, $J$=0.78 Hz, 1 H) 6.28 (s, 2 H) 4.00 (s, 3 H) 3.75 - 3.80 (m, 4 H) 3.20 - 3.25 (m, 4 H) 1.99 (s, 1 H) 0.77 - 0.83 (m, 12 H); ES-LCMS: 565.5 (M+1).

Example 13

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-cyclobutyl-2-(methyloxy)-3-pyridinesulfonamide
Example 14
5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-(cyclopentylmethyl)-2-(methyloxy)-3-pyridinesulfonamide

Example 15
5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-(tetrahydro-2H-pyran-4-yl)-3-pyridinesulfonamide
Example 16

2-amino-5-(2-amino-1-cyclopentyl-1H-benzimidazol-6-yl)-N-cyclopropyl-3-pyridinesulfonamide

A degassed mixture of 2-amino-N-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (64 mg, 0.189 mmol), 6-bromo-1-cyclopentyl-1H-benzimidazol-2-amine (52.9 mg, 0.189 mmol), Pd(dppf)Cl$_2$ CH$_2$Cl$_2$ adduct (15.41 mg, 0.019 mmol) and potassium acetate (55.5 mg, 0.566 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90°C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain 2-amino-5-(2-amino-1-cyclopentyl-1H-benzimidazol-6-yl)-N-cyclopropyl-3-pyridinesulfonamide (25 mg, 0.056 mmol, 29.9 % yield): $^1$H NMR (400 MHz, DMSO-cf$_2$) $\delta$ ppm 0.35 - 0.56 (m, 4 H) 1.70 (br. s., 2 H) 1.95
2-amino-5-(2-amino-1-phenyl-1H-benzimidazol-6-yl)-N-cyclopropyl-3-pyridinesulfonamide

Example 17

2-amino-5-(2-amino-1^henyl-1H-benzimidazol-6-yl)-N-cyclopropyl-3^yridinesulfonamide

[001 57] A degassed mixture of 2-amino-N-cyclopropyl-5-(4,4,5,5-tetramethyl-1^3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (64 mg, 0.189 mmol), 6-bromo-1-phenyl-1H-benzimidazol-2-amine (54.4 mg, 0.189 mmol), Pd(dppf)2CI2 CH2Cl2 adduct (15.41 mg, 0.019 mmol) and potassium acetate (55.5 mg, 0.566 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH2Cl2 and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain 2-amino-5-(2-amino-1-phenyl-1H-benzimidazol-6-yl)-N-cyclopropyl-3-pyridinesulfonamide (11 mg, 0.026 mmol, 13.59 % yield): 1H NMR (400 MHz, DMSO-d6) δ ppm 0.39 (d, J=2.64 Hz, 4 H) 6.36 (s, 2 H) 6.58 (br. s., 2 H) 6.96 (s, 1 H) 7.20 - 7.35 (m, 2 H) 7.48 - 7.60 (m, 3 H) 7.60 - 7.69 (m, 2 H) 7.93 (s, 1 H) 8.08 - 8.13 (m, 1 H) 8.15 (s, 1 H) 8.44 (s, 1 H); ES LC-MS m/z =421.4 (M+H)+.

Example 18

2-amino-5-[2-amino-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-6-yl]-N-cyclopropyl-3-pyridinesulfonamide
A degassed mixture of 2-amino-N-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (63.0 mg, 0.186 mmol), 6-bromo-1-[3-(4-morpholiny1)propyl]-1H-benzimidazol-2-amine (63 mg, 0.186 mmol), Pd(dppf)\(_2\)Cl\(_2\)CH\(_2\)Cl\(_2\) adduct (15.17 mg, 0.019 mmol) and potassium acetate (54.7 mg, 0.557 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH\(_2\)Cl\(_2\) and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain 2-amino-5-[2-amino-1-[3-(4-morpholiny1)propyl]-1H-benzimidazol-6-yl]-N-cyclopropyl-3-pyridinesulfonamide (23 mg, 0.046 mmol, 24.95 % yield): \(^1\)H NMR (400 MHz, DMSO-cf) \(\delta\) ppm 0.32 - 0.56 (m, 4 H) 1.90 (s, 2 H) 2.07 - 2.40 (m, 7 H) 3.55 (br. s., 4 H) 4.05 (br. s., 2 H) 6.58 (br. s., 2 H) 7.09 - 7.22 (m, 2 H) 7.39 (s, 1 H) 8.06 (d, \(J=2.15\) Hz, 1 H) 8.14 (s, 1 H) 8.55 (d, \(J=2.25\) Hz, 1 H); ES LC-MS m/z =472.5 (M+H)⁺.

**Example 19**

2-amino-5-(2-amino-1-cyclopentyl-1H-benzimidazol-6-yl)-N-phenyl-3-pyridinesulfonamide

![Chemical structure](image)

A degassed mixture of 2-amino-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (70 mg, 0.187 mmol), 6-bromo-1-cyclopentyl-1H-benzimidazol-2-amine (52.3 mg, 0.187 mmol), Pd(dppf)\(_2\)Cl\(_2\)CH\(_2\)Cl\(_2\) adduct (15.23 mg, 0.019 mmol) and potassium acetate (54.9 mg, 0.560 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH\(_2\)Cl\(_2\) and filtered through a plug of Celite. The filtrate was concentrated. The residue was dissolved in DMF (1 mL) and a drop of TFA and purified by HPLC (10-60% CH\(_3\)CN/H\(_2\)O, both containing 0.1% formic acid) to obtain 2-amino-5-(2-amino-1-cyclopentyl-1H-benzimidazol-6-yl)-N-phenyl-3-pyridinesulfonamide (27 mg, 0.057 mmol, 30.7 % yield): \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 1.71 (br. s., 2 H) 1.85 - 2.18 (m, 6 H)
4.75 (quin, $J=8.77$ Hz, 1 H) 6.42 (s, 2 H) 6.69 (br. s., 2 H) 6.98 - 7.08 (m, 2 H) 7.12 (d, $J=7.52$ Hz, 2 H) 7.15 - 7.20 (m, 2 H) 7.21 - 7.28 (m, 2 H) 7.96 (d, $J=2.44$ Hz, 1 H) 8.43 (d, $J=2.35$ Hz, 1 H) 10.50 (br. s., 1 H); ES LC-MS m/z =449.4 (M+H)^+.

Example 20

2-amino-5-[2-amino-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-6-yO-N-^henyl-3-pyridinesulfonamide

[00160] A degassed mixture of 2-amino-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (69.7 mg, 0.186 mmol), 6-bromo-1-[3-(4-morpholinyl)propyl]-1 H-benzimidazol-2-amine (63 mg, 0.186 mmol), Pd(dpff)$_2$Cl$_2$ CH$_2$Cl$_2$ adduct (15.17 mg, 0.019 mmol) and 6-bromo-1-[3-(4-morpholinyl)propyl]-1 H-benzimidazol-2-amine (63 mg, 0.186 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a small amount of MeOH, and filtered through a plug of Celite. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain 2-amino-5-[2-amino-1-[3-(4-morpholinyl)propyl]-1 H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide (26 mg, 0.049 mmol, 26.2% yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.85 (br. s., 2 H) 2.15 - 2.38 (m, 6 H) 3.53 (br. s., 4 H) 4.04 (br. s., 2 H) 6.58 (s, 2 H) 6.64 - 6.75 (m, 2 H) 6.96 - 7.03 (m, 1 H) 7.05 (d, $J=8.1$ Hz, 1 H) 7.10 (d, $J=7.91$ Hz, 2 H) 7.15 (d, $J=8.10$ Hz, 1 H) 7.19 - 7.27 (m, 2 H) 7.29 (s, 1 H) 8.00 (d, $J=2.25$ Hz, 1 H) 8.45 (d, $J=2.25$ Hz, 1 H) 10.47 (br. s., 1 H); ES LC-MS m/z =508.5 (M+H)^+.

Example 21

2-amino-5-(2-amino-1^henyl-1H-benzimidazol-6-yO-N^henyl-3^yridine sulfonamide
A degassed mixture of 2-amino-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (70 mg, 0.187 mmol), 6-bromo-1-phenyl-1H-benzimidazol-2-amine (53.8 mg, 0.187 mmol), Pd(dppf)$_2$C$_2$I$_2$C$_2$I$_2$ adduct (15.23 mg, 0.019 mmol) and potassium acetate (54.9 mg, 0.560 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/ EtOAc) to obtain 2-amino-5-(2-amino-1-phenyl-1H-benzimidazol-6-yl)-N-phenyl-3-pyridinesulfonamide (11 mg, 0.023 mmol, 12.27% yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 6.36 (s, 2 H) 6.67 (br. s., 2 H) 6.80 (d, J=1.17 Hz, 1 H) 6.91 - 6.99 (m, 1 H) 7.02 - 7.09 (m, 2 H) 7.10 - 7.19 (m, 3 H) 7.26 (d, J=8.10 Hz, 1 H) 7.49 - 7.60 (m, 3 H) 7.62 - 7.71 (m, 2 H) 7.83 (d, J=2.34 Hz, 1 H) 8.34 (d, J=2.24 Hz, 1 H) 10.42 (br. s., 1 H); ES LC-MS m/z = 457.4 (M+H)$^+$. 

**Example 22**

2-amino-5-{2-amino-1-[(1S)-1-phenylethyl]-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide

A degassed mixture of 2-amino-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (71.2 mg, 0.190 mmol), 6-bromo-1-[(1S)-1-phenylethyl]-1H-benzimidazol-2-amine (60 mg, 0.190 mmol), Pd(dppf)$_2$C$_2$I$_2$C$_2$I$_2$ adduct (15.50 mg, 0.019 mmol) and potassium acetate (55.9 mg, 0.569 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room...
temperature and concentrated. The residue was dissolved in CH₂Cl₂ and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain 2-amino-5-[2-amino-1-[(1S)-1-phenylethyl]-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide (20 mg, 0.039 mmol, 20.66 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.83 - 1.89 (m, 3 H) 5.81 (q, J=6.89 Hz, 1 H) 6.55 - 6.73 (m, 5 H) 7.06 (d, J=7.80 Hz, 2 H) 7.14 (d, J=8.19 Hz, 1 H) 7.17 - 7.26 (m, 2 H) 7.26 - 7.43 (m, 5 H) 7.73 (d, J=2.34 Hz, 1 H) 8.18 (d, J=2.34 Hz, 1 H) 10.45 (br. s., 1 H); ES LC-MS m/z = 485.5 (M+H)⁺.

Example 23

2-amino-5-[2-amino-1-[(1S)-1-phenylethyl]-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide

[001 63] A degassed mixture of 2-amino-N-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (64 mg, 0.189 mmol), 6-bromo-1-[(1S)-1-phenylethyl]-1H-benzimidazol-2-amine (59.7 mg, 0.189 mmol), Pd(dppf)₂Cl₂ CH₂Cl₂ adduct (15.41 mg, 0.019 mmol) and potassium acetate (55.5 mg, 0.566 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH₂Cl₂ and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc, then HPLC, 10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 2-amino-5-[2-amino-1-[(1S)-1-phenylethyl]-1H-benzimidazol-6-yl]-N-cyclopropyl-3-pyridinesulfonamide (14 mg, 0.030 mmol, 15.72 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-cf) δ ppm 0.32 - 0.52 (m, 4 H) 1.86 (d, J=7.02 Hz, 3 H) 2.11 (d, J=3.71 Hz, 1 H) 5.82 (q, J=6.76 Hz, 1 H) 6.54 (br. s., 2 H) 6.60 (br. s., 2 H) 6.79 (s, 1 H) 7.05 - 7.12 (m, 1 H) 7.13 - 7.22 (m, 1 H) 7.24 - 7.32 (m, 1 H) 7.32 - 7.42 (m, 4 H) 7.82 (d, J=2.24 Hz, 1 H) 8.11 (br. s., 1 H) 8.19 - 8.29 (m, 1 H); ES LC-MS m/z = 449.5 (M+H)⁺.

Example 24

5-[2-amino-1-[4-(4-morpholiny)phenyl]-1H-benzimidazol 6-yl]-N,N-dimethyl-2-
A degassed mixture of [5-[(dimethylamino)sulfonyl]-6-(methyloxy)-3-pyridinyl]boronic acid (111 mg, 0.214 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (80 mg, 0.214 mmol), Pd(dppf)2CIC2H2Cl2 adduct (17.50 mg, 0.021 mmol) and potassium acetate (63.1 mg, 0.643 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH2Cl2 and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/ETIOAc, then HPLC, 10-60% CH3CN/H2O, both containing 0.1% formic acid) to obtain 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N,N-dimethyl-2-(methyloxy)-3-pyridinesulfonamide (12 mg, 0.023 mmol, 10.90 % yield) as a white solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 2.78 (s, 6 H) 3.19 - 3.26 (m, 4 H) 3.72 - 3.81 (m, 4 H) 3.99 (s, 3 H) 6.30 (s, 2 H) 6.97 (s, 1 H) 7.15 (d, J=8.98 Hz, 2 H) 7.30 (s, 2 H) 7.35 (d, J=8.88 Hz, 2 H) 8.12 (d, J=2.34 Hz, 1 H) 8.61 (d, J=2.44 Hz, 1 H); ES LC-MS m/z =509.4 (M+H)+.

Example 25
2-amino-5-{2-amino-1-[2-(4-morpholinyl)cyclopentyl]-1H-benzimidazol-6-yl}-N-phenyl-3-pyridinesulfonamide formic acid salt
A degassed mixture of 2-amino-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-
dioxaborolan-2-yl)-3-pyridinesulfonamide (61.6 mg, 0.164 mmol), 6-bromo-1-[2-(4-
morpholinyl)cyclopentyl]-1H-benzimidazol-2-amine (60 mg, 0.164 mmol), Pd(dppf)\(_2\)Cl\(_2\)CH\(_2\)Cl\(_2\) adduct (13.41 mg, 0.016 mmol) and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH\(_2\)Cl\(_2\) and a small amount of MeOH, filtered through a pipette plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF, filtered and purified by HPLC (10-60% CH\(_3\)CN/H\(_2\)O, both containing 0.1% formic acid) to obtain 2-amino-5-[2-amino-1-[2-(4-morpholinyl)cyclopentyl]-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide formic acid salt (38 mg, 0.060 mmol, 36.2 % yield) as a white solid: \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) ppm 1.72 (br. s., 2 H) 1.90 (br. s., 1 H) 1.96 - 2.16 (m, 3 H) 2.24 - 2.43 (m, 3 H) 2.43 - 2.58 (m, 1 H) 3.46 (br. s., 5 H) 3.56 (br. s., 1 H) 4.59 - 4.75 (m, 1 H) 6.70 (br. s., 4 H) 6.97 - 7.16 (m, 4 H) 7.16 - 7.32 (m, 4 H) 7.97 (d, J=2.34 Hz, 1 H) 8.13 (s, 1 H) 8.46 (d, J=2.44 Hz, 1 H) 10.51 (br. s., 1 H); ES LC-MS \(m/z = 534.5\) (M+H).
Example 27

2-amino-5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-N,N-dimethyl-3-pyridinesulfonamide formic acid salt

NMR (400 MHz, DMSO-d$_6$) δ ppm 0.37 - 0.58 (m, 4 H) 1.78 (s, 9 H) 2.16 (td, J=6.44, 3.12 Hz, 1 H) 6.07 (s, 2 H) 6.58 (br. s., 2 H) 7.09 - 7.24 (m, 2 H) 7.58 (d, J=1.07 Hz, 1 H) 8.00 (d, J=2.34 Hz, 1 H); ES LC-MS m/z = 401.2 (M+H)$^+$. 

Example 28

2-amino-5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide formic acid salt
A degassed mixture of 2-amino-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (84 mg, 0.224 mmol), 6-bromo-1-(1,1-dimethylethyl)-1H-benzimidazol-2-amine (60 mg, 0.224 mmol), Pd(dppf)$_2$C$_2$I$_2$ adduct (18.27 mg, 0.022 mmol) and potassium acetate (65.9 mg, 0.671 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a small amount of MeOH, filtered through a pipette plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF, filtered and purified by HPLC (10-60% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain 2-amino-5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide formic acid salt (30 mg, 0.069 mmol, 30.7% yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.73 - 1.80 (m, 9 H) 6.04 (s, 2 H) 6.68 (br. s., 2 H) 6.04 - 6.19 (m, 3 H) 7.21 - 7.30 (m, 2 H) 7.43 (d, J=1.27 Hz, 1 H) 7.92 (d, J=2.44 Hz, 1 H) 8.15 (s, 1 H) 8.41 (d, J=2.34 Hz, 1 H); ES LC-MS m/z =437.3 (M+H)$^+$.  

**Example 29**

5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-N,N-dimethyl-2-(methyloxy)-3-pyridinesulfonamide formic acid salt

![Chemical Structure](image)

A degassed mixture of [5-[(dimethylamino)sulfonyl]-6-(methyloxy)-3-pyridinyl]boronic acid (58.2 mg, 0.224 mmol), 6-bromo-1-(1,1-dimethylethyl)-1H-benzimidazol-2-amine (60 mg, 0.224 mmol), Pd(dppf)$_2$C$_2$I$_2$ adduct (18.27 mg, 0.022 mmol) and potassium acetate (65.9 mg, 0.671 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a small amount of MeOH, filtered through a pipette plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF, filtered and purified by HPLC (10-60% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain 5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-N,N-dimethyl-2-(methyloxy)-3-
pyridinesulfonamide formic acid salt (12 mg, 0.027 mmol, 11.93 % yield) as a white solid: \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) \textit{\delta} ppm 1.79 (s, 9 H) 2.81 (s, 6 H) 4.02 (s, 3 H) 6.11 (s, 2 H) 7.22 (s, 2 H) 7.67 (s, 1 H) 8.18 (s, 1 H) 8.20 (d, \textit{J}=2.44 Hz, 1 H) 8.68 (d, \textit{J}=2.34 Hz, 1 H); ES LC-MS \textit{m/z} =404.3 (M+H\textsuperscript{+}).

**Example 30**

5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazoL6-yl]-N-(2,4-difluorophenyl)-2-(methyloxy)-3-pyridinesulfonamide formic acid salt

\[ \text{Example 30} \]

A degassed mixture of [5-[(2,4-difluorophenyl)amino]sulfonyl]-6-(methyloxy)-3-pyridinyl]boronic acid (77 mg, 0.224 mmol), 6-bromo-1-(1,1-dimethylethyl)-1H-benzimidazol-2-amine (60 mg, 0.224 mmol), Pd(dppf)\textsubscript{2}Cl\textsubscript{2} CH\textsubscript{2}Cl\textsubscript{2} adduct (18.27 mg, 0.022 mmol) and potassium acetate (65.9 mg, 0.671 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH\textsubscript{2}Cl\textsubscript{2} and a small amount of MeOH, filtered through a pipette plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF, filtered and purified by HPLC (10-60% CH\textsubscript{3}CN/H\textsubscript{2}O, both containing 0.1% formic acid) to obtain 5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-N-(2,4-difluorophenyl)-2-(methyloxy)-3-pyridinesulfonamide formic acid salt (24 mg, 0.048 mmol, 21.56 % yield) as a grey solid: \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) \textit{\delta} ppm 1.76 (s, 9 H) 3.96 (s, 3 H) 6.11 (s, 2 H) 7.02 (br. s., 1 H) 7.09 - 7.27 (m, 3 H) 7.32 (td, \textit{J}=8.98, 6.15 Hz, 1 H) 7.56 (s, 1 H) 8.07 (d, \textit{J}=2.44 Hz, 1 H) 8.15 (s, 1 H) 8.64 (d, \textit{J}=2.34 Hz, 1 H); ES LC-MS \textit{m/z} =488.4 (M+H\textsuperscript{+}).

**Example 31**

5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-N-phenyl-3-pyridinesulfonamide formic acid salt

\[ \text{Example 31} \]
A degassed mixture of 6-(methyloxy)-5-[(phenylamino)sulfonyl]-3-pyridinyl}boronic acid (68.9 mg, 0.224 mmol), 6-bromo-1-(1,1-dimethylethyl)-1 H-benzimidazol-2-amine (60 mg, 0.224 mmol), Pd(dppf)\(_2\)Cl\(_2\)CH\(_2\)Cl\(_2\) adduct (18.27 mg, 0.022 mmol) and potassium acetate (65.9 mg, 0.671 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH\(_2\)Cl\(_2\) and a small amount of MeOH, filtered through a pipette plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF, filtered and purified by HPLC (10-60% CH\(_3\)CN/H\(_2\)O, both containing 0.1% formic acid) to obtain 5-[2-amino-1-(1,1-dimethylethyl)-1 H-benzimidazol-6-yl]-2-(methyloxy)-N-phenyl-3-pyridinesulfonamide formic acid salt (34 mg, 0.068 mmol, 30.2% yield) as a grey solid: \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) ppm 1.77 (s, 9 H) 4.00 (s, 3 H) 6.13 - 7.04 (m, 1 H) 7.10 - 7.27 (m, 6 H) 7.58 (s, 1 H) 8.15 (s, 1 H) 8.20 (d, J=2.34 Hz, 1 H) 8.60 (d, J=2.34 Hz, 1 H) 10.37 (br. s., 1 H); ES LC-MS \(m/z = 452.4\) (M+H)+.

**Example 32**

2-amino-5-[2-ammo-1-(phenylsulfonyl)-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide

A degassed mixture of 2-amino-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (65.8 mg, 0.175 mmol), 6-iodo-1-(phenylsulfonyl)-1 H-benzimidazol-2-amine (70 mg, 0.175 mmol), Pd(dppf)\(_2\)Cl\(_2\)CH\(_2\)Cl\(_2\) adduct (14.32 mg, 0.018 mmol) and potassium acetate (51.6 mg, 0.526 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 50 °C overnight. The resulting mixture was allowed to cool to room temperature,
diluted with EtOAc (50 ml) and water (50 ml). The aq. layer was washed with CH₂Cl₂ (50 mL). The organic layers were combined, dried (Na₂S0₄), filtered and concentrated. The residue was taken up into DMF and purified by HPLC (0-100% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 2-amino-5-[2-amino-1-(phenylsulfonyl)-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide (13 mg, 0.024 mmol, 13.67 % yield): ¹H NMR (400 MHz, DMSO-d₆) δ ppm 6.79 (br. s., 2 H) 7.00 - 7.08 (m, 1 H) 7.10 - 7.21 (m, 3 H) 7.22 - 7.33 (m, 5 H) 7.62 - 7.70 (m, 3 H) 7.78 (m, J=7.12 Hz, 1 H) 7.96 (d, J=1.56 Hz, 1 H) 8.07 (d, J=8.10 Hz, 2 H) 8.45 (d, J=1.56 Hz, 1 H) 10.53 (br. s., 1 H); ES LC-MS m/z =521.3 (M+H)⁺.

**Example 33**

5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(2,4-difluorophenyl)-2-(methyloxy)-3-pyridinesulfonamide formic acid salt

![Chemical Structure](image)

[00173] A degassed mixture of N-(2,4-difluorophenyl)-2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (103 mg, 0.241 mmol), 6-bromo-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (60 mg, 0.161 mmol), Pd(dppf)₂Cl₂ CH₂Cl₂ adduct (13.13 mg, 0.016 mmol) and potassium acetate (47.3 mg, 0.482 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The reaction mixture was allowed to cool to room temperature then was diluted with EtOAc (50 mL) and washed with H₂O (25 mL). The organic layer was dried (Na₂S0₄) and filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (0-100% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(2,4-difluorophenyl)-2-(methyloxy)-3-pyridinesulfonamide formic acid salt (34 mg, 0.057 mmol, 35.7 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.17 - 3.27 (m, 4 H) 3.73 - 3.82 (m, 4 H) 3.93 (s, 3 H) 6.32 (s, 2 H) 6.88 (d, J=1.27 Hz, 1 H) 6.94 - 7.04 (m, 1 H) 7.10 - 7.39 (m, 8 H) 7.99 (d, J=2.44 Hz, 1 H) 8.14 (s, 1 H) 8.59 (d, J=2.44 Hz, 1 H); ES LC-MS m/z =593.5 (M+H)⁺.
Example 34

5-[2-amino-1-(phenylsulfonyl)-1H-benimidazol-6-yl]-N,N-dimethyl-2-(methyloxy)-3-pyridinesulfonamide

[00174] A degassed mixture of N,N-dimethyl-2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (90 mg, 0.263 mmol), 6-iodo-1-(phenylsulfonyl)-1H-benimidazol-2-amine (70 mg, 0.175 mmol), Pd(dppf)Cl2 adduct (14.32 mg, 0.018 mmol) and potassium acetate (51.6 mg, 0.526 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 50 °C overnight. The resulting mixture was allowed to cool to room temperature then diluted with EtOAc (50 mL) and water (50 mL). The aq. layer was washed with CH2Cl2 (50 mL). The organic layers were combined, dried (Na2SO4), filtered and concentrated. The residue was taken up into DMF and purified by HPLC (0-100% CH3CN/H2O, both containing 0.1% formic acid) to obtain 5-[2-amino-1-(phenylsulfonyl)-1H-benimidazol-6-yl]-N,N-dimethyl-2-(methyloxy)-3-pyridinesulfonamide (5 mg, 9.23 μmol, 5.26% yield): 1H NMR (400 MHz, DMSO-d6) δ ppm 2.82 (s, 6 H) 4.05 (s, 3 H) 7.25 (d, J=8.19 Hz, 1 H) 7.34 (s, 2 H) 7.46 (d, J=8.19, 1.76 Hz, 1 H) 7.62 - 7.70 (m, 2 H) 7.74 - 7.81 (m, 1 H) 7.87 (d, J=1.56 Hz, 1 H) 8.10 - 8.17 (m, 2 H) 8.22 (d, J=2.44 Hz, 1 H) 8.73 (d, J=2.44 Hz, 1 H); ES LC-MS m/z =488.4 (M+H)+.

Example 35

5-[2-amino-1-[2-(4-morpholinyl)cyclopentyl]-1H-benimidazol-6-yl]-2-(methyloxy)-N-phenyl-3-pyridinesulfonamide

[00175] A degassed mixture of 2-(methyloxy)-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (70 mg, 0.179 mmol), 6-bromo-1-[2-(4-
morpholinyl)cyclopentyl]-1H-benzimidazol-2-amine (65.5 mg, 0.179 mmol), Pd(dppf)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (14.65 mg, 0.018 mmol) and potassium acetate (52.8 mg, 0.538 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The reaction mixture was allowed to cool to room temperature then diluted with EtOAc (50 mL) and H$_2$O (50 mL). The organic layer was dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-90% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain 5-{2-amino-1-[2-(4-morpholinyl)cyclopentyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-phenyl-3-pyridinesulfonamide (43 mg, 0.076 mmol, 42.4% yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 1.73 (br. s., 2 H), 2.44 (m, 8 H), 3.35 (br. s., 8 H), 4.00 - 4.06 (m, 3 H), 6.93 - 7.04 (m, 1 H), 7.10 - 7.17 (m, 1 H), 7.17 - 7.25 (m, 2 H), 7.48 (br. s., 2 H), 7.66 (br. s., 1 H); ES LC-MS m/z = (M+H)$^+$. 

**Example 36**

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-N-phenyl-3-pyridinesulfonamide

![Chemical Structure](image)

[00176] A degassed mixture of 2-(methyloxy)-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)-3-pyridinesulfonamide (70 mg, 0.179 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (66.9 mg, 0.179 mmol), Pd(dppf)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (14.65 mg, 0.018 mmol) and potassium acetate (52.8 mg, 0.538 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The reaction mixture was allowed to cool to room temperature then was diluted with EtOAc (50 mL) and H$_2$O (50 mL). The organic layer was dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-90% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-N-phenyl-3-pyridinesulfonamide (38 mg, 0.068 mmol, 38.1% yield) as a grey solid: $^1$H NMR (400 MHz,
DMSO-cfe) δ ppm 3.17 - 3.27 (m, 6 H) 3.72 - 3.82 (m, 4 H) 3.96 (s, 3 H) 6.89 (s, 1 H) 6.93 - 7.00 (m, 1 H) 7.06 - 7.12 (m, 2 H) 7.12 - 7.20 (m, 4 H) 7.21 - 7.30 (m, 2 H) 7.34 (d, J=8.88 Hz, 2 H) 8.11 (d, J=2.44 Hz, 1 H) 8.53 (d, J=2.44 Hz, 1 H) 10.33 (s, 1 H); ES LC-MS m/z = (M+H)⁺.

**Example 37**

5-(2-amino-1-[[4-(dimethylamino)tetrahydro-2H^yran-4-yl]methyl]-1H-benimidazol-6-yl)-2-(methyloxy)-N-phenyl-3-pyridinesulfonamide

[00177] A degassed mixture of 2-(methyloxy)-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (60 mg, 0.154 mmol), 6-bromo-1-[[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl]-1H-benzimidazol-2-amine (54.3 mg, 0.154 mmol), Pd(dpff)₂Cl₂ CH₂Cl₂ adduct (12.56 mg, 0.015 mmol) and potassium acetate (45.3 mg, 0.461 mmol) in 4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The reaction mixture was allowed to cool to room temperature then was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-90% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-[[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl]-1H-benzimidazol-6-yl)-2-(methyloxy)-N-phenyl-3-pyridinesulfonamide (10 mg, 0.019 mmol, 12.12 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-cie) δ ppm 1.24 (br. s., 2 H) 1.90 (d, J=13.47 Hz, 2 H) 2.42 (s, 6 H) 3.40 - 3.66 (m, 4 H) 4.00 (s, 3 H) 4.07 (s, 2 H) 6.61 (br. s., 2 H) 6.93 - 7.02 (m, 1 H) 7.10 - 7.25 (m, 6 H) 7.39 (s, 1 H) 8.26 (d, J=2.34 Hz, 1 H) 8.64 (d, J=2.34 Hz, 1 H) 10.03 - 10.73 (m, 1 H); ES LC-MS m/z = 537.4(M+H)⁺.

**Example 38**

5-(2-amino-1-[[4-(dimethylamino)tetrahydro-2H^yran-4-yl]methyl]-1H-benzimidazol-6-yl)-N-(4-fluorophenyl)-2-(methyloxy)-3-pyridinesulfonamide

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A degassed mixture of N-(4-fluorophenyl)-2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (62.4 mg, 0.153 mmol), 6-bromo-1-[(4-dimethylamino)tetrahydro-2H-pyran-4-yl]methyl]-1H-benzimidazol-2-amine (54 mg, 0.153 mmol), Pd(dppf)Cl2 CH2Cl2 adduct (12.48 mg, 0.015 mmol) and potassium acetate (45.0 mg, 0.459 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 hr. The reaction mixture was allowed to cool to room temperature then was diluted with H2O (50 mL) and extracted with EtOAc (50 mL) and CH2Cl2 (50 mL). The organic layers were filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (90-90% CH3CN/H2O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-(tert-butyl)-1H-benzo[d]imidazol-6-yl)-N-(4-fluorophenyl)-2-(methyloxy)-3-pyridinesulfonamide (16 mg, 0.029 mmol, 18.87% yield) as a white solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.24 (br. s., 2 H) 1.88 (br. s., 2 H) 2.42 (s, 6 H) 3.47 (br. s., 4 H) 4.00 (s, 3 H) 4.07 (s, 2 H) 6.61 (br. s., 2 H) 7.00 - 7.11 (m, 3 H) 7.10 - 7.25 (m, 4 H) 7.39 (s, 1 H) 8.22 (d, J=2.34 Hz, 1 H) 8.65 (d, J=2.25 Hz, 1 H); ES LC-MS m/z =555.3 (M+H)+.

**Example 39**

5-(2-amino-1-(tert-butyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

[00179] A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (50 mg, 0.135 mmol), 6-bromo-1-(tert-butyl)-1H-benzo[d]imidazol-2-amime (36.2 mg, 0.135 mmol), Pd(dppf)Cl2 CH2Cl2 adduct (11.03 mg, 0.014 mmol) and potassium acetate (39.8 mg, 0.405 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The resulting mixture was allowed
to cool to room temperature, diluted with EtOAc (50 mL) and washed with H₂O (50 mL). The organic layer was filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-70% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-(tert-butyl)-1 H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (26 mg, 0.060 mmol, 44.6% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.12 (s, 9 H), 1.74 - 1.83 (m, 9 H), 4.04 (s, 3 H), 6.13 (br. s., 2 H), 7.21 (s, 1 H), 7.47 (s, 1 H), 7.66 (s, 1 H), 8.15 (s, 1 H), 8.22 (d, J=2.54 Hz, 1 H), 8.64 (d, J=2.54 Hz, 1 H), 12.86 (br. s, 1 H); ES-LC-MS m/z = (M+H)+.

Example 40

5-(2-amino-1-phenyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

[00180] A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (50 mg, 0.135 mmol), 6-bromo-1-phenyl-1H-benzo[d]imidazol-2-amine (38.9 mg, 0.135 mmol), Pd(dppf)₂Cl₂CH₂Cl₂ adduct (11.03 mg, 0.014 mmol) and potassium acetate (39.8 mg, 0.405 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (50 mL) and washed with H₂O (50 mL). The organic layer was filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-70% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-phenyl-1 H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (34 mg, 0.075 mmol, 55.8% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.05 - 1.10 (m, 9 H), 4.01 (s, 3 H), 6.44 (s, 2 H), 7.04 (s, 1 H), 7.32 (s, 2 H), 7.45 (s, 1 H), 7.50 - 7.58 (m, 3 H), 7.60 - 7.67 (m, 2 H), 8.12 - 8.17 (m, 2 H), 8.59 (d, J=2.54 Hz, 1 H); ES-LC-MS m/z = (M+H)+.

Example 41

5-(2-amino-1-((4-(dimethylamino)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yloxy)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

[00180] A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (50 mg, 0.135 mmol), 6-bromo-1-phenyl-1H-benzo[d]imidazol-2-amine (38.9 mg, 0.135 mmol), Pd(dppf)₂Cl₂CH₂Cl₂ adduct (11.03 mg, 0.014 mmol) and potassium acetate (39.8 mg, 0.405 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (50 mL) and washed with H₂O (50 mL). The organic layer was filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-70% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-phenyl-1 H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (34 mg, 0.075 mmol, 55.8% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.05 - 1.10 (m, 9 H), 4.01 (s, 3 H), 6.44 (s, 2 H), 7.04 (s, 1 H), 7.32 (s, 2 H), 7.45 (s, 1 H), 7.50 - 7.58 (m, 3 H), 7.60 - 7.67 (m, 2 H), 8.12 - 8.17 (m, 2 H), 8.59 (d, J=2.54 Hz, 1 H); ES-LC-MS m/z = (M+H)+.
A degassed mixture of 2-(methylamino)-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (80 mg, 0.205 mmol), 6-bromo-1-((4-(dimethylamino)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzimidazol-2-amine (72.4 mg, 0.205 mmol), Pd(dppf)₂Cl₂CH₂Cl₂ adduct (16.74 mg, 0.020 mmol) and potassium acetate (60.4 mg, 0.615 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. LCMS indicated complete reaction. The reaction mixture was allowed to cool to room temperature then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-((4-(dimethylamino)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-phenylpyridine-3-sulfonamide formic acid salt (12 mg, 0.020 mmol, 9.75% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.19 - 1.31 (m, 2 H) 1.88 (br. s., 2 H) 2.42 (s, 6 H) 3.46 (d, J=10.85 Hz, 2 H) 3.51 - 3.62 (m, 2 H) 4.00 (s, 3 H) 4.07 (s, 2 H) 6.61 (br. s., 2 H) 6.95 - 7.01 (m, 1 H) 7.10 - 7.24 (m, 6 H) 7.40 (s, 1 H) 8.16 (s, 1 H) 8.26 (d, J=2.05 Hz, 1 H) 8.64 (d, J=2.05 Hz, 1 H); ES LC-MS m/z =537.2 (M+H)⁺.

Example 42
5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-methyl-N-phenylpyridine-3-sulfonamide formic acid salt
Step A

5-bromo-N-(4-morpholinophenyl)-2-nitroaniline

[00182] A solution of 4-bromo-2-fluoro-1-nitrobenzene (2.66 g, 12.09 mmol), [4-(4-morpholinyl)phenyl]amine (2.155 g, 12.09 mmol), and potassium carbonate (3.34 g, 24.18 mmol) in N,N-dimethylformamide (DMF) (30 mL) was maintained at 90°C for 3 hours. The mixture was diluted with ethyl acetate and washed three times with 5% LiCl (aq). The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford (5-bromo-2-nitrophenyl)[4-(4-morpholinyl)phenyl]amine (3.45 g, 9.12 mmol, 75% yield) as a bright orange solid.

Step B

5-bromo-N1-(4-morpholinophenyl)benzene-1,2-diamine

[00183] A solution of (5-bromo-2-nitrophenyl)[4-(4-morpholinyl)phenyl]amine (2060 mg, 5.45 mmol) in tetrahydrofuran (THF) (100 mL) was maintained with stirring at room temperature while sodium dithionite (9477 mg, 54.5 mmol) in Water (100 mL) was added dropwise by addition funnel over 25 minutes. The mixture was maintained with vigorous stirring for 3 hours, poured into ethyl acetate, and diluted with water. The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column...
chromatography to afford (2-amino-5-bromophenyl)[4-(4-morpholinyl)phenyl]amine (987 mg, 2.83 mmol, 52.0 % yield) as a yellow solid.

**Step C**

6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine

[00184] A solution of cyanogen bromide (400 mg, 3.77 mmol) in acetonitrile (2 mL) and water (12 mL) was treated with (2-amino-5-bromophenyl)[4-(4-morpholinyl)phenyl]amine (750 mg, 2.154 mmol) as a solution in methanol/acetonitrile (12 mL). Stirring was continued for 2 hours the the mixture was poured into ethyl acetate and diluted with saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and triturated with DCM to afford 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (365 mg, 0.978 mmol, 45.4% yield) as a white solid. The filtrates were collected, concentrated onto celite, and purified by column chromatography to afford additional 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (155 mg, 0.415 mmol, 19.28% yield) as a white foam.

**Step D**

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-methyl-N-phenylpyridine-3-sulfonamide formic acid salt

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A degassed mixture of 2-methoxy-N-methyl-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (60 mg, 0.148 mmol), 6-bromo-1-(4-morpholinophenyl)-1 H-benzo[d]imidazol-2-amine (60.9 mg, 0.163 mmol), Pd(dppf)Cl₂CH₂Cl₂ adduct (12.12 mg, 0.015 mmol) and potassium acetate (43.7 mg, 0.445 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The resulting mixture was diluted with EtOAc (50 mL) and washed with H₂O (50 mL). The organic layer was filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-70% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-(4-morpholinophenyl)-1 H-benzo[d]imidazol-6-yl)-2-methoxy-N-methyl-N-phenylpyridine-3-sulfonamide formic acid salt (31 mg, 0.050 mmol, 33.5 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.19 - 3.28 (m, 4 H) 3.32 (s, 3 H) 3.73 - 3.82 (m, 4 H) 3.91 (s, 3 H) 6.32 (br. s., 2 H) 6.80 (d, J=1.47 Hz, 1 H) 7.11 - 7.24 (m, 6 H) 7.24 - 7.38 (m, 5 H) 7.88 (d, J=2.44 Hz, 1 H) 8.14 (s, 1 H) 8.59 (d, J=2.44 Hz, 1 H); ES LC-MS m/z =571.2 (M+H)⁺.

**Example 43**

5-(2-amino-1-((4-(dimethylamino) tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (80 mg, 0.216 mmol), 6-bromo-1-[[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl]-1H-benimidazol-2-amine (84 mg, 0.238 mmol), Pd(dppf)Cl₂CH₂Cl₂ adduct (17.64 mg, 0.022 mmol) and potassium acetate (63.6 mg, 0.648 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-70% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-((4-(dimethylamino)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (27 mg, 0.048 mmol, 21.99 % yield) as a white
solid: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 1.11 (s, 9 H) 1.19 - 1.35 (m, 2 H) 1.92 (d, $J$=13.56 Hz, 2 H) 2.43 (s, 6 H) 3.47 (d, $J$=10.83 Hz, 2 H) 3.56 (d, $J$=10.63 Hz, 2 H) 4.04 (s, 3 H) 4.10 (s, 2 H) 6.64 (br. s., 2 H) 7.23 (s, 2 H) 7.46 (d, $J$=7.51 Hz, 2 H) 8.14 (s, 1 H) 8.27 (d, $J$=2.44 Hz, 1 H) 8.68 (d, $J$=2.44 Hz, 1 H); ES LC-MS $m/z$ =517.5 (M+H)$^+$. 

Example 44
5-(2-amino-1-isobutyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

[00187] A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (80 mg, 0.216 mmol), 6-bromo-1-isobutyl-1H-benzo[d]imidazol-2-amine (63.7 mg, 0.238 mmol), Pd(dppf)$_2$C$_2$I$_2$CH$_2$I$_2$ adduct (17.64 mg, 0.022 mmol) and potassium acetate (63.6 mg, 0.648 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H$_2$O (50 mL) and extracted with EtOAc (50 mL) and CH$_2$Cl$_2$ (50 mL). The organic layers were filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-isobutyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (43 mg, 0.089 mmol, 41.3 % yield) as a white solid: $^1$H NMR (400 MHz, DMSO-de) $\delta$ ppm 0.88 (d, $J$=6.63 Hz, 6 H) 1.11 (s, 9 H) 2.07 - 2.23 (m, 1 H) 3.87 (d, $J$=7.61 Hz, 2 H) 4.04 (s, 3 H) 6.56 (s, 2 H) 7.16 - 7.25 (m, 2 H) 7.46 (s, 1 H) 7.49 (s, 1 H) 8.16 (s, 1 H) 8.27 (d, $J$=2.44 Hz, 1 H) 8.68 (d, $J$=2A4 Hz, 1 H); ES LC-MS $m/z$ =432.4 (M+H)$^+$. 

Example 45
5-(2-amino-1-cyclopentyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

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A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (80 mg, 0.216 mmol), 6-bromo-1-cyclopentyl-1H-benzo[d]imidazol-2-amine (66.6 mg, 0.238 mmol), Pd(dppf)Cl₂CH₂Cl₂ adduct (17.64 mg, 0.022 mmol) and potassium acetate (63.6 mg, 0.648 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-cyclopentyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (58 mg, 0.118 mmol, 54.8 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.12 (s, 9 H) 1.69 (d, J=5.56 Hz, 2 H) 1.86 - 2.05 (m, 4 H) 2.12 (d, J=8.29 Hz, 2 H) 4.04 (s, 3 H) 4.78 (quin, J=8.78 Hz, 1 H) 6.57 (br. s., 2 H) 7.24 (s, 2 H) 7.37 (s, 1 H) 7.48 (s, 1 H) 8.14 (s, 1 H) 8.24 (d, J=2.44 Hz, 1 H) 8.67 (d, J=2.44 Hz, 1 H); ES LC-MS m/z =444.4 (M+H)+.

Example 46
5-(2-amino-1-(pyridin-3-ylmethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (80 mg, 0.216 mmol), 6-bromo-1-(pyridin-3-ylmethyl)-1H-benzo[d]imidazol-2-amine (72.0 mg, 0.238 mmol), Pd(dppf)Cl₂CH₂Cl₂ adduct (17.64 mg, 0.022 mmol) and potassium acetate (63.6 mg, 0.648 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was
allowed to cool to room temperature then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-(pyridin-3-ylmethyl)-1 H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypridine-3-sulfonamide formic acid salt (29 mg, 0.056 mmol, 25.9 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.09 (s, 9 H) 4.02 (s, 3 H) 5.44 (s, 2 H) 6.69 (s, 2 H) 7.11 (d, J=7.80 Hz, 1 H) 7.20 - 7.32 (m, 3 H) 7.44 (d, J=4.49 Hz, 2 H) 7.75 (td, J=7.71, 1.76 Hz, 1 H) 8.15 (s, 1 H) 8.22 (d, J=2.54 Hz, 1 H) 8.51 - 8.56 (m, 1 H) 8.60 (d, J=2.44 Hz, 1 H); ES LC-MS m/z =467.4 (M+H)⁺.

**Example 47**
5-(2-amino-1-((1r,4r)-4-hydroxycyclohexyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

![Chemical structure](image)

[00190] A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (80 mg, 0.216 mmol), (1r,4r)-4-(2-amino-6-bromo-1 H-benzo[d]imidazol-1-yl)cyclohexanol (73.7 mg, 0.238 mmol), Pd(dppf)₂Cl₂ CH₂Cl₂ adduct (17.64 mg, 0.022 mmol) and potassium acetate (63.6 mg, 0.648 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-((1r,4r)-4-hydroxycyclohexyl)-1 H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (51 mg, 0.106 mmol, 45 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.12 (s, 9 H) 1.42 (br. s., 2 H) 1.72 (br. s., 2 H) 1.93 (br. s., 2 H) 2.16 - 2.40 (m, 2 H) 3.70 (br. s., 1 H) 4.04 (s, 3 H) 4.23 (br. s., 1 H) 4.67 (br. s., 1 H) 6.55 (br. s., 2 H) 7.20 (br. s., 2
H) 7.48 (s, 1 H) 7.52 - 7.64 (m, 1 H) 8.14 (s, 1 H) 8.24 (br. s., 1 H) 8.71 (br. s., 1 H); ES LC-MS m/z = 474.4 (M+H)⁺.

Example 48

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(^N^rt-butyl)-2-methoxy-N-methylpyridine-3-sulfonamide formic acid salt

Step A

5-bromo-N-(tert-butyl)-2-methoxy-N-methylpyridine-3-sulfonamide

[00191] A solution of 5-bromo-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide (460 mg, 1.423 mmol), potassium carbonate (983 mg, 7.12 mmol), and methyl iodide (0.267 mL, 4.27 mmol) in N,N-dimethylformamide (8 mL) was maintained at 80°C for 45 minutes. The solution was cooled to room temperature, poured into ethyl acetate, and washed three times with 5% aq. LiCl (aq). The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography (20% EtOAc in hexanes) to afford 5-bromo-N-(tert-butyl)-2-methoxy-N-methylpyridine-3-sulfonamide (400 mg, 1.186 mmol, 83% yield) as a yellow solid: ¹H NMR (DMSO-d₆) δ: 8.56 (d, J = 2.5 Hz, 1H), 8.20 (d, J = 2.5 Hz, 1H), 4.01 (s, 3H), 3.01 (s, 3H), 1.21 (s, 9H).

Step B

N-(tert-butyl)-2-methoxy-N-methyl-5-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)pyridine-3-
A degassed mixture of 5-bromo-N-(tert-butyl)-2-methoxy-N-methylpyridine-3-sulfonamide (334 mg, 0.990 mmol), 4,4,4',4',5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (277 mg, 1.089 mmol), Pd(dppf)₂Cl₂ CH₂Cl₂ adduct (81 mg, 0.099 mmol) and potassium acetate (292 mg, 2.97 mmol) in 1,4-dioxane (10 mL) was heated at 95 °C for 10 h, allowed to cool to room temperature and stirred over the weekend. The resulting mixture was filtered through pad of Celite® with the aid of EtOAc. The filtrate was concentrated, reevaporated twice from CH₂Cl₂/hexane. The residue was dissolved in CH₂Cl₂, concentrated onto Celite® and purified by column chromatography (silica gel, 0-30% EtOAc/hexane) to obtain N-(tert-butyl)-2-methoxy-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (356 mg, 0.741 mmol, 74.8 % yield) as a pale yellow oil: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.27 - 1.35 (m, 12 H) 3.01 (s, 3 H) 4.04 (s, 3 H) 8.24 (d, J=1.86 Hz, 1 H) 8.56 (d, J=1.76 Hz, 1 H); ES LC-MS m/z =385.2 (M+H)⁺.

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxy-N-methylpyridine-3-sulfonamide formic acid salt

A degassed mixture of N-(tert-butyl)-2-methoxy-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (80 mg, 0.208 mmol), 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (85 mg, 0.229 mmol), Pd(dppf)₂Cl₂ CH₂Cl₂
adduct (17.00 mg, 0.021 mmol) and potassium acetate (61.3 mg, 0.625 mmol) in 1,4-dioxane (4 ml) and water (1 ml) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then was diluted with H₂O (50 ml) and extracted with EtOAc (50 ml) and CH₂Cl₂ (50 ml). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-70% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxy-N-methylpyridine-3-sulfonamide formic acid salt (33 mg, 0.055 mmol, 26.6 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.19 (s, 9 H) 3.02 (s, 3 H) 3.19 - 3.27 (m, 4 H) 3.73 - 3.81 (m, 4 H) 4.02 (s, 3 H) 6.55 (br. s., 2 H) 6.98 (s, 1 H) 7.16 (d, J=8.98 Hz, 2 H) 7.32 (s, 2 H) 7.37 (d, J=8.88 Hz, 2 H) 8.10 - 8.16 (m, 2 H) 8.59 (d, J=2.44 Hz, 1 H); ES LC-MS m/z =551.3 (M+H)+.

**Example 49**

tert-butyl 3-(2-amino-6-(5-(N-(tert-butyl)sulfamoyl)-6-methoxypyridin-3-yl)-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate formic acid salt

![Chemical structure](image)

[00194] A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (80 mg, 0.216 mmol), tert-butyl 3-(2-amino-6-bromo-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate (91 mg, 0.238 mmol), Pd(dppf)₂Cl₂, CH₂Cl₂ adduct (17.64 mg, 0.022 mmol) and potassium acetate (63.6 mg, 0.648 mmol) in 1,4-dioxane (4 mL) and water (1 ml.) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-70% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain tert-butyl 3-(2-amino-6-(5-(N-(tert-butyl)sulfamoyl)-6-methoxypyridin-3-yl)-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate formic acid salt (66 mg, 0.112 mmol, 51.7 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.10 (s, 9 H) 1.24 (d, J=7.51 Hz, 1 H) 1.39 (br. s., 9 H) 2.19 (br. s., 1 H) 2.53 - 2.65 (m, 1 H) 3.34 (br. s., 1 H) 3.54 - 3.80 (m, 2 H) 4.03 (s, 3 H) 5.06 (m, J=7.32 Hz, 1 H) 6.61 (br. s.,
Example 50

55-(2-amino-1-(pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide trifluoroacetate

[00195] A solution of tert-butyl 3-(2-amino-6-(5-(N-(tert-butyl)sulfamoyl)-6-methoxypyridin-3-yl)-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate formic acid salt (80 mg, 0.135 mmol) in CH₂Cl₂ (2 mL) was treated with TFA (1 mL). After 2 h at room temperature the reaction mixture was concentrated to obtain 5-(2-amino-1-(pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide trifluoroacetate (73 mg, 0.128 mmol, 95 % yield) as a grey solid: ¹H NMR (400 MHz, DMSO-c₆) δ ppm 1.10 (s, 9 H) 2.35 - 2.69 (m, 2 H) 3.20 (d, J=6.24 Hz, 1 H) 3.69 (br., 3 H) 4.07 (s, 3 H) 5.36 (quin, J=9.22 Hz, 1 H) 7.48 - 7.62 (m, 3 H) 7.82 (s, 1 H) 8.33 (d, J=2.54 Hz, 1 H) 8.78 (d, J=2.34 Hz, 1 H) 8.91 (s, 2 H) 9.22 (br. s., 1 H); ES LC-MS m/z =545.3 (M+H)⁺.

Example 51

5-(2-amino-1-(2-phenylpropan-2-yl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

[00196] A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (70 mg, 0.189 mmol), 6-bromo-1-(2-phenylpropan-2-yl)-1 H-benzo[d]imidazol-2-amine (68.7 mg, 0.208 mmol), Pd(dppf)₂Cl₂ CH₂Cl₂ adduct (15.44 mg,
0.019 mmol) and potassium acetate (55.7 mg, 0.567 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-(2-phenylpropan-2-yl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (18 mg, 0.032 mmol, 17.1 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.07 - 1.12 (m, 9 H) 2.06 (s, 6 H) 4.00 (s, 3 H) 5.82 (s, 2 H) 6.71 (s, 1 H) 7.14 - 7.25 (m, 2 H) 7.27 - 7.44 (m, 6 H) 7.94 (d, J=2.34 Hz, 1 H) 8.16 (s, 1 H) 8.34 (d, J=2.34 Hz, 1 H); ES LC-MS m/z = 494.5 (M+H)⁺.

**Example 52**

(S)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N^rt-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

![Chemical Structure](image)

[00197] A degassed mixture of N-(tert-butyl)-2-methoxy-5-(3,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (70 mg, 0.189 mmol), (S)-6-bromo-1-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine (65.8 mg, 0.208 mmol), Pd(dppe)₂Cl₂ CH₂Cl₂ adduct (15.44 mg, 0.019 mmol) and potassium acetate (55.7 mg, 0.567 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-70% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain (S)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (27 mg, 0.051 mmol, 26.9 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.09 (s, 9 H) 1.87 (d, J=7.02 Hz, 3 H) 3.96 - 4.03 (m, 3 H) 5.84 (q, J=6.96 Hz, 1 H) 6.65 (s, 2 H) 6.87 (s, 1 H)
7.13 - 7.23 (m, 2 H) 7.26 - 7.32 (m, 1 H) 7.33 - 7.43 (m, 5 H) 8.02 (d, \( J=2.54 \) Hz, 1 H) 8.16 (s, 1 H) 8.41 (d, \( J=2.34 \) Hz, 1 H); ES LC-MS \( m/z = 480.5 \) (M+H)^+.

**Example 53**

5-(2-amino-1-(2,3-dihydro-1H-inden-1-yl)-1H-benzo[d]imidazol-6-yl)-N^rt-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

![Chemical Structure]

[00198] A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (70 mg, 0.189 mmol), 6-bromo-1-(2,3-dihydro-1H-inden-1-yl)-1H-benzo[d]imidazol-2-amine (68.3 mg, 0.208 mmol), \( \text{Pd(dppf)}_2 \text{Cl}_2 \text{CH}_2 \text{Cl}_2 \) adduct (15.44 mg, 0.019 mmol) and potassium acetate (55.7 mg, 0.567 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with \( \text{H}_2\text{O} \) (50 mL) and extracted with \( \text{EtOAc} \) (50 mL) and \( \text{CH}_2\text{Cl}_2 \) (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-70% \( \text{CH}_3\text{CN/H}_2\text{O} \), both containing 0.1% formic acid) to obtain 5-(2-amino-1-(2,3-dihydro-1H-inden-1-yl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (20 mg, 0.037 mmol, 19.48 % yield) as a white solid: \(^1\text{H NMR} \) (400 MHz, DMSO-d$_6$) \( \delta \) ppm 1.08 (s, 9 H) 2.17 - 2.36 (m, 1 H) 2.59 - 2.72 (m, 1 H) 2.94 - 3.09 (m, 1 H) 3.12 - 3.24 (m, 1 H) 3.98 (s, 3 H) 5.98 - 6.32 (m, 2 H) 6.68 (br. s., 2 H) 7.00 (d, \( J=7.41 \) Hz, 1 H) 7.13 - 7.25 (m, 3 H) 7.33 (t, \( J=7.32 \) Hz, 1 H) 7.38 (s, 1 H) 7.42 (d, \( J=7.61 \) Hz, 1 H) 7.88 (br. s., 1 H) 8.16 (s, 1 H) 8.25 (br. s., 1 H); ES LC-MS \( m/z = 492.5 \) (M+H)^+.

**Example 54**

5-(2-amino-1-((4-(dimethylamino)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-N-(3-fluorophenyl)-2-methoxypyridine-3-sulfonamide formic acid salt
A degassed mixture of N-(3-fluorophenyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (75 mg, 0.184 mmol), 6-bromo-1-[(4-(dimethylamino)tetrahydro-2H-pyran-4-yl)methyl]-1H-benzimidazol-2-amine (64.9 mg, 0.184 mmol), Pd(dpdpf)₂C₂H₂Cl₂ adduct (15.00 mg, 0.018 mmol) and potassium acetate (54.1 mg, 0.551 mmol) in 1,4-dioxane (4 ml) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-((4-(dimethylamino)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-N-(3-fluorophenyl)-2-methoxypyridine-3-sulfonamide formic acid salt (18 mg, 0.030 mmol, 16.15 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.19 - 1.32 (m, 2 H) 1.90 (d, J=13.27 Hz, 2 H) 2.43 (s, 6 H) 3.46 (d, J=10.73 Hz, 2 H) 3.51 - 3.62 (m, 2 H) 3.99 (s, 3 H) 4.08 (s, 2 H) 6.61 (br. s., 2 H) 6.81 (td, J=8.39, 2.15 Hz, 1 H) 6.90 - 7.02 (m, 2 H) 7.16 - 7.29 (m, 3 H) 7.42 (s, 1 H) 8.15 (s, 1 H) 8.32 (d, J=2.34 Hz, 1 H) 8.67 (d, J=2.34 Hz, 1 H); ES LC-MS m/z =555.44 (M+H)⁺.

Example 55

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-(1-phenylethyl)pyridine-3-sulfonamide formic acid salt
A degassed mixture of 2-methoxy-N-(1-phenylethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (80 mg, 0.191 mmol), 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (79 mg, 0.210 mmol), Pd(dppf)$_2$C$_I$$_2$CH$_2$C$_I$$_2$ adduct (15.62 mg, 0.019 mmol) and potassium acetate (56.3 mg, 0.574 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H$_2$O (50 mL) and extracted with EtOAc (50 mL) and CH$_2$C$_I$$_2$ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-(1-phenylethyl)pyridine-3-sulfonamide formic acid salt (52 mg, 0.082 mmol, 42.7 % yield) as a white solid: $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 1.32 (d, J=7.02 Hz, 3 H) 3.18 - 3.28 (m, 4 H) 3.73 - 3.82 (m, 4 H) 3.88 (s, 3 H) 4.33 - 4.43 (m, 1 H) 6.69 (br. s., 2 H) 6.84 (d, J=1.37 Hz, 1 H) 6.93 - 7.05 (m, 3 H) 7.05 - 7.11 (m, 2 H) 7.15 - 7.25 (m, 3 H) 7.32 (d, J=8.00 Hz, 1 H) 7.39 (d, J=8.98 Hz, 2 H) 7.83 (d, J=2.54 Hz, 1 H) 8.13 (s, 1 H) 8.19 (d, J=8.98 Hz, 1 H) 8.33 (d, J=2.54 Hz, 1 H); ES LC-MS m/z =585.5 (M+H)$^+$.

Example 56

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-benzyl-2-methoxypyrindine-3-sulfonamide formic acid salt

A degassed mixture of N-benzyl-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (80 mg, 0.198 mmol), 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (81 mg, 0.218 mmol), Pd(dppf)$_2$C$_I$$_2$CH$_2$C$_I$$_2$ adduct (16.16 mg, 0.020 mmol) and potassium acetate (58.3 mg, 0.594 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H$_2$O (50 mL) and extracted.
with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-benzyl-2-methoxypyridine-3-sulfonamide formic acid salt (46 mg, 0.075 mmol, 37.7% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.17 - 3.28 (m, 4 H) 3.72 - 3.81 (m, 4 H) 3.92 (s, 3 H) 4.11 (d, J=6.24 Hz, 2 H) 6.91 (s, 3 H) 7.03 - 7.15 (m, 4 H) 7.18 (d, J=8.98 Hz, 2 H) 7.27 - 7.33 (m, 1 H) 7.33 - 7.38 (m, 1 H) 7.40 (d, J=8.98 Hz, 2 H) 7.93 (d, J=2.54 Hz, 1 H) 8.13 (s, 1 H) 8.17 (t, J=6.34 Hz, 1 H) 8.43 (d, J=2.34 Hz, 1 H) 12.79 (br. s., 1 H); ES LC-MS m/z = 571.4 (M+H)+.

**General Scheme 2**

![Chemical Structures]
Example 57

5-(2-amino-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

Step A

6-bromo-1-(2-chloroethyl)-1H-benzo[d]imidazol-2-amine hydrochloride

[00202] A mixture of 2-(2-amino-6-bromo-1H-benzo[d]imidazol-1-yl)ethanol (1 g, 3.90 mmol) and thionyl chloride (3.99 ml, 54.7 mmol) was heated in an 85 °C bath for 30 min. The resulting mixture was concentrated. The residue was treated with water, sonicated and filtered to obtain 6-bromo-1-(2-chloroethyl)-1H-benzo[d]imidazol-2-amine hydrochloride (1.164 g, 3.74 mmol, 96% yield) as a tan solid: \(^{1}H\) NMR (400 MHz, DMSO-cf) \(\delta\) ppm 3.99 (t, 2 H) 4.58 (t, \(J=5.86\) Hz, 2 H) 7.31 - 7.39 (m, 1 H) 7.39 - 7.46 (m, 1 H) 7.93 (d, \(J=1.56\) Hz, 1 H) 9.10 (s, 2 H) 13.09 (br.s., 1 H); ES LC-MS \(m/z = 274.0\) (CI\(^{35}\), Br\(^{79}\), M+H)\(^{+}\), ES LC-MS \(m/z = 276.0\) (CI\(^{35}\), Br\(^{81}\), M+H)\(^{+}\).

Step B

6-bromo-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-2-amine
A mixture of 6-bromo-1-(2-chloroethyl)-1H-benzo[d]imidazol-2-amine hydrochloride (100 mg, 0.322 mmol) and pyrrolidine (229 mg, 3.22 mmol) was heated at 80 °C overnight. The resulting mixture was allowed to cool to room temperature. The resulting solids were taken up into EtOAc (50 mL) and washed with a sat. NaHCO₃ solution. The organic layer was concentrated to obtain 6-bromo-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-2-amine (91 mg, 0.277 mmol, 86 % yield) as a beige solid: ¹H NMR (400 MHz, DMSO-cf) δ ppm 1.58 - 1.72 (m, 4 H) 2.45 - 2.54 (m, 4 H, overlaps with DMSO-d₆) 2.66 (t, J=6.54 Hz, 2 H) 4.07 (t, J=6.54 Hz, 2 H) 6.60 (s, 2 H) 7.04 (s, 2 H) 7.33 (s, 1 H); ES LC-MS m/z =309.3 (Br⁺, M+H)⁺, ES LC-MS m/z =31.13 (Br⁺, M+H)⁺.

Step C
5-(2-amino-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-6-yl)-N-tert-butyl-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide formic acid salt

A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (80 mg, 0.216 mmol), 6-bromo-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-2-amine (78 mg, 0.238 mmol), Pd(dppf)₂Cl₂ CH₂Cl₂ adduct (17.64 mg, 0.022 mmol) and potassium acetate (63.6 mg, 0.648 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (47 mg, 0.089 mmol, 41.1 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.11 (s, 9 H) 1.63 - 1.72 (m, 4 H) 2.53 - 2.62 (m, 4 H) 2.76 (t, J=6.44 Hz, 1 H) 4.04 (s, 3 H) 4.18 (t, J=6.44 Hz, 1 H) 6.64 (br. s., 2 H) 7.17 - 7.28 (m, 2 H) 7.43 (s, 1 H) 7.47 (d, J=0.98 Hz, 1 H) 8.15 (s, 2
H) 8.29 (d, J=2.54 Hz, 1 H) 8.67 (d, J=2.34 Hz, 1 H) 12.08 - 13.76 (m, 1 H); ES LC-MS m/z =473.5 (M+H)^+.

**Example 58**

5-(2-amino-1-(2-morpholinoethyl)-1H-benzo[d]imidazol-6-yl)-N-(t^rt-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

![Structure](image)

**Step A**

6-bromo-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-2-amine

![Structure](image)

[00205] A mixture of 6-bromo-1-(2-chloroethyl)-1 H-benzo[d]imidazol-2-amine hydrochloride (100 mg, 0.322 mmol) and pyrrolidine (229 mg, 3.22 mmol) was heated at 80 °C overnight. The resulting mixture was allowed to cool to room temperature. The resulting solids were taken up into EtOAc (50 mL) and washed with a sat. NaHCO₃ solution. The organic layer was concentrated to obtain 6-bromo-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-2-amine (91 mg, 0.277 mmol, 86 % yield) as a beige solid: ^1^H NMR (400 MHz, DMSO-cf6) δ ppm 1.58 - 1.72 (m, 4 H) 2.45 - 2.54 (m, 4 H, overlaps with DMSO-d₆) 2.66 (t, J=6.54 Hz, 2 H) 4.07 (t, J=6.54 Hz, 2 H) 6.60 (s, 2 H) 7.04 (s, 2 H) 7.33 (s, 1 H); ES LC-MS m/z =309.3 (Br^79^, M+H)⁺; ES LC-MS m/z =31.3 (Br^81^, M+H)⁺.

**Step B**

5-(2-amino-1-(2-morpholinoethyl)-1H-benzo[d]imidazol-6-yl)-N-(t^rt-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

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A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (69.3 mg, 0.180 mmol), (R)-6-bromo-1-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine (60 mg, 0.190 mmol), Pd(dppf)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (15.50 mg, 0.019 mmol) and potassium acetate (55.9 mg, 0.569 mmol) in 1,4-dioxane (4 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H$_2$O (50 mL) and extracted with EtOAc (50 mL) and CH$_2$Cl$_2$ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (54 mg, 0.101 mmol, 46.7 % yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.11 (s, 9 H) 4 protons obscured by DMSO-d$_6$ signal 2.59 (t, J=6.35 Hz, 2 H) 3.53 (t, J=4.20 Hz, 4 H) 4.04 (s, 3 H) 4.17 (t, J=6.16 Hz, 2 H) 6.63 (br. s., 2 H) 7.17 - 7.27 (m, 2 H) 7.44 (s, 1 H) 7.50 (s, 1 H) 8.16 (s, 1 H) 8.30 (d, J=2.15 Hz, 1 H) 8.68 (d, J=2.15 Hz, 1 H); ES LC-MS m/z =489.5 (M+H)$^+$. 

**Example 59**

(R)-5-(2-amino-1-(1^henylethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-b^tyl)-2-methoxy-N-methylpyridine-3-sulfonamide formic acid salt
and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain (R)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxy-3-sulfonamide formic acid salt (50 mg, 0.093 mmol, 48.8 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.16 - 1.32 (m, 9 H) 1.86 (d, J=7.04 Hz, 3 H) 3.02 (s, 3 H) 4.01 (s, 3 H) 5.84 (q, J=6.91 Hz, 1 H) 6.68 (br. s., 2 H) 6.85 (s, 1 H) 7.13 - 7.24 (m, 2 H) 7.26 - 7.33 (m, 1 H) 7.34 - 7.43 (m, 4 H) 7.99 (d, J=2.35 Hz, 1 H) 8.14 (d, J=2.35 Hz, 1 H); ES LC-MS m/z =494.4 (M+H)^+.

**Example 60**

(R)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-benzyl-2^- ethoxypyridine-3-sulfonamide formic acid salt

![Chemical Structure](image)

[00208] A degassed mixture of N-benzyl-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (72.9 mg, 0.180 mmol), (R)-6-bromo-1-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine (60 mg, 0.190 mmol), Pd(dppf)Cl₂ CH₂Cl₂ adduct (15.50 mg, 0.019 mmol) and potassium acetate (55.9 mg, 0.569 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain (R)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-benzyl-2-methoxypyridine-3-sulfonamide formic acid salt (50 mg, 0.089 mmol, 47.1 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.89 (d, J=7.04 Hz, 3 H) 3.90 (s, 3 H) 4.10 (d, J=6.25 Hz, 2 H) 5.84 (q, J=6.97 Hz, 1 H) 6.65 (s, 2 H) 6.79 (d, J=1.56 Hz, 1 H) 6.98 - 7.15 (m, 5 H) 7.20 (d, J=8.01 Hz, 1 H) 7.25 - 7.33 (m, 1 H) 7.34 -
7.44 (m, 4 H) 7.83 (d, J=2.54 Hz, 1 H) 8.10 - 8.18 (m, 3 H) 8.24 (d, J=2.35 Hz, 1 H); ES LC-MS m/z =514.4 (M+H)+.

**Example 61**

(R)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yO-N-(3-fluorophenyl)-2-methoxypyridine-3-sulfonamide formic acid salt

![Chemical structure](image)

[00209] A degassed mixture of N-(3-fluorophenyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (73.6 mg, 0.180 mmol), (R)-6-bromo-1-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine (60 mg, 0.190 mmol), Pd(dppf)2Cl2 CH2Cl2 adduct (15.50 mg, 0.019 mmol) and potassium acetate (55.9 mg, 0.569 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H2O (50 mL) and extracted with EtOAc (50 mL) and CH2Cl2 (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH3CN/H2O, both containing 0.1% formic acid) to obtain (R)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-(3-fluorophenyl)-2-methoxypyridine-3-sulfonamide formic acid salt (53 mg, 0.094 mmol, 49.6 % yield) as a white solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.87 (d, J=7.04 Hz, 3 H) 3.96 (s, 3 H) 5.83 (q, J=6.97 Hz, 1 H) 6.67 (s, 2 H) 6.77 - 6.88 (m, 2 H) 6.88 - 6.97 (m, 2 H) 7.10 - 7.44 (m, 8 H) 8.04 (d, J=2.34 Hz, 1 H) 8.14 (s, 1 H) 8.41 (d, J=2.35 Hz, 1 H) 10.73 (br. s., 1 H); ES LC-MS m/z =518.4 (M+H)+.

**Example 62**

(R)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-benzyl-2-methoxy-N-methylpyridine-3-sulfonamide formic acid salt
A degassed mixture of N-benzyl-2-methoxy-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (75 mg, 0.180 mmol), (R)-6-bromo-1-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine (60 mg, 0.190 mmol), Pd(dppf)2Cl2CH2Cl2 adduct (15.50 mg, 0.019 mmol) and potassium acetate (55.9 mg, 0.569 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then was diluted with H2O (50 mL) and extracted with EtOAc (50 mL) and CH2Cl2 (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH3CN/H2O, both containing 0.1% formic acid) to obtain (R)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-benzyl-2-methoxy-N-methylpyridine-3-sulfonamide formic acid salt (36 mg, 0.063 mmol, 33.1 % yield) as a white solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.87 (d, J=7.02 Hz, 3 H) 2.71 (s, 3 H) 4.01 (s, 3 H) 4.34 (s, 2 H) 5.84 (q, J=6.76 Hz, 1 H) 6.65 (s, 2 H) 6.89 (s, 1 H) 7.20 (s, 2 H) 7.24 - 7.43 (m, 10 H) 8.05 (d, J=2.34 Hz, 1 H) 8.14 (s, 1 H) 8.45 (d, J=2.34 Hz, 1 H); ES LC-MS m/z =528.4 (M+H)+.

Example 63
5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt

[00210] A degassed mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (140 mg, 0.378 mmol), 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (155 mg, 0.416 mmol), Pd(dppf)2Cl2CH2Cl2
adduct (30.9 mg, 0.038 mmol) and potassium acetate (111 mg, 1.134 mmol) in 1,4-dioxane (6 mL) and water (1.5 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain 5-(2-amino-1-(4-morpholinophenyl)-1 H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide formic acid salt (70 mg, 0.117 mmol, 30.8 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.41 (d, 1H), 7.30 (7.30 - 7.43 (m, 4 H)) 4.01 (s, 3 H) 6.78 (br. s., 2 H) 7.00 (s, 1 H) 7.15 (s, 1 H) 7.17 (s, 1 H) 7.30 - 7.43 (m, 4 H) 7.45 (s, 1 H) 8.11 - 8.18 (m, 2 H) 8.59 (d, J=2.54 Hz, 1 H); ES LC-MS m/z =537.4 (M+H)+.

Example 64

(R)-5-(2-amino-1-(1-phenylethyl)-1H-benzo[cqimidazol-6-yl]-N-fart-butyl)-2-methoxypyridine-3-sulfonamide

[0021] A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (30 mg, 0.081 mmol) and 6-bromo-1-(3-morpholinophenyl)-1 H-benzo[d]imidazol-2-amine (30 mg, 0.081 mmol) and potassium acetate (24 mg, 0.243 mmol) in dioxane (4 mL) and water (0.75 mL) was sparged with nitrogen as PdC(dppe) DCN adduct (7 mg, 0.008 mmol) was added. The reaction mixture was then heated to 130°C for 15 minutes. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na₂S⁰₄, filtered and the filtrate concentrated. The residue was purified by silica gel chromatography (0-5% MeOH in DCM). Fractions containing the product were combined and concentrated to and the residue was slurried in hexane - DCM then concentrated to yield (R)-5-(2-amino-1-(1-phenylethyl)-1 H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide as a tan solid (15 mg, 39 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.41 (d,
Example 65

5-(2-amino-1-(3-(oxazol-5-yl)phenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide

[00213] A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (30 mg, 0.081 mmol) and 6-bromo-1-(3-(oxazol-5-yl)phenyl)-1H-benzo[d]imidazol-2-amine (29 mg, 0.081 mmol) and potassium acetate (24 mg, 0.243 mmol) in dioxane (4 mL) and water (0.75 mL) was sparged with nitrogen as PdCl₂(dppf) DCM adduct (7 mg, 0.008 mmol) was added. The reaction mixture was then heated to 130°C for 15 minutes. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na₂SO₄, filtered and the filtrate concentrated. The residue was purified by silica gel chromatography (0-5% MeOH in DCM). Center cut fractions containing the product were combined and concentrated to and the residue was slurred in hexane - DCM and then concentrated to yield 5-(2-amino-1-(3-(oxazol-5-yl)phenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide as a tan glass (14 mg, 33 % yield). ¹H NMR (400 MHz, DMSO-de) 6ppm 8.59 (d, J=2.3 Hz, 1 H) 8.50 (s, 1 H) 8.16 (d, J=2.3 Hz, 1 H) 7.82 - 7.94 (m, 3 H) 7.73 (t, J=7.9 Hz, 1 H) 7.50 - 7.60 (m, 1 H) 7.44 (s, 1 H) 7.33 (s, 2 H) 7.09 (s, 1 H) 6.54 (s, 2 H) 4.00 (s, 3 H) 1.06 (s, 9 H). ES-LCMS: m/z 519.3 (M+H⁺).

Example 66

5-(2-amino-1-(3-morpholinophenyO-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide
A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (30 mg, 0.081 mmol) and 6-bromo-1-(3-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (30 mg, 0.081 mmol) and potassium acetate (24 mg, 0.243 mmol) in dioxane (4 mL) and water (0.75 mL) was sparged with nitrogen as PdCl$_2$(dppe) DCM adduct (7 mg, 0.008 mmol) was added. The reaction mixture was then heated to 130°C for 15 minutes in the microwave. The solution was then partitioned between EtOAc and brine. The organic layer was concentrated. The residue was purified by silica gel chromatography (0-5% MeOH in DCM) The sample was further purified by HPLC (10-70% MeCN water with 0.1% Formic acid) to yield 5-(2-amino-1-(3-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2- methoxypyridine-3-sulfonamide (8 mg, 18 % yield) as an-off white solid. $^1$H NMR (400 MHz, DMSO-d$_6$) 5ppm 8.59 (d, J=2.5 Hz, 1 H) 8.22 - 8.11 (m, 1 H) 7.51 - 7.40 (m, 2 H) 7.31 (s, 2 H) 7.13 - 6.99 (m, 3 H) 6.92 (d, J=7.6 Hz, 1 H) 6.41 (s, 2 H) 4.01 (s, 3 H) 3.82 - 3.66 (m, 4 H) 3.24 - 3.18 (m, 4 H) 1.08 (s, 9 H). ES-LCMS: m/z 537.3 (M+H$^+$).

**Example 67**

(R)-5-(2-amino-5-fluoro-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-buty) methoxypyridine-3-sulfonamide

Step A

(R)-5-bromo-4-fluoro-2-nitro-N-(1-phenylethyl)aniline
An orange mixture of 1-bromo-2,5-difluoro-4-nitrobenzene (2.163 g, 9.09 mmol), (R)-1-phenylethanamine (1.212 g, 10 mmol) and Hunig’s base (1.91 mL, 36.4 mmol) in butanol (23.3 mL) was allowed to stir in an 80°C sand bath for 17 hours. The resulting orange solution was concentrated and the residue partitioned between EtOAc and NaHCO₃ solution. The organic layer was washed with brine, dried with Na₂SO₄ filtered and concentrated to yield (R)-5-bromo-4-fluoro-2-nitro-N-(1-phenylethyl)aniline as an orange oil, (3.09 g, 94% crude yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.19 (d, J=6.8 Hz, 1 H) 8.05 (d, J=9.2 Hz, 1 H) 7.40 - 7.48 (m, 2 H) 7.36 (t, J=7.5 Hz, 2 H) 7.23 - 7.31 (m, 1 H) 7.18 (d, J=6.1 Hz, 1 H) 4.97 (t, J=6.7 Hz, 1 H) 1.55 (d, J=6.8 Hz, 3 H). LCMS: m/z 339.0 (M+H⁺).

**Step β**

(R)-5-bromo-4-fluoro-N1-(1-phenylethyl)benzene-1,2-diamine

To a bright yellow solution of (R)-5-bromo-4-fluoro-2-nitro-N-(1-phenylethyl)aniline (3.08 g, 9.08 mmol) in EtOH (100 mL) was added drop wise a solution of sodium hydrosulphite (14.97 g, 85.98 mmol) in H₂O (80 mL). After ~1 h from start of addition LCMS shows no starting material remaining. The pale yellow slurry was filtered and the solid was washed with EtOH. The filtrate was concentrated down to about 80 mL, diluted with EtOAc (100 mL) and water (50 mL). The organic layer was washed with a sat. NaCl solution (100 mL) and then concentrated. The residue was purified by purified by silica gel chromatography (0-70% EtOAc/hexane) to obtain (R)-5-bromo-4-fluoro-N1-(1-phenylethyl)benzene-1,2-diamine, as a dark oil (1.34 g, 3.94 mmol, as 0.35 ethyl acetate (solvent) 43.4 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.25 - 7.43 (m, 4 H) 7.12 - 7.24 (m, 1 H) 6.46 (d, J=10.7 Hz, 1 H) 6.19 (d, J=6.8 Hz, 1 H) 5.23 (br. s., 2 H) 5.02 (d, J=6.2 Hz, 1 H) 4.43 (t, J=6.5 Hz, 1 H) 1.43 (d, J=6.6 Hz, 3 H). LCMS: m/z 309.0 (M+H⁺).
Step C

(R)-6-bromo-5-fluoro-1-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine

[00217] A solution of (R)-5-bromo-4-fluoro-N1-(1-phenylethyl)benzene-1,2-diamine, 0.35 ethyl acetate (solvate) (1.34 g, 3.94 mmol) in MeOH (6.1 mL) was treated with cyanogen bromine (0.835 g, 7.88 mmol). The reaction mixture was maintained at room temperature for 2 hours. Additional CNBr (83 mg) was added and the solution was allowed to stir for another 30 minutes. The reaction mixture was then partitioned between EtOAc (100 mL) a sat. NaHCO₃ solution (100 mL) and water (20 mL). The organic layer was washed with a sat. NaCl solution and concentrated to obtain a brown solid. The residue was purified by silica gel chromatography (0-5% MeOH in DCM). Fractions containing the product were combined and concentrated. The residue was dissolved in DCM/hexanes and concentrated. The sample was then slurried in DCM/hexanes and filtered to yield (R)-6-bromo-5-fluoro-1-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine as a light tan solid (1.012 g, 3.03 mmol, 77 % yield). ¹H NMR (400 MHz, DMSO-d6) δ ppm 7.35 - 7.42 (m, 2 H) 7.25 - 7.34 (m, 3 H) 7.07 (d, J=9.8 Hz, 1 H) 6.75 - 6.85 (m, 3 H) 5.65 - 5.85 (m, 1 H) 1.81 (d, J=7.2 Hz, 3 H).

Step D

(R)-5-(2-amino-5-fluoro-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide

[00218] A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (111 mg, 0.299 mmol) and (R)-6-bromo-5-fluoro-1-(1-phenylethyl)-1H-
benzo[d]imidazol-2-amine (100 mg, 0.299 mmol) and potassium acetate (88 mg, 0.896 mmol) in dioxane (10 mL) and water (2.5 mL) was sparged with nitrogen as PdC^dppf DCM adduct (24 mg, 0.03 mmol) was added. The reaction mixture was then heated to 130°C for 15 minutes. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na_2SO_4, filtered and the filtrate concentrated. The residue was purified by silica gel chromatography (0-5% MeOH in DCM). Fractions containing the product were combined and concentrated to and the residue was slurried in hexane - DCM then concentrated. The sample was further purified by silica gel chromatography (0-5 % MeOH in DCM). Centercut fractions were combined and concentrated. The residue was dissolved in DCM/hexanes and concentrated to yield (R)-5-(2-amino-5-fluoro-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide as a tan solid (62 mg, 39 % yield). 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.26 (s, 1 H) 8.02 (d, J=1.4 Hz, 1 H) 7.45 (s, 1 H) 7.24 - 7.42 (m, 5 H) 7.03 (d, J=11.9 Hz, 1 H) 6.81 (br. s., 2 H) 6.70 (d, J=7.0 Hz, 1 H) 5.77 - 5.88 (m, 1 H) 4.02 (s, 3 H) 1.86 (d, J=6.8 Hz, 3 H) 1.09 (s, 9 H) LCMS: m/z 498.3 (M+H^+).

Example 68
5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(3-chlorophenyl)-2-methoxypyridine-3-sulfonamide

[00219] A mixture of N-(3-chlorophenyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (127 mg, 0.30 mmol) and 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (112 mg, 0.30 mmol) and potassium acetate (88 mg, 0.90 mmol) in dioxane (10 mL) and water (2.5 mL) was sparged with nitrogen as PdCl_2(dppf) DCM adduct (24 mg, 0.03 mmol) was added. The reaction mixture was then heated to 130°C for 15 minutes. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na_2SO_4, filtered and the filtrate concentrated. The residue was
dissolved in DMF (2 mL) and filtered. The filtrate was concentrated and the residue slurried in
EtOAc. The dark solid was purified by reverse phase (HPLC 10-70% MeCN in water with 0.1 %
formic acid). Fractions containing the product were combined and concentrated and the residue
was slurried in hexane - DCM then concentrated to yield 5-(2-amino-1-(4-morpholinophenyl)-
1H-benzo[d]imidazol-6-yl)-N-(3-chlorophenyl)-2-methoxypyridine-3-sulfonamide as a tan solid
(40 mg, 21 % yield). 1H NMR (400 MHz, DMSO-d6) δ ppm 8.56 (d, J=2.1 Hz, 1 H) 8.06 - 8.27
(m, 2 H) 7.35 (d, J=8.6 Hz, 2 H) 7.10 - 7.30 (m, 6 H) 6.99 - 7.09 (m, 2 H) 6.92 (s, 1 H) 6.31 (br.
s., 2 H) 3.95 (s, 3 H) 3.77 (d, J=3.7 Hz, 4 H) 3.23 (d, J=3.9 Hz, 4 H). LCMS: m/z 591.2 (M+H+).

**Example 69**

(R)-5-(2-amino-1-(1-phenylpropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-
methoxypyridine-3-sulfonamide

![Chemical Structure](image)

**Step A**

(R)-5-bromo-2-nitro-N-(1-phenylpropyl)aniline

![Chemical Structure](image)

**[00220]** An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), (R)-1-
phenylpropan-1-amine (1.229 g, 9.09 mmol) and K2CO3 (2.51 g, 18.18 mmol) in DMF (20 mL)
was heated at 90 °C. After 2 hours the resulting mixture was allowed to cool to room
temperature, diluted with EtOAc (100 mL) and washed with a 5% LiCl solution (3x100 mL). The
organic layer was concentrated to obtain an yellow oil, which was purified by silica gel
chromatography (0-20% EtOAc in hexanes) to obtain (R)-5-bromo-2-nitro-N-(1-
phenylpropyl)aniline as a yellow oil (3.75 g, 9.10 mmol, 0.5 ethyl acetate assume 100 % yield).
^1^H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.39 (d, J=7.0 Hz, 1 H) 7.99 (d, J=9.2 Hz, 1 H) 7.39 - 7.46 (m, 2 H) 7.36 (t, J=7.6 Hz, 2 H) 7.22 - 7.30 (m, 1 H) 7.04 (d, J=2.0 Hz, 1 H) 6.82 (dd, J=9.2, 2.0 Hz, 1 H) 4.03 (q, J=7.2 Hz, 1 H) 6.82 (dd, J=9.2, 2.0 Hz, 1 H) 1.69 - 2.08 (m, 2 H) 0.91 (t, J=7.3 Hz, 3 H).

Step B

(R)-5-bromo-N$_1$-(1-phenylpropyl)benzene-1,2-diamine

[00221] To a bright yellow solution of (R)-5-bromo-2-nitro-N-(1-phenylpropyl)aniline (3.05 g, 9.09 mmol) in EtOH (104 mL) was added dropwise a solution of sodium hydrosulfite (14.99 g, 86.1 mmol) in H$_2$O (83 mL). After ~1 h from start of addition the pale yellow slurry was filtered and the solid was washed with EtOH. The filtrate was concentrated down to about 80 mL, diluted with EtOAc (100 mL) and water (50 mL). The organic layer was washed with a sat. NaCl solution (100 mL) and concentrated. The residue was purified by silica gel chromatography (0-70% EtOAc/hexane) to obtain (R)-5-bromo-N$_1$-(1-phenylpropyl)benzene-1,2-diamine as a dark oil (1.92 g, 5.79 mmol, 0.3 ethyl acetate 63.7 % yield). ^1^H NMR (400 MHz, DMSO-d$_6$) δ ppm 7.26 - 7.38 (m, 4 H) 7.15 - 7.23 (m, 1 H) 6.41 (d, J=0.8 Hz, 2 H) 6.24 (s, 1 H) 5.10 (d, J=7.0 Hz, 1 H) 4.86 (s, 2 H) 4.20 (q, J=7.0 Hz, 1 H) 1.76 - 1.95 (m, 1 H) 1.68 (dt, J=13.8, 6.7 Hz, 1 H) 0.91 (t, J=7.3 Hz, 3 H). LCMS: m/z 305.0 (M+H$^+$).

Step C

(R)-6-bromo-1-(1-phenylpropyl)-1H-benzo[d]imidazol-2-amine

[00222] Cyanogen bromide (1.22 g, 11.52 mmol) was added to a solution of (R)-5-bromo-N$_1$-(1-phenylpropyl)benzene-1,2-diamine, 0.3 ethyl acetate (solvate) (1.91 g, 5.76 mmol) in methanol (8.9 mL). The resulting dark solution was allowed to stir at room temperature for 2 hours. The solution was then partitioned between EtOAc and NaHCO$_3$ solution. The organic
layer was dried with Na₂SO₄, filtered and concentrated to yield a brown solid. The residue was purified by silica gel chromatograph (0-5% MeOH in DCM) to yield (R)-6-bromo-1-(1-phenylpropyl)-1H-benzo[d]imidazol-2-amine (0.64 g, 33.7% yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.34 - 7.41 (m, 2 H) 7.26 - 7.34 (m, 3 H) 7.03 - 7.07 (m, 1 H) 6.98 - 7.02 (m, 1 H) 6.91 (d, J=1.8 Hz, 1 H) 6.68 (s, 2 H) 5.52 (t, J=7.9 Hz, 1 H) 2.36 (quin, J=7.5 Hz, 2 H) 0.80 (t, J=7.2 Hz, 3 H). LCMS: m/z 330.3 (M+H⁺).

Step D
(R)-5-(2'-amino-1-(1-phenylpropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide

A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (111 mg, 0.299 mmol) and (R)-6-bromo-5-fluoro-1-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine (100 mg, 0.299 mmol) and potassium acetate (88 mg, 0.896 mmol) in dioxane (10 ml) and water (2.5 ml) was sparged with nitrogen as PdCl₂(dppf) DCM adduct (24 mg, 0.03 mmol) was added. The reaction mixture was then heated to 130°C for 15 minutes. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na₂SO₄, filtered and the filtrate concentrated. The residue was purified by reverse phase (HPLC 10-70% MeCN / water with 0.1% formic acid) to yield (R)-5-(2-amino-1-(1-phenylpropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide: formic acid salt as an off white solid (46 mg, 28 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.45 (d, J=2.5 Hz, 1 H) 8.07 (d, J=2.5 Hz, 1 H) 7.33 - 7.45 (m, 5 H) 7.24 - 7.30 (m, 1 H) 7.15 - 7.23 (m, 2 H) 7.05 (s, 1 H) 6.68 (s, 2 H) 5.59 (dd, J=10.1, 5.6 Hz, 1 H) 4.01 (s, 3 H) 2.37 - 2.48 (m, 2 H) 1.09 (s, 9 H) 0.85 (t, J=7.2 Hz, 3 H). LCMS: m/z 494.3 (M+H⁺).

Example 70
(R)-5-(2-amino-1-(2-methyl-1-phenylpropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide
Step A

(R)-5-bromo-N-(2-methyl-1-phenylpropyl)-2-nitroaniline

Step B

(R)-5-bromo-N 1-(2-methyl-1-phenylpropyl)benzene-1,2-diamine

[00224] An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), (R)-2-methyl-1-phenylpropan-l-amine, Hydrochloride (1.357 g, 9.09 mmol) and K2CO3 (2.51 g, 18.18 mmol) in DMF (20 mL) (1.51 g) The mixture was heated overnight at 90°C. The mixture was allowed to cool to room temperature then diluted with EtOAc. The mixture was then washed with 5% LiCl solution 3 x 100 mL then brine. The organic layer was dried with Na2SO4, filtered and purified by silica gel chromatography (0-20 % EtOAc in hexanes). Fractions containing the product were combined and concentrated to obtain 3.48 g of a yellow oil. The sample was dissolved in DMF (20mL) and (R)-2-methyl-1-phenylpropan-1-amine, Hydrochloride (543 mg) was added followed by K2CO3 (1.51 g). The mixture was heated overnight at 90°C. The mixture was allowed to cool to room temperature then diluted with EtOAc. The mixture was then washed with 5% LiCl solution 3 x 100 mL then brine. The organic layer was dried with Na2SO4, filtered and purified by silica gel chromatography (0-20 % EtOAc in hexanes) to obtain (R)-5-bromo-N-(2-methyl-1-phenylpropyl)-2-nitroaniline as a yellow oil, (3.1 g, 8.11 mmol as 0.3 ethyl acetate, 89 % yield). 1H NMR (400 MHz, DMSO-d6) δ ppm 8.55 (d, J=7.2 Hz, 1 H) 7.99 (d, J=9.0 Hz, 1 H) 7.30 - 7.44 (m, 4 H) 7.22 - 7.30 (m, 1 H) 7.04 (d, J=2.0 Hz, 1 H) 6.81 (dd, J=9.1 , 2.0 Hz, 1 H) 4.65 (t, J=7.0 Hz, 1 H) 2.07 - 2.24 (m, 1 H) 0.68 - 1.07 (m, 6 H). LCMS: m/z 349.1 (M+H+).

Step B

(R)-5-bromo-N 1-(2-methyl-1-phenylpropyl)benzene-1,2-diamine

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To a bright yellow solution of (R)-5-bromo-N-(2-methyl-1-phenylpropyl)-2-nitroaniline (3.10 g, 8.25 mmol as 0.3 ETHYL ACETATE) in EtOH (87 mL) was added drop wise a solution of sodium hydrosulfite (12.98 g, 74.6 mmol) in H$_2$O (69 mL). After ~2 hours from start of addition, the pale yellow slurry was filtered and the solid was washed with EtOH. The filtrate was concentrated down to about 80 mL; diluted with EtOAc (100 mL) and water (50 mL). The organic layer was washed with a sat. NaCl solution (100 mL) and concentrated. The residue was purified by silica gel chromatography (0-50% EtOAc/hexane) to obtain (R)-5-bromo-N1-(2-methyl-1-phenylpropyl)benzene-1,2-diamine as a dark oil, (1.96 g, 5.53 mmol, as 0.4 ethyl acetate 67.0 % yield). $^1$H NMR (400 MHz, DMSO-c$_6$) δ ppm 7.32 - 7.37 (m, 2 H) 7.26 - 7.32 (m, 2 H) 7.15 - 7.23 (m, 1 H) 6.41 (s, 2 H) 6.28 (s, 1 H) 5.00 (d, J=7.4 Hz, 1 H) 4.85 (s, 2 H) 3.90 - 4.12 (m, 1 H) 1.86 - 2.11 (m, 1 H) 1.04 (d, J=6.6 Hz, 3 H) 0.74 (d, J=6.6 Hz, 3 H). LCMS: m/z 319.3 (M+H $^+$).

Step C

(R)-6-bromo-1-(2-methyl-1-phenylpropyl)-1H-benzo[d]imidazol-2-amine

Cyanogen bromide (0.598 g, 5.64 mmol) was added to a solution of (R)-5-bromo-N1-(2-methyl-1-phenylpropyl)benzene-1,2-diamine, (1.00 g, 2.82 mmol as 0.4 ethyl acetate) in methanol (4.4 mL). The resulting dark solution was allowed to stir at room temperature for 2 hours. The solution was then partitioned between EtOAc and NaHCO$_3$ solution. The organic layer was dried with Na$_2$SO$_4$, filtered and concentrated. The residue was slurred in EtOAc and filtered to yield (R)-6-bromo-1-(2-methyl-1-phenylpropyl)-1H-benzo[d]imidazol-2-amine as an off white solid (206 mg, 21% yield). $^1$H NMR (400 MHz, DMSO-$c_6$) δ PPM 7.57 (d, J=7.4 Hz, 2 H) 7.31 - 7.44 (m, 3 H) 7.20 - 7.32 (m, 1 H) 6.99 (d, J=0.8 Hz, 2
Step D

(R)-5-(2-amino-1-(2-methyl-1-phenylpropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide

A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (111 mg, 0.30 mmol) and (R)-6-bromo-1-(2-methyl-1-phenylpropyl)-1H-benzo[d]imidazol-2-amine (103 mg, 0.30 mmol) and potassium acetate (88 mg, 0.896 mmol) in dioxane (10 ml) and water (2.5 mL) was sparged with nitrogen as PdC\textsuperscript{dpdf} DCM adduct (24 mg, 0.03 mmol) was added. The reaction mixture was then heated to 130°C for 15 minutes. The solution was then partitioned between EtOAc and brine. The organic layer was dried with \textit{Na}_2\textit{SO}_4, filtered and the filtrate concentrated. The residue was purified by reverse phase HPLC (10-70% MeCN / water with 0.1% formic acid). Clean fractions were combined and concentrated. The residue was dissolved in dcm/hexanes and concentrated to yield (R)-5-(2-amino-1-(2-methyl-1-phenylpropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide as an off white solid. (45 mg, 27 % yield as the formic acid salt). \textit{^1}H NMR (400 MHz, DMSO-\textit{d}_6) \delta ppm 8.59 (d, \textit{J}=2.5 Hz, 1 H) 8.14 - 8.21 (m, 2 H) 7.65 (d, \textit{J}=7.4 Hz, 2 H) 7.52 (s, 1 H) 7.45 (s, 1 H) 7.37 (t, \textit{J}=7.6 Hz, 2 H) 7.21 - 7.30 (m, 1 H) 7.15 (s, 1 H) 6.74 (s, 2 H) 5.17 (d, \textit{J}=11.1 Hz, 1 H) 4.04 (s, 3 H) 1.24 (br. s., 1 H) 1.12 (s, 9 H) 1.04 (d, \textit{J}=6.4 Hz, 3 H) 0.82 (d, \textit{J}=6.4 Hz, 3 H). LCMS: m/z 508.2 (M+H\textsuperscript{+}).

Example 71

5-(2-amino-1-benzyl-5-methyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide

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Step A

6-bromo-5-methyl-1H-benzo[d]imidazol-2-amine

[00228] A cooled 0 °C solution of 4-bromo-5-methylbenzene-1,2-diamine (0.86 g, 4.28 mmol) in acetonitrile (4 mL) and water (2 mL) was treated with cyanogen bromine (0.498 g, 4.70 mmol). The reaction mixture was allowed to warm slowly to room temperature and stir overnight. The reaction mixture was partitioned between DCM (100 mL) a sat. NaHCO₃ solution (100 mL) and water (20 mL). The organic layer was dried with Na₂SO₄, filtered and concentrated to obtain a brown solid. 67-1 The aqueous layer was filtered to yield a light tan solid. The Na₂SO₄ contained a tan solid as well. The salts were dissolved in water, sonicated then filtered to yield a pink solid. Spectra of the pink solid and the material from the aqueous filtration were comparable so the samples were combined to yield 6-bromo-5-methyl-1H-benzo[d]imidazol-2-amine as a light tan solid (825 mg, 3.28 mmol, 77 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.83 (br. s., 1 H) 7.21 - 7.40 (m, 1 H) 7.02 - 7.16 (m, 1 H) 6.67 (br. s., 2 H) 2.24 - 2.39 (m, 3 H). LCMS: m/z 225.9 (M+H⁺).

Step B

1-benzyl-6-bromo-5-methyl-1H-benzo[d]imidazol-2-amine and 1-benzyl-5-bromo-6-methyl-1H-benzo[d]imidazol-2-amine
A mixture of 6-bromo-5-methyl-1H-benzo[d]imidazol-2-amine (822 mg, 3.27 mmol) in MeCN (174 mL) was stirred at room temperature as sodium hydroxide (131 mg, 3.27 mmol) was added. The mixture was allowed to stir for one hour before the addition of benzyl bromide (0.39 mL, 3.27 mmol). The mixture was then heated at reflux for 18 hours. The solution was allowed to cool to room temperature. A solid precipitated. The mixture was filtered to yield an off white solid. The filtrate was concentrated and the residue was partitioned between DCM and water. Organic layer was purified by silica gel chromatography (0-10% 2N NH₃ in MeOH in DCM). Fractions containing the product were combined and concentrated. The residue was further purified by HPLC (10 - 70% MeCN in water with 0.1% formic acid). Fractions containing the product were combined and concentrated to yield a mixture of 1-benzyl-6-bromo-5-methyl-1H-benzo[d]imidazol-2-amine (85 mg, 8.2 %). ¹H NMR (400 MHz, DMSO-cf) δ ppm 7.88 (br. s., 2H) 7.42 - 7.57 (m, 1H) 7.32 - 7.39 (m, 2H) 7.26 - 7.32 (m, 2H) 7.21 (d, J=7.2 Hz, 2H) 5.33 (d, J=13.5 Hz, 2H) 2.34 (d, J=1.9 Hz, 3H). LCMS: m/z 316.0 (M+H⁺).

Step C

5-(2-amino-1-benzyl-5-methyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide

A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (94 mg, 0.253 mmol) and 1-benzyl-6-bromo-5-methyl-1H-benzo[d]imidazol-2-amine and 1-benzyl-5-bromo-6-methyl-1H-benzo[d]imidazol-2-amine (80 mg, 0.253 mmol) and potassium acetate (74.5 mg, 0.759 mmol) in dioxane (8 mL) and water (2.0 mL) was sparged with nitrogen as PdC^dppf) DCM adduct (21 mg, 0.03 mmol) was added. The reaction mixture was then heated to 130°C for 15 minutes. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na₂SO₄, filtered and the filtrate concentrated. The residue was purified by HPLC (10-70% MeCN - water with 0.1% Formic acid). Fractions were containing both regioisomers combined and concentrated. The
regioisomers were separated by additional HPLC (MeCN-water with TFA modifier). Fractions containing the first peak were combined and concentrated. The residue was dissolved in DCM/hexanes and concentrated to yield (R)-5-{2-amino-1-(1-phenylethyl)-1H-benzo[d]imidazol-6-yl}-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide as an off-white solid (5 mg, 3 % yield as the TFA salt). \[^1H\] NMR (500 MHz, DMSO-\(_d_6\)) \(\delta\) ppm 8.82 (br. s., 2 H), 8.30 (d, \(J=2\) Hz, 1 H), 7.96 (d, \(J=2.3\) Hz, 1 H), 7.49 (s, 1 H), 7.36 - 7.38 (m, 4 H), 7.29 - 7.31 (m, 3 H), 5.43 (br. s., 2 H), 4.05 (s, 3 H), 2.25 (s, 3 H), 1.10 (s, 9 H). LCMS: m/z 480.3 (M+H\(^+\)).

Example 72

\[
\text{2-amino-5-\{2-amino-1-\{4-(4-morpholunyl)phenyl\}-1H-benzimidazol-6-yl\}-N,N-dimethyl-3-pyridinesulfonamide}
\]

[00231] A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzo[d]imidazol-2-amine (0.029 g, 0.076 mmol), 2-amino-N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (0.025 g, 0.076 mmol) and \(\text{PdCl}_2(\text{dppf})-\text{CH}_2\text{Cl}_2\) adduct (6.24 mg, 7.64 \(\mu\)mol) in 1,4-dioxane (3 mL) and \(\text{NaHCO}_3\) solution (sat. aq. 2 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over \(\text{Na}_2\text{SO}_4\), filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/\(\text{H}_2\text{O}\) + formic acid) to give the product 2-amino-5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzo[d]imidazol-6-yl]-N,N-dimethyl-3-pyridinesulfonamide (7.7 mg, 0.014 mmol, 18.38 % yield) as a white solid. \[^1H\] NMR (400 MHz, DMSO-cf6) \(\delta\) ppm 8.45 (d, \(J=2.35\) Hz, 1 H), 7.80 (d, \(J=2.54\) Hz, 1 H), 7.35 (d, \(J=8.99\) Hz, 2 H), 7.19 - 7.28 (m, 2 H), 7.15 (d, \(J=8.99\) Hz, 2 H), 6.90 (d, \(J=1.37\) Hz, 1 H), 6.67 (br. s., 2 H), 6.24 (s, 2 H), 3.72 - 3.82 (m, 4H), 3.18 - 3.28 (m, 4 H), 2.69 (s, 6 H); ES-LCMS: 494.4 (M+1).

Example 73
A mixture of 6-bromo-1-(4-(4-morpholinyl)phenyl)-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), 2-amino-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (37.5 mg, 0.100 mmol) and PdCl\(_2\)(dppf)-CH\(_2\)Cl\(_2\) adduct (8.16 mg, 9.99 μmol) in 1,4-dioxane (3 mL) and NaHCO\(_3\) solution (sat. aq. 2 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na\(_2\)SO\(_4\), filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H\(_2\)O + formic acid) to give the product 2-amino-5-[2-amino-1-(4-(4-morpholinyl)phenyl)-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide as a white solid (19.2 mg, 35.5%). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) ppm: 10.43 (br. s., 1 H), 8.34 (d, J = 1.95 Hz, 1 H), 7.82 (d, J = 2.15 Hz, 1 H), 7.34 (d, J = 8.79 Hz, 2 H), 7.04 - 7.26 (m, 8 H), 6.85 - 7.02 (m, 1 H), 6.72 (s, 1 H), 6.67 (br. s., 2 H), 6.25 (br. s., 2 H), 3.67 - 3.84 (m, 4 H), 3.07 - 3.28 (m, 4 H); ES-LCMS: 542.3 (M+1).
A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), 2-amino-N-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (33.9 mg, 0.100 mmol) and PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (8.16 mg, 9.99 µmol) in 1,4-dioxane (3 mL) and NaHCO$_3$ solution (sat. aq. 2 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-cyclopropyl-3-pyridinesulfonamide as a white solid (7.6 mg, 15.04%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.44 (br. s., 1 H), 8.12 (br. s., 1 H), 7.93 (br. s., 1 H), 7.35 (d, J = 8.40 Hz, 2 H), 7.20 - 7.31 (m, 2 H), 7.15 (d, J = 8.40 Hz, 2 H), 6.89 (s, 1 H), 6.58 (br. s., 2 H), 6.29 (br. s., 2 H), 3.73-3.81 (m, 4 H). LCMS: 506.3 (M+1).

**Example 75**

6-[6-amino-5-(4-morpholinylsulfonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

A mixture of 3-(4-morpholinylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridinamine (36.9 mg, 0.100 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (8.16 mg, 9.99 µmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H$_2$O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 6-[6-amino-5-(4-morpholinylsulfonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine as a white solid (25.6 mg, 97%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm
8.48 (d, J = 2.35 Hz, 1 H), 7.80 (d, J = 2.35 Hz, 1 H), 7.11 - 7.37 (m, 6 H), 6.91 (s, 1 H), 6.70 (br. s., 2 H), 6.27 (br. s., 2 H), 3.70 - 3.92 (m, 4 H), 3.49 - 3.67 (m, 4 H), 3.14 - 3.26 (m, 4 H), 2.87 - 3.12 (m, 4 H); LCMS: 536.5 (M+1).

**Example 76**

6-[6-amino-5-(1-piperidinylsulfonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

![Chemical structure of Example 76](image)

[00235] A mixture of 3-(1-piperidinylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridinamine (36.7 mg, 0.100 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (8.16 mg, 9.99 µmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 6-[6-amino-5-(1-piperidinylsulfonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine as a white solid (16.7 mg, 31.3%). ¹H NMR (400 MHz, DMSO-cf6) δ ppm 8.44 (d, J = 2.34 Hz, 1 H), 7.78 (d, J = 2.34 Hz, 1 H), 7.12 - 7.37 (m, 6 H), 6.77 - 6.99 (m, 1 H), 6.66 (br. s., 2 H), 6.26 (s, 2 H), 3.69 - 3.85 (m, 4 H), 3.16 - 3.30 (m, 4 H), 3.02 (m, 4H), 1.46-1.54 (m, 4 H), 1.34-1.43 (m, 2 H); LCMS: 534.3 (M+1).

**Example 77**

6-[6-amino-5-[(1,1-dioxido-4-thiomorpholinyl)sulfonyl]-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine
A mixture of 3-[(1,1-dioxido-4-thiomorpholinyl)sulfonyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridinamine (41.7 mg, 0.100 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (8.16 mg, 9.99 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H$_2$O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H$_2$O + formic acid) to give the product 6-[6-amino-5-[(1,1-dioxido-4-thiomorpholinyl)sulfonyl]-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine as a white solid (17.0mg, 28.6%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.50 (d, $J$ = 2.35 Hz, 1 H), 7.91 (d, $J$ = 2.35 Hz, 1 H), 7.12 - 7.37 (m, 4 H), 6.96 - 7.04 (m, 1 H), 6.93 (s, 1 H), 6.87 (m, 1 H), 6.69 - 6.81 (m, 2 H), 6.20 - 6.40 (m, 2 H), 3.71 - 3.83 (m, 4 H), 3.59-3.65 (m, 1 H), 3.22 (q, $J$ = 4.95 Hz, 6 H); LCMS: 584.5 (M+1).

Example 78

2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(4-cyanophenyl)-3-pyridinesulfonamide
A mixture of 2-amino-N-(4-cyanophenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (40.0 mg, 0.100 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl₂(dpff)-CH₂Cl₂ adduct (8.16 mg, 9.99 μmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 ml), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(4-cyanophenyl)-3-pyridinesulfonamide as a white solid (13.7 mg, 23.7%).

<sup>1</sup>H NMR (400 MHz, DMSO-d₆) δ ppm 8.37 (d, J = 1.95 Hz, 1 H), 7.98 (d, J = 2.34 Hz, 1 H), 7.60 (d, J = 8.01 Hz, 2 H), 7.36 (d, J = 8.79 Hz, 2 H), 7.04 - 7.28 (m, 7 H), 6.78 - 6.85 (m, 7 H), 6.71 (br. s., 2 H), 6.45 (br. s., 2 H), 3.71 - 3.80 (m, 4 H), 3.10 - 3.31 (m, 4 H); LCMS: 567.3 (M+1).

**Example 79**

2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(tetrahydro-2H-pyran-4-yl)-3-pyridinesulfonamide
A mixture of 2-amino-N-(tetrahydro-2H-pyran-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (38.3 mg, 0.100 mmol), 6-bromo-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (8.16 mg, 9.99 μmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 2-amino-5-(2-amino-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl)-N-(tetrahydro-2H-pyran-4-yl)-3-pyridinesulfonamide as a white solid (9.6 mg, 16.9%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.40 (d, J = 2.54 Hz, 0.5 H), 8.35 (d, J = 2.34 Hz, 1 H), 8.15 (d, J = 2.34 Hz, 0.5 H), 8.09 (d, J = 2.34 Hz, 1 H), 7.35 - 7.45 (m, 4 H), 7.21 (d, J = 8.98 Hz, 2 H), 6.98 (s, 1 H), 4.05-4.12 (m, 4 H), 3.82 - 3.89 (m, 4 H), 3.76 - 3.81 (m, 4 H), 3.23 - 3.28 (m, 4 H), 1.61 - 1.73 (m, 2 H), 1.40-1.54 (m, 2 H); LCMS: 550.5 (M+1).

Example 80

2-amino-5-[2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl]-N-(2,4-difluorophenyl)-3-pyridinesulfonamide

A mixture of 2-amino-N-(2,4-difluorophenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (41.1 mg, 0.100 mmol), 6-bromo-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (8.16 mg, 9.99 μmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 2-amino-5-[2-amino-1-[4-(4-morpholiny1)phenyl]-1H-benzimidazol-6-yl]-N-(2,4-difluorophenyl)-3-pyridinesulfonamide as a white solid (5.0 mg, 8.23
%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.12 (d, J = 2.34 Hz, 1 H), 8.04 (d, J = 2.34 Hz, 1 H), 7.15 - 7.39 (m, 7 H), 6.81 - 7.01 (m, 1 H), 6.60 - 6.73 (m, 1 H), 6.51-6.59 (m, 1 H), 3.83-3.91 (m, 4 H), 3.26-3.29 (m, 4 H); LCMS: 578.2 (M+1).

**Example 81**

2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-3-pyridinyl-3-pyridinesulfonamide

[00240] A mixture of 2-amino-N-3-pyridinyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (37.6 mg, 0.100 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (8.16 mg, 9.99 µmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H$_2$O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-3-pyridinyl-3-pyridinesulfonamide as a white solid (9.5mg, 17.5%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.36 (d, J = 2.15 Hz, 1 H), 8.24 (d, J = 2.34 Hz, 1 H), 8.18 (d, J = 2.24 Hz, 1 H), 7.85 (d, J = 2.15 Hz, 1 H) 7.44-7.50 (m, 1 H), 7.33 (d, J = 8.78 Hz, 2 H), 7.24 (d, J = 8.00 Hz, 1 H), 7.00 - 7.20 (m, 4 H), 6.78 (s, 1 H) 6.68 (br. s., 2 H), 6.27 (br. s., 2 H), 3.69 - 3.83 (m, 4 H), 3.21 - 3.28 (m, 4 H); LCMS: 543.3 (M+).
A mixture of N-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (32.4 mg, 0.100 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (8.16 mg, 9.99 µmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-cyclopropyl-3-pyridinesulfonamide as a white solid (14.2 mg, 27.5%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.07 (br. s., 1 H), 8.81 (br. s., 1 H), 8.20 (br. s., 1 H), 8.12 (br. s., 1 H), 7.26 - 7.53 (m, 4 H), 7.15 (d, J = 8.00 Hz, 2 H), 7.08 (br. s., 1 H), 6.40 (br. s., 2 H), 3.77 (br. s., 4 H), 3.22 (br. s., 4 H), 2.17 (br. s., 1 H), 0.38-0.49 (m, 4 H); LCMS: 491.4 (M+1).

**Example 83**

5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N,N-dimethyl-3-pyridinesulfonamide

A mixture of N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (31.2 mg, 0.100 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-
benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (8.16 mg, 9.99 µmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H$_2$O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-{2-amino-1-[2,4-difluorophenyl]}-3-pyridinesulfonamide as a white solid (9.9 mg, 19.46%).  

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 9.09 (s, 1 H), 8.78 (s, 1 H), 8.12 (br. s., 1 H), 7.26 - 7.53 (m, 4 H), 6.97 - 7.23 (m, 3 H), 6.39 (br. s., 2 H), 3.33 (br. s., 4 H), 3.22 (br. s., 4 H), 2.67 (s, 6 H); LCMS: 479.3 (M+1).

Example 84
5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(2,4-difluorophenyl)-3-pyridinesulfonamide

A mixture of N-(2,4-difluorophenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (39.6 mg, 0.100 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (8.16 mg, 9.99 µmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H$_2$O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(2,4-difluorophenyl)-3-pyridinesulfonamide as a white solid (9.9 mg, 17.26%).  

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 9.05 (d, J = 1.95 Hz, 1 H), 8.61 (d, J = 2.15 Hz, 1 H), 8.09 - 8.13 (m, 1 H), 7.20 - 7.44 (m, 6 H), 7.16 (d, J = 8.98 Hz, 2 H), 6.99 - 7.07 (m, 2 H), 6.42 (br. s., 2 H) 3.73 - 3.83 (m, 4 H), 3.20 - 3.28 (m, 4 H); LCMS: 563.3 (M+1).
Example 85
5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-ethyl-3-
pyridinesulfonamide

[00244] A mixture of N-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-
pyridinesulfonamide (31.2 mg, 0.100 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-
benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (8.16 mg, 9.99 µmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H$_2$O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-[2-aminop-1-[4-(4-morpholinyl)phenyl]-1 H-benzimidazol-6-yl]-N-ethyl-3-
pyridinesulfonamide as a white solid (10.0 mg, 20.5%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 9.04 (d, $J = 1.95$ Hz, 1 H), 8.79 (d, $J = 1.95$ Hz, 1 H), 8.20 (t, $J = 2.15$ Hz, 1 H), 7.80 (t, $J = 5.56$ Hz, 1 H), 7.31 - 7.45 (m, 4 H), 7.16 (d, $J = 8.98$ Hz, 2 H), 7.08 (d, $J = 1.37$ Hz, 1 H), 6.38 (s, 2 H), 3.72 - 3.82 (m, 4 H), 3.15 - 3.29 (m, 4 H), 2.78 - 2.87 (m, 2 H), 0.97 (t, $J = 7.22$ Hz, 3 H); LCMS: 479.4 (M+1).

Example 86
5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-ethyl-3-
pyridinesulfonamide
A mixture of N,N-diethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (34.0 mg, 0.100 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (8.16 mg, 9.99 µmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H$_2$O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N,N-diethyl-3-pyridinesulfonamide as a white solid (22.0 mg, 41.7%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 9.03 (br. s., 1 H), 8.82 (br. s., 1 H), 8.17 (br. s., 1 H), 7.36 (br. s., 4 H), 7.15 (br. s., 2 H), 7.09 (br. s., 1 H), 6.40 (br. s., 2 H), 4.02 (br. s., 5 H), 3.77 (br. s., 4 H), 3.34 (br. s., 4 H), 1.98 (br. s., 2 H) 1.90 (br. s., 2 H) 1.17 (br. s., 3 H) 1.05 (br. s., 3 H); LCMS: 507.4 (M+1).

Example 87

2-amino-5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-methyl-N-phenyl-3-pyridinesulfonamide

[00246] A mixture of 2-amino-N-methyl-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (78 mg, 0.201 mmol), 6-bromo-1-[4-(4-
morpholinyl]phenyl]-1H-benzimidazol-2-amine (75.0 mg, 0.201 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (16.41 mg, 0.020 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 2-amino-5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-methyl-N-phenyl-3-pyridinesulfonamide as a white solid (24.5 mg, 21.5%).

\[\text{H NMR (400 MHz, DMSO-d₆) } \delta \text{ ppm 8.43 (d, } J = 2.34 \text{ Hz, 1 H), 7.28-7.34 (m, 2 H), 7.24-7.27 (m, 2 H), 7.17-7.23 (m, 5 H), 7.10-7.15 (m, 1 H), 7.06 (dd, } J = 8.19, 1.76 \text{ Hz, 1 H), 6.50-6.61 (m, 2 H), 6.20 (s, 2 H), 3.75-3.83 (m, 4 H) 3.23-3.30 (m, 4 H), 3.20 (s, 3 H); LCMS: 556.3 (M+1).}\]

**Example 88**

2-amino-6-{6-amino-5-{[(phenylamino)sulfonyl]-3-pyridinyl}-N,N-dimethyl-1H-benzimidazole-1-sulfonamide

[00247] A mixture of 2-amino-6-iodo-N,N-dimethyl-1H-benzimidazole-1-sulfonamide (39.0 mg, 0.107 mmol), 2-amino-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (40 mg, 0.107 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (8.70 mg, 0.020 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 2-amino-6-{6-amino-5-{[(phenylamino)sulfonyl]-3-pyridinyl}-N,N-dimethyl-1H-benzimidazole-1-sulfonamide (9.5 mg, 0.018 mmol, 17.18 % yield) as a white solid. \[\text{H NMR (400 MHz, DMSO-cf) } \delta \text{ ppm 10.51 (s, 1 H), 8.41 (d, } J = 2.35 \text{ Hz, 1 H), 7.93 (d, } J = 2.35 \text{ Hz, 1}\]
Example 89

2-amino-5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide

A mixture of 1-(cyclopropylsulfonyl)-6-iodo-1H-benzimidazol-2-amine (38.7 mg, 0.107 mmol), 2-amino-N-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (40 mg, 0.107 mmol), PdCl₂(dpff)-CH₂Cl₂ adduct (8.70 mg, 10.66 µmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 2-amino-5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N-phenyl-3-pyridinesulfonamide (5.8 mg, 0.012 mmol, 11.00 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-de) δ ppm 10.50 (s, 1 H), 8.44 (d, J = 2.54 Hz, 1 H), 7.98 (d, J = 2.35 Hz, 1 H), 7.56 (d, J = 1.37 Hz, 1 H), 7.21 - 7.40 (m, 3 H), 7.12 (d, J = 7.62 Hz, 2 H), 6.94 - 7.07 (m, 2H), 6.77 (br. s., 2 H), 3.23 - 3.32 (m, 1 H), 1.24 - 1.45 (m, 2H), 1.03 - 1.24 (m, 2 H); LCMS: 485.2 (M+1).

Example 90

2-amino-6-[5-[(dimethylamino)sulfonyl]J-6-(methyloxy)-3-pyridinyl]-N,N-dimethyl-1H-benzimidazole-1-sulfonamide

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A mixture of 2-amino-6-iodo-N,N-dimethyl-1H-benzimidazole-1-sulfonamide (26.8 mg, 0.073 mmol), N,N-dimethyl-2-(methoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (25 mg, 0.073 mmol), PdCl$_2$(dpff)-CH$_2$CI$_2$ adduct (8.70 mg, 10.66 µmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H$_2$O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 2-amino-6-[5-[dimethylamino)sulfonyl]-6-(methoxy)-3-pyridinyl]-N,N-dimethyl-1H-benzimidazol-1-sulfonamide (2.8 mg, 6.04 µmol, 8.26 % yield) as a white solid. $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 8.51 (d, J = 2.34 Hz, 1 H), 8.38 (d, J = 2.34 Hz, 1 H), 7.78 (s, 1 H), 7.36 - 7.50 (m, 2 H), 7.27 (s, 2 H), 5.73 (br. s., 1 H), 4.11 (s, 3 H), 3.00 (s, 6 H), 2.93 (s, 6 H); LCMS: 455.2 (M+1).

**Example 91**

5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N,N-dimethyl-2-(methoxy)-3-pyridinesulfonamide

[00250] A mixture of 1-(cyclopropylsulfonyl)-6-iodo-1H-benzimidazol-2-amine (26.5 mg, 0.073 mmol), N,N-dimethyl-2-(methoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (25 mg, 0.073 mmol), PdCl$_2$(dpff)-CH$_2$CI$_2$ adduct (8.70 mg, 10.66 µmol)
and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N,N-dimethyl-2-(methylxylo)-3-pyridinesulfonamide (6.1 mg, 0.013 mmol, 17.75 % yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.53 (d, J = 2.54 Hz, 1 H), 8.39 (d, J = 2.34 Hz, 1 H), 7.80 (s, 1 H), 7.35 - 7.60 (m, 2 H), 7.27 (s, 1 H), 5.85 (br. s., 2 H), 4.11 (s, 3 H), 2.93 (s, 18 H), 2.84 (m, 1 H), 1.51 (dd, J = 4.68, 1.76 Hz, 2 H); 1.15 (d, J = 6.44 Hz, 2 H); LCMS: 452.3 (M+1).

**Example 92**

2-amino-6-{6-amino-5-[(tetrahydro-2H-pyran-4-ylamino)sulfonyl]-3-yridin yl]-N,N-dimethyl-1H-benzimidazole-1-sulfonamide

![Structural diagram](image)

[00251] A mixture of 2-amino-6-iodo-N,N-dimethyl-1H-benzimidazole-1-sulfonamide (66.9 mg, 0.183 mmol), 2-amino-N-(tetrahydro-2H-pyran-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (70 mg, 0.183 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 2-amino-6-{6-amino-5-[(tetrahydro-2H-pyran-4-ylamino)sulfonyl]-3-pyridinyl}-N,N-dimethyl-1H-benzimidazole-1-sulfonamide (34.6 mg, 0.069 mmol, 37.8 % yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.50 (d, J = 2.34 Hz, 1 H), 8.19 (d, J = 2.34 Hz, 1 H), 7.76 (d, J = 1.56 Hz, 1 H), 7.45 (d, J = 8.19 Hz, 1 H), 7.37 (dd, J = 8.19, 1.76 Hz, 1 H), 5.66 (br. s., 2 H), 5.62 (s, 2 H), 3.89 (m, 2 H), 3.29 - 3.43 (m, 2 H), 3.00 (s, 6 H), 1.73 - 1.83 (m, 2 H), 1.45 - 1.53 (m, 2 H); LCMS: 496.0 (M+1).
Example 93

2-amino-5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N-cyclopropyl-3-
pyridinesulfonamide

![Chemical structure](image)

[00252] A mixture of 1-(cyclopropylsulfonyl)-6-iodo-1H-benzimidazol-2-amine (37.5 mg, 0.103 mmol), 2-amino-N-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-
pyridinesulfonamide (35 mg, 0.103 mmol), PdCl₂(dpff)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H₂O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 2-amino-5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N-cyclopropyl-3-
pyridinesulfonamide (1.0 mg, 0.024 mmol, 22.82 % yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.51 (d, J = 2.34 Hz, 1 H), 8.22 (d, J = 2.34 Hz, 1 H), 7.77 (d, J = 1.37 Hz, 1 H), 7.37 - 7.48 (m, 2 H), 5.71 (br. s., 2 H), 5.63 (br. s., 2 H), 2.79 - 2.87 (m, 1 H), 2.26-2.34 (m, 1 H), 1.47 - 1.53 (m, 2 H), 1.15 (m, 2 H), 0.61 - 0.70 (m, 4 H); LCMS: 449.3 (M+1).

Example 94

2-amino-6-{6-amino-5-[(cyclopropylamino)sulfonyl]-3-pyridinyl}-N,N-dimethyl-1H-
benzimidazole-1-sulfonamide
A mixture of 2-amino-6-iodo-N,N-dimethyl-1H-benzimidazole-1-sulfonamide (32.4 mg, 0.088 mmol), 2-amino-N-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (30 mg, 0.088 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H$_2$O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H$_2$O + formic acid) to give the product 2-amino-6-[6-amino-5-[(cyclopropylamino)sulfonyl]-3-pyridinyl]-N,N-dimethyl-1H-benzimidazole-1-sulfonamide (6.2 mg, 0.013 mmol, 15.22% yield) as a white solid. $^1$H NMR (400 MHz, CDC$_3$) δ ppm 8.49 (d, $J$ = 2.34 Hz, 1 H), 8.21 (d, $J$ = 2.34 Hz, 1 H), 7.75 (d, $J$ = 1.56 Hz, 1 H), 7.34 - 7.45 (m, 2 H), 5.88 (br. s., 2 H), 5.75 (s, 2 H), 2.99 (s, 6 H), 2.27 - 2.36 (m, 1 H), 0.61 - 0.70 (m, 4 H); LCMS: 452.4 (M+1).

Example 95
2-amino-5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N-(tetrahydro-2H-pyran-4-yl)-3-pyridinesulfonamide

A mixture of 1-(cyclopropylsulfonyl)-6-iodo-1H-benzimidazol-2-amine (37.9 mg, 0.1 0 4 mmol), 2-amino-N-(tetrahydro-2H-pyran-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)−3-pyridinesulfonamide (30 mg, 0.088 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (1.5 mL) and H$_2$O (0.5 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H$_2$O + formic acid) to give the product 2-amino-5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N-(tetrahydro-2H-pyran-4-yl)-3-pyridinesulfonamide (6.2 mg, 0.013 mmol, 15.22% yield) as a white solid. $^1$H NMR (400 MHz, CDC$_3$) δ ppm 8.49 (d, $J$ = 2.34 Hz, 1 H), 8.21 (d, $J$ = 2.34 Hz, 1 H), 7.75 (d, $J$ = 1.56 Hz, 1 H), 7.34 - 7.45 (m, 2 H), 5.88 (br. s., 2 H), 5.75 (s, 2 H), 2.99 (s, 6 H), 2.27 - 2.36 (m, 1 H), 0.61 - 0.70 (m, 4 H); LCMS: 452.4 (M+1).
yl)-3-pyridinesulfonamide (40 mg, 0.104 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 2-amino-5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-N-(tetrahydro-2H-pyran-4-yl)-3-pyridinesulfonamide (14.7 mg, 0.030 mmol, 28.3 % yield) as a white solid.

**Example 96**

2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(phenylmethyl)-3-pyridinesulfonamide

![Structural diagram]

[00255] A mixture of 2-amino-N-(phenylmethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (52.1 mg, 0.134 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (50 mg, 0.134 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(phenylmethyl)-3-pyridinesulfonamide (35.7 mg, 0.063 mmol, 47.0 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.37 (t, J = 6.15 Hz, 1 H), 8.33 (d, J =
Example 97

5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-methyl-3-
pyridinesulfonamide

[00256] A mixture of N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-
pyridinesulfonamide (55.9 mg, 0.188 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-
benzimidazol-2-amine (70 mg, 0.188 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018
mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL)
was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with
EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The
crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid)
to give the product 5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-methyl-3-
pyridinesulfonamide (36.4 mg, 0.077 mmol, 40.9 % yield) as a white solid. ¹H NMR (400 MHz,
DMSO-d₆) δ ppm 9.30 (d, J = 2.15 Hz, 0.5 H), 9.05 (d, J = 2.15 Hz, 0.5 H), 9.02 (d, J = 2.15 Hz,
0.5 H), 8.78 (d, J = 1.95 Hz, 0.5 H), 8.52 (t, J = 2.15 Hz, 0.5 H), 8.18 (t, J = 2.15 Hz, 0.5 H), 7.79
(q, J = 4.88 Hz, 0.5 H), 7.71 (q, J = 4.88 Hz, 0.5 H), 7.32 - 7.45(m, 3 H), 7.16 (d, J = 8.98 Hz, 2
H), 7.08 (d, J = 1.56 Hz, 1 H), 6.40 (s, 2 H), 3.72 - 3.80 (m, 4 H), 3.18 - 3.26 (m, 4 H), 2.45 (d, J =
4.88 Hz, 3 H); LCMS: 465.3 (M+1).

Example 98

2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-methyl-3-
pyridinesulfonamide
A mixture of 2-amino-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (58.7 mg, 0.188 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (70 mg, 0.188 mmol), PdCl\textsubscript{2}(dppf)-CH\textsubscript{2}Cl\textsubscript{2} adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H\textsubscript{2}O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H\textsubscript{2}O + formic acid) to give the product 2-amino-5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-methyl-3-pyridinesulfonamide (36.5 mg, 0.075 mmol, 39.8 % yield) as a white solid. \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_{6}) δ ppm 8.42 (d, J = 2.34 Hz, 1 H), 7.89 (d, J = 2.15 Hz, 1 H), 7.67 (q, J = 4.68 Hz, 1 H), 7.35 (d, J = 8.78 Hz, 2 H), 7.21 - 7.30 (m, 2 H), 7.15 (d, J = 8.98 Hz, 2 H), 6.89 (s, 1 H), 6.58 (br. s., 2 H), 6.33 (br. s., 2 H), 3.70 - 3.84 (m, 4 H), 3.20 - 3.27 (m, 4 H), 2.41 (d, J = 5.07 Hz, 3 H); LCMS: 480.4 (M+1).

**Example 99**

5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-2-(ethyloxy)-N,N-dimethyl-3-pyridinesulfonamide

A mixture of 2-(ethyloxy)-N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (35.3 mg, 0.099 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37 mg, 0.099 mmol), potassium acetate (97 mg, 0.991 mmol) and...
PdCl₂(dppf)-CH₂Cl₂ adduct (8.10 mg, 9.91 μmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(ethyloxy)-N,N-dimethyl-3-pyridinesulfonamide (12.3 mg, 0.024 mmol, 23.74 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.59 (d, J = 2.54 Hz, 1 H), 8.13 (d, J = 2.54 Hz, 1 H), 7.35 (d, J = 8.98 Hz, 2 H), 7.29 (s, 2 H), 7.15 (d, J = 8.98 Hz, 2 H), 6.97 (s, 1 H), 6.30 (s, 2 H), 4.46 (d, J = 7.22 Hz, 2 H), 3.74 - 3.81 (m, 4 H), 3.20 - 3.26 (m, 4 H), 2.79 (s, 6 H), 1.36 (t, J = 7.02 Hz, 3 H); LCMS: 523.3 (M+1).

**Example 100**

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-(cyclopropylmethyl)-2-(methyloxy)-3-pyridinesulfonamide

[00259] A mixture of N-(cyclopropylmethyl)-2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (35 mg, 0.095 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1 H-benzimidazol-2-amine (35.5 mg, 0.095 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N-(cyclopropylmethyl)-2-(methyloxy)-3-pyridinesulfonamide (19.4 mg, 0.036 mmol, 37.4 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.58 (d, J = 2.54 Hz, 1 H), 8.17 (s, 1 H), 8.11 (d, J = 2.54 Hz, 1 H), 7.71 (t, J = 5.95 Hz, 1 H), 7.35 (m, J = 8.98 Hz, 2 H), 7.29 (s, 2 H), 7.15 (m, J = 8.98 Hz, 2 H), 6.95 (s, 1 H), 6.30 (s, 2 H), 4.00 (s, 3 H), 3.73 -
3.81 (m, 4 H), 3.19 - 3.26 (m, 4 H), 2.76 (t, J = 6.44 Hz, 2 H), 0.72 (m, 1 H), 0.22 - 0.29 (m, 2 H), -0.01 - 0.07 (m, 2 H); LCMS: 535.3 (M+1).

**Example 101**

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(dim ethylamino)-N,N-dimethyl-3-pyridinesulfonamide

![Chemical structure](image)

[00260] A mixture of 2-(dimethylamino)-N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (35.2 mg, 0.099 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.0 mg, 0.099 mmol), PdCl$_2$(dpff)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(dimethylamino)-N,N-dimethyl-3-pyridinesulfonamide (15.8 mg, 0.029 mmol, 29.7 % yield) as a white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 8.66 (br. s., 1 H), 8.04 (br. s., 1 H), 7.35 (m, J = 8.00 Hz, 2 H), 7.30 (br. s., 2 H), 7.15 (m, J = 8.00 Hz, 2 H), 6.97 (s, 1 H), 6.31 (br. s., 2 H), 3.77 (m, 4 H), 3.22 (m, 4 H), 2.89 (m, 6 H), 2.72 (m, 6 H); LCMS: 522.5 (M+1).

**Example 102**

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-N,N-dimethyl-2-(methylamino)-3-pyridinesulfonamide
[00261] A mixture of N,N-dimethyl^-imethylaminoJ-S^\cdot S.S-tetramethyl-I.S^-dioxaborolan-2-yl)-3-pyridinesulfonamide (33.8 mg, 0.099 mmol), 6-bromo-1-[4-(4-morpholiny]phenyl]-1 H-benzimidazol-2-amine (37 mg, 0.099 mmol), PdCl$_2$(dppO-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) i
1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-[2-amino-1-[4-(4-morpholiny]phenyl]-1H-benzimidazol-6-yl]-N,N-dimethyl-2-(methyloxy)-3-pyridinesulfonamide (21.8 mg, 0.041 mmol, 41.2 % yield) as a white solid. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.54 (d, J = 2.15 Hz, 1 H), 7.80 (d, J = 2.34 Hz, 1 H), 7.35 (m, J = 8.78 Hz, 2 H), 7.19 - 7.29 (m, 2 H), 7.15 (m, J = 8.98 Hz, 2 H), 6.90 (s, 1 H), 6.78 (s, 1 H), 6.25 (s, 2 H), 3.74 - 3.81 (m, 4 H), 3.20 - 3.24 (m, 4 H), 2.92 (d, J = 4.68 Hz, 3 H), 2.68 (s, 6 H); LCMS: 508.4 (M+1).

Example 103
5-[2-amino-1-[4-(4-morpholiny]phenyl]-1H-benzimidazol-6-yl]-N-(1,1-dimethylethyl)-2-(methyloxy)-3-pyridinesulfonamide

[00262] A mixture of N-(1,1-dimethylethyl)-2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (50 mg, 0.135 mmol), 6-bromo-1-[4-(4-
morpholinyl)phenyl]-1H-benzimidazol-2-amine (50.4 mg, 0.135 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(1,1-dimethylethyl)-2-(methyloxy)-3-pyridinesulfonamide (18.5 mg, 0.034 mmol, 25.3 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.58 (d, J = 2.15 Hz, 1 H), 8.13 (d, J = 2.54 Hz, 1 H), 7.45 (s, 1 H), 7.35 (d, J = 8.78 Hz, 2 H), 7.29 (s, 2 H), 7.15 (d, J = 8.98 Hz, 2 H), 6.96 (s, 1 H), 6.31 (s, 2 H), 4.01 (s, 3 H), 3.74 - 3.84 (m, 4 H), 3.16 - 3.26 (m, 4 H), 1.08 (s, 9 H); LCMS: 537.7 (M+1).

Example 104
5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(4-fluorophenyl)-2-(methyloxy)-3-pyridinesulfonamide

[00263] A mixture of N-(4-fluorophenyl)-2-(methylxoy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (49.8 mg, 0.122 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (45.5 mg, 0.122 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(4-fluorophenyl)-2-(methyloxy)-3-pyridinesulfonamide (36.5 mg, 0.062 mmol, 51.0 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.55 (d, J = 2.34 Hz, 1 H), 8.09 (d, J = 2.34 Hz, 1 H), 7.34 (d, J = 8.78 Hz, 2 H), 7.21 - 7.29 (m, 2 H), 7.08 - 7.19 (m, 4 H), 7.01 (s, 4 H), 1.41 (s, 9 H), 1.09 (s, 9 H); LCMS: 537.7 (M+1).
H), 6.99 - 7.07 (m, 2 H), 6.90 (s, 1 H), 6.31 (s, 2 H), 3.96 (s, 3 H), 3.74 - 3.81 (m, 4 H), 3.19 - 3.25 (m, 4 H); LCMS: 575.7 (M+1).

Example 105

6-{6-(methyloxy)-5-(1\text{\textsuperscript{y}}rrolidinylsulfonyl)-3-pyridinyl}-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

[00264] A mixture of 2-(methyloxy)-3-(1-pyrrolidinylsulfone)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (50 mg, 0.136 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (50.7 mg, 0.136 mmol), PdCl\textsubscript{2}(dpdpf)-CH\textsubscript{2}Cl\textsubscript{2} adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H\textsubscript{2}O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H\textsubscript{2}O + formic acid) to give the product 6-{6-(methyloxy)-5-(1-pyrrolidinylsulfone)-3-pyridinyl}-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (31.6 mg, 0.057 mmol, 42.2 % yield) as a white solid. \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) δ ppm 8.61 (d, J = 2.34 Hz, 1 H), 8.13 (d, J = 2.34 Hz, 1 H), 7.35 (m, J = 8.78 Hz, 2 H), 7.30 (s, 2 H), 7.15 (m, J = 8.98 Hz, 2 H), 6.96 (s, 1 H), 6.30 (s, 2 H), 5.76 (s, 1 H), 4.00 (s, 3 H), 3.73 - 3.80 (m, 4 H), 3.26 - 3.31 (m, 4 H), 3.20 - 3.26 (m, 4 H), 1.72 - 1.81 (m, 4 H); LCMS: 535.5 (M+1).

Example 106

6-{6-(methyloxy)-5-[(4-methyl-1-piperazinyl)sulfonyl]-3-pyridinyl}-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

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[00265] A mixture of 1-methyl-4-[[2-(methyloxy)-5,4,5,4-tetramethyl-1,3,2-dioxaborolan-2-yl]-3-pyridinyl]sulfonyl]piperazine (40 mg, 0.101 mmol), 6-bromo-1-[4-(4-morpholiny))-phenyl]-1H-benzimidazol-2-amine (37.6 mg, 0.101 mmol), PdCl$_2$(dppO-CH$_2$Cl)$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H$_2$O + formic acid) to give the product 6-{6-(methyloxy)-5-[(4-methyl-1-piperazinyl)sulfonyl]-3-pyridinyl}-1-[4-(4-morpholiny))-phenyl]-1H-benzimidazol-2-amine (16.9 mg, 0.029 mmol, 29.2 % yield) as a white solid. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.62 (d, J = 2.34 Hz, 1 H), 8.15 (s, 2 H), 8.12 (d, J = 2.34 Hz, 1 H), 7.35 (d, J = 8.78 Hz, 2 H), 7.30 (s, 2 H), 7.12 - 7.19 (m, 3 H), 6.98 (s, 1 H), 6.32 (s, 2 H), 3.99 (s, 3 H), 3.75 - 3.80 (m, 4 H), 3.21 - 3.26 (m, 4 H), 3.13 - 3.19 (m, 4 H), 2.28 - 2.34 (m, 4 H), 2.15 (s, 3 H); LCMS: 564.4 (M+1).

**Example 107**

5-{2-amino-1-[4-(4-morpholiny))-phenyl]-1H-benzimidazol-6-yl}-N-(2-hydroxyethyl)-3-pyridinesulfonamide

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A mixture of N-(2-hydroxyethyl)-2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (70 mg, 0.195 mmol), 6-bromo-1-[4-(4-morpholiny]lphenyl]-1H-benzimidazol-2-amine (72.9 mg, 0.195 mmol), PdCl$_2$(dpdf)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-[2-amino-1-[4-(4-morpholiny]lphenyl]-1H-benzimidazol-6-yl]-N-(2-hydroxyethyl)-2-(methyloxy)-3-pyridinesulfonamide (40.6 mg, 0.075 mmol, 38.4 % yield) as a white solid. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.58 (d, $J = 2.34$ Hz, 1H), 8.15 (s, 1H), 8.12 (d, $J = 2.54$ Hz, 1H), 7.49 (t, $J = 5.85$ Hz, 1H), 7.35 (m, $J = 8.98$ Hz, 2H), 7.30 (s, 2H), 7.15 (m, $J = 8.98$ Hz, 2H), 6.96 (s, 1H), 6.30 (s, 2H), 4.65 (br. s., 1H), 3.99 (s, 3H), 3.72 - 3.80 (m, 4H), 3.20 - 3.25 (m, 4H), 2.89 (q, $J = 6.24$ Hz, 2H); LCMS: 525.5 (M+1).

**Example 108**

5-[2-amino-1-[4-(4-morpholiny]lphenyl]-1H-benzimidazol-6-yl]-N-cyclopentyl-2-(methyloxy)-3-pyridinesulfonamide

[00267] A mixture of N-cyclopentyl-2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (50 mg, 0.131 mmol), 6-bromo-1-[4-(4-morpholiny]lphenyl]-1H-benzimidazol-2-amine (48.8 mg, 0.131 mmol), PdCl$_2$(dpdf)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-[2-amino-1-[4-(4-morpholiny]lphenyl]-1H-benzimidazol-6-yl]-N-cyclopentyl-2-(methyloxy)-3-pyridinesulfonamide (19.3 mg, 0.035 mmol,
Example 109

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-[3-(methyloxy)phenyl]-3-pyridinesulfonamide

[00268] A mixture of 2-(methyloxy)-N-[3-(methyloxy)phenyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-3-pyridinesulfonamide (50 mg, 0.119 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (44.4 mg, 0.119 mmol), PdCl\(_2\)(dpdf)-CH\(_2\)Cl\(_2\) adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H\(_2\)O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na\(_2\)SO\(_4\), filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H\(_2\)O + formic acid) to give the product 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-[3-(methyloxy)phenyl]-3-pyridinesulfonamide (26.5 mg, 0.045 mmol, 37.6 % yield) as a white solid. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) ppm 8.55 (d, \(J = 2.34\) Hz, 1 H), 8.12 - 8.18 (m, 2 H), 7.34 (m, \(J = 8.78\) Hz, 2 H), 7.22 - 7.30 (m, 2 H), 7.15 (m, \(J = 8.78\) Hz, 2 H), 7.06 (t, \(J = 8.10\) Hz, 1 H), 6.90 (s, 1 H), 6.64 - 6.71 (m, 2 H), 6.54 (dd, \(J = 8.29, 1.85\) Hz, 1 H), 6.31 (s, 2 H), 3.97 (s, 3 H), 3.75 - 3.81 (m, 4 H), 3.59 (s, 3 H), 3.20 - 3.25 (m, 4 H); LCMS: 587.3 (M+1).
A mixture of 2-(methyloxy)-N-(4-methylphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (48.7 mg, 0.121 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (45 mg, 0.121 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H$_2$O + formic acid) to give the product 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-(4-methylphenyl)-3-pyridinesulfonamide (23.0 mg, 0.038 mmol, 31.8% yield) as a white solid. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 10.19 (br. s., 1 H), 8.44 - 8.73 (m, 1 H), 7.42 - 7.67 (m, 2 H), 7.34 (m, J = 8.59 Hz, 2 H), 7.24 (br. s., 2 H), 7.15 (m, J = 8.79 Hz, 2 H), 6.95 (m, 3 H), 6.39 (br. s., 2 H) 3.97 (s, 3 H), 3.67-3.86 (m, 4 H), 3.19-3.26 (m, 4 H), 2.12 (s, 3 H); LCMS: 571.3 (M+1).

Example 111

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-(4-methylphenyl)-3-pyridinesulfonamide
A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (45 mg, 0.121 mmol), 2-(methoxy)-N-(2-methylphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (48.7 mg, 0.121 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-(2-methylphenyl)-3-pyridinesulfonamide (24.3 mg, 0.040 mmol, 33.2 % yield) as a white solid. H NMR (400 MHz, DMSO-d₆) δ ppm 9.67 (s, 1 H), 8.58 (d, J = 2.34 Hz, 1 H), 7.92 - 7.35 (m, 2 H), 7.29 - 7.26 (m, 2 H), 7.09 - 7.17 (m, 3 H), 6.98 - 7.07 (m, 3 H), 6.81 - 6.84 (m, 1 H), 6.29 (s, 2 H), 3.96 (s, 3 H), 3.75 - 3.81 (m, 4 H), 3.21 - 3.26 (m, 4 H), 2.10 (s, 3 H); LCMS: 571.3 (M+1).

Example 112

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-(3-methylphenyl)-3-pyridinesulfonamide

A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (45 mg, 0.121 mmol), 2-(methoxy)-N-(3-methylphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (48.7 mg, 0.121 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-N-(3-methylphenyl)-3-pyridinesulfonamide (22.4 mg, 0.037 mmol, 30.9 % yield) as a white solid. H NMR (400 MHz, DMSO-d₆) δ ppm 8.53 (d, J = 2.34 Hz, 1 H), 8.11 (d,
J = 2.34 Hz, 1 H), 7.34 (m, J = 8.98 Hz, 2 H), 7.25 (d, J = 7.61 Hz, 2 H), 7.15 (m, J = 8.98 Hz, 2 H), 7.02 (d, J = 7.61 Hz, 1 H), 6.85 - 6.94 (m, 3 H), 6.78 (d, J = 7.41 Hz, 1 H), 6.30 (br. s., 2 H), 3.96 (s, 3 H), 3.74 - 3.83 (m, 4 H), 3.19 - 3.26 (m, 4 H), 2.13 (s, 3 H); LCMS: 571.4 (M+1).

Example 113

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-4-methoxy-N-(4-methoxyphenyl)pyridine-3-sulfonamide

[00272] A mixture of 6-bromo-1-(4-morpholinophenyl)-1 H-benzo[d]imidazol-2-amine (73 mg, 0.196 mmol), 4-methoxy-N-(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (82 mg, 0.196 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-4-methoxy-N-(4-methoxyphenyl)pyridine-3-sulfonamide (40.9 mg, 0.069 mmol, 35.3 % yield) as a white solid. 

¹H NMR (400 MHz, DMSO-cf) δ ppm 9.98 (s, 1 H), 8.54 (d, J = 2.34 Hz, 1 H), 8.03 (d, J = 2.34 Hz, 1 H), 7.33 (m, J = 8.98 Hz, 2 H), 7.19 - 7.27 (m, 2 H), 7.15 (m, J = 8.78 Hz, 2 H), 7.00 (m, J = 8.98 Hz, 2 H), 6.89 (s, 1 H), 6.75 (m, J = 8.98 Hz, 2 H), 6.30 (s, 2 H), 3.99 (s, 3 H), 3.73 - 3.83 (m, 4 H), 3.61 (s, 3 H), 3.18 - 3.27 (m, 4 H); LCMS: 587.3 (M+1).

Example 114

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-4-methoxy-N-(2-methoxyphenyl)pyridine-3-sulfonamide
A mixture of 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (73 mg, 0.196 mmol), 2-methoxy-N-(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (82 mg, 0.196 mmol), PdCl$_2$(dpff)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-(2-methoxyphenyl)pyridine-3-sulfonamide (43.2 mg, 0.073 mmol, 37.3% yield) as a white solid. 

$^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 9.27 (br. s., 1 H), 8.53 (d, J = 2.34 Hz, 1 H), 7.91 (d, J = 2.34 Hz, 1 H), 7.32 (d, J = 8.98 Hz, 2 H), 7.22 - 7.27 (m, 2 H), 7.13 - 7.20 (m, 3 H), 7.01 - 7.09 (m, 1 H), 6.77 - 6.87 (m, 3 H), 6.29 (s, 2 H), 3.97 (s, 3 H), 3.75 - 3.84 (m, 4 H), 3.49 (s, 3 H), 3.19 - 3.28 (m, 4 H); LCMS: 587.3 (M+1).

**Example 115**

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(3-fluorophenyl)-2-methoxypyrindine-3-sulfonamide

A mixture of 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (73 mg, 0.196 mmol), N-(3-fluorophenyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (82 mg, 0.196 mmol), PdCl$_2$(dpff)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy-N-(2-methoxyphenyl)pyridine-3-sulfonamide (43.2 mg, 0.073 mmol, 37.3% yield) as a white solid. 

$^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 9.27 (br. s., 1 H), 8.53 (d, J = 2.34 Hz, 1 H), 7.91 (d, J = 2.34 Hz, 1 H), 7.32 (d, J = 8.98 Hz, 2 H), 7.22 - 7.27 (m, 2 H), 7.13 - 7.20 (m, 3 H), 7.01 - 7.09 (m, 1 H), 6.77 - 6.87 (m, 3 H), 6.29 (s, 2 H), 3.97 (s, 3 H), 3.75 - 3.84 (m, 4 H), 3.49 (s, 3 H), 3.19 - 3.28 (m, 4 H); LCMS: 587.3 (M+1).
yl)pyridine-3-sulfonamide (80 mg, 0.196 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(3-fluorophenyl)-2-methoxypyridine-3-sulfonamide (41.6 mg, 0.071 mmol, 36.3 % yield) as a white solid. H NMR (400 MHz, DMSO-d₆) δ ppm 10.65 (s, 1 H), 8.56 (d, J = 2.34 Hz, 1 H), 8.18 (d, J = 2.54 Hz, 1 H), 7.34 (m, J = 8.98 Hz, 2 H), 7.25 - 7.29 (m, 2 H), 7.15 (m, J = 8.98 Hz, 2 H), 6.87 - 6.97 (m, 3 H), 6.80 (t, J = 8.00 Hz, 1 H), 6.31 (s, 2 H), 3.95 (s, 3 H), 3.74 - 3.83 (m, 4 H), 3.20 - 3.26 (m, 4 H); LCMS: 575.2 (M+1).
Example 117

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(2-fluoro-3-methylphenyl)-2-methoxypyridine-3-sulfonamide

A mixture of N-(2-fluoro-3-methylphenyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (42.2 mg, 0.100 mmol), 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (37.3 mg, 0.100 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(2-fluoro-3-methylphenyl)-2-methoxypyridine-3-sulfonamide (35.2 mg, 0.059 mmol, 59.2 % yield) as a yellow solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.08 (br. s., 1 H), 8.58 (d; J = 1.95 Hz, 1 H), 7.99 (d, J = 2.34 Hz, 1 H), 7.33 (m, J = 8.59 Hz, 2 H), 7.24 (q, J = 8.06 Hz, 2 H), 7.15 (m, J = 8.78 Hz, 2 H), 6.98 - 7.10 (m, 2 H), 6.90 - 6.98 (m, 1 H), 6.86 (s, 1 H), 6.30 (br. s., 2 H), 3.86 - 3.99 (m, 3 H), 3.66 - 3.83 (m, 4 H), 3.15 - 3.28 (m, 4 H), 2.11 (s, 3 H); LCMS: 589.3 (M+1).

Example 118

5-(2-amino-1-isopropyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide

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A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (37 mg, 0.100 mmol), 6-bromo-1-isopropyl-1H-benzo[d]imidazol-2-amine (25.4 mg, 0.100 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-(2-amino-1-isopropyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide (24.2 mg, 0.057 mmol, 56.8 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.68 (d, J = 2.34 Hz, 1 H), 8.26 (d, J = 2.54 Hz, 1 H), 8.16 (s, 1 H), 7.57 (s, 1 H), 7.46 (s, 1 H), 7.21 (s, 2 H), 6.49 (s, 2 H), 4.65 (m, 1 H), 4.04 (s, 3 H), 4.04 (s, 3 H), 1.53 (d, J = 6.83 Hz, 6 H), 1.12 (s, 9 H); LCMS: 418.6 (M+1).

**Example 119**

5-(2-amino-1-(3-morpholinopropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide

[00278] A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (37 mg, 0.100 mmol), 6-bromo-1-(3-morpholinopropyl)-1H-benzo[d]imidazol-2-amine (33.9 mg, 0.100 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-(2-amino-1-(3-morpholinopropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide (24.2 mg, 0.057 mmol, 56.8 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.68 (d, J = 2.34 Hz, 1 H), 8.26 (d, J = 2.54 Hz, 1 H), 8.16 (s, 1 H), 7.57 (s, 1 H), 7.46 (s, 1 H), 7.21 (s, 2 H), 6.49 (s, 2 H), 4.65 (m, 1 H), 4.04 (s, 3 H), 4.04 (s, 3 H), 1.53 (d, J = 6.83 Hz, 6 H), 1.12 (s, 9 H); LCMS: 418.6 (M+1).
mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and \( \text{H}_2\text{O} \) (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na\(_2\)SO\(_4\), filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ \( \text{H}_2\text{O} \) + formic acid) to give the product 5-(2-amino-1-(3-morpholinopropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide (19.6 mg, 0.038 mmol, 38.2% yield) as a white solid. \( ^1\text{H} \) NMR (400 MHz, DMSO-\( \text{d}_6 \)) \( \delta \) ppm 8.68 (d, \( J = 2.34 \) Hz, 1 H), 8.28 (d, \( J = 2.54 \) Hz, 1 H), 7.51 (s, 1 H), 7.46 (s, 1 H), 7.19 - 7.27 (m, 2 H), 6.71 (br. s., 2 H), 4.08 (t, \( J = 6.34 \) Hz, 2 H), 4.04 (s, 3 H), 3.49 - 3.59 (m, 4 H), 2.29-2.33 (m, 4 H), 2.21-2.27 (t, \( J = 6.24 \) Hz, 2 H), 1.83 - 1.90 (m, 2 H), 1.10 (s, 9 H); LCMS: 503.4 (M+1).

**Example 120**

5-(2-amino-1-methyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide

[00279] A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (37 mg, 0.100 mmol), 6-bromo-1-methyl-1H-benzo[d]imidazol-2-amine (22.59 mg, 0.100 mmol), PdCl\(_2\)(dppe)-CH\(_2\)Cl\(_2\) adduct (8.16 mg, 9.99 umol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and \( \text{H}_2\text{O} \) (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na\(_2\)SO\(_4\), filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ \( \text{H}_2\text{O} \) + formic acid) to give the product 5-(2-amino-1-methyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide (29.3 mg, 0.074 mmol, 73.8% yield) as a white solid. \( ^1\text{H} \) NMR (400 MHz, DMSO-\( \text{d}_6 \)) \( \delta \) ppm 8.68 (d, \( J = 2.54 \) Hz, 1 H), 8.30 (d, \( J = 2.34 \) Hz, 1 H), 7.42 - 7.56 (m, 2 H), 7.17 - 7.33 (m, 2 H), 6.65 (br. s., 2 H), 4.04 (s, 3 H), 3.57 (s, 3 H), 1.10 (s, 9 H); LCMS: 390.3 (M+1).
Example 121

5-(2-amino-1-(2-hydroxyethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-
methoxypyridine-3-sulfonamide

[00280] A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-
dioxaborolan-2-yl)pyridine-3-sulfonamide (37 mg, 0.100 mmol), 2-(2-amino-6-bromo-1H-benzo[d]imidazol-1-
yl)ethanol (25.6 mg, 0.100 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (8.16 mg, 9.99 umol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-(2-amino-1-(2-hydroxyethyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-
methoxypyridine-3-sulfonamide (16.8 mg, 0.039 mmol, 39.3 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.67 (d, J = 2.34 Hz, 1 H), 8.29 (d, J = 2.54 Hz, 1 H), 8.15 (s, 1 H), 7.49- 7.53 (m, 1 H), 7.45 (s, 1 H), 7.17 - 7.27 (m, 2 H), 6.46 (s, 2 H), 4.97 (br. s., 1 H), 4.11 (s, 2 H), 4.04 (s, 3 H), 3.66 - 3.72 (m, 2 H),1.10 (s, 9 H); LCMS: 420.3 (M+1).

Example 122

5-(2-amino-1-((tetrahydro-2H^yran-4-yl)methyl)-1H-benzo[cf]imidazol^y)-N-(tert-butyl)-
2-methoxypyridine-3-sulfonamide
A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (37 mg, 0.100 mmol), 6-bromo-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-2-amine (41.9 mg, 0.135 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (8.16 mg, 9.99 umol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 5-(2-amino-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide (34.2 mg, 0.071 mmol, 52.9 % yield) as a white solid. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.70 (d, J = 2.34 Hz, 1 H), 8.28 (d, J = 2.54 Hz, 1 H), 7.55 (s, 1 H), 7.46 (s, 1 H), 7.16 - 7.23 (m, 2 H), 6.56 (s, 2 H), 4.04 (s, 3 H), 3.91 - 3.98 (m, 2 H), 3.78 - 3.84 (m, 2 H), 3.14 - 3.25 (m, 2 H) 1.35 - 1.42 (m, 4 H) 1.11 (s, 9H); LCMS: 474.3 (M+1).

**Example 123**

5-(2-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-benzo[d]imidazol-6-ylO-N-ft^rt-butyl)-2-methoxypyridine-3-sulfonamide
A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (37 mg, 0.100 mmol), 6-bromo-1-(tetrahydro-2H-pyran-4-yl)-1H-benzo[d]imidazol-2-amine (40.0 mg, 0.135 mmol), PdCl\(_2\)(dppf)-CH\(_2\)Cl\(_2\) adduct (8.16 mg, 9.99 umol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H\(_2\)O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na\(_2\)SO\(_4\), filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H\(_2\)O + formic acid) to give the product 5-(2-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide (45.4 mg, 0.097 mmol, 71.7 % yield) as a white solid. 

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) δ ppm 8.69 (d, \(J = 2.34\) Hz, 1 H), 8.24 (d, \(J = 2.34\) Hz, 1 H), 8.14 (s, 1 H), 7.54 (s, 1 H), 7.48 (s, 1 H), 7.22 (s, 2 H), 6.53 (s, 2 H), 4.04 (s, 3 H), 4.00 - 4.07 (m, 2 H), 3.49 (t, \(J = 11.32\) Hz, 2 H), 2.37 - 2.47 (m, 2 H), 1.65 - 1.74 (m, 2 H), 1.12 (s, 9 H); LCMS: 460.3 (M+1).

**Example 124**

5-(2-amino-1-phenethyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide

[00283] A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (37 mg, 0.100 mmol), 6-bromo-1-phenethyl-1H-benzo[d]imidazol-2-amine (42.7 mg, 0.135 mmol), PdCl\(_2\)(dppf)-CH\(_2\)Cl\(_2\) adduct (8.16 mg, 9.99 umol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H\(_2\)O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na\(_2\)SO\(_4\), filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H\(_2\)O + formic acid) to give the product 5-(2-amino-1-phenethyl-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide (45.3 mg, 0.094 mmol, 69.2 % yield) as a white solid. 

\(^1\)H NMR (400 MHz, DMSO-
Example 125

5-(2-amino-1-(3-phenylpropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-
methoxypyridine-3-sulfonamide

[00284] A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-
yl)pyridine-3-sulfonamide (50 mg, 0.135 mmol), 6-bromo-1-(3-phenylpropyl)-1H-
benzo[d]imidazol-2-amine (44.6 mg, 0.135 mmol), PdCl₂(dpff)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with ETOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-(2-amino-1-(3-phenylpropyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-
methoxypyridine-3-sulfonamide (39.7 mg, 0.080 mmol, 59.0 % yield) as a white solid. 1 H NMR (400 MHz, DMSO-de) δ ppm 8.66 (d, J = 2.34 Hz, 1 H), 8.26 (d, J = 2.34 Hz, 1 H), 7.46 (s, 1 H), 7.40 (s, 1 H), 7.13 - 7.30 (m, 6 H), 6.64 (br. s., 2 H), 4.09 (t, J = 7.32 Hz, 2 H), 4.04 (s, 3 H), 2.61 - 2.70 (m, 2 H), 1.92 - 2.03 (m, 2 H), 1.11 (s, 9 H); LCMS: 494.3 (M+1).

Example 126

2-amino-6-(5-(N-(tert-butyl)sulfamoyl)-6-methoxypyridin-3-yl)-N,N-dimethyl-1H-
benzol[d]imidazole-1-sulfonamide
A mixture of N-(tert-butyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (37 mg, 0.100 mmol), 2-amino-6-bromo-N,N-dimethyl-1H-benzo[d]imidazole-1-sulfonamide (43.1 mg, 0.135 mmol), (dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 2-amino-6-(5-(N-(tert-butyl)sulfamoyl)-6-methoxypyridin-3-yl)-N,N-dimethyl-1H-benzo[d]imidazole-1-sulfonamide (20.5 mg, 0.042 mmol, 31.5 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.64 (br. s., 1 H), 8.22 (br. s., 1 H), 7.70 (br. s., 1 H), 7.53 (br. s., 2 H), 7.33 (br. s., 1 H), 7.04 (br. s., 2 H), 4.04 (s, 3 H), 2.92 (br. s., 6 H), 1.12 (s., 9 H); LCMS: 483.3 (M+1).
General Scheme 3

X : OH, NH₂, NHR'

1. NH₂ → NHNH₂

2. R-X → R'X

Pd
Example 127
5-(2-amino-1-(4-morphoHnophenyO-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-(methylamino)pyridine-3-sulfonamide

Step A
5-bromo-N-(tert-butyl)-2-(methylamino)pyridine-3-sulfonamide
A solution of 5-bromo-2-chloro-3-pyridinesulfonyl chloride (0.5 g, 1.719 mmol), pyridine (0.570 mL, 7.05 mmol) and 2-methylpropan-2-amine (0.402 mL, 7.05 mmol) in dichloromethane (DCM) (5 mL) was stirred at room temperature for 30 minutes then it was evaporated, the residue dissolved in EtOAc, washed with water and brine, dried over magnesium sulfate and was evaporated to give brown semisolid intermediate. It was dissolved in Tetrahydrofuran (THF) (5.00 mL), 2M Methylamine in THF (2.58 mL, 5.16 mmol) was added and the solution was heated at 50 °C for 2 hrs. The reaction mixture was then evaporated, the residue dissolved in EtOAc and water, the organic phase was separated and washed with brine, dried over magnesium sulfate and was evaporated to give 5-bromo-N-(tert-butyl)-2-(methylamino)pyridine-3-sulfonamide (330 mg, 1.024 mmol, 59.6 % yield) as a brown solid.

**Step B**

\[
N-(\text{tert-butyl})-2-(\text{methylamino})-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)\text{pyridine-3-sulfonamide}
\]

**Step C**

The mixture of 5-bromo-N-(tert-butyl)-2-(methylamino)pyridine-3-sulfonamide (330 mg, 1.024 mmol), bis(pinacolato)diboron (312 mg, 1.229 mmol), potassium acetate (302 mg, 3.07 mmol) and PdCl\(_2\)(dpdpf)-CH\(_2\)Cl\(_2\) adduct (84 mg, 0.102 mmol) in 1,4-dioxane (6 mL) was heated under nitrogen atmosphere at 100 °C overnight. The mixture was filtered through Celite® and was evaporated to dryness to give the crude N-(tert-butyl)-2-(methylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (646 mg, 1.749 mmol, 171 % yield) as a black solid, which was used without further purification. MS (ES+) m/z 288 (corresponding boronic acid).
5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-(methylamino)pyridine-3-sulfonamide

[00288] The mixture of 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (50 mg, 0.134 mmol), N-(tert-butyl)-2-(methylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (99 mg, 0.268 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (10.94 mg, 0.013 mmol) and Cs$_2$CO$_3$ (43.6 mg, 0.134 mmol) in Tetrahydrofuran (THF) (1 mL) and Water (0.25 mL) was heated at 80 °C overnight then it was evaporated and purified on a RP-HPLC to give 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-(methylamino)pyridine-3-sulfonamide (20.2 mg, 0.038 mmol, 28.2 % yield) as a gray solid. MS (ES$^+$) m/z 536; $^1$H NMR (400MHz, DMSO-d$_6$) $\delta$ = 8.48 (br. s., 1 H), 8.14 (br. s., 2 H), 7.96 (br. s., 1 H), 7.68 (br. s., 1 H), 7.52 - 7.05 (m, 6 H), 6.89 (br. s., 1 H), 6.47 (br. s., 3 H), 3.77 (br. s., 5 H), 2.96 (br. s., 4 H), 1.07 (br. s., 9 H).

**Example 128**

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-(dimethylamino)pyridine-3-sulfonamide

Step A
A solution of 5-bromo-2-chloro-3-pyridinesulfonyl chloride (0.5 g, 1.719 mmol), pyridine (0.142 mL, 1.753 mmol) and 2-methylpropan-2-amine (0.402 mL, 7.05 mmol) in dichloromethane (DCM) (5 mL) was stirred at room temperature for 20 minutes then the mixture was evaporated, the residue dissolved in EtOAc, washed with water and brine, dried over magnesium sulfate and was evaporated again to give a yellow crystalline intermediate. It was dissolved in tetrahydrofuran (THF) (5.00 mL), 2M dimethylamine in THF (2.58 mL, 5.16 mmol) was added and the solution was heated at 50 °C for 2 hrs. The reaction mixture was then evaporated, the residue dissolved in EtOAc and water, the organic phase was separated and washed with brine, dried over magnesium sulfate and was evaporated again to give 5-bromo-N-(tert-butyl)-2-(dimethylamino)pyridine-3-sulfonamide (452 mg, 1.344 mmol, 78 % yield) as a brown solid. MS (ES+) m/z 336, 338 (M+H); 1H NMR (400MHz ,DMSO-d6) δ = 8.38 (d, J = 2.2 Hz, 1 H), 8.23 (d, J = 2.3 Hz, 1 H), 7.67 (s, 1 H), 3.02 (s, 6 H), 1.05 (s, 9 H).

Step B
N-(tert-butyl)-2-(dimethylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide

The mixture of 5-bromo-N-(tert-butyl)-2-(dimethylamino)pyridine-3-sulfonamide (450 mg, 1.338 mmol), bis(pinacolato)diboron (408 mg, 1.606 mmol), potassium acetate (394
mg, 4.01 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (109 mg, 0.134 mmol) in 1,4-dioxane (6 mL) was heated under nitrogen atmosphere at 100 °C overnight. The mixture was filtered through Celite® and was evaporated to dryness to give the crude N-(tert-butyl)-2-(dimethylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (1.01 g, 2.63 mmol, 197 % yield) as a black solid, which was used without further purification. MS (ES+) m/z 302 (M+H of the corresponding boronic acid).

Step C

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-(dimethylamino)pyridine-3-sulfonamide

The mixture of 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (50 mg, 0.134 mmol), N-(tert-butyl)-2-(dimethylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (103 mg, 0.268 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (10.94 mg, 0.013 mmol) and Cs₂CO₃ (43.6 mg, 0.134 mmol) in Tetrahydrofuran (THF) (1 mL) and Water (0.25 mL) was heated at 80 °C overnight then it was evaporated and purified on a RP-HPLC to give 5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-(dimethylamino)pyridine-3-sulfonamide (19.2 mg, 0.035 mmol, 26.1 % yield) as a gray solid. MS (ES+) m/z 550; ¹H NMR (400MHz, DMSO-d₆) δ = 8.55 (br. s., 1 H), 8.43 - 8.03 (m, 3 H), 7.80 - 6.87 (m, 7 H), 6.44 (br. s., 1 H), 3.77 (br. s., 7 H), 2.99 (br. s., 7 H), 1.02 (br. s., 9 H).

Example 129

5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-ethoxypyridine-3-sulfonamide, formate salt
A solution of 5-bromo-2-chloro-3-pyridinesulfonyl chloride (0.5 g, 1.719 mmol), pyridine (0.142 mL, 1.753 mmol) and 2-methylpropan-2-amine (0.402 mL, 7.05 mmol) in dichloromethane (DCM) (5 mL) was stirred at room temperature for 20 minutes then the mixture was evaporated, the residue dissolved in EtOAc, washed with water and brine, dried over magnesium sulfate and was evaporated again to give a yellow crystalline intermediate. It was dissolved in Ethanol (5.00 mL) then 21 wt% sodium ethanolate in ethanol (1.925 mL, 5.16 mmol) was added and the mixture was heated at 50 °C 1 day. The reaction was only about 60% complete therefore 21 wt% sodium ethanolate in ethanol (1.925 mL, 5.16 mmol) was added one more time and the heating continued overnight when the mixture was evaporated, dissolved in EtOAc, washed with water and brine, dried over magnesium sulfate then evaporated again to give 5-bromo-N-(tert-butyl)-2-ethoxypyridine-3-sulfonamide (435 mg, 1.290 mmol, 75 % yield) as a yellow solid. MS (ES+) m/z 337, 339 (M+H); ¹H NMR (400MHz, DMSO-d₆) δ = 8.52 (d, J = 2.5 Hz, 1 H), 8.18 (d, J = 2.4 Hz, 1 H), 7.50 (s, 1 H), 4.51 (q, J = 7.0 Hz, 2 H), 1.36 (t, J = 7.0 Hz, 3 H), 1.11 (s, 9 H).

Step B
N-(tert-butyl)-2-ethoxy-5-(4, 4, 5, 5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide

[00293] The mixture of 5-bromo-N-(tert-butyl)-2-ethoxypyridine-3-sulfonamide (435 mg, 1.290 mmol), bis(pinacolato)diboron (393 mg, 1.548 mmol), potassium acetate (380 mg, 3.87 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (105 mg, 0.129 mmol) in 1,4-dioxane (6 mL) was heated under nitrogen atmosphere at 100 °C overnight. The mixture was filtered through Celite® and was evaporated to dryness to give the crude N-(tert-butyl)-2-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (742 mg, 1.931 mmol, 150 % yield) as a black solid, which was used without further purification. MS (ES+) m/z 385.

Step C
5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-ethoxypyridine-3-sulfonamide, formate salt

[00294] The mixture of 6-bromo-1-(4-morpholinophenyl)-1 H-benzo[d]imidazol-2-amine (50 mg, 0.134 mmol), N-(tert-butyl)-2-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (103 mg, 0.268 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (10.94 mg, 0.013 mmol) and Cs₂CO₃ (43.6 mg, 0.134 mmol) in Tetrahydrofuran (THF) (1 mL) and Water (0.25 mL) was heated at 80 °C overnight then it was evaporated and purified on a RP-HPLC to give 5-(2-amino-1-(4-morpholinophenyl)-1 H-benzo[d]imidazol-6-yl)-N-(tert-butyl)-2-ethoxypyridine-3-sulfonamide, formate salt (25 mg, 0.042 mmol, 31.3 % yield), as a gray solid. MS (ES+) m/z
$\text{H NMR (400MHz, DMSO-d}_6\text{)} \delta = 8.53 (d, J = 2.0 \text{ Hz, 1 H}), 8.26 - 8.06 (m, 2 \text{ H}), 7.49 - 7.24 (m, 4 \text{ H}), 7.21 - 7.07 (m, 2 \text{ H}), 7.06 - 6.93 (m, 2 \text{ H}), 6.18 (\text{br. s., 2 H}), 4.54 (q, J = 6.9 \text{ Hz, 2 H}), 3.81 - 3.75 (m, 4 \text{ H}), 3.30 - 3.20 (m, 4 \text{ H}), 1.39 (t, J = 6.9 \text{ Hz, 3 H}), 1.13 (s, 9 \text{ H}).$

General Scheme 4

[Diagram of chemical reactions and structures]
Example 130

N-[5-[2-amino-1-(2-methylpropyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridyl]-2,4-difluorobenzenesulfonamide

Step A

(5-bromo-2-nitrophenyl)(2-methylpropyl)amine

[00295] A solution of 4-bromo-2-fluoro-1-nitrobenzene (7 g, 31.8 mmol), isobutylamine (4.78 mL, 47.7 mmol), and DIPEA (11.1 mL, 63.6 mmol) in DMF (60 mL) was stirred at room temperature for 3 hours. The solution was poured into water and extracted three times with ethyl acetate. The combined organic layers were washed three times with 5% aq. LiCl (aq), separated, dried over sodium sulfate, filtered, and concentrated to afford (5-bromo-2-nitrophenyl)(2-methylpropyl)amine (9.02 g, 33.0 mmol, quant. yield) as a yellow oil: \(^1\)H NMR (DMSO-de) \(\delta\) ppm 8.20 (t, \(J = 5.4\) Hz, 1H), 7.97 (d, \(J = 9.2\) Hz, 1H), 7.25 (d, \(J = 2.0\) Hz, 1H), 6.81 (dd, \(J = 9.1, 2.0\) Hz, 1H), 3.11 - 3.26 (m, 2H), 1.83 - 1.98 (m, 1H), 0.94 (d, \(J = 6.6\) Hz, 6H).
Step B

\((2\text{-amino-5-bromophenyl})(2\text{-methylpropyl})\text{amine}\)

\[
\text{HNMR (DMSO-}d_6\text{) } \delta \text{ ppm}
\]

6.38 - 6.54 (m, 3H), 4.71 (s, 2H), 4.65 (t, J = 5.4 Hz, 1H), 2.80 (t, J = 6.1 Hz, 2H), 1.87 (dt, J = 13.4, 6.7 Hz, 1H), 0.95 (d, J = 6.6 Hz, 6H).

[00296] A solution of (5-bromo-2-nitrophenyl)(2-methylpropyl)amine (9.04 g, 33.1 mmol) in tetrahydrofuran (175 mL) was treated dropwise with sodium dithionite (28.8 g, 165 mmol) in water (175 mL) over one hour. After stirring for 8 hours additional sodium dithionite (28.8 g, 165 mmol) in water (175 mL) was added and the mixture was stirred overnight. The mixture was diluted with ethyl acetate and washed three times with saturated NaCl (aq). The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford (2-amino-5-bromophenyl)(2-methylpropyl)amine (4.8 g, 19.74 mmol, 59.6 % yield) as a clear oil:

\[
\text{ES LC-MS } m/z = 268.5 \text{ (Br}^7\text{9, M+H)}^+; \text{ ES LC-MS } m/z = 270.5 \text{ (Br}^8\text{1, M+H)}^+.
\]

Step C

\(6\text{-bromo-1-(2-methylpropyl)-1H-benzimidazol-2-amine}\)

[00297] A solution of (2-amino-5-bromophenyl)(2-methylpropyl)amine (1 g, 4.11 mmol) in MeOH (40 mL) was treated with cyanogen bromine (0.871 g, 8.23 mmol). The reaction mixture was maintained at room temperature for 2 h. The resulting mixture was partitioned between EtOAc (100 mL), a sat. NaHCO\textsubscript{3} solution (100 mL) and water (20 mL). The organic layer was washed with a sat. NaCl solution, dried (Na\textsubscript{2}S\textsubscript{0}\textsubscript{4}) and then concentrated. The residue was triturated using CH\textsubscript{2}Cl\textsubscript{2} to obtain 6-bromo-1-(2-methylpropyl)-1H-benzimidazol-2-amine (800 mg, 2.98 mmol, 72.5 % yield) as a beige solid: ES LC-MS m/z = 268.5 (Br\textsuperscript{79}, M+H\textsuperscript{+}); ES LC-MS m/z = 270.5 (Br\textsuperscript{81}, M+H\textsuperscript{+}).

Step D
Tin (II) chloride dihydrate (87 g, 386.2 mmol) was added into a solution of 5-bromo-2-methoxy-3-nitropyridine (18 g, 72.2 mmol) in acetyl acetate (450 mL) at r.t. and the resulting mixture was refluxed for 3 hours with TLC monitoring. After the full conversion of starting material, the reaction mixture was cooled to r.t. and slowly poured into 6 N NaOH (500 mL) and stirred for a period of 10 minutes. The precipitate was filtered out with suction, and the filtrate was extracted with EtOAc (500 mL x 3). The combined organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated to dry to give a residue which was purified with column chromatography (EtOAc: petroleum ether = 1 : 4 as eluent) to give the product as a white solid (12 g, 77%). LC/MS, ESI, m/z, 203, 205 (m+1)+, Br pattern found.

**Step E**

\( N-(5\text{-bromo-2-methoxypyridin-3-yl})-2,4\text{-difluorobenzene-sulfonamide} \)

[00299] 2,4-difluorobenzene-1-sulfonyl chloride (6.8 g, 32 mmol) was added into a solution of 5-bromo-2-methoxypyridin-3-amine (6.5 g, 32 mmol) in pyridine (10 mL) and the reaction mixture was stirred at r.t. for 20 hours before the reaction solution was concentrated to dry in vacuo to give a crude product which was purified with column chromatography (EtOAc : Petroleum ether = 1:2 as eluent) to give the product as a brown solid (10 g, 83%). 1H-NMR (300 MHz, DMSO-\(d_6\)), $\delta$ 10.46 (s, 1H), 8.52 (s, 1H), 7.80-7.72 (m, 2H), 7.56 (m, 1H), 7.20 (m, 1H), 3.62 (s, 3H). LC/MS, ESI, m/z, 379, 381 (m+1)+, Br pattern found.

**Step F**

\( 2,4\text{-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide} \)
Pd(dppf)Cl₂ (3.53 g, 4.3 mmol) was added into a suspension of N-(5-bromo-2-methoxypyrindin-3-yl)-2,4-difluorobenzene-sulfonamide (30 g, 86.5 mmol), 4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (24.2 g, 95.2 mmol), KOAc (25.4 g, 259.6 mmol) in dioxane (500 mL). The reaction mixture was then stirred at reflux under N₂ protection overnight before cooled down to r.t. and concentrated to dry. The residue was taken up with 200 mL for dichloromethane and filtered to collect the filtrate which was concentrated to dry to give a residue. The crude was applied on silica gel column (EtOAc : petroleum ether = 1:10 to 1:4 as eluent) to give the product as a white solid (30 g, 81%). ¹H-NMR (300 MHz, CD₃OD), δ 8.22 (s, 1H), 7.94 (s, 1H), 7.80 (m, 1H), 7.22 (m, 1H), 7.02 (m, 1H), 3.77 (s, 3H), 1.37 (s, 12H).

LC/MS, ESI, m/z, 427 (M+1)+.

Step G

N-[5-[2-amino-1-(2-methylpropyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

A degassed mixture of 6-bromo-1-(2-methylpropyl)-1 H-benzimidazol-2-amine (60 mg, 0.224 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (119 mg, 0.280 mmol), Pd(dppf)Cl₂ adduct (18.27 mg, 0.022 mmol) and potassium acetate (65.9 mg, 0.671 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 80 °C for 2 h. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (50 mL) and washed with a sat. NaCl solution (50 mL). The organic layer was concentrated. The residue was dissolved in DMF (1 mL), filtered and purified by reverse phase chromatography (10-90% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain N-[5-[2-amino-1-(2-methylpropyl)-1 H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-
difluorobenzenesulfonamide (73 mg, 67 % yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 0.88 (d, J=6.64 Hz, 6 H) 2.07 - 2.22 (m, 1 H) 3.62 (s, 3 H) 3.86 (d, J=7.52 Hz, 2 H) 6.61 (br. s., 2 H) 7.11 - 7.24 (m, 3 H) 7.40 (s, 1 H) 7.51 - 7.60 (m, 1 H) 7.70 - 7.78 (m, 1 H) 7.80 (d, J=2.05 Hz, 1 H) 8.14 (s, 1 H) 8.26 (d, J=1.95 Hz, 1 H); ES LC-MS $m/z$ =488.4 (M+H$^+$).

Example 131

$N$-[5-(2-amino-1-methyl-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

![Chemical Structure][1]

Step A

5-bromo-N-methyl-2-nitroaniline

[00302] An orange mixture of 4-bromo-2-fluoro-1 -nitrobenzene (2 g. 9.09 mmol), a 2 M methylamine solution in THF (5.00 mL, 10.00 mmol) and $K_2CO_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 3 h. More methylamine solution in THF (10.00 mL, 20.00 mmol) was added and the reaction mixture was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated onto Celite® and purified by column chromatography (silica gel, 0-40% EtOAc/hexane) to obtain 5-bromo-N-methyl-2-nitroaniline (1.56 g, 6.75 mmol, 74.3 % yield) as an orange solid: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 2.94 (d, 3 H) 6.82 (dd, J=9.07, 2.05 Hz, 1 H) 7.16 (d, J=1.95 Hz, 1 H) 7.98 (d, J=9.07 Hz, 1 H) 8.24 (d, J=4.19 Hz, 1 H).

Step B

(2-amino-5-bromophenyl)methylamine
To a bright yellow solution of 5-bromo-N-methyl-2-nitroaniline (1.56 g, 6.75 mmol) in EtOH (100 mL) was added dropwise a solution of sodium dithionate (8.35 g, 40.5 mmol) in H$_2$O (80 mL). The resulting pale yellow slurry was filtered and the solid was washed with EtOH. The filtrate was concentrated. The residue was partitioned between EtOAc (100 mL) and water (100 mL). The organic layer was washed with a sat. NaCl solution (100 mL) and concentrated to obtain (2-amino-5-bromophenyl)methylamine (996 mg, 4.95 mmol, 73.4 % yield) as a brown oil:

$^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.68 (s, 3 H) 4.62 (br. s., 2 H) 4.89 (br. s., 1 H) 6.40 (d, J=2.15 Hz, 1 H) 6.42 - 6.46 (m, 1 H) 6.49 - 6.54 (m, 1 H); ES LC-MS m/z =201.5 (Br$^{79}$, M+H)$^+$; ES LC-MS m/z =203.4 (Br$^{81}$, M+H)$^+$.

Step C

6-bromo-1-methyl-1H-benzimidazol-2-amine

A solution of (2-amino-5-bromophenyl)methylamine (992 mg, 4.93 mmol) in MeOH (10 mL) was treated with cyanogen bromine (1045 mg, 9.87 mmol). The reaction mixture was maintained at room temperature for 1 h, then partitioned between EtOAc (100 mL), a sat. NaHCO$_3$ solution (100 mL) and water (20 mL). The organic layer was washed with a sat. NaCl solution, dried (Na$_2$SO$_4$) and concentrated. The residue was triturated using CH$_2$Cl$_2$ to obtain 6-bromo-1-methyl-1H-benzimidazol-2-amine (952 mg, 4.21 mmol, 85 % yield) as a beige solid:

$^1$H NMR (400 MHz, DMSO-cf$_2$) δ ppm 3.48 (s, 3 H) 6.57 (s, 2 H) 7.04 (d, J=0.98 Hz, 2 H) 7.30 - 7.38 (m, 1 H) ES LC-MS m/z =226.1 (Br$^{79}$, M+H)$^+$; ES LC-MS m/z =228.1 (Br$^{81}$, M+H)$^+$.

Step D

N-[5-(2-amino-1-methyl-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide
A degassed mixture of 6-bromo-1-methyl-1H-benzimidazol-2-amine (50.6 mg, 0.224 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (119 mg, 0.280 mmol), Pd(dppf)Cl₂CH₂Cl₂ adduct (18.29 mg, 0.022 mmol) and potassium acetate (66.0 mg, 0.672 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 80 °C. After 2 h the reaction mixture was allowed to cool to room temperature. The resulting slurry was filtered and the solid was washed with water to obtain N-[5-(2-amino-1-methyl-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (18 mg, 0.040 mmol, 17.86 % yield) as a light brown solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.55 (s, 3 H) 3.62 (s, 3 H) 6.57 (br. s., 2 H) 7.11 - 7.26 (m, 3 H) 7.36 (s, 1 H) 7.49 - 7.62 (m, 1 H) 7.70 - 7.86 (m, 2 H) 8.25 (br. s., 1 H) 10.30 (br. s., 1 H); ES LC-MS m/z =446.2 (M+H)+.

Example 132

N-[5-(2-amino-1-cyclopentyl-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

Step A

5-bromo-N-cyclopentyl-2-nitroaniline
[00306] An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol),
cyclopentylamine (0.897 mL, 9.09 mmol) and K$_2$CO$_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was
heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature, diluted
with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer
was concentrated to obtain 5-bromo-N-cyclopentyl-2-nitroaniiline (2.58 g, 9.05 mmol, 100 %
yield) as a yellow solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.44 - 1.77 (m, 6 H) 2.06 (dq, J=12.08, 5.96 Hz, 2 H) 4.08 (sxt, J=6.38 Hz, 1 H) 6.84 (dd, J=9.12, 2.00 Hz, 1 H) 7.27 (d, J=2.05 Hz, 1 H) 7.95 - 8.04 (m, 2 H); ES LC-MS m/z =285.1 (Br$^79$, M+H)$^+$; ES LC-MS m/z =287.2 (Br$^81$, M+H)$^+$

Step B

(2-amino-5-bromophenyl)cyclopentylamine

![Diagram](image)

[00307] To a yellow solution of 5-bromo-N-cyclopentyl-2-nitroaniiline (2.58 g, 9.05 mmol) in
EtOH (100 mL) was added dropwise a solution of sodium dithionate (14.92 g, 72.4 mmol) in
H$_2$O (80 mL). The resulting slurry was stirred at room temperature for 3 h, then filtered. The
solid was washed with EtOH. The filtrate was concentrated. The residue was partitioned
between EtOAc (100 mL), and water (100 mL). The organic layer was washed with a sat. NaCl
solution (100 mL), concentrated onto Celite® and purified by column chromatography (silica gel,
0-40% EtOAc/hexane) to obtain (2-amino-5-bromophenyl)cyclopentylamine (1.66 g, 6.51 mmol,
71.9 % yield) as a brown oil: $^1$H NMR (400 MHz, DMSO-cfe) δ ppm 1.37 - 1.61 (m, 4 H) 1.61 -
1.74 (m, 2 H) 1.92 (dq, J=1 1.95, 6.10 Hz, 2 H) 3.66 (sxt, J=6.05 Hz, 1 H) 4.54 (d, J=5.95 Hz, 1
H) 4.71 (s, 2 H) 6.41 - 6.47 (m, 2 H) 6.47 - 6.51 (m, 1 H); ES LC-MS m/z =255.2 (Br$^79$, M+H)$^+$; ES LC-MS m/z =257.2 (Br$^81$, M+H)$^+$

Step C

6-bromo-1-cyclopentyl-1H-benzimidazol-2-amine

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A solution of (2-amino-5-bromophenyl)cyclopentylamine (1.66 g, 6.51 mmol) in MeOH (17 mL) was treated with cyanogen bromine (1.378 g, 13.01 mmol). The reaction mixture was maintained at room temperature for 1 h, then partitioned between EtOAc (100 mL), a sat. NaHCO₃ solution (100 mL) and water (20 mL). The organic layer was washed with a sat. NaCl solution, dried (Na₂SO₄) and concentrated. The residue was triturated using CH₂Cl₂ to obtain 6-bromo-1-cyclopentyl-1H-benzimidazol-2-amine (947 mg, 3.38 mmol, 52.0 % yield) as a beige solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.54 - 1.77 (m, 2 H) 1.81 - 2.09 (m, 6 H) 4.71 (quin, J=8.71 Hz, 1 H) 6.59 (s, 2 H) 7.08 (s, 2 H) 7.28 (s, 1 H); ES LC-MS m/z =280.5 (Br⁺79, M+H)^+; ES LC-MS m/z =282.5 (Br⁺81, M+H)^+.

Step D

N-[5-(2-amino-1-cyclopentyl-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl]-2, 4-difluorobenzenesulfonamide

A degassed mixture of 6-bromo-1-cyclopentyl-1H-benzimidazol-2-amine (62.8 mg, 0.224 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (119 mg, 0.28 mmol), Pd(dpff)₂Cl₂ CH₂Cl₂ adduct (18.29 mg, 0.022 mmol) and potassium acetate (66.0 mg, 0.672 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 80 °C for 4 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (50 mL) and washed with a sat. NaCl solution (50 mL). The organic layer was concentrated. The residue was dissolved in DMF (1 mL), filtered and purified by HPLC (10-90% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain N-[5-(2-amino-1-cyclopentyl-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (10 mg, 0.020 mmol, 8.76 % yield): ¹H NMR (400 MHz, DMSO-cf) δ ppm 1.70 (br. s., 2 H) 1.96 (br. s., 4 H) 2.10 (br. s., 2 H) 3.65 (s, 3 H) 4.77 (quin, J=8.73 Hz, 1 H) 6.55 (br. s., 2 H) 7.12 -
7.25 (m, 3 H) 7.28 (s, 1 H) 7.51 - 7.63 (m, 1 H) 7.70 - 7.83 (m, 2 H) 8.14 (s, 1 H) 8.24 (d, 7=1.56 Hz, 1 H); ES LC-MS m/z =500.4 (M+H) +.

**Example 133**

*N-[5-[2-amino-1-(1-methylethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyr^ndyl]-2,4-difluorobenzenesulfonamide formic acid salt*

\[
\begin{align*}
\text{Step A} \\
\text{5-bromo-N-(1-methylethyl)-2-nitroaniline}
\end{align*}
\]

An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), isopropylamine (0.774 mL, 9.09 mmol) and K$_2$CO$_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was stirred at room temperature overnight. The resulting mixture was diluted with ethyl acetate and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated to obtain 5-bromo-N-(1-methylethyl)-2-nitroaniline (2.32 g, 8.95 mmol, 98% yield) as a bright orange solid: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 1.24 (d, 6 H) 3.93 - 4.02 (m, 1 H) 6.83 (dd, J=9.12, 2.00 Hz, 1 H) 7.29 (d, J=1.95 Hz, 1 H) 7.90 (d, J=7.71 Hz, 1 H) 7.99 (d, J=9.07 Hz, 1 H); ES LC-MS m/z =259.2 (Br$^{79}$, M+H)$^+$; ES LC-MS m/z =261.2 (Br$^{81}$, M+H)$^+$.

**Step B**

*(2-amino-5-bromophenyl)(1-methylethyl)amine*
To a bright yellow solution of 5-bromo-N-(1-methylethyl)-2-nitroaniline (2.32 g, 8.95 mmol) in EtOH (100 mL) was added a solution of sodium dithionate (9.23 g, 44.8 mmol) in H2O (40 mL). The reaction mixture was stirred at room temperature overnight. The resulting pale yellow slurry was filtered, and the solid was washed with EtOAc. The filtrate was concentrated to about 50 mL. EtOAc (100 mL) was added and the mixture was washed with water (50 mL) and a sat. NaCl solution (50 mL). The organic layer was concentrated to obtain (2-amino-5-bromophenyl)(1-methylethyl)amine (2.05 g, 8.95 mmol, 100 % yield) as a brown semisolid: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.14 (d, J=6.24 Hz, 6 H) 3.45 - 3.57 (m, 1 H) 4.70 (br. s., 3 H) 6.39 - 6.55 (m, 3 H); ES LC-MS m/z =229.1 (Br79, M+H)+; ES LC-MS m/z =231.1 (Br81, M+H)+.

**Step C**

6-bromo-1-(1-methylethyl)-1H-benzimidazol-2-amine

A solution of (2-amino-5-bromophenyl)(1-methylethyl)amine (2.05 g, 8.95 mmol) in MeOH (20 mL) was treated with cyanogen bromine (1.895 g, 17.89 mmol). The reaction mixture was maintained at room temperature for 1 h. The resulting mixture was partitioned between EtOAc (100 mL) and a sat. NaHCO3 solution (100 mL). The organic layer was washed with a sat. NaCl solution and concentrated. The residue was triturated using CH2Cl2 to obtain 6-bromo-1-(1-methylethyl)-1H-benzimidazol-2-amine (1.214 g, 4.78 mmol, 53.4 % yield) as a grey solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.45 (d, J=6.93 Hz, 6 H) 4.57 (spt, J=6.85 Hz, 1 H) 6.47 (s, 2 H) 7.04 (s, 2 H) 7.45 (s, 1 H); ES LC-MS m/z =254.2 (Br79, M+H)+; ES LC-MS m/z =256.2 (Br81, M+H)+.

**Step D**

N-[5-[2-amino-1-(1-methylethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt
A degassed mixture of 6-bromo-1-(1-methylethyl)-1H-benzimidazol-2-amine (57 mg, 0.224 mmol), 2,4-difluoro-N-[2-(m ethyloxy)-5-[2-(4-morpholino)ethyl]amino]-1H-benz imidazol-5-yl]-3-pyridinyl]benzenesulfonamide (0.119 g, 0.280 mmol), Pd(dp pflu2Cl2CH2Cl2 adduct (0.018 g, 0.022 mmol) and potassium acetate (0.066 g, 0.672 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C. After 1 h added more 6-bromo-1-(1-methylethyl)-1H-benzimidazol-2-amine (25 mg, 0.098 mmol) and Pd(dp pflu2Cl2CH2Cl2 adduct (0.018 g, 0.022 mmol). The mixture was degassed and heated at 90 °C for 1 h. The resulting mixture was allowed to cool to room temperature. The layers were separated, the organic layer was concentrated. The residue was dissolved in DMF and purified by HPLC (10-50% CH3CN/H2O, both containing 0.1% formic acid) to obtain N-[5-[2-amino-1-(1-methylethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorob enzenesulfonamide formic acid salt (35 mg, 0.074 mmol, 33.0 % yield): 1H NMR (400 MHz, DMSO-d6) δ ppm 1.52 (d, J=6.83 Hz, 6 H) 3.64 (s, 3 H) 4.64 (m, J=13.66, 6.73, 6.73, 6.73 Hz, 1 H) 6.55 (br. s., 2 H) 7.11 - 7.26 (m, 3 H) 7.44 (s, 1 H) 7.53 - 7.61 (m, 1 H) 7.70 - 7.83 (m, 2 H) 8.14 (s, 1 H) 8.25 (d, J=2.05 Hz, 1 H); ES LC-MS m/z =474.3 (M+H)+.

Example 134
2,4-difluoro-N-[2-(methyloxy)-5-{2-(4-morpholino)ethylamino]-1H-benzimidazol-5-yl]-3-pyridinyl]benzenesulfonamide

Step A
5-bromo-N-[2-(4-morpholino)ethyl]-1H-benzimidazol-2-amine
A solution of 5-bromo-2-chloro-1H-benzimidazole (200 mg, 0.864 mmol) and 2-(4-morpholinyl)ethanamine (337 mg, 2.59 mmol) in toluene (4 mL) was heated at 120 °C for 20 h. The toluene was decanted, the oily residue was dissolved in CH₂Cl₂ and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain 5-bromo-N-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-2-amine (157 mg, 0.483 mmol, 55.9 % yield) as a beige solid: ¹H NMR (400 MHz, DMSO-de) δ ppm 2.42 (br. s., 4 H) 2.50 - 2.54 (m, 2 H) 3.39 (q, J=6A5 Hz, 2 H) 3.51 - 3.67 (m, 4 H) 6.59 (s, 1 H) 6.91 - 7.01 (m, 1 H) 7.01 - 7.09 (m, 1 H) 7.25 (d, J=1.86 Hz, 1 H) 10.88 (br. s., 1 H); ES LC-MS m/z =325.2 (Br⁺, M+H)⁺; ES LC-MS m/z =327.3 (Br³⁺, M+H)⁺.

Step B

2,4-difluoro-N-[2-(methyloxy)-5-[(2-(4-morpholinyl)ethyl)amino]-1H-benzimidazol-5-yl]-3-pyridinyl]benzenesulfonamide

A degassed mixture of 5-bromo-N-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-2-amine (0.073 g, 0.224 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (0.119 g, 0.280 mmol), Pd(dppf)₂Cl₂ CH₂Cl₂ adduct (0.018 g, 0.022 mmol) and potassium acetate (0.066 g, 0.672 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 80 °C for 4 h. The reaction mixture was allowed to cool to room temperature then diluted with EtOAc (50 mL) and washed with a sat. NaCl solution (50 mL). The organic layer was concentrated. The residue was dissolved in DMF (1 mL), filtered and purified by HPLC (10-90% CH₃CN/H₂O , both containing 0.1% formic acid) to obtain 2,4-difluoro-N-[2-(methyloxy)-5-[(2-(4-morpholinyl)ethyl)amino]-1H-benzimidazol-5-yl]-3-pyridinyl]benzenesulfonamide: ¹H NMR (400 MHz, chloroform-d) δ ppm 2.73 - 3.19 (m, 6 H) 3.75 (br. s., 2 H) 3.93 (s, 7 H) 6.96 (q, J=9.43 Hz, 2 H) 7.21 - 7.32 (m, 1 H) 7.36 (d, J=4.88 Hz, 2 H) 7.49 - 8.39 (m, 4 H) 8.50 (s, 2 H); ES LC-MS m/z =545.4 (M+H)⁺.

Example 135

2,4-difluoro-N-[2-(methyloxy)-5-[(2-(1-pyrrolidinyl)ethyl)amino]-1H-benzimidazol-5-yl]-3-pyridinyl]benzenesulfonamide
**Step A**

5-bromo-N-[2-(1-pyrrolidinyl)ethyl]-1H-benzimidazol-2-amine

[00316] A solution of 5-bromo-2-chloro-1H-benzimidazole (200 mg, 0.864 mmol) and 2-(1-pyrrolidinyl)ethanamine (296 mg, 2.59 mmol) in toluene (4 mL) was heated at 120 °C for 20 h. The resulting mixture was allowed to cool to room temperature and purified by column chromatography (silica gel, 0-30%MeOH/EtOAc) to obtain 5-bromo-N-[2-(1-pyrrolidinyl)ethyl]-1H-benzimidazol-2-amine (161 mg, 0.521 mmol, 60.3 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.73 (br. s., 4 H) 2.55 - 2.70 (m, 4 H) 2.74 (br. s., 2 H) 3.42 (q, J=6.24 Hz, 2 H) 6.72 (t, J=5.07 Hz, 1 H) 6.94 - 7.00 (m, 1 H) 7.03 - 7.08 (m, 1 H) 7.26 (d, J=1.85 Hz, 1 H) 10.82 (br. s., 1 H); ES LC-MS m/z =309.2 (Br⁺97, M+H)⁺; ES LC-MS m/z =311.2 (Br⁺111, M+H)⁺.

**Step B**

2A-difluoro-N-[2-(methyloxy)-5-(2-[[2-(1-pyrrolidinyl)ethyl]amino]-1H-benzimidazol-5-yl)-3-pyridinyl]benzenesulfonamide

[00317] A degassed mixture of 5-bromo-N-[2-(1-pyrrolidinyl)ethyl]-1H-benzimidazol-2-amine (80 mg, 0.258 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (110 mg, 0.258 mmol), Pd(dppf)₂Cl₂ CH₂Cl₂ adduct (21.07 mg, 0.026 mmol) and potassium acetate (76 mg, 0.774 mmol) in 1,4-dioxane (2
mL) and water (0.5 mL) was heated at 80 °C for 2 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in DMF (1 mL), filtered and purified by HPLC (10-40% CH3CN/H2O, both containing 0.1% formic acid) to obtain 2,4-difluoro-N-[2-(methyloxy)-5-(2-(1-pyrrolidinyl)ethylamino)-1H-benzimidazol-5-yl)-3-
pyridinyl]benzenesulfonamide (22 mg, 0.041 mmol, 15.97% yield): 1H NMR (400 MHz, DMSO-
68x717d6) δ ppm 1.79 (br. s., 4 H) 2.81 (br. s., 4 H) 2.86 - 2.96 (m, 2 H) 3.49 (br. s., 2 H) 3.66 (s, 3 H) 6.80 (br. s., 1 H) 7.08 (s, 1 H) 7.19 (d, J=8.00 Hz, 2 H) 7.29 (s, 1 H) 7.49 (s, 1 H) 7.67 - 7.82 (m, 2 H) 8.05 - 8.12 (m, 1 H) 8.17 (br. s., 2 H); ES LC-MS m/z =529.4 (M+H)+.

Example 136

N-[5-{2-amino-1-[3-(2-oxo-1-pyrrolidinyl)propyl]-1H-benzimidazol-6-yl}-(methyloxy)-3-
pyridinyl]-2,4-difluorobenzenesulfonamide

Step A

2,4-difluoro-N-[5-(3-fluoro-4-nitrophenyl)-2-(methyloxy)-3-pyridinyl]benzenesulfonamide

[00318] A degassed mixture of 4-bromo-2-fluoro-1-nitrobenzene (0.413 g, 1.877 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-
pyridinyl]benzenesulfonamide (1 g, 2.346 mmol), Pd(dpff)2Cl2 CH2Cl2 adduct (0.153 g, 0.188 mmol) and potassium acetate (0.553 g, 5.63 mmol) in 1,4-dioxane (20 mL) and water (5 mL) was heated at 90 °C for 90 minutes. The reaction mixture was allowed to cool to room temperature then diluted with EtOAc (100 mL) and washed with a sat. NaCl solution (100 mL). The organic layer was concentrated. The residue was dissolved in CH2Cl2, concentrated onto Celite® and purified by column chromatography (silica gel, 0-50% EtOAc/hexane) to obtain 2,4-
difluoro-N-[5-(3-fluoro-4-nitrophenyl)-2-(methyloxy)-3-pyridinyl]benzenesulfonamide (705 mg, 1.605 mmol, 85% yield) as a yellow solid: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 3.62 - 3.69 (m, 3 H) 7.20 (td, J=8.49, 2.24 Hz, 1 H) 7.54 - 7.62 (m, 1 H) 7.70 - 7.80 (m, 2 H) 7.99 (dd, >12.93, 1.80 Hz, 1 H) 8.07 (d, J=2.34 Hz, 1 H) 8.24 (t, J=8.39 Hz, 1 H) 8.52 (d, J=2.34 Hz, 1 H) 10.40 (s, 1 H); ES LC-MS m/z =440.2 (M+H)$^+$.  

Step B

2,4-difluoro-N-[2-(methyloxy)-5-(4-nitro-3-[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]phenyl)-3-pyridinyl]benzenesulfonamide

[00319] A mixture of 2,4-difluoro-N-[5-(3-fluoro-4-nitrophenyl)-2-(methyloxy)-3-pyridinyl]benzenesulfonamide (400 mg, 0.910 mmol) and K$_2$CO$_3$ (377 mg, 2.73 mmol) in DMF (4 mL) was heated at 90 °C for 1 h. The resulting mixture was partitioned between EtOAc (100 mL) and water (100 mL). The layers were separated, and the aq. layer was treated with con. HCl solution until the orange color changed to greenish brown then was extracted with EtOAc (100 mL). The organic layers were concentrated to obtain 2,4-difluoro-N-[2-(methyloxy)-5-(4-nitro-3-[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]phenyl)-3-pyridinyl]benzenesulfonamide (376 mg, 0.670 mmol, 73.5 % yield) as a yellow solid: $^1$H NMR (400 MHz, DMSO-d6) $\delta$ ppm 1.82 (quin, J=6.74 Hz, 2 H) 1.91 (quin, J=7.52 Hz, 2 H) 2.17 - 2.25 (m, 2 H) 3.29 (t, J=6.64 Hz, 2 H) 3.36 (t, J=7.04 Hz, 2 H) 3.46 (q, J=6.51 Hz, 2 H) 3.66 (s, 3 H) 6.92 (dd, J=8.99, 1.66 Hz, 1 H) 7.16 (d, J=1.56 Hz, 1 H) 7.21 (td, J=8.48, 2.10 Hz, 1 H) 7.53 - 7.63 (m, 1 H) 7.75 (td, J=8.53, 6.40 Hz, 1 H) 7.95 (d, J=2.34 Hz, 1 H) 8.15 (d, J=8.89 Hz, 1 H) 8.33 (t, J=5.86 Hz, 1 H) 8.45 (d, J=2.25 Hz, 1 H) 10.37 (s, 1 H); ES LC-MS m/z =562.3 (M+H)$^+$.  

Step C

N-[5-(4-amino-3-[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]phenyl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide
To a bright yellow solution of 2,4-difluoro-N-[2-(methyloxy)-5-(4-nitro-3-[3-(2-oxo-1-pyrrolidinyl)propyl]amino)phenyl]-3-pyridinyl]benzenesulfonamide (183 mg, 0.326 mmol) in EtOH (5 mL) was added a solution of sodium dithionate (537 mg, 2.61 mmol) in H2O (10 mL). After stirring for 17 h at room temperature the reaction mixture was partitioned between EtOAc (50 mL) and water (25 mL). The organic layer was washed with a sat. NaCl solution (25 mL) and concentrated to obtain N-[5-(4-amino-3-[3-(2-oxo-1-pyrrolidinyl)propyl]amino)phenyl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (105 mg, 0.198 mmol, 60.6 % yield) as a yellow solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.81 (quin, J=6.90 Hz, 2 H) 1.92 (quin, J=7.44 Hz, 2 H) 2.15 - 2.27 (m, 2 H) 3.03 - 3.16 (m, 2 H) 3.61 (s, 3 H) 6.58 - 6.68 (m, 1 H) 6.72 (br. s., 2 H) 7.22 (m, J=8.49, 8.49 Hz, 1 H) 7.53 - 7.62 (m, 1 H) 7.65 - 7.79 (m, 2 H) 8.18 (d, J=7.03 Hz, 1 H) 10.17 (br. s., 1 H); ES LC-MS m/z =532.4 (M+H)+.

Step D
N-[5-{2-amino-1-[3-(2-oxo-1-pyrrolidinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

A solution of N-[5-(4-amino-3-[3-(2-oxo-1-pyrrolidinyl)propyl]amino)phenyl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (80 mg, 0.150 mmol) in MeOH (1 mL) was treated with cyanogen bromine (31.9 mg, 0.301 mmol). After 1 h at room temperature the reaction mixture was purified by HPLC (10-60% CH3CN/H2O, both containing 0.1% formic acid) to obtain N-[5-{2-amino-1-[3-(2-oxo-1-pyrrolidinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (32 mg, 0.055 mmol, 36.7 % yield) as a white solid: 1H NMR (400 MHz, DMSO-c6) δ ppm 1.89 (br. s., 4 H) 2.19 (t, J=7.86 Hz, 2 H) 3.27 (t, J=7.03 Hz, 2 H).
Hz, 2 H) 3.32 (t, J=6.83 Hz, 2 H) 3.61 (s, 3 H) 4.03 (t, J=6.25 Hz, 2 H) 6.74 (br. s., 2 H) 7.19 (s, 3 H) 7.42 (s, 1 H) 7.58 (t, J=9.76 Hz, 1 H) 7.74 (q, J=7.58 Hz, 1 H) 7.84 (s, 1 H) 8.11 - 8.17 (m, 1 H) 8.29 (s, 1 H); ES LC-MS m/z =557.4 (M+H)^+.

Example 137

\[ \text{N-[5-{2-amino-1-[2-(methyloxy)phenyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-}
\]
\[ \text{2,4-difluorobenzenesulfonamide} \]

\[
\text{\includegraphics[width=0.5\textwidth]{example137.png}}
\]

\text{Step A}

\text{5-bromo-N-[2-(methyloxy)phenyl]-2-nitroaniline}

[00322] An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), a 2-(methyloxy)aniline (1.036 mL, 9.19 mmol) and K$_2$CO$_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 13 h. The resulting mixture was diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated onto Celite® and purified by column chromatography (silica gel, 0-30% EtOAc/hexane) to obtain 5-bromo-N-[2-(methyloxy)phenyl]-2-nitroaniline (704 mg, 2.179 mmol, 23.72 % yield): $^1$H NMR (400 MHz, DMSO-\textit{d}_6) \delta ppm 3.80 (s, 3 H) 6.99 (d, J=2.05 Hz, 1 H) 7.01 (s, 1 H) 7.05 (td, J=7.61, 1.27 Hz, 1 H) 7.19 (dd, J=8.29, 1.07 Hz, 1 H) 7.27 - 7.34 (m, 1 H) 7.39 (dd, J=7.76, 1.41 Hz, 1 H) 8.06 (d, J=9.27 Hz, 1 H) 9.38 (s, 1 H); ES LC-MS m/z =323.3 (Br$^7$, M+H)$^+$; ES LC-MS m/z =325.1 (Br$^8$, M+H)$^+$.

\text{Step B}

\text{(2-amino-5-bromophenyl)[2-(methyloxy)phenyl]amine}

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To a bright orange solution of 5-bromo-N-[2-(methyloxy)phenyl]-2-nitroaniline (700 mg, 2.166 mmol) in EtOH (50 mL) was added a solution of sodium dithionate (3572 mg, 17.33 mmol) in H₂O (20 mL). The reaction mixture was stirred at room temperature for 4 days. The resulting pale yellow slurry was filtered, the solid was washed with EtOH. The filtrate was concentrated. The residue was partitioned between EtOAc (100 mL) and water (100 mL). The organic layer was washed with a sat. NaCl solution (100 mL) and concentrated to obtain (2-amino-5-bromophenyl)[2-(methyloxy)phenyl]amine (554 mg, 1.890 mmol, 87% yield) as a brown oil: ES LC-MS m/z =293.2 (Br⁺, M+H)⁺; ES LC-MS m/z =295.2 (Br⁺, M+H)⁺.

Step C
6-bromo-1-[2-(methyloxy)phenyl]-1H-benzimidazol-2-amine

A solution of (2-amino-5-bromophenyl)[2-(methyloxy)phenyl]amine (550 mg, 1.876 mmol) in MeOH (10 mL) was treated with cyanogen bromine (397 mg, 3.75 mmol). The reaction mixture was maintained at room temperature for 2 h, then partitioned between EtOAc (50 mL) and a sat. NaHCO₃ solution (50 mL). The organic layer was concentrated. The residue was purified by column chromatography (silica gel, 0-30%MeOH/EtOAc) to obtain 6-bromo-1-[2-(methyloxy)phenyl]-1H-benzimidazol-2-amine (296 mg, 0.930 mmol, 49.6% yield) as a beige solid: 1H NMR (400 MHz, DMSO-d₆) δ ppm 3.70 - 3.80 (m, 3 H) 6.28 (s, 2 H) 6.64 (d, J=1.56 Hz, 1 H) 7.06 - 7.17 (m, 3 H) 7.30 (dd, J=8.39, 0.98 Hz, 1 H) 7.36 (dd, J=7.71, 1.66 Hz, 1 H) 7.49 - 7.59 (m, 1 H); ES LC-MS m/z =318.1 (Br⁺, M+H)⁺; ES LC-MS m/z =320.1 (Br⁺, M+H)⁺.

Step D
N-[5-{2-amino-1-[2-(methyloxy)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3^yrid inyl]-2,4-
A degassed mixture of 6-bromo-1-[2-(methyloxy)phenyl]-1H-benzimidazol-2-amine (67.2 mg, 0.211 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (90 mg, 0.211 mmol), Pd(dppf)\(_2Cl_2\)\(CH_2Cl_2\) adduct (17.24 mg, 0.021 mmol) and potassium acetate (62.2 mg, 0.633 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 2 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in DMF (1 mL), filtered and purified by HPLC (10-60% CH\(_3\)CN/H\(_2\)O, both containing 0.1% formic acid) to obtain N-[5-{2-amino-1-[2-(methyloxy)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (10 mg, 0.019 mmol, 8.81% yield). ¹H NMR (400 MHz, DMSO-d\(_6\)) δ ppm 3.61 (s, 3 H) 3.77 (s, 3 H) 6.26 (br. s., 2 H) 6.68 (br. s., 1 H) 7.05 - 7.23 (m, 3 H) 7.25 (br. s., 1 H) 7.29 - 7.38 (m, 1 H) 7.38 - 7.45 (m, 1 H) 7.47 - 7.59 (m, 2 H) 7.61 (br. s., 1 H) 7.65 - 7.79 (m, 1 H) 8.06 - 8.22 (m, 2 H); ES LC-MS m/z = 538.3 (M+H)+.

Example 138

N-[5-{2-amino-1-[3-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(^6ethyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt

Step A

5-bromo-N-[3-(4-morpholinyl)phenyl]-2-nitroaniline
An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), a 3-(4-morpholinyl)aniline (1.632 g, 9.16 mmol) and K$_2$CO$_3$ (2.51 g, 18.18 mmol) in DMF (10 mL) was heated at 90 °C for 10 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated onto Celite® and purified by column chromatography (silica gel, 0-50% EtOAc/hexane) to obtain 5-bromo-N-[3-(4-morpholinyl)phenyl]-2-nitroaniline (2.26 g, 5.98 mmol, 65.2 % yield) as a bright orange solid: $^1$H NMR (400 MHz, DMSO-cfe) δ ppm 3.10 - 3.17 (m, 4 H) 3.70 - 3.77 (m, 4 H) 6.78 (dd, J=7.72, 1.47 Hz, 1 H) 6.86 (dd, J=8.26, 2.10 Hz, 1 H) 6.91 (t, J=2.00 Hz, 1 H) 6.99 (dd, J=9.09, 2.05 Hz, 1 H) 7.20 (d, J=2.05 Hz, 1 H) 7.30 (t, J=8.06 Hz, 1 H) 8.04 (d, J=9.09 Hz, 1 H) 9.43 (s, 1 H); ES LC-MS m/z =378.2 (Br$^79$, M+H)$^+$; ES LC-MS m/z =380.2 (Br$^81$, M+H)$^+$.

Step B

(2-amino-5-bromophenyl)[3-(4-morpholinyl)phenyl]amine

To a bright orange solution of 5-bromo-N-[3-(4-morpholinyl)phenyl]-2-nitroaniline (2.26 g, 5.98 mmol) in EtOH (80 mL) was added a solution of sodium dithionate (7.39 g, 35.9 mmol) in H$_2$O (20 mL). The reaction mixture was maintained at room temperature for 7 days. The resulting slurry was filtered, solid washed with EtOH. The filtrate was concentrated. The residue was partitioned between EtOAc (200 mL), and water (100 mL). The organic layer was concentrated. The residue was dissolved in CH$_2$Cl$_2$ and purified by column chromatography (silica gel, 0-100% EtOAc/hexane) to obtain (2-amino-5-bromophenyl)[3-(4-
morpholinyl)phenyl]amine (330 mg, 0.948 mmol, 15.86 % yield) as a white solid: \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) ppm 2.95 - 3.07 (m, 4 H) 3.66 - 3.76 (m, 4 H) 4.91 (s, 2 H) 6.27 (dd, \(J=7.80, 1.56\) Hz, 1 H) 6.34 - 6.41 (m, 2 H) 6.66 (d, \(J=8.39\) Hz, 1 H) 6.90 (dd, \(J=8.44, 2.29\) Hz, 1 H) 6.99 - 7.08 (m, 2 H) 7.10 (s, 1 H); ES LC-MS \(m/z = 348.2\) (Br\(^79\), M+H); ES LC-MS \(m/z = 350.2\) (Br\(^{81}\), M+H).

**Step C**

6-bromo-1-[3-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

![Chemical Structure](image)

[00328] A solution of (2-amino-5-bromophenyl)[3-(4-morpholinyl)phenyl]amine (327 mg, 0.939 mmol) in MeOH (5 mL) was treated with cyanogen bromine (199 mg, 1.878 mmol). The reaction mixture was maintained at room temperature for 6 h, then partitioned between EtOAc (100 mL), a sat. NaHCO\(_3\) solution (100 mL) and water (20 mL). The organic layer was washed with a sat. NaCl solution and concentrated. The residue was taken up into Et\(_2\)O. The liquid was decanted from a black oily residue. The liquid was concentrated to obtain 6-bromo-1-[3-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (229 mg, 0.614 mmol, 65.3 % yield) as a grey solid: \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) ppm 3.15 - 3.23 (m, 4 H) 3.69 - 3.78 (m, 4 H) 6.40 (s, 2 H) 6.84 (dd, \(J=7.61, 1.27\) Hz, 1 H) 6.90 (d, \(J=1.37\) Hz, 1 H) 6.95 (t, \(J=2.05\) Hz, 1 H) 7.07 - 7.16 (m, 3 H) 7.45 (t, \(J=8.05\) Hz, 1 H); ES LC-MS \(m/z = 373.2\) (Br\(^79\), M+H); ES LC-MS \(m/z = 375.2\) (Br\(^{81}\), M+H).

**Step D**

N-[5-[2-amino-1-[3-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt

![Chemical Structure](image)
A degassed mixture of 6-bromo-1-[3-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (61.3 mg, 0.164 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (70 mg, 0.164 mmol), Pd(dppf)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (13.41 mg, 0.016 mmol) and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 2 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in DMF (2 mL), filtered and purified by HPLC (10-60% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain N-[5-[2-amino-1-[3-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt (17 mg, 0.028 mmol, 17.12 % yield): $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 3.16 - 3.25 (m, 4 H) 3.62 (s, 3 H) 3.70 - 3.78 (m, 4 H) 6.35 (s, 2 H) 6.91 (dd, J=7.72, 1.17 Hz, 1 H) 6.95 (s, 1 H) 7.01 (t, J=1.95 Hz, 1 H) 7.04 - 7.15 (m, 2 H) 7.18 - 7.24 (m, 1 H) 7.24 - 7.30 (m, 1 H) 7.48 (t, J=8.06 Hz, 2 H) 7.64 (d, J=1.56 Hz, 1 H) 7.71 (td, J=8.50, 6.45 Hz, 1 H) 8.14 (s, 2 H); ES LC-MS m/z =593.3 (M+H$^+$).

Example 139

$N$-[5-[2-amino-1-(phenylmethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide hydrobromide

Step A

2,4-difluoro-$N$-[5-(3-fluoro-4-nitrophenyl)-2-(methyloxy)-3-pyridinyl]benzenesulfonamide

A degassed mixture of 4-bromo-2-fluoro-1-nitrobenzene (0.413 g, 1.877 mmol), 2,4-difluoro-$N$-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (1 g, 2.346 mmol), Pd(dppf)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (0.153 g, 0.188 mmol) and potassium acetate (0.553 g, 5.63 mmol) in 1,4-dioxane (20 mL) and water (5 mL)
was heated at 90 °C for 90 minutes. The reaction mixture was allowed to cool to room temperature then diluted with EtOAc (100 mL) and washed with a sat. NaCl solution (100 mL). The organic layer was concentrated. The residue was dissolved in CH$_2$Cl$_2$, concentrated onto Celite® and purified by column chromatography (silica gel, 0-50% EtOAc/hexane) to obtain 2,4-difluoro-N-[5-(3-fluoro-4-nitrophenyl)-2-(methyloxy)-3-pyridinyl]benzenesulfonamide (705 mg, 1.605 mmol, 85 % yield) as a yellow solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 3.62 - 3.69 (m, 3 H) 7.20 (td, J=8.49, 2.24 Hz, 1 H) 7.54 - 7.62 (m, 1 H) 7.70 - 7.80 (m, 2 H) 7.99 (dd, J=12.93, 1.80 Hz, 1 H) 8.07 (d, J=2.34 Hz, 1 H) 8.24 (t, J=8.39 Hz, 1 H) 8.52 (d, J=2.34 Hz, 1 H) 10.40 (s, 1 H); ES LC-MS m/z =440.2 (M+H)$^+$. 

**Step B**

2,4-difluoro-N-(2-(methyloxy)-5-[4-nitro-3-[(phenylmethyl)amino]phenyl]-3-pyridinyl]benzenesulfonamide

[00331] A mixture of 2,4-difluoro-N-[5-(3-fluoro-4-nitrophenyl)-2-(methyloxy)-3-pyridinyl]benzenesulfonamide (100 mg, 0.228 mmol), benzylamine (24.39 mg, 0.228 mmol) and K$_2$CO$_3$ (94 mg, 0.683 mmol) in DMF (1 mL) was heated at 90 °C for 2 h. The resulting mixture was allowed to cool to room temperature and filtered. The solids were washed with DMF. The filtrate was concentrated and used as is. ES LC-MS m/z =527.3 (M+H)$^+$. 

**Step C**

N-[5-{4-amino-3-[(phenylmethyl)amino]phenyl}-2-(methyloxy)-3^\textsuperscript{\textdagger} pyridinyl]-2,4-difluorobenzenesulfonamide

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To a bright yellow solution of 2,4-difluoro-N-(2-(methylene)-5-[4-nitro-3-
[(phenylmethyl)amino]phenyl]-3-pyridinyl]benzenesulfonamide (160 mg, 0.228 mmol) in EtOH (10 mL) was added a solution of sodium dithionate (376 mg, 1.823 mmol) in H$_2$O (10 mL). After 3 days at room temperature EtOH (20 mL) and THF (10 mL) were added to aid solubility. After another day more sodium dithionate (376 mg, 1.823 mmol) in H$_2$O (10 mL) was added and the reaction mixture was stirred for 1 day. The resulting slurry was filtered, the solid washed with EtOH. The filtrate was concentrated, reevaporated from CH$_2$Cl$_2$/hexane. The residue was taken up into CH$_2$Cl$_2$. The yellow liquid was decanted and purified by column chromatography (silica gel, 0-100% EtOAc/hexane) to obtain N-[5-[4-amino-3-[(phenylmethyl)amino]phenyl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzensulfonamide (43 mg, 0.087 mmol, 38.0 % yield): $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 3.58 (s, 3 H) 4.37 (d, J=5.66 Hz, 2 H) 4.81 (br. s., 2 H) 5.31 (t, J=5.7 Hz, 1 H) 6.53 (s, 1 H) 6.58 - 6.65 (m, 2 H) 7.13 - 7.22 (m, 1 H) 7.23 (d, J=7.32 Hz, 1 H) 7.33 (t, J=7.51 Hz, 2 H) 7.42 (d, J=7.22 Hz, 2 H) 7.51 - 7.62 (m, 2 H) 7.69 (td, J=8.51 , 6.39 Hz, 1 H) 8.00 (d, J=2.24 Hz, 1 H) 10.17 (br. s., 1 H); ES LC-MS m/z =497.3 (M+H)$^+$. 

Step D

\[ N-[5-[2-amino-1-(phenylmethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3pyridinyl]-2,4-difluorobenzensulfonamide hydrobromide \]

N-[5-[2-amino-1-(phenylmethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3pyridinyl]-2,4-difluorobenzensulfonamide hydrobromide (42 mg, 0.085 mmol) in MeOH (1 mL) was treated with cyanogen bromine (22.40 mg, 0.211 mmol). After 2 h at room temperature the reaction mixture was concentrated. The residue was taken up into CH$_2$Cl$_2$ and diluted with Et$_2$O. The resulting slurry was allowed to sit overnight, then filtered to obtain N-[5-[2-amino-1-(phenylmethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3pyridinyl]-2,4-difluorobenzensulfonamide hydrobromide (46 mg, 0.076 mmol, 90 % yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 3.56 - 3.64 (m, 3 H) 5.51 (s, 2 H) 7.18 (td, J=8.48, 2.10 Hz, 1 H) 7.28 - 7.36 (m, 3 H) 7.36 - 7.44 (m, 2 H) 7.45 - 7.63 (m, 3 H) 7.71 (td, J=8.55, 6.35 Hz, 1 H) 7.78 (d, J=0.98 Hz, 1 H) 7.89 (d, J=2.34 Hz, 1 H) 8.29 (d, J=2.35 Hz, 1 H) 8.86 (s, 2 H) 10.31 (br. s., 1 H) 12.83 (br. s., 1 H) ES LC-MS m/z =522.3 (M+H)$^+$. 

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**Example 140**

*N*-5-{2-amino-1-[4-(methyloxy)phenyl]-1H-benzimidazol-6-yl}-2-(methylo^2,4-difluorobenzenesulfonamide formic acid salt

![Chemical Structure]

**Step A**

5-bromo-N-[4-(methyloxy)phenyl]-2-nitroaniline

![Chemical Structure]

[00334] An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), a 4-(methyloxy)aniline (1.187 g, 9.64 mmol) and K$_2$CO$_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 5 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated to obtain 5-bromo-N-[4-(methyloxy)phenyl]-2-nitroaniline (2.92 g, 9.04 mmol, 99% yield) as a dark orange solid: H NMR (400 MHz, DMSO-$d_6$) δ ppm 3.76 - 3.83 (m, 3 H) 6.91 - 6.98 (m, 2 H) 7.00 - 7.07 (m, 2 H) 7.24 - 7.31 (m, 2 H) 8.01 - 8.06 (m, 1 H) 9.46 (s, 1 H); ES LC-MS $m/z$ = 323.3 (Br$^{79}$, M+H)$^+$; ES LC-MS $m/z$ = 325.2 (Br$^{81}$, M+H)$^+$.  

Step B

(2-amino-5-bromophenyl)[4-(methyloxy)phenyl]amine

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To a bright yellow solution of 5-bromo-N-[4-(methyloxy)phenyl]-2-nitroaniline (2.91 g, 9.01 mmol) in EtOH (100 mL) was added a solution of sodium dithionate (14.85 g, 72.0 mmol) in H₂O (80 mL). THF (50 mL) was then added to aid solubility. The reaction mixture was stirred at room temperature for 90 min. The resulting pale yellow slurry was filtered. The filtrate was concentrated. The residue was partitioned between EtOAc (50 mL), and water (25 mL). The organic layer was washed with a sat. NaCl solution (25 mL) and concentrated. The residue was dissolved in CH₂Cl₂ and purified by column chromatography (silica gel, 0-100% CH₂Cl₂/hexane) to obtain (2-amino-5-bromophenyl)[4-(methyloxy)phenyl]amine (1.47 g, 5.01 mmol, 55.7% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.69 (s, 3 H) 4.89 (s, 2 H) 6.62 (d, J=8.39 Hz, 1 H) 6.79 (dd, J=8.39, 2.24 Hz, 1 H) 6.85 (s, 4 H) 6.86 - 6.92 (m, 2 H); ES LC-MS m/z =293.2 (Br⁺, M+H)⁺; ES LC-MS m/z =295.2 (Br⁺, M+H)⁺.

Step C

6-bromo-1-[4-(methyloxy)phenyl]-1H-benzimidazol-2-amine

[00335] A solution of (2-amino-5-bromophenyl)[4-(methyloxy)phenyl]amine (1.47 g, 5.01 mmol) in MeOH (10 mL) was treated with cyanogen bromine (1.062 g, 10.03 mmol). The reaction mixture was maintained at room temperature for 4 h, then partitioned between EtOAc (100 mL), a sat. NaHCO₃ solution (100 mL) and water (20 mL). The organic layer was washed with a sat. NaCl solution and concentrated. The residue was triturated using CH₂Cl₂. The filtrate was purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain 6-bromo-1-[4-(methyloxy)phenyl]-1H-benzimidazol-2-amine (1.04 g, 3.27 mmol, 65.2% yield) as a pink solid.
\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) \( \delta \text{ ppm } 3.85 \) (s, 3 H) 6.58 (s, 2 H) 6.84 (s, 1 H) 7.08 - 7.21 (m, 4 H) 7.35 - 7.45 (m, 2 H); ES LC-MS \( m/z = 318.1 \) (Br\textsuperscript{79}, M+H\textsuperscript{+}); ES LC-MS \( m/z = 320.1 \) (Br\textsuperscript{81}, M+H\textsuperscript{+})

\textbf{Step D}

\( N\{-[2\text{-amino-1-[4-(methyloxy)phenyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl}\}-2,4\text{-difluorobenzenesulfonylamide formic acid salt} \)

[00337] A degassed mixture of 6-bromo-1-[4-(methyloxy)phenyl]-1 H-benzimidazol-2-amine (52.3 mg, 0.164 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (70 mg, 0.164 mmol), \( \text{Pd(dppf)}\text{Cl}_2 \text{CH}_2\text{Cl}_2 \) adduct (13.41 mg, 0.016 mmol) and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in \( \text{CH}_2\text{Cl}_2 \) and filtered through a plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF (1 mL) and a drop of TFA and purified by HPLC (10-60% CH\textsubscript{3}CN/H\textsubscript{2}O, both containing 0.1% formic acid) to obtain \( N\{-[2\text{-amino-1-[4-(methyloxy)phenyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl}\}-2,4\text{-difluorobenzenesulfonylamide formic acid salt} \) (47 mg, 0.083 mmol, 50.6 % yield) as a grey solid: \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) \( \delta \text{ ppm } 3.60 \) (s, 3 H) 3.86 (s, 3 H) 6.76 (br. s., 2 H) 6.91 (s, 1 H) 7.10 - 7.24 (m, 3 H) 7.24 - 7.36 (m, 2 H) 7.43 - 7.60 (m, 3 H) 7.66 - 7.76 (m, 2 H) 8.13 (s, 1 H) 8.18 (d, \( J=2.34 \) Hz, 1 H) 10.27 (br. s., 1 H); ES LC-MS \( m/z = 538.3 \) (M+H\textsuperscript{+}).

\textbf{Example 141}

\( N\{-[2\text{-amino-1-[}(1R)-1\text{-phenylethyi]}\}-1\text{H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl\}-2,4\text{-difluorobenzenesulfonylamide formic acid salt} \)
Step A

5-bromo-2-nitro-N-[(1R)-1-phenylethyl]aniline

[00338] An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), (1R)-1-phenylethylamine (1.102 g, 9.09 mmol) and K₂CO₃ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 2 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated to obtain an orange oil, which later crystallized under vacuo to obtain 5-bromo-2-nitro-N-[(1 R)-1-phenylethyl]aniline (2.88 g, 8.97 mmol, 99% yield) as an orange solid:

1H NMR (400 MHz, DMSO-d₆) δ ppm 1.54 (d, 3 H) 4.95 (quin, J=6.68 Hz, 1 H) 6.83 (dd, J=9.07, 1.95 Hz, 1 H) 7.03 (d, J=2.05 Hz, 1 H) 7.22 - 7.30 (m, 1 H) 7.32 - 7.39 (m, 2 H) 7.40 - 7.46 (m, 2 H) 7.99 (d, J=9.07 Hz, 1 H) 8.31 (d, J=6.63 Hz, 1 H).

Step B

(2-amino-5-bromophenyl)[(1R)-1-phenylethyl]amine

[00339] To a bright yellow solution of 5-bromo-2-nitro-N-[(1 R)-1-phenylethyl]aniline (2.88 g, 8.97 mmol) in EtOH (100 mL) was added dropwise a solution of sodium dithionate (14.79 g, 71.7 mmol) in H₂O (80 mL). The reaction mixture was stirred at room temperature for 3 h. The resulting pale yellow slurry was filtered, and the solid was washed with EtOH. The filtrate was concentrated down to about 80 mL, diluted with EtOAc (100 mL) and water (50 mL). The organic layer was washed with a sat. NaCl solution (100 mL) and concentrated. The residue was dissolved in CH₂Cl₂ and purified by column chromatography (silica gel, 0-100% EtOAc/hexane) to obtain (2-amino-5-bromophenyl)[(1 R)-1-phenylethyl]amine (1.87 g, 6.42
mmol, 71.6 % yield) as a pale yellow oil: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 1.45 (d, 3 H) 4.46 (quin, $J=6.61$ Hz, 1 H) 4.86 (s, 2 H) 5.15 (d, $J=6.54$ Hz, 1 H) 6.20 (s, 1 H) 6.43 (s, 2 H) 7.13 - 7.24 (m, 1 H) 7.25 - 7.42 (m, 4 H); ES LC-MS $m/z=291.1$ (Br$^{81}$, M+H)$^+$; ES LC-MS $m/z=293$ (Br$^{81}$, M+H)$^+$.

Step C
6-bromo-1-[(1R)-1-phenylethyl]-1H-benzimidazol-2-amine

[00340] A solution of (2-amino-5-bromophenyl)[(1R)-1-phenylethyl]amine (1.87 g, 6.42 mmol) in MeOH (10 mL) was treated with cyanogen bromine (1.360 g, 12.84 mmol). The reaction mixture was maintained at room temperature for 2 h, then partitioned between EtOAc (100 mL) a sat. NaHCO$_3$ solution (100 mL) and water (20 mL). The organic layer was washed with a sat. NaCl solution and concentrated to obtain 6-bromo-1-[(1R)-1-phenylethyl]-1H-benzimidazol-2-amine (1.86 g, 5.88 mmol, 92 % yield) as a grey solid: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 1.81 (d, 3 H) 5.71 - 5.82 (m, 1 H) 6.67 (s, 2 H) 6.76 (d, $J=1.76$ Hz, 1 H) 6.95 - 7.02 (m, 1 H) 7.02 - 7.08 (m, 1 H) 7.24 - 7.34 (m, 3 H) 7.34 - 7.43 (m, 2 H); ES LC-MS $m/z=316.2$ (Br$^{79}$, M+H)$^+$; ES LC-MS $m/z=318.2$ (Br$^{81}$, M+H)$^+$.

Step D
N-[5-{2-amino-1-[(1R)-1-phenylethyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2, 4-difluorobenzenesulfonamide formic acid salt

[00341] A degassed mixture of 6-bromo-1-[(1R)-1-phenylethyl]-1H-benzimidazol-2-amine (51.9 mg, 0.164 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (70 mg, 0.164 mmol), Pd(dpff)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (13.41 mg, 0.016 mmol) and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 mL) and
water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH₂Cl₂ and filtered through a plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF (1 mL) and a drop of TFA and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain N-[5-[2-amino-1-[(1R)-1-phenylethyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt (15 mg, 0.027 mmol, 16.20% yield) as a white solid:

\[ \text{H NMR (400 MHz, DMSO-CH₂Cl₂) } \delta \text{ ppm } 1.88 (d, J=7.02 \text{ Hz, } 3 \text{ H}), 3.61 (s, 3 \text{ H}), 5.84 (d, J=7.22 \text{ Hz, } 3 \text{ H}), 6.68 - 6.94 (m, 3 \text{ H}), 7.11 (d, J=8.39 \text{ Hz, } 1 \text{ H}), 7.14 - 7.25 (m, 2 \text{ H}), 7.25 - 7.43 (m, 5 \text{ H}), 7.51 - 7.62 (m, 2 \text{ H}), 7.70 (td, J=8.49, 6.44 \text{ Hz, } 1 \text{ H}), 7.99 (d, J=2.15 \text{ Hz, } 1 \text{ H}), 8.13 (s, 1 \text{ H}), 10.22 (br. s., 1 \text{ H}); \text{ ES LC-MS } m/z = 536.3 (M+H)⁺.

**Example 142**

**N-[5-[2-amino-1-(3-pyridinylmethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt**

[00342] An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), (2-pyridinylmethyl)amine (0.983 g, 9.09 mmol) and K₂CO₃ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 2 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated onto Celite® and purified by column chromatography (silica gel, 0-40% EtOAc/hexane) to obtain 5-bromo-2-nitro-N-(2-pyridinylmethyl)aniline (1.82 g, 5.91 mmol, 65.0
% yield) as a yellow solid: ^1^H NMR (400 MHz, DMSO-^d_6) δ ppm 4.72 (d, 2 H) 6.86 (dd, J=9.07, 1.95 Hz, 1 H) 7.22 (d, J=1.85 Hz, 1 H) 7.34 (dd, J=7.22, 5.07 Hz, 1 H) 7.42 (d, J=7.90 Hz, 1 H) 7.82 (td, J=7.66, 1.66 Hz, 1 H) 8.02 (d, J=9.07 Hz, 1 H) 8.60 (d, J=4.78 Hz, 1 H) 9.11 (t, J=5.12 Hz, 1 H); ES LC-MS m/z =308 (Br^79, M+H)^+; ES LC-MS m/z =310 (Br^81, M+H)^+.

**Step B**

(2-amino-5-bromophenyl)(3-pyridinylmethyl)amine

![Structure of (2-amino-5-bromophenyl)(3-pyridinylmethyl)amine](image)

[00343] To a bright yellow solution of 5-bromo-2-nitro-N-(3-pyridinylmethyl)aniline (1.82 g, 5.91 mmol) in EtOH (50 mL) was added a solution of sodium dithionate (9.74 g, 47.3 mmol) in H_2O (40 mL). The reaction mixture was stirred at room temperature for 17 h. The resulting thick pale yellow slurry was filtered. The filtrate was concentrated, then the residue was partitioned between EtOAc (100 mL) and water (100 mL). The organic layer was washed with a sat. NaCl solution (100 mL) and concentrated to obtain (2-amino-5-bromophenyl)(3-pyridinylmethyl)amine (1.14 g, 4.10 mmol, 69.4 % yield) as a yellow solid: ^1^H NMR (400 MHz, DMSO-^d_6) δ ppm 4.36 (d, 2 H) 4.76 (s, 2 H) 5.60 (t, J=5.76 Hz, 1 H) 6.35 (d, J=1.85 Hz, 1 H) 6.46 - 6.54 (m, 2 H) 7.23 - 7.30 (m, 1 H) 7.35 (d, J=7.90 Hz, 1 H) 7.75 (td, J=7.68, 1.80 Hz, 1 H) 8.54 (dd, J=4.83, 0.73 Hz, 1 H); ES LC-MS m/z =278.3 (Br^79, M+H)^+; ES LC-MS m/z =280.3 (Br^81, M+H)^+.

**Step C**

6-bromo-1-(3-pyridinylmethyl)-1H-benzimidazol-2-amine

![Structure of 6-bromo-1-(3-pyridinylmethyl)-1H-benzimidazol-2-amine](image)

[00344] A solution of (2-amino-5-bromophenyl)(3-pyridinylmethyl)amine (1.14 g, 4.10 mmol) in MeOH (10 mL) was treated with cyanogen bromine (0.868 g, 8.20 mmol). The reaction mixture was maintained at room temperature for 3 h. The resulting mixture was partitioned between EtOAc (100 mL), a sat. NaHC0_3 solution (100 mL) and water (20 mL). The organic
layer was washed with a sat. NaCl solution and concentrated. The residue was triturated using CH$_2$Cl$_2$ to obtain 6-bromo-1-(3-pyridinylmethyl)-1H-benzimidazol-2-amine (886 mg, 2.92 mmol, 71.3 % yield) as a grey solid: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 5.34 (s, 2 H) 6.68 (s, 2 H) 6.99 - 7.14 (m, 3 H) 7.24 - 7.33 (m, 2 H) 7.77 (td, J=7.71, 1.76 Hz, 1 H) 8.53 (dd, J=4.78, 0.78 Hz, 1 H); ES LC-MS m/z =303.2 (Br$^79$, M+H)$^+$; ES LC-MS m/z =305.2 (Br$^81$, M+H)$^+$.  

Step D  

$N$-[5-{2-amino-1-(3-pyridinylmethyl)-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt  

![Diagram](https://example.com/diagram.png)  

[00345] A degassed mixture of 6-bromo-1-(3-pyridinylmethyl)-1 H-benzimidazol-2-amine (54.8 mg, 0.181 mmol), 2,4-difluoro-$N$-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (70 mg, 0.164 mmol), Pd(dpff)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (13.41 mg, 0.016 mmol) and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a few drops of MeOH, then filtered through a plug of CeliteO. The filtrate was concentrated. The residue was dissolved in DMF (1 mL) and purified by HPLC (10-50% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain $N$-[5-{2-amino-1-(3-pyridinylmethyl)-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt (32 mg, 0.061 mmol, 37.3 % yield) as a grey solid: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 3.61 (s, 3 H) 5.42 (s, 2 H) 6.72 (br. s., 2 H) 7.11 (d, J=7.82 Hz, 1 H) 7.14 - 7.24 (m, 3 H) 7.30 (dd, J=7.23, 5.08 Hz, 1 H) 7.33 (s, 1 H) 7.49 - 7.59 (m, 1 H) 7.68 - 7.80 (m, 3 H) 8.15 (s, 1 H) 8.17 (d, J=2.15 Hz, 1 H) 8.55 (d, J=4.50 Hz, 1 H); ES LC-MS m/z =523.4 (M+Hf).  

Example 143  

$N$-[5-{2-amino-1-[3-(3-oxo-4-morpholinyl)propyl]-1H-benzimidazol^+ yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt
Step A

4-{3-[(5-bromo-2-nitrophenyl)amino]propyl}-3-morpholinone

Step B

4-{3-[(2-amino-5-bromophenyl)amino]propyl}-3-morpholinone

[00346] An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), 4-(3-aminopropyl)-3-morpholinone hydrochloride (0.849 g, 4.36 mmol) and K₂CO₃ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 2 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (50 mL) and a 5% aq. LiCl solution. Thick slurry formed at the interphase. The mixture was filtered, solid washed with water. The organic layer was washed with a 5% aq. LiCl solution (2x50 mL), concentrated down to a slurry which was filtered. The solids were combined and dried in vacuo to obtain 4-{3-[(5-bromo-2-nitrophenyl)amino]propyl}-3-morpholinone (1.274 g, 3.56 mmol, 82 % yield) as a yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.69 (t, 2 H) 3.39 - 3.49 (m, 4 H) 3.49 - 3.65 (m, 6 H) 6.83 (dd, J=9.07, 1.76 Hz, 1 H) 7.31 (d, J=1.76 Hz, 1 H) 7.98 (d, J=9.07 Hz, 1 H) 8.38 (t, J=5.85 Hz, 1 H); ES LC-MS m/z =358.2 (Br⁺, M+H)⁺; ES LC-MS m/z =360.2 (Br⁺, M+H)⁺.

Step B

4-{3-[(2-amino-5-bromophenyl)amino]propyl}-3-morpholinone
To a bright yellow solution of 4-[(5-bromo-2-nitrophenyl)amino]propyl]-3-morpholinone (1.27 g, 3.55 mmol) in EtOH (30 mL) was added a solution of sodium dithionate (5.85 g, 28.4 mmol) in H2O (30 mL). The reaction mixture was stirred at room temperature for 4 h and was filtered. The filtrate concentrated, the residue was partitioned between EtOAc (100 mL), and water (100 mL). The organic layer was washed with a sat. NaCl solution (100 mL) and concentrated to obtain 4-[(2-amino-5-bromophenyl)amino]propyl]-3-morpholinone (705 mg, 2.148 mmol, 60.6 % yield) as a pale yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.60 (t, 2 H), 3.25 (q, J=6.44 Hz, 2 H) 3.39 - 3.49 (m, 4 H), 3.54 (dd, J=4A4, 2.68 Hz, 4 H) 4.64 (s, 2 H) 4.74 (t, J=5.7 Hz, 1 H) 6.43 - 6.50 (m, 2 H) 6.50 - 6.56 (m, 1 H); ES LC-MS m/z =328.3 (Br⁺, M+H)⁺; ES LC-MS m/z =330.3 (Br⁺⁺, M+H)⁺.

Step C
4-[(2-amino-6-bromo-1H-benzimidazol-1-yl)propyl]-3-morpholinone

A solution of 4-[(2-amino-5-bromophenyl)amino]propyl]-3-morpholinone (702 mg, 2.139 mmol) in MeOH (5 mL) was treated with cyanogen bromine (453 mg, 4.28 mmol). The reaction mixture was maintained at room temperature for 4 h, then partitioned between EtOAc (50 mL), a sat. NaHCO₃ solution (50 mL) and water (20 mL). The organic layer was washed with a sat. NaCl solution (50 mL) and concentrated. The residue was triturated using CH₂Cl₂ to obtain 4-[(2-amino-6-bromo-1H-benzimidazol-1-yl)propyl]-3-morpholinone (575 mg, 1.628 mmol, 76 % yield) as a pink solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.73 (t, J=6.68
Hz, 2 H) 3.19 - 3.37 (m, 2 H) 3.37 - 3.55 (m, 6 H) 4.18 (t, J=6.68 Hz, 2 H) 6.60 (s, 2 H) 7.05 (s, 2 H) 7.37 (s, 1 H); ES LC-MS m/z =353.2 (Br\(^7\), M+H)⁺; ES LC-MS m/z =355.2 (Br\(^8\), M+H)⁺.

**Step D**

*N-[5-[2-amino-1-[3-(3-oxo-4-morpholinyl)propyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt*

![Chemical Structure](image)

[00349] A degassed mixture of 4-[3-(2-amino-6-bromo-1H-benzimidazol-1-yl)propyl]-3-morpholinone (63.8 mg, 0.181 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (70 mg, 0.164 mmol), Pd(dppf)\(_2\)Cl\(_2\) CH\(_2\)Cl\(_2\) adduct (13.41 mg, 0.016 mmol) and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH\(_2\)Cl\(_2\), filtered through a plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF (1 mL) and purified by HPLC (10-50% CH\(_3\)CN/H\(_2\)O, both containing 0.1% formic acid) to obtain N-[5-[2-amino-1-[3-(3-oxo-4-morpholinyl)propyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt (27 mg, 0.047 mmol, 28.7% yield): \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) δ ppm 2.78 (t, J=6.60 Hz, 2 H) 3.33 (d, J=4.30 Hz, 2 H) 3.37 - 3.50 (m, 6 H) 3.62 (s, 3 H) 4.27 (t, J=6.50 Hz, 2 H) 6.61 (br. s., 2 H) 7.13 - 7.25 (m, 3 H) 7.40 (s, 1 H) 7.55 (m, J=8.84, 8.84 Hz, 1 H) 7.71 - 7.80 (m, 1 H) 7.82 (d, J=1.86 Hz, 1 H) 8.15 (s, 1 H) 8.26 (d, J=1.56 Hz, 1 H); ES LC-MS m/z =573.5 (M+H)⁺.

**Example 144**

*N-[5-[2-amino-1-(trans-4-hydroxycyclohexyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt*
Step A

5-bromo-N-isobutyl-2-nitroaniline

An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), trans-4-aminocyclohexanol (1.047 g, 9.09 mmol) and K₂CO₃ (2.51 g, 18.18 mmol) in DMF (20 mL) was maintained at room temperature overnight, then heated at 90 °C for 1 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated. The residue was dissolved in CH₂Cl₂ and purified by column chromatography (silica gel, 50-100% CH₂Cl₂/hexane) to obtain trans-4-[(5-bromo-2-nitrophenyl)amino]cyclohexanol (2.2 g, 6.98 mmol, 77% yield) as a bright yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.28 - 1.46 (m, 4 H) 1.74 - 1.88 (m, 2 H) 1.88 - 2.03 (m, 2 H) 3.39 - 3.54 (m, 1 H) 3.66 (d, J=3.61 Hz, 1 H) 4.62 (d, J=4.19 Hz, 1 H) 6.81 (dd, J=9.07, 1.95 Hz, 1 H) 7.34 (d, J=1.85 Hz, 1 H) 7.83 - 8.02 (m, 2 H); ES LC-MS m/z =315.2 (Br⁺, M+H)⁺; ES LC-MS m/z =317.2 (Br²⁺, M+H)⁺.

Step B

trans-4-[(2-amino-5-bromophenyl)amino]cyclohexanol
[00351] To a bright yellow solution of trans-4-[(5-bromo-2-nitrophenyl)amino]cyclohexanol (2.2 g, 6.98 mmol) in EtOH (100 mL) was added a solution of sodium dithionate (1.151 g, 55.8 mmol) in H₂O (80 mL). The reaction mixture was stirred at room temperature for 3 h. The resulting pale yellow slurry was filtered. The filtrate was concentrated, and then the residue was partitioned between EtOAc (100 mL) and water (50 mL). The organic layer was washed with a sat. NaCl solution (50 mL) and concentrated to obtain trans-4-[(2-amino-5-bromophenyl)amino]cyclohexanol (1.565 g, 5.49 mmol, 79 % yield) as a white foamy solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.07 - 1.37 (m, 4 H) 1.83 (d, J=1.12 Hz, 2 H) 1.93 (d, J=12.00 Hz, 2 H) 3.03 - 3.20 (m, 1 H) 3.36 - 3.48 (m, 1 H) 4.36 (d, J=7.51 Hz, 1 H) 4.55 (d, J=4.29 Hz, 1 H) 4.60 - 4.73 (m, 2 H) 6.38 - 6.51 (m, 3 H); ES LC-MS m/z =287.2 (Br⁺, M+H)⁺; ES LC-MS m/z =287.2 (Br⁺, M+H)⁺.

Step C

trans-4-(2-amino-6-bromo-1H-benzimidazol-1-yl)cyclohexanol

[00352] A solution of trans-4-[(2-amino-5-bromophenyl)amino]cyclohexanol (1.56 g, 5.47 mmol) in MeOH (10 mL) was treated with cyanogen bromine (1.159 g, 10.94 mmol). The reaction mixture was maintained at room temperature for 2 h, then partitioned between EtOAc (100 mL) a sat. NaHCO₃ solution (100 mL) and water (20 mL). The organic layer was washed with a sat. NaCl solution and concentrated to obtain trans-4-(2-amino-6-bromo-1H-benzimidazol-1-yl)cyclohexanol (1.44 g, 4.64 mmol, 85 % yield) as an off-white solid: ¹H NMR (400 MHz, DMSO-cf) δ ppm 1.27 - 1.50 (m, 2 H) 1.66 (d, J=1.13 Hz, 2 H) 1.93 (d, J=10.35 Hz, 2 H) 2.04 - 2.26 (m, 2 H) 3.66 (d, J=3.91 Hz, 1 H) 4.07 - 4.24 (m, 1 H) 4.67 (d, J=4.10 Hz, 1 H) 6.52 (s, 2 H) 7.03 (s, 2 H) 7.49 (s, 1 H); ES LC-MS m/z =31.0.3 (Br⁺, M+H)⁺; ES LC-MS m/z =31.2.6 (Br⁺, M+H)⁺.

Step D

N-[5-[(trans-4-hydroxycyclohexyl)-1H-benzimidazol-6-yl]-2-(methyl^α^-)-3-pyridinyl]-
A degassed mixture of trans-4-(2-amino-6-bromo-1H-benzimidazol-1-yl)cyclohexanol (56 mg, 0.181 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (70 mg, 0.164 mmol), Pd(dppf)₂Cl₂CH₂Cl₂ adduct (13.41 mg, 0.016 mmol), and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH₂Cl₂ and a few drops of MeOH, then filtered through a plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF (1 mL) and purified by HPLC (10-50% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain N-[5-{2-amino-1-(trans-4-hydroxycyclohexyl)-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt (44 mg, 0.083 mmol, 50.6 % yield) as a grey solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 1.33 - 1.53 (m, 2 H) 1.71 (d, J=10.75 Hz, 2 H) 1.96 (d, J=10.36 Hz, 2 H) 2.14 - 2.38 (m, 2 H) 3.58 - 3.77 (m, 4 H) 4.13 - 4.31 (m, 1 H) 4.66 (br. s., 1 H) 6.51 (br. s., 2 H) 7.06 - 7.15 (m, 1 H) 7.15 - 7.24 (m, 2 H) 7.48 (s, 1 H) 7.51 - 7.63 (m, 1 H) 7.68 - 7.83 (m, 2 H) 8.14 (s, 1 H) 8.26 (d, J=2.05 Hz, 1 H); ES LC-MS m/z =530.2 (M+H)⁺.

**Example 145**

**N-[5-{2-amino-1-[(1S)-1-phenylethyl]-1H-benzimidazoL6-yl}-2-(methyl^3^γ)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt**

**Step A**

5-bromo-2-nitro-N-[1(1S)-1-phenylethyl]aniline
An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), (1S)-1-phenylethanamine (1.102 g, 9.09 mmol) and K$_2$CO$_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated to obtain an orange oil, which later crystallized to obtain 5-bromo-2-nitro-N-[(1S)-1-phenylethyl]aniline (2.99 g, 9.31 mmol, 102 % yield) as an orange solid:

\[ \text{HNMR (400 MHz, DMSO-de)} \delta \text{ppm} \]

1.54 (d, 3 H)
4.95 (quin, J=6.71 Hz, 1 H)
6.83 (dd, J=9.12, 2.00 Hz, 1 H)
7.03 (d, J=1.95 Hz, 1 H)
7.23 - 7.30 (m, 1 H)
7.32 - 7.40 (m, 2 H)
7.40 - 7.46 (m, 2 H)
8.00 (d, J=9.07 Hz, 1 H)

Step B

(2-amino-5-bromophenyl)[(1S)-1-phenylethyl]amine

To a bright yellow solution of 5-bromo-2-nitro-N-[(1S)-1-phenylethyl]aniline (2.99 g, 9.31 mmol) in EtOH (100 mL) was added a solution of sodium dithionate (15.35 g, 74.5 mmol) in H$_2$O (80 mL). The reaction mixture was stirred at room temperature for 3 h. The resulting pale yellow slurry was filtered. The filtrate was concentrated, the residue was partitioned between EtOAc (100 mL) and water (50 mL). The organic layer was washed with a sat. NaCl solution (50 mL) and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and purified by column chromatography (silica gel, 0-100% EtOAc/hexane) to obtain (2-amino-5-bromophenyl)[(1S)-1-phenylethyl]amine (1.79 g, 6.15 mmol, 66.0 % yield) as a light brown oil:

\[ \text{HNMR (400 MHz, DMSO-d$_6$)} \delta \text{ppm} \]

1.44 (d, 3 H)
4.46 (quin, J=6.59 Hz, 1 H)
5.15 (d, J=6.34 Hz, 1 H)
6.20 (s, 1 H)
6.43 (s, 2 H)
7.12 - 7.24 (m, 1 H)
7.24 - 7.45 (m, 4 H); ES LC-MS m/z =291.2 (Br$^{79}$, M+H)$^+$; ES LC-MS m/z =293.2 (Br$^{81}$, M+H)$^+$. 251
Step C

6-bromo-1-[(1S)-1-phenylethyl]-1H-benzimidazol-2-amine

[00356] A solution of (2-amino-5-bromophenyl)[(1S)-1-phenylethyl]amine (1.79 g, 6.15 mmol) in MeOH (10 ml) was treated with cyanogen bromine (1.302 g, 12.29 mmol). The reaction mixture was maintained at room temperature for 2 h, then partitioned between EtOAc (100 ml), a sat. NaHCO₃ solution (100 ml) and water (20 ml). The organic layer was washed with a sat. NaCl solution and concentrated to obtain 6-bromo-1-[(1S)-1-phenylethyl]-1H-benzimidazol-2-amine (1.45 g, 4.59 mmol, 74.6 % yield) as a beige solid: ¹H NMR (400 MHz, DMSO-de) δ ppm 1.79 (d, 3 H) 5.78 (q, J=6.94 Hz, 1 H) 6.64 - 6.83 (m, 3 H) 6.95 - 7.03 (m, 1 H) 7.03 - 7.11 (m, 1 H) 7.24 - 7.35 (m, 3 H) 7.35 - 7.45 (m, 1 H) 7.46 - 7.51 (m, 3 H) 7.51 - 7.60 (m, 2 H); ES LC-MS m/z =316.6 (Br⁻, M+H⁺); ES LC-MS m/z =318.6 (Br⁻⁻, M+H⁺).

Step D

N-[5-{2-amino-1-[(1S)-1-phenylethyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt

[00357] A degassed mixture of 6-bromo-1-[(1S)-1-phenylethyl]-1H-benzimidazol-2-amine (57.1 mg, 0.181 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (70 mg, 0.164 mmol), Pd(dppf)₂Cl₂ CH₂Cl₂ adduct (13.41 mg, 0.016 mmol) and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 ml) and water (0.5 ml) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH₂Cl₂ plus a few drops of MeOH, then filtered through a plug of Celite®. The resulting filtrate was then concentrated. The residue was dissolved in DMF (1 ml) and purified by HPLC (10-50% CH₃CN/H₂O), both containing 0.1%
formic acid) to obtain N-[5-[2-amino-1-[(1S)-1-phenylethyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt (17 mg, 0.032 mmol, 19.33 % yield) as a grey solid: $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 1.87 (d, $J=7.04$ Hz, 3 H) 3.61 (s, 3 H) 5.83 (q, $J=6.94$ Hz, 1 H) 6.66 (br. s., 2 H) 6.82 (d, $J=1.17$ Hz, 1 H) 6.82 (m, 5 H) 7.49 - 7.62 (m, 2 H) 7.70 (td, $J=8.16, 1.51$ Hz, 1 H) 7.96 (d, $J=1.76$ Hz, 1 H) 8.14 (s, 1 H); ES LC-MS m/z =356.2 (M+H)$^+$. 

Example 146

$N$-[5-[2-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

Step A

(5-bromo-2-nitrophenyl)tetrahydro-2H-pyran-4-ylamine

[00358] An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), tetrahydro-2H-pyran-4-amine (0.920 g, 9.09 mmol) and $K_2$CO$_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 90 min. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated onto Celite® and purified by column chromatography (silica gel, 0-40% EtOAc/hexane) obtain (5-bromo-2-nitrophenyl)tetrahydro-2H-pyran-4-ylamine (2.68 g, 8.90 mmol, 98 % yield) as a yellow solid: $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 1.45 - 1.67 (m, 2 H) 1.91 (dd, $J=12.51, 1.95$ Hz, 2 H) 3.49 (td, $J=11.43, 2.05$ Hz, 2 H) 3.77 - 4.03 (m, 3 H) 6.84 (dd, $J=9.09, 1.95$ Hz, 1 H) 7.42 (d, $J=1.86$ Hz, 1 H) 7.85 - 8.06 (m, 2 H); ES LC-MS m/z =301.4 (Br$_7^+$, M+H)$^+$; ES LC-MS m/z =303.4 (Br$_8^+$, M+H)$^+$. 253
Step B
(2-amino-5-bromophenyl)tetrahydro-2H-pyran-4-ylamine

To a bright yellow solution of (5-bromo-2-nitrophenyl)tetrahydro-2H-pyran-4-ylamine (2.68 g, 8.90 mmol) in EtOH (100 mL) was added a solution of sodium dithionate (14.67 g, 71.2 mmol) in H\textsubscript{2}O (80 mL). The reaction mixture was stirred at room temperature for 17 h. The resulting pale yellow slurry was filtered. The filtrate was concentrated and the residue was partitioned between EtOAc (100 mL) and water (100 mL). The organic layer was washed with a sat. NaCl solution (25 mL) and concentrated. The residue was dissolved in CH\textsubscript{2}Cl\textsubscript{2} and purified by column chromatography (silica gel, 0-100% EtOAc/hexane) to obtain (2-amino-5-bromophenyl)tetrahydro-2H-pyran-4-ylamine (1.48 g, 5.46 mmol, 61.3 % yield): \textsuperscript{1}H NMR (400 MHz, DMSO-de) \( \delta \) ppm 1.29 - 1.48 (m, 2 H) 1.87 (dd, J=12.63, 1.80 Hz, 2 H) 3.36 - 3.50 (m, 2 H) 3.86 (dt, J=11.24, 3.11 Hz, 2 H) 4.49 (d, J=7.71 Hz, 1 H) 6.43 - 6.48 (m, 1 H) 6.48 - 6.53 (m, 1 H) 6.55 (d, J=2.05 Hz, 1 H) ES LC-MS m/z =271.4 (Br\textsuperscript{79}, M+H)\textsuperscript{+}; ES LC-MS m/z =273.4 (Br\textsuperscript{81}, M+H)\textsuperscript{+}.

Step C
6-bromo-1-(tetrahydro-2H-pyran-4-yl)-1H-benzimidazol-2-amine

A solution of (2-amino-5-bromophenyl)tetrahydro-2H-pyran-4-ylamine (1.48 g, 5.46 mmol) in MeOH (10 mL) was treated with cyanogen bromine (1.156 g, 10.92 mmol). The reaction mixture was maintained at room temperature for 2 h. The resulting slurry was filtered and the solid was washed with Et\textsubscript{2}O. More solid precipitated in the filtrate which was filtered again. Solids were combined to obtain 6-bromo-1-(tetrahydro-2H-pyran-4-yl)-1H-benzimidazol-
2-amine (1.45 g, 3.85 mmol, 70.5 % yield) as a pink solid: H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.81 (d, $J=11.32$ Hz, 2 H) 2.36 (qd, $J=12.03$, 4.19 Hz, 2 H) 3.49 (t, $J=1.56$ Hz, 2 H) 4.04 (dd, $J=11.17$, 3.37 Hz, 2 H) 4.73 (t, $J=12.10$ Hz, 1 H) 7.32 - 7.40 (m, 1 H) 7.40 - 7.49 (m, 1 H) 7.87 (s, 1 H) 8.79 (s, 2 H) 12.78 (br. s., 1 H); ES LG-MS $m/z$ =296.3 (Br$_7$9 Br$_7$9, M+H)$^+$; ES LC-MS $m/z$ =298.3 (Br$_8$1, M+H)$^+$.

Step D

N-[5-[2-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

[00361] A degassed mixture of 6-bromo-1-(tetrahydro-2H-pyran-4-yl)-1H-benzimidazol-2-amine (61.9 mg, 0.164 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (70 mg, 0.164 mmol), Pd(dppf)$_2$C$_2$I$_2$CH$_2$Cl$_2$ adduct (13.41 mg, 0.016 mmol) and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 ºC for 3h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a small amount of MeOH, and filtered through a plug of CeliteO. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain N-[5-[2-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (32 mg, 0.059 mmol, 35.9 % yield) as a white solid: H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.72 (d, $J=9.58$ Hz, 2 H) 2.36 - 2.48 (m, 2 H) 3.43 - 3.58 (m, 2 H) 3.64 (s, 3 H) 4.05 (dd, $J=11.04$, 3.91 Hz, 2 H) 4.41 - 4.59 (m, 1 H) 6.55 (br. s., 2 H) 7.12 - 7.18 (m, 1 H) 7.18 - 7.26 (m, 2 H) 7.43 (s, 1 H) 7.52 - 7.68 (m, 1 H) 7.71 - 7.86 (m, 2 H) 8.26 (d, $J=1.95$ Hz, 1 H) 10.33 (br. s., 1 H); ES LC-MS $m/z$ =516.4 (M+H)$^+$.

Example 147

N-[5-[2-amino-1-[3-(4-morpholinylmethyl)phenyl]-1H-benzimidazol-6-yl]-2-ethyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt
Step A

5-bromo-N-[3-(4-morpholinylmethyl)phenyl]-2-nitroaniline

![Chemical Structure](image)

[00362] An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), 3-(4-morpholinylmethyl)aniline (1.748 g, 9.09 mmol) and K$_2$CO$_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 5 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated onto Celite® and purified by column chromatography (silica gel, 0-100% EtOAc/hexane) to obtain 5-bromo-N-[3-(4-morpholinylmethyl)phenyl]-2-nitroaniline (1.71 g, 4.36 mmol, 48.0 % yield) as an orange solid: $^1$H NMR (400 MHz, DMSO-d6) δ ppm 2.27 - 2.45 (m, 4 H) 3.49 (s, 2 H) 3.58 (t, J=4.54 Hz, 4 H) 7.02 (dd, J=9.09, 2.05 Hz, 1 H) 7.15 - 7.26 (m, 3 H) 7.30 (s, 1 H) 7.37 - 7.44 (m, 1 H) 7.97 - 8.12 (m, 1 H) 9.49 (s, 1 H); ES LC-MS m/z =392.4 (Br$^+$, M+H)$^+$; ES LC-MS m/z =394.4 (Br$^+$, M+H)$^+$. 

Step B

(2-amino-5-bromophenyl)[3-(4-morpholinylmethyl)phenyl]amine

![Chemical Structure](image)

[00363] To a bright yellow solution of 5-bromo-N-[3-(4-morpholinylmethyl)phenyl]-2-nitroaniline (1.71 g, 4.36 mmol) in EtOH (50 mL) was added a solution of sodium dithionate (7.19 g, 34.9 mmol) in H$_2$O (40 mL). The reaction mixture was stirred at room temperature for 17
The resulting pale yellow slurry was filtered and the filtrate was concentrated. The residue was partitioned between EtOAc (100 mL) and water (50 mL). The organic layer was washed with a sat. NaCl solution (50 mL) and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and purified by column chromatography (silica gel, 0-100% EtOAc/hexane) to obtain (2-amino-5-bromophenyl)[3-(4-morpholinylmethyl)phenyl]amine (450 mg, 1.242 mmol, 28.5 % yield) as a white solid: $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.34 (br. s., 4 H) 3.34 - 3.39 (m, 2 H) 3.57 (t, $J$=4.49 Hz, 4 H) 4.94 (s, 2 H) 6.68 - 6.71 (m, 3 H) 6.81 (br. s, 1 H) 6.91 (dd, $J$8.49, 2.24 Hz, 1 H) 7.06 (d, $J$=2.24 Hz, 1 H) 7.11 (t, $J$=7.76 Hz, 1 H) 7.22 (s, 1 H); ES LC-MS m/z =362.4 (Br$^79$, M+H)$^+$; ES LC-MS m/z =364.4 (Br$^81$, M+H)$^+$.  

Step C  
6-bromo-1-[3-(4-morpholinylmethyl)phenyl]-1H-benzimidazol-2-amine

A solution of (2-amino-5-bromophenyl)[3-(4-morpholinylmethyl)phenyl]amine (447 mg, 1.234 mmol) in MeOH (10 mL) was treated with cyanogen bromine (261 mg, 2.468 mmol). The reaction mixture was stirred at room temperature for 3 days. The resulting mixture was partitioned between EtOAc (100 mL), a sat. NaHCO$_3$ solution (100 mL) and water (20 mL). The organic layer was concentrated. The residue was dissolved in CH$_2$Cl$_2$ and purified by column chromatography (silica gel, 0-40% MeOH/EtOAc) to obtain 6-bromo-1-[3-(4-morpholinylmethyl)phenyl]-1 H-benzimidazol-2-amine (100 mg, 0.258 mmol, 20.93 % yield) as a grey solid: $^1$H NMR (400 MHz, DMSO-cf$_6$) δ ppm 2.45 (d, $J$=1.95 Hz, 4 H) 3.53 - 3.63 (m, 6 H) 6.46 (s, 2 H) 6.89 (d, $J$=1.27 Hz, 1 H) 7.13 - 7.16 (m, 2 H) 7.34 - 7.42 (m, 2 H) 7.45 (d, $J$=7.71 Hz, 1 H) 7.53 - 7.60 (m, 1 H) ES LC-MS m/z =387.2 (Br$^79$, M+H)$^+$; ES LC-MS m/z =389.2 (Br$^81$, M+H)$^+$.  

Step D  
N-[5-[2-amino-1-[3-(4-morpholinylmethyl)phenyl]-1H-benzimidazol-6-yl]-2-(meth$^\text{ox}$)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt
A degassed mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (66.0 mg, 0.155 mmol), 6-bromo-1-[3-(4-morpholinylmethyl)phenyl]-1H-benzimidazol-2-amine (60 mg, 0.155 mmol), Pd(dppf)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (12.65 mg, 0.015 mmol) and potassium acetate (45.6 mg, 0.465 mmol) in 1,4-dioxane (2 ml) and water (0.5 ml) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and filtered through a plug of Celite®. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain N-[5-{2-amino-1-[3-(4-morpholinylmethyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt (44 mg, 0.069 mmol, 44.5% yield) as a white solid:

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.37 - 2.47 (m, 4 H) 3.51 - 3.64 (m, 9 H) 6.43 (br. s., 2 H) 6.95 (s, 1 H) 7.12 (br. s., 1 H) 7.25 (s, 1 H) 7.27 - 7.34 (m, 1 H) 7.34 - 7.64 (m, 6 H) 7.64 - 7.75 (m, 2 H) 8.15 (br. s., 1 H) 10.25 (br. s., 1 H); ES LC-MS m/z =607.4 (M+H)$^+$.}

**Example 148**

N-[5-{2-amino-1-[3-(4-morpholinypropyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-3-pyridinesulfonamide formic acid salt

A degassed mixture of {6-(methyloxy)-5-[(3-pyridylsulfonyl)amino]-3-pyridinyl}boronic acid (57.4 mg, 0.186 mmol), 6-bromo-1-[3-(4-morpholinypropyl]-1H-benzimidazol-2-amine (63 mg, 0.186 mmol), Pd(dppf)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (15.17 mg, 0.019 mmol) and potassium acetate (54.7 mg, 0.557 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and
concentrated. The residue was partitioned between water and EtOAc. The resulting slurry was filtered. The solid was dissolved in DMF, filtered and purified by HPLC (10-50% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain N-[5-[2-amino-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-3-pyridinesulfonamide formic acid salt (25 mg, 0.048 mmol, 25.7 % yield) as a grey solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.01 (br. s., 2 H) 2.54 - 2.95 (m, 6 H) 3.56 (s, 7 H) 4.23 (t, J=6.10 Hz, 2 H) 7.40 - 7.53 (m, 2 H) 7.63 (dd, J=8.00, 4.88 Hz, 1 H) 7.80 (s, 1 H) 7.95 (d, J=1.07 Hz, 1 H) 8.10 (d, J=8.00 Hz, 1 H) 8.14 (s, 1 H) 8.36 (d, J=1.27 Hz, 1 H) 8.54 (br. s., 2 H) 8.74 - 8.91 (m, 2 H) 10.37 (br. s., 1 H); ES LC-MS m/z = 524.3 (M+H)⁺.

**Example 149**

\[
N\{5-(2-amino-1-[(4-(dimethylamino)tetrahydro-2H-pyran-4-y]methyl]-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl\}-2,4-difluorobenzenesulfonamide
\]

**Step A**

(5-bromo-2-nitrophenyl)\{[4-(dimethylamino)tetrahydro-2H-pyran-4-y]methyl\}amine

[00367] A mixture of 4-bromo-2-fluoro-1-nitrobenzene (2.82 g, 12.83 mmol), 4-(aminomethyl)-N,N-dimethyltetrahydro-2H-pyran-4-amine (2.03 g, 12.83 mmol) and K₂CO₃ (3.55 g, 25.7 mmol) in DMF (20 mL) was maintained at room temperature for 3 days. The resulting mixture was partitioned between water (100 mL) and EtOAc (100 mL). The organic layer was washed with a 5% aq. LiCl solution (2x100 mL) and concentrated to obtain 4-)(((5-bromo-2-nitrophenyl)amino)methyl)-N,N-dimethyltetrahydro-2H-pyran-4-amine (3.95 g, 11.03 mmol, 86 % yield): ¹H NMR (400 MHz, DMSO-cfe) δ ppm 1.39 (d, J=13.27 Hz, 2 H) 1.81 (ddd,
A solution of 4-(((5-bromo-2-nitrophenyl)amino)methyl)-N,N-dimethyltetrahydro-2H-pyran-4-amine (3.95 g, 11.03 mmol) in EtOH (150 mL) was added a solution of sodium dithionate (18.18 g, 88 mmol) in water (80 mL). The reaction mixture was maintained at room temperature overnight. The resulting slurry was filtered, solid washed with EtOH. The filtrate was concentrated to about 60 mL, its pH adjusted to basic using solid K$_2$CO$_3$, then extracted with EtOAc (150 mL). The organic layer was washed with a sat. NaCl solution (100 mL) and concentrated. The residue was triturated using CH$_2$Cl$_2$ to obtain 5-bromo-N1-((4-(dimethylamino)tetrahydro-2H-pyran-4-yl)methyl)benzene-1,2-diamine (1.76 g, 5.36 mmol, 48.6 % yield): ES LC-MS m/z =328.0 (Br$^{79}$, M+H)$^+$; ES LC-MS m/z =330.0 (Br$^{81}$, M+H)$^+$.

Step C

6-bromo-1-[[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl]-1H-benzimidazol-2-amine

A solution of (2-amino-5-bromophenyl){[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl}amine (1.76 g, 5.36 mmol) in MeOH (20 mL) was treated with cyanogen bromine (0.625 g, 5.90 mmol). The reaction mixture was maintained at room temperature overnight. The resulting mixture was diluted with EtOAc (100 mL), washed with a sat. NaHCO$_3$ solution and a sat. NaCl solution. The organic layer was concentrated and the residue was triturated
using CH₂Cl₂ to obtain 6-bromo-1-[[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl]-1H-benzimidazol-2-amine (1.078 g, 3.05 mmol, 56.9 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-de) δ ppm 1.12 - 1.28 (m, 2 H) 1.87 (d, J=13.58 Hz, 2 H) 2.40 (s, 6 H) 3.41 - 3.51 (m, 2 H) 3.51 - 3.63 (m, 2 H) 3.99 (s, 2 H) 6.61 (s, 2 H) 7.05 (s, 2 H) 7.34 (s, 1 H); ES LC-MS m/z =353.4 (Br⁺, M+H)⁺; ES LC-MS m/z =355.4 (Br⁺, M+H)⁺.

Step D
N-[5-(2-amino-1-[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl]-1H-benzimidazol-6-yl]-2-(methylxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

A degassed mixture of 6-bromo-1-[[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl]-1H-benzimidazol-2-amine (58.0 mg, 0.164 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (70 mg, 0.164 mmol), Pd(dppf)₂CH₂Cl₂ adduct (13.41 mg, 0.016 mmol) and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 ml.) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH₂Cl₂ and a small amount of MeOH, and filtered through a plug of CeliteO. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain N-[5-(2-amino-1-[4-(dimethylamino)tetrahydro-2H-pyran-4-yl]methyl]-1H-benzimidazol-6-yl]-2-(methylxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (14 mg, 0.023 mmol, 14.29 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.19 - 1.33 (m, 2 H) 1.91 (m, J=5.85 Hz, 2 H) 2.43 (s, 6 H) 3.47 (d, J=10.63 Hz, 2 H) 3.57 (s, 2 H) 3.63 (s, 3 H) 4.08 (s, 2 H) 6.63 (br. s., 2 H) 7.10 - 7.25 (m, 3 H) 7.37 (s, 1 H) 7.50 - 7.63 (m, 1 H) 7.74 (td, J=8.49, 6.44 Hz, 1 H) 7.82 (d, J=2.24 Hz, 1 H) 8.26 (d, J=1.66 Hz, 1 H) 10.32 (br. s., 1 H); ES LC-MS m/z =573.5 (M+H)⁺.

Example 150
N-[5-(2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-2-(methylxy)-3-pyridinyl]-3-pyridinesulfonamide formic acid salt
[00371] A degassed mixture of {6-(methyloxy)-5-[3-pyridinylsulfonyl]amino}-3-pyridinylboronic acid (60 mg, 0.194 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1 H-benzimidazol-2-amine (72.5 mg, 0.194 mmol), Pd(dppf)$_2$Cl$_2$ adduct (15.85 mg, 0.019 mmol) and potassium acetate (57.2 mg, 0.582 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF, filtered and purified by HPLC (10-60% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain N-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1 H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-3-pyridinesulfonamide formic acid salt (25 mg, 0.043 mmol, 22.17% yield): $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 3.19 - 3.29 (m, 4 H) 3.55 (s, 3 H) 3.73 - 3.83 (m, 4 H) 6.70 (br. s., 2 H) 6.89 (s, 1 H) 7.18 (d, J=8.98 Hz, 2 H) 7.23 - 7.34 (m, 2 H) 7.38 (d, J=8.88 Hz, 2 H) 7.56 (dd, J=8.05, 4.83 Hz, 1 H) 7.66 (d, J=2.24 Hz, 1 H) 8.05 (dt, J=8.05, 1.88 Hz, 1 H) 8.16 (s, 1 H) 8.18 (d, J=2.24 Hz, 1 H) 8.77 (dd, J=4.78, 1.37 Hz, 1 H) 8.83 (d, J=2.15 Hz, 1 H) 10.29 (br. s., 1 H); ES LC-MS $m/z = 558.4$ (M+H)$^+$.

**Example 151**

N-[5-(2-amino-1-methyl-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

![Chemical Structure](image)

**Step A**

5-bromo-N-[2-(4-morpholinyl)cyclopentyl]-2-nitroaniline
An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), 2-(4-morpholinyl)cyclopentanamine (1.548 g, 9.09 mmol) and K$_2$CO$_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated. The residue was dissolved in CH$_2$Cl$_2$ and purified by column chromatography (silica gel, 0-100% EtOAc/hexane) to obtain 5-bromo-N-[2-(4-morpholinyl)cyclopentyl]-2-nitroaniline (2.23 g, 6.02 mmol, 66.3% yield) as an orange solid:

**$^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.48 (dq, J=12.63, 6.32 Hz, 1 H) 1.54 - 1.72 (m, 3 H) 1.74 - 1.86 (m, 1 H) 2.05 - 2.20 (m, 1 H) 2.36 - 2.47 (m, 4 H) 2.76 - 2.87 (m, 1 H) 3.48 - 3.66 (m, 4 H) 3.99 (quin, J=6.56 Hz, 1 H) 6.85 (dd, J=9.12, 1.71 Hz, 1 H) 7.54 (d, J=1.56 Hz, 1 H) 7.98 (d, J=9.07 Hz, 1 H) 8.04 - 8.18 (m, 1 H); ES LC-MS m/z =370.4 (Br$^{79}$, M+H)$^+$; ES LC-MS m/z =372.4 (Br$^{81}$, M+H)$^+$.**

**Step B**

(2-amino-5-bromophenyl)[2-(4-morpholinyl)cyclopentyl]amine

To a bright yellow solution of 5-bromo-N-[2-(4-morpholinyl)cyclopentyl]-2-nitroaniline (2.32 g, 6.27 mmol) in EtOH (100 mL) was added a solution of sodium dithionate (10.33 g, 50.1 mmol) in H$_2$O (80 mL). The reaction mixture was stirred at room temperature for 2 h. The resulting pale yellow slurry was filtered. The filtrate was concentrated to about 100 mL, then partitioned between EtOAc (100 mL) and water (50 mL). The organic layer was washed with a sat. NaCl solution (50 mL) and concentrated to obtain (2-amino-5-bromophenyl)[2-(4-morpholinyl)cyclopentyl]amine (1.39 g, 4.09 mmol, 65.2% yield) as a white solid: ES LC-MS m/z =340.3 (Br$^{79}$, M+H)$^+$; ES LC-MS m/z =342.3 (Br$^{81}$, M+H)$^+$. 263
Step C

6-bromo-1-[2-(4-morpholiny)cyclopentyl]-1H-benzimidazol-2-amine

A solution of racemic (2-amino-5-bromophenyl)[2-(4-morpholiny)cyclopentyl]amine (1.39 g, 4.09 mmol) in MeOH (10 mL) was treated with cyanogen bromine (0.865 g, 8.17 mmol). The reaction mixture was maintained at room temperature for 2 h. The resulting mixture was partitioned between EtOAc (100 mL), a sat. NaHCO₃ solution (100 mL) and water (20 mL). The organic layer was washed with a sat. NaCl solution and concentrated. The residue was dissolved in CH₂Cl₂ and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain 6-bromo-1-[2-(4-morpholiny)cyclopentyl]-1H-benzimidazol-2-amine (782 mg, 2.141 mmol, 52.4 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-de) δ ppm 1.57 - 1.76 (m, 2 H) 1.78 - 1.93 (m, 1 H) 1.93 - 2.11 (m, 3 H) 2.31 (m, J=7.15, 15.47, 15.47, 4.29 Hz, 4 H) 3.39 - 3.56 (m, 5 H) 4.62 (q, J=8.98 Hz, 1 H) 6.59 (s, 2 H) 7.06 (s, 2 H) 7.32 (s, 1 H); ES LC-MS m/z =365.3 (Br⁻⁺, M+H)⁺; ES LC-MS m/z =367.3 (Br⁻⁻¹, M+H)⁺.

Step D

N-[5-(2-amino-1-methyl-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

A degassed mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (70.0 mg, 0.164 mmol), 6-bromo-1-[2-(4-morpholiny)cyclopentyl]-1 H-benzimidazol-2-amine (60 mg, 0.164 mmol), Pd(dpdpf)₂Cl₂ CH₂Cl₂ adduct (13.41 mg, 0.016 mmol) and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool
to room temperature and concentrated. The residue was dissolved in CH₂Cl₂ and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF, filtered and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain N-[5-[2-amino-1-[2-(4-morpholinyl)cyclopentyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide formic acid salt (47 mg, 0.066 mmol, 40.2% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.61 - 1.78 (m, 2 H) 1.82 - 1.98 (m, 1 H) 2.06 (dd, J=19.90, 7.61 Hz, 3 H) 2.26 - 2.43 (m, 4 H) 3.41 - 3.54 (m, 4 H) 3.54 - 3.73 (m, 4 H) 4.68 (q, J=8.91 Hz, 1 H) 6.56 (br. s., 2 H) 7.11 - 7.25 (m, 3 H) 7.31 (s, 1 H) 7.51 - 7.60 (m, 1 H) 7.70 - 7.81 (m, 2 H) 8.14 (s, 2 H) 8.20 - 8.28 (m, 1 H); ES LC-MS m/z =585.5 (M+H)⁺.

Example 152
N-[5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-3-pyridinesulfonamide

A degassed mixture of N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]-3-pyridinesulfonamide (88 mg, 0.224 mmol), 6-bromo-1-(1,1-dimethylethyl)-1 H-benzimidazol-2-amine (60 mg, 0.224 mmol), Pd(dppf)₂Cl₂ CH₂Cl₂ adduct (18.27 mg, 0.022 mmol) and potassium acetate (65.9 mg, 0.671 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH₂Cl₂ and a small amount of MeOH, filtered through a plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF, filtered and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain N-[5-[2-amino-1-(1,1-dimethylethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-3-pyridinesulfonamide (8 mg, 0.017 mmol, 7.51% yield) as a grey solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.78 (s, 9 H) 3.61 (s, 3 H) 6.12 (br. s., 2 H) 7.11 - 7.16 (m, 1 H) 7.16 - 7.23 (m, 1 H) 7.55 (s, 1 H) 7.61 (dd, J=7.96, 4.74 Hz, 1 H) 7.73 (d, J=2.25 Hz, 1 H) 8.06 - 8.22 (m, 3 H) 8.80 (dd, J=4.74, 1.22 Hz, 1 H) 8.88 (d, J=1.95 Hz, 1 H); ES LC-MS m/z =453.3 (M+H)⁺.
Example 153

N-[5-[2-amino-1-(phenylsulfonyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridyl]-3-pyridinesulfonamide

![Chemical structure diagram]

Step A

l-(phenylsulfonyl)-1H-benzo[d]imidazol-2-amine

[00377] A solution of 2-amino benzimidazole (3 g, 22.53 mmol) in acetonitrile (40 mL) and water (4 mL) was treated with sodium hydroxide (1.983 g, 49.6 mmol), after everything was in solution phenyl sulphonyl chloride (3.98 g, 22.53 mmol) was added and the mixture stirred for 4 hours at RT. The reaction was poured into water and the precipitate collected and used directly. ES-LCMS: 274.0 (M+1).

Step B

6-iodo-l-(phenylsulfonyl)-1H-benzo[d]imidazol-2-amine

[00378] A solution of 1-(phenylsulfonyl)-1 H-benzo[d]imidazol-2-amine (4.1 g, 15.00 mmol) in acetic acid (40 mL) was treated with NIS (4.39 g, 19.50 mmol) and the reaction stirred at 55 C for 16 hours. The reaction was poured into a solution of Na2S03 (aq) and the resulting precipitate collected and dried to give the crude product, which was used directly. ^1^H NMR (400
MHz, DMSO-\(d_6\) \(\delta\) ppm 8.05 (m, 2 H), 7.78 (m, 1 H), 7.56 (m, 2 H), 7.18 (br s, 2 H), 7.12 (m, 2 H), 7.05 (m, 1 H).

Step C

\(N-[5-[2\text{-amino-1-(phenylsulfonyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-3-pyridinesulfonamide}\)

![Chemical structure of the compound](image)

**[00379]** In a dry microwave tube \{(6-(methyloxy)-5-{[3-pyridinylsulfonfyl]amino}-3-pyridinyl)boronic acid (77 mg, 0.249 mmol), 6-iodo-1-(phenylsulfonyl)-1H-benzimidazol-2-amine (99 mg, 0.249 mmol), potassium acetate (73.3 mg, 0.747 mmol) \(\text{dried in oven overnight), Pd(dppf)}_2\text{Cl}_2 \text{CH}_2\text{Cl}_2 \text{adduct (20.34 mg, 0.025 mmol) in anh. dioxane (1 mL) was heated in a microwave apparatus at 130 °C for 20 min. The resulting mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL) and CH\(_2\)Cl\(_2\) (50 mL). The organic layers were combined, dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The residue was taken up into DMF and purified by HPLC (0-100\% CH\(_3\)CN/H\(_2\)O, both containing 0.1\% formic acid) to obtain \(N-[5-[2\text{-amino-1-(phenylsulfonyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-3-pyridinesulfonamide}\) (9 mg, 0.016 mmol, 6.26 \% yield) as a white solid: \(^1\text{H NMR (400 MHz, DMSO-}\text{d}_6\text{)} \delta\) ppm 3.62 (s, 3 H) 7.22 (d, J=8.19 Hz, 1 H) 7.32 (s, 2 H) 7.37 (dd, J=1.76 Hz, 1 H) 7.60 - 7.71 (m, 3 H) 7.75 - 7.83 (m, 3 H) 8.08 - 8.16 (m, 3 H) 8.28 (d, J=2.34 Hz, 1 H) 8.82 (dd, J=4.83, 1.51 Hz, 1 H) 8.90 (d, J=2.15 Hz, 1 H) 10.31 (s, 1 H); ES LC-MS \(m/z =537.3\) (M+H)\^+.

**Example 154**

\(N-[5-[2\text{-amino-1-(phenylsulfonyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide}\)

![Chemical structure of the compound](image)
A degassed mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (149 mg, 0.35 mmol), Pd(dppf)Cl2 adduct (28.6 mg, 0.036 mmol), potassium acetate (103 mg, 1.05 mmol) and 6-iodo-1-(phenylsulfonyl)-1 H-benzimidazol-2-amine (140 mg, 0.35 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated in a microwave apparatus at 130 °C for 20 min. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (25 mL). The organic layer was dried (Na2SO4), filtered and concentrated. The residue was dissolved in DMF, filtered and purified by HPLC (0-100% CH3CN/H2O, both containing 0.1% formic acid) to obtain N-[5-[2-amino-1-(phenylsulfonyl)-1 H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (11 mg, 0.018 mmol, 10.21 % yield) as a white solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 3.69 (s, 3 H) 7.21 (d, J=8.11 Hz, 2 H) 7.30 (s, 2 H) 7.48 - 7.61 (m, 1 H) 7.61 - 7.72 (m, 3 H) 7.72 - 7.85 (m, 4 H) 8.02 - 8.28 (m, 3 H) 10.32 (br. s., 1 H); ES LC-MS m/z =572.4 (M+H)+.

**Example 155**

N-[5-[2-amino-1-(2-phenylethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

![Chemical structure](attachment:image.png)

**Step A**

5-bromo-2-nitro-N-(2-phenylethyl)aniline
An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), 2-phenylethanamine (1.102 g, 9.09 mmol) and K₂C₂O₃ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 3 h, then was allowed to cool to room temperature. The resulting mixture was diluted with EtOAc (100 mL) and washed with a 5% LiCl solution (3x100 mL). The organic layer was concentrated. The residue was triturated with Et₂O to obtain 5-bromo-2-nitro-N-(2-phenylethyl)aniline (1.70 g, 5.29 mmol, 58.2 % yield) as a yellow solid: ¹H NMR (400 MHz, DMSO-de) δ ppm 2.93 (t, J=7.13 Hz, 2 H) 3.57 - 3.66 (m, 2 H) 6.82 (dd, J=9.4, 2.00 Hz, 1 H) 7.18 - 7.25 (m, 1 H) 7.25 - 7.35 (m, 5 H) 7.96 (d, J=9.18 Hz, 1 H) 8.09 - 8.19 (m, 1 H); ES LC-MS m/z =321.2 (Br⁷⁹, M+H); ES LC-MS m/z =323.2 (Br⁸¹, M+H).

Step B

(2-amino-5-bromophenyl)(2-phenylethyl)amine

To a bright yellow solution of 5-bromo-2-nitro-N-(2-phenylethyl)aniline (1.70 g, 5.29 mmol) in EtOH (100 mL) was added a solution of sodium dithionate (8.73 g, 42.3 mmol) in H₂O (80 mL). The reaction mixture was stirred at room temperature overnight. The resulting pale yellow slurry was filtered. The filtrate was concentrated to about 100 mL and diluted with EtOAc (100 mL). The organic layer was filtered through a pad of silica gel. The filtrate was concentrated, the residue was dissolved in CH₂Cl₂ and purified by column chromatography (silica gel, 0-20% EtOAc/hexane) to obtain (2-amino-5-bromophenyl)(2-phenylethyl)amine (1.06 g, 3.64 mmol, 68.8 % yield) as a brown oil: ¹H NMR (400 MHz, DMSO-cf) δ ppm 2.88 (t, 2 H) 3.18 - 3.28 (m, 2 H) 4.68 (s, 2 H) 4.79 (t, J=5.33 Hz, 1 H) 6.43 - 6.48 (m, 1 H) 6.48 - 6.55 (m, 2 H) 7.17 - 7.25 (m, 1 H) 7.26 - 7.35 (m, 4 H); ES LC-MS m/z =291.4 (Br⁷⁹, M+H); ES LC-MS m/z =293.4 (Br⁸¹, M+H).

Step C

6-bromo-1-(2-phenylethyl)-1H-benzimidazol-2-amine
A solution of (2-amino-5-bromophenyl)(2-phenylethyl)amine (1.06 g, 3.64 mmol) in MeOH (10 mL) was treated with cyanogen bromine (0.771 g, 7.28 mmol). The reaction mixture was stirred at room temperature for 1 h, and then partitioned between EtOAc (50 mL) and a sat. NaHCO₃ solution (50 mL). The organic layer was washed with a sat. NaCl solution (50 mL) and concentrated. The residue was dissolved in CH₂Cl₂ and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain 6-bromo-1-(2-phenylethyl)-1H-benzimidazol-2-amine (0.94 g, 2.97 mmol, 82% yield) as a beige solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.88 (t, 2 H), 4.18 (t, J=7.71 Hz, 2 H), 6.58 (s, 2 H), 7.01 (s, 2 H), 7.15 - 7.37 (m, 6 H); ES LC-MS m/z =316.6 (Br⁺, M+H)⁺; ES LC-MS m/z =318.6 (Br⁻, M+H)⁺.

Step D

N-[5-[2-amino-1-(2-phenylethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

A degassed mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (80 mg, 0.188 mmol), 6-bromo-1-(2-phenylethyl)-1H-benzimidazol-2-amine (59.3 mg, 0.188 mmol), Pd(dppf)₂Cl₂-C₂H₂Cl₂ adduct (15.33 mg, 0.019 mmol) and potassium acetate (55.3 mg, 0.563 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was diluted with EtOAc (100 mL) and washed with H₂O (50 mL). The organic layer was dried (Na₂SO₄) and filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (0-100% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain N-[5-[2-amino-1-(2-phenylethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (55 mg, 0.103
mmol, 54.7 % yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.94 (t, J=7.41 Hz, 2 H) 3.62 (s, 3 H) 4.26 (t, J=7.51 Hz, 2 H) 6.64 (br. s., 2 H) 7.08 - 7.23 (m, 4 H) 7.23 - 7.39 (m, 5 H) 7.51 - 7.61 (m, 1 H) 7.69 - 7.82 (m, 2 H) 8.14 (s, 1 H) 8.22 (s, 1 H); ES LC-MS m/z =536.5 (M+H)$^+$. 

**Example 156**

* N-[5-[2-amino-1-(3'-henylpropy0-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridin yl]-2,4-difluorobenzenesulfonamide

An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), (3-phenylpropyl)amine (1.229 g, 9.09 mmol) and K$_2$C$_7$O$_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 3 h, then was allowed to cool to room temperature. The resulting mixture was diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated to obtain 5-bromo-2-nitro-N-(3-phenylpropyl)aniline (2.5 g, 7.46 mmol, 82 % yield) as an orange oil: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.92 (quin, J=7.40 Hz, 2 H) 2.68 (t, J=7.62 Hz, 2 H) 3.33 - 3.41 (m, 2 H) 6.78 - 6.84 (m, 1 H) 7.14 - 7.26 (m, 4 H) 7.26 - 7.32 (m, 2 H) 7.97 (d, J=9.18 Hz, 1 H) 8.20 (t, J=5.57 Hz, 1 H); ES LC-MS m/z =335.2 (Br$^{79}$, M+H)$^+$; ES LC-MS m/z =337.2 (Br$^{81}$, M+H)$^+$. 

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To a bright yellow solution of 5-bromo-2-nitro-N-(3-phenylpropyl)aniline (2.5 g, 7.46 mmol) in EtOH (100 mL) was added a solution of sodium dithionate (12.30 g, 59.7 mmol) in H2O (80 mL). The reaction mixture was stirred at room temperature overnight. The resulting pale yellow slurry was filtered. The filtrate was concentrated to about 100 mL and diluted with EtOAc (100 mL). The organic layer was filtered through a pad of silica gel to obtain (2-amino-5-bromophenyl)(3-phenylpropyl)amine (1.97 g, 6.45 mmol, 87 % yield) as a brown oil: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.88 (quin, 2 H) 2.70 (t, J=7.66 Hz, 2 H) 2.92 - 3.04 (m, 2 H) 4.63 - 4.76 (m, 3 H) 6.38 (d, J=2.05 Hz, 1 H) 6.42 - 6.47 (m, 1 H) 6.48 - 6.53 (m, 1 H) 7.11 - 7.37 (m, 5 H); ES LC-MS m/z =305.3 (Br79, M+H)+; ES LC-MS m/z =307.3 (Br81, M+H)+.

A solution of (2-amino-5-bromophenyl)(3-phenylpropyl)amine (1.97 g, 6.45 mmol) in MeOH (10 mL) was treated with cyanogen bromine (1.367 g, 12.91 mmol). The reaction mixture was stirred at room temperature for 1 h. The resulting mixture was partitioned between EtOAc (50 mL) and a sat. NaHCO3 solution (50 mL). The organic layer was washed with a sat. NaCl solution (50 mL) and concentrated. The residue was triturated using CH2Cl2 to obtain 6-bromo-1-(3-phenylpropyl)-1H-benzimidazol-2-amine (1.47 g, 4.45 mmol, 69.0 % yield) as a beige solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 1.90 (quin, 2 H) 2.57 - 2.65 (m, 2 H) 4.01 (t,
J=7.37 Hz, 2 H) 6.59 (s, 2 H) 7.03 (s, 2 H) 7.14 - 7.23 (m, 3 H) 7.24 - 7.32 (m, 3 H); ES LC-MS m/z =330.4 (Br⁻, M+H)⁺; ES LC-MS m/z =332.4 (Br⁺, M+H)⁺.

Step D

\[ N-[5-[2-amino-1-(3-phenylpropyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide \]

[00388] A degassed mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (80 mg, 0.188 mmol), 6-bromo-1-(3-phenylpropyl)-1H-benzimidazol-2-amine (62.0 mg, 0.188 mmol), Pd(dppf)₂Cl₂C₂H₂Cl₂ adduct (15.33 mg, 0.019 mmol) and potassium acetate (55.3 mg, 0.563 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was diluted with EtOAc (50 mL) and washed with H₂O (25 mL). The organic layer was dried (Na₂SO₄) and filtered. The filtrate was then concentrated. The residue was dissolved in DMF and purified by HPLC (0-100% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain N-[5-[2-amino-1-(3-phenylpropyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (80 mg, 0.146 mmol, 78 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.97 (m, \( J=7.90 \) Hz, 2 H) 2.59 - 2.70 (m, 2 H) 3.61 (s, 3 H) 4.08 (t, \( J=7.02 \) Hz, 2 H) 6.68 (br. s., 2 H) 7.13 - 7.35 (m, 9 H) 7.56 (t, \( J=9.61 \) Hz, 1 H) 7.68 - 7.78 (m, 1 H) 7.80 (s, 1 H) 8.14 (d, \( J=0.98 \) Hz, 1 H) 8.26 (s, 1 H); ES LC-MS m/z =550.5 (M+H)⁺.

Example 157

\[ N-(5-(2-amino-1-(2,3-dihydro-1H-inden-1-yl)-1H-benzo[d]imidazol-6-yl)-2-methyloxy-pyridin-3-yl)-2,4-difluorobenzenesulfonamide formic acid salt \]
Step A

(5-bromo-2-nitrophenyl)2,3-dihydro-1H-inden-1-ylamine

A mixture of 4-bromo-2-fluoro-1-nitrobenzene (1.35 g, 6.14 mmol), 2,3-dihydro-1H-inden-1-amine (0.817 g, 6.14 mmol), and K$_2$CO$_3$ (1.696 g, 12.27 mmol) in DMF (10 mL) was maintained at room temperature for 5 days. The resulting mixture was diluted with EtOAc (100 mL) and washed with a 5% aq. LiCl solution (3x100 mL). The organic layer was concentrated to obtain (5-bromo-2-nitrophenyl)2,3-dihydro-1H-inden-1-ylamine (1.97 g, 5.91 mmol, 96% yield) as a yellow solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.86 - 1.99 (m, 1 H) 2.61 - 2.72 (m, 1 H) 2.83 - 2.95 (m, 1 H) 2.96 - 3.05 (m, 1 H) 5.40 (q, J=7.22 Hz, 1 H) 6.84 - 6.97 (m, 1 H) 7.20 - 7.40 (m, 4 H) 7.54 (d, J=1.85 Hz, 1 H) 7.98 - 8.07 (m, 1 H) 8.20 (d, J=7.61 Hz, 1 H); ES LC-MS m/z = 333.3 (Br$^{79}$, M+H)$^+$; ES LC-MS m/z = 335.2 (Br$^{81}$, M+H).

Step B

(2-amino-5-bromophenyl)methylamine

To a bright yellow solution of (5-bromo-2-nitrophenyl)2,3-dihydro-1H-inden-1-ylamine (1.97 g, 5.91 mmol) in EtOH (50 mL) and THF (50 mL) was added a solution of sodium dithionate (9.75 g, 47.3 mmol) in H$_2$O (40 mL). The reaction mixture was stirred at room temperature overnight. The resulting pale yellow slurry was filtered. The filtrate was partitioned between EtOAc (50 mL) and water (25 mL). The organic layer was washed with a sat. NaCl solution (25 mL) and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and purified by column chromatography (silica gel, 0-100% EtOAc/hexane) to obtain (2-amino-5-bromophenyl)2,3-
dihydro-1 H-inden-1 -ylamine (1.08 g, 3.56 mmol, 60.2 % yield) as a thick yellow oil: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.69 - 1.86 (m, 1 H) 2.51 - 2.57 (m, 1 H) 2.76 - 2.90 (m, 1 H) 2.90 - 3.02 (m, 1 H) 4.76 (s, 2 H) 4.88 - 5.00 (m, 2 H) 6.44 - 6.51 (m, 1 H) 6.51 - 6.60 (m, 1 H) 6.75 (d, J=2.05 Hz, 1 H) 7.11 - 7.36 (m, 4 H); ES LC-MS m/z =303.3 (Br²⁺, M+H)⁺; ES LC-MS m/z =305.3 (Br³⁺, M+H)⁺.

Step C
6-bromo-1-(2,3-dihydro-1H-inden-1-yl)-1H-benzo[d]imidazol-2-amine

A solution of 5-bromo-N1 -(2,3-dihydro-1 H-inden-1 -yl)benzene-1 ,2-diamine (1.08 g, 3.56 mmol) in MeOH (10 mL) was treated with cyanogen bromine (0.755 g, 7.12 mmol). The reaction mixture was maintained at room temperature for 3 h, and then partitioned between EtOAc (100 mL) and a sat. NaHCO₃ solution (100 mL). The organic layer was washed with a sat. NaCl solution (50 mL) and concentrated. The residue was triturated using CH₂Cl₂ to obtain 6-bromo-1 -(2,3-dihydro-1 H-inden-1 -yl)-1 H-benzo[d]imidazol-2-amine (738 mg, 2.249 mmol, 63.1 % yield) as a beige solid: ¹H NMR (400 MHz, DMSO-cf) δ ppm 3.85 (s, 3 H) 6.58 (s, 2 H) 6.84 (s, 1 H) 7.08 - 7.21 (m, 4 H) 7.35 - 7.45 (m, 2 H); ES LC-MS m/z =328.0 (Br²⁺, M+H)⁺; ES LC-MS m/z =330.1 (Br³⁺, M+H)⁺.

Step D
N-(5-(2-amino-1-(2,3-dihydro-1H-inden-1-yl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide formic acid salt

A degassed mixture of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (70 mg, 0.164 mmol), 6-bromo-1 -(2,3-dihydro-1 H-inden-1 -yl)-1 H-benzo[d]imidazol-2-amine (53.9 mg, 0.164 mmol), Pd(dppf)₂Cl₂
CH$_2$Cl$_2$ adduct (13.41 mg, 0.016 mmol) and potassium acetate (48.4 mg, 0.493 mmol) in 1,4-dioxane (2 ml.) and water (0.5 mL) was heated at 90 ºC for 3 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (50 mL) and washed with H$_2$O (50 mL). The organic layer was dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-70% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain N-(5-(2-amino-1-(2,3-dihydro-1H-inden-1-yl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide formic acid salt (33 mg, 0.059 mmol, 36.0 % yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.21 - 2.35 (m, 1 H) 2.58 - 2.70 (m, 1 H) 3.04 (s, 1 H) 3.16 - 3.27 (m, 1 H) 3.59 (s, 3 H) 6.09 (s, 1 H) 6.13 - 6.27 (m, 1 H) 6.68 (br. s., 2 H) 6.97 (d, J=7.52 Hz, 1 H) 7.01 - 7.10 (m, 1 H) 7.13 - 7.24 (m, 3 H) 7.34 (t, J=7.38 Hz, 1 H) 7.44 (d, J=7.62 Hz, 3 H) 7.50 - 7.59 (m, 1 H) 7.67 (td, J=8.50, 6.45 Hz, 1 H) 7.72 - 7.82 (m, 1 H) 8.14 (s, 1H); ES LC-MS m/z =548.4 (M+H)$^+$. 

**Example 158**

N-(5-(2-amino-1-(4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide formic acid salt

![Chemical Structure](image)

**Step A**

5-bromo-2-nitro-N-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)aniline

![Chemical Structure](image)

[00393] An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (1.134 g, 5.16 mmol), (4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methanamine (0.95 g, 5.16 mmol) and K$_2$CO$_3$ (1.425 g, 10.53 mmol) was...
10.31 mmol) in DMF (20 mL) was heated at 90 °C for 2 h. The resulting mixture was allowed to cool to room temperature, diluted with EtOAc (50 mL) and washed with a 5% aq. LiCl solution (3x50 mL). The organic layer was concentrated to obtain 5-bromo-2-nitro-N-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)aniline (1.94 g, 5.05 mmol, 98% yield) as a yellow solid. 

**Step B**

**5-bromo-N1-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)benzene-1,2-diamine**

[00394] To a bright orange solution of 5-bromo-2-nitro-N-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)aniline (1.94 g, 5.05 mmol) in EtOH (30 mL) and THF (30 mL) was added a solution of sodium dithionate (8.32 g, 40.4 mmol) in H2O (40 mL). After 5 min the pale yellow slurry was filtered. The filtrate was partitioned between EtOAc (100 mL) and water (50 mL). The organic layer was washed with a sat. NaCl solution (50 mL) and concentrated. The aqueous layers was neutralized with K2CO3 and extracted with EtOAc. Combined the two batches and concentrated to obtain 5-bromo-N1-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)benzene-1,2-diamine (1.47 g, 4.15 mmol, 82% yield) as a white solid: ES LC-MS m/z =354.3 (Br79, M+H)+; ES LC-MS m/z =356.3 (Br81, M+H)+.

**Step C**

**6-bromo-1-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-2-amine:**
A solution of 5-bromo-N1-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)benzene-1,2-diamine (1.47 g, 4.15 mmol) in MeOH (10 mL) was treated with cyanogen bromine (0.879 g, 8.30 mmol). The reaction mixture was maintained at room temperature for 2 h, and then treated with a sat. NaHCO₃ solution. The resulting slurry was filtered, solid washed with water to obtain crude 6-bromo-1-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-2-amine: ES LC-MS m/z = 379.4 (Br⁺, M+H)⁺; ES LC-MS m/z = 381.3 (Br⁺, M+H)⁺.

Step D

N-(5-(2-amino-1-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy pyridin-3-yl)-2,4-difluorobenzenesulfonamide formic acid salt

A degassed mixture of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (75 mg, 0.176 mmol), 6-bromo-1-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-2-amine (70.1 mg, 0.185 mmol), Pd(dppf)₂Cl₂CH₂Cl₂ adduct (14.37 mg, 0.018 mmol) and potassium acetate (51.8 mg, 0.528 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The resulting mixture was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain N-(5-(2-amino-1-((4-(pyrrolidin-1-yl)tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy pyridin-3-yl)-2,4-difluorobenzenesulfonamide formic acid salt (53 mg, 0.082 mmol, 46.7% yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.40 (br. s., 2 H) 1.75 (br. s., 6 H) 2.86 (br. s., 4 H) 3.46 - 3.62 (m, 4 H) 3.63 (s, 3 H) 4.18 (br. s., 2 H) 7.21 (td, J=8.54, 2.24 Hz, 1 H) 7.29 (s, 2 H) 7.39 - 7.85 (m, 5 H) 7.87 (d, J=2.24 Hz, 1 H) 8.13 (s, 1 H) 8.31 (d, J=2.24 Hz, 1 H) 9.89 - 10.82 (m, 1 H); ES LC-MS m/z = 599.2 (M+H)⁺.
General Scheme 5

\[ \text{Compound A} \xrightarrow{\text{NaOH, CH}_3\text{CN, H}_2\text{O}} \text{Compound B} \xrightarrow{\text{NIS, AcOH}} \]

\[ \text{Compound C} \xrightarrow{\text{Pd(dppe)Cl}_2, \text{KOAc}, 1,4\text{-dioxane, H}_2\text{O}}} \text{Compound D} \]
Example 159

\[ N-(5\text{-}(2\text{-amino-1-}(\text{morpholinosulfonyl})\text{-}1\text{H-benzo}[d]\text{imidazol-6-yl})\text{-}2\text{-methoxy}pyridin-3-yl)\text{-}2,4\text{-difluorobenzenesulfonamide} \]

Step A

\[ 1\text{-}(\text{morpholinosulfonyl})\text{-}1\text{H-benzo}[d]\text{imidazol-2-amine} \]
A solution of 1H-benzo[d]imidazol-2-amine (0.36 g, 2.70 mmol) in CH₃CN (10 mL) and water (1 mL) was treated with sodium hydroxide (0.238 g, 5.95 mmol). After everything dissolved morpholine-4-sulfonyl chloride (0.502 g, 2.70 mmol) was added and the mixture was stirred at room temperature overnight. The resulting slurry was filtered, solid washed with CH₃CN to obtain 1-(morpholinosulfonyl)-1H-benzo[d]imidazol-2-amine (557 mg, 1.973 mmol, 73.0 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.20 - 3.29 (m, 4 H) 3.49 - 3.58 (m, 4 H) 6.91 (s, 2 H) 6.97 - 7.05 (m, 1 H) 7.11 - 7.19 (m, 1 H) 7.19 - 7.27 (m, 1 H) 7.52 (d, J=8.00 Hz, 1 H); ES LC-MS m/z =283.07 (M+H)+.

Step B
6-iodo-1-(morpholinosulfonyl)-1H-benzo[d]imidazol-2-amine

A mixture of 1-(morpholinosulfonyl)-1H-benzo[d]imidazol-2-amine (550 mg, 1.948 mmol) and NIS (482 mg, 2.143 mmol) in AcOH (15 mL) was heated at 50 °C for 3 h. The reaction mixture was poured into water. The resulting slurry was filtered, solid washed with water to obtain 6-iodo-1-(morpholinosulfonyl)-1H-benzo[d]imidazol-2-amine (710 mg, 1.739 mmol, 89 % yield) as a light brown solid: ¹H NMR (400 MHz, DMSO-cie) δ ppm 3.23 - 3.31 (m, 4 H) 3.54 - 3.61 (m, 4 H) 7.07 (d, J=8.29 Hz, 1 H) 7.14 (br. s., 2 H) 7.47 (dd, J=8.29, 1.56 Hz, 1 H) 7.75 (d, J=1.56 Hz, 1 H); ES LC-MS m/z =409.2 (M+H)+.

Step C
N-(5-(2-amino-1-(morpholinosulfonyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

A degassed mixture of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (79 mg, 0.185 mmol), 6-iodo-1-
(morpholinosulfonyl)-1H-benzo[d]imidazol-2-amine (79 mg, 0.195 mmol), Pd(dppf)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (15.14 mg, 0.019 mmol) and potassium acetate (18.19 mg, 0.185 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The resulting mixture was diluted with H$_2$O (50 mL) and extracted with EtOAc (50 mL) and CH$_2$Cl$_2$ (50 mL). The organic layers were filtered through paper. The filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-60% CH$_3$CN/H$_2$O, both containing 0.1% formic acid) to obtain N-(5-(2-amino-1-(morpholinosulfonyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (21 mg, 0.035 mmol, 19.13 % yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 3.26 - 3.31 (m, 4 H) 3.57 (br. s., 4 H) 3.66 (s, 3 H) 7.04 (br. s., 2 H) 7.16 - 7.25 (m, 1 H) 7.28 - 7.35 (m, 1 H) 7.35 - 7.42 (m, 1 H) 7.62 (s, 2 H) 7.71 - 7.81 (m, 2 H) 8.25 (br. s., 1 H) 10.29 (s, 1 H); ES LC-MS m/z = 581.1 (M+H)$^+$. 

**General Scheme 6**
Example 160

N-(6-(5-(2,4-difluorophenylsulfonamido)-6-methoxypyridin-3-yl)-1H-benzo[d]imidazol-2-yl)acetamide

[00400] A deep brown solution of 4-bromo-1,2-benzenediamine (4 g, 21.39 mmol) in MeOH (20 mL) was treated with cyanic bromide (2.492 g, 23.52 mmol). The reaction was exothermic, and the methanol began to boil after a few seconds. After 5 minutes the reaction
mixture was diluted with EtOAc (100 mL), washed with a sat. NaHCO$_3$ solution (100 mL) and a sat. NaCl solution (100 mL). The organic layer was concentrated to a few mL, loaded onto silica cartridge and purified by column chromatography (0-20% MeOH/EtOAc) to obtain 5-bromo-1H-benzimidazol-2-amine (3.9 g, 18.39 mmol, 86 % yield) as a black solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 6.47 (br. s., 2 H) 6.94 - 7.00 (m, 1 H) 7.01 - 7.06 (m, 1 H) 7.23 (d, J=1.85 Hz, 1 H) 8.70 - 11.33 (m, 1 H); ES LC-MS m/z =212.2 (Br$^{79}$, M+H)$^+$, ES LC-MS m/z =214.2 (Br$^{81}$, M+H).

Step B

$N$-(5-bromo-1H-benzimidazol-2-yl)acetamide

A mixture of 5-bromo-1 H-benzimidazol-2-amine (1 g, 4.72 mmol) and Ac$_2$O (8.90 mL, 94 mmol) was stirred at room temperature overnight. The resulting mixture was diluted with water (50 mL) and stirred for 2 h. The resulting slurry was filtered, solid washed with water and hexane to obtain $N$-(5-bromo-1 H-benzimidazol-2-yl)acetamide (970 mg, 3.82 mmol, 81 % yield) as a light brown solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.13 (s, 3 H) 7.21 (d, J=8.49 Hz, 1 H) 7.29 - 7.48 (m, 1 H) 7.59 (d, J=19.90 Hz, 1 H) 11.61 (s, 1 H) 12.15 (d, J=16.88 Hz, 1 H); ES LC-MS m/z =254.2 (Br$^{79}$, M+H)$^+$, ES LC-MS m/z =256.2 (Br$^{81}$, M+H).

Step C

$N$-(6-(5-(2,4-difluorophenyl)sulfonamido)-6-methoxypyridin-3-yl)-1H-benzo[d]imidazol-2-yl)acetamide

A degassed mixture of 2,4-difluoro-$N$-(2-methoxy-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (80 mg, 0.188 mmol), $N$-(6-bromo-1 H-benzo[d]imidazol-2-yl)acetamide (47.7 mg, 0.188 mmol), Pd(dpff)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (15.33 mg, 0.019 mmol) and potassium acetate (55.3 mg, 0.563 mmol) in 1,4-dioxane (2 mL) and water (.5
mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature then diluted with EtOAc (50 mL) and H₂O (50 mL). The organic layer was dried (Na₂SO₄) and filtered, and then the filtrate was concentrated. The residue was dissolved in DMF and purified by HPLC (10-70% CH₃CN/H₂O, both containing 0.1% formic acid) to obtain N-(6-(5-(2,4-difluorophenylsulfonamido)-6-methoxypyridin-3-yl)-1H-benzo[d]imidazol-2-yl)acetamide (17 mg, 0.034 mmol, 18.37 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-cf) δ ppm 2.17 (s, 3 H) 3.66 (s, 3 H) 7.19 (t, J=7.95 Hz, 1 H) 7.23 - 7.38 (m, 1 H) 7.38 - 7.88 (m, 6 H) 8.14 (s, 1 H) 11.58 (br. s., 1 H) 12.08 (br. s., 1 H); ES LC-MS m/z =474.3 (M+H)+.

**General Scheme 7**
Example 16.1

*N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxy pyridin-3-*
**Step A**

2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine

---

[00403] A degassed mixture of 5-bromo-2-methoxypyridin-3-amine (2 g, 9.85 mmol), 4,4',4',5,5,5,5'-octamethyl-2,2'-bi-3,2-dioxaborolane (3.0 g, 11.82 mmol), Pd(dppf)Cl₂ adduct (0.804 g, 0.985 mmol) and potassium acetate (3.87 g, 39.4 mmol) in 1,4-dioxane (50 mL) was heated at 100 °C for 18 h, then stirred at room temperature over the weekend. The resulting mixture was filtered through pad of Celite® with the aid of EtOAc. The filtrate was concentrated and reevaporated from CH₂Cl₂/hexane. The residue was dissolved in CH₂Cl₂ and purified by column chromatography (silica gel, 0-100% EtOAc/hexane) to obtain 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine (3.9 g, 9.36 mmol, 95 % yield) as a light brown solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.26 (s, 12 H) 3.87 (s, 3 H) 4.92 (s, 2 H) 7.12 (d, J=1.46 Hz, 1 H) 7.63 (d, J=1.37 Hz, 1 H); ES LC-MS m/z =251 .4 (M+H)⁺.

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**Step B**

6-(5-amino-6-methoxypyridin-3-yl)-1-(4-morpholinophenyl)-1H-benzimidazo[2-amine

---
A degassed mixture of 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (300 mg, 0.723 mmol), 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (270 mg, 0.723 mmol), Pd(dppf)₂Cl₂CH₂Cl₂ adduct (59.0 mg, 0.072 mmol) and potassium acetate (213 mg, 2.168 mmol) in 1,4-dioxane (16 mL) and water (4 mL) was heated in a microwave apparatus at 130 °C for 15 min. The resulting mixture was diluted with H₂O (100 mL) and extracted with EtOAc (100 mL) and CH₂Cl₂ (100 mL). The organic layers were filtered through paper, and then the filtrate was concentrated. The residue was triturated using EtOAc to obtain 6-(5-amino-6-methoxy-3-pyridyl)-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (85 mg, 0.163 mmol, 22.60 % yield) as a dark grey solid. The insoluble solids from the extraction were dissolved in a mixture of MeOH and CH₂Cl₂ and combined with the filtrate from the trituration. The mixture was concentrated onto Celite® and purified by column chromatography (0-40% MeOH/ CH₂Cl₂) to obtain an additional 6-(5-amino-6-methoxypyridin-3-yl)-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (95 mg, 0.167 mmol, 23.05 % yield): ES LC-MS m/z =417.3 (M+H)⁺.

Step C

N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide formic acid salt
A solution of cyclopropanesulfonyl chloride (27.0 mg, 0.192 mmol) and 6-(5-amino-6-methoxypyridin-3-yl)-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (50 mg, 0.120 mmol) in pyridine (1 mL) was maintained at room temperature. After 19 h more cyclopropanesulfonyl chloride (20 mg, 0.144 mmol) was added. After 6 h the reaction mixture was treated with MeOH (1 mL) and concentrated. The residue was dissolved in DMF and purified by HPLC (10-90% CH3CN/H2O, both containing 0.1% formic acid) to obtain N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide formic acid salt (11 mg, 0.019 mmol, 15.69 % yield) as a white solid:

\[ ^1\text{H NMR} (400 \text{ MHz}, \text{DMSO-}d_6) \delta \text{ ppm} 0.82 - 0.95 \text{ (m, 4 H)} 2.62 - 2.73 \text{ (m, 1 H)} 3.16 - 3.26 \text{ (m, 4 H)} 3.71 - 3.82 \text{ (m, 4 H)} 3.88 - 3.95 \text{ (m, 3 H)} 6.28 \text{ (br. s., 2 H)} 6.91 \text{ (d, J}=1.07 \text{ Hz, 1 H}) 7.15 \text{ (d, J}=8.88 \text{ Hz, 2 H}) 7.21 - 7.30 \text{ (m, 2 H)} 7.35 \text{ (d, J}=8.88 \text{ Hz, 2 H}) 7.72 \text{ (d, J}=2.2A \text{ Hz, 1 H}) 8.15 \text{ (s, 1 H)} 8.17 \text{ (d, J}=2.34 \text{ Hz, 1 H}) 9.30 \text{ (br. s., 1 H)}; \text{ES LC-MS } m/z =521.4 \text{ (M+H)}.\]

**Example 162**

\[ \text{N-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzipimidazol-6-yl}-2-(methyloxy)-3-pyridyl]-2,4-difluorobenzenesulfonamide} \]

**Step A**

(5-bromo-2-nitrophenyl)[4-(4-morpholinyl)phenyl]amine
A solution of 4-bromo-2-fluoro-1-nitrobenzene (2.66 g, 12.09 mmol), [4-(4-morpholinyl)phenyl]amine (2.155 g, 12.09 mmol), and potassium carbonate (3.34 g, 24.18 mmol) in N,N-dimethylformamide (30 mL) was maintained at 90°C for 3 hours. The mixture was diluted with ethyl acetate and washed three times with 5% LiCl (aq). The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and then purified by column chromatography to afford (5-bromo-2-nitrophenyl)[4-(4-morpholinyl)phenyl]amine (3.45 g, 9.12 mmol, 75% yield) as a bright orange solid. LCMS (m/z, ES+) = 379 (M+H).

Step B

(2-amino-5-bromophenyl)[4-(4-morpholinyl)phenyl]amine

A solution of (5-bromo-2-nitrophenyl)[4-(4-morpholinyl)phenyl]amine (2060 mg, 5.45 mmol) in tetrahydrofuran (100 mL) was maintained with stirring at room temperature while sodium dithionite (9477 mg, 54.5 mmol) in water (100 mL) was added dropwise by addition funnel over 25 minutes. The mixture was maintained with vigorous stirring for 3 hours, poured into ethyl acetate, and then diluted with water. The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford (2-amino-5-bromophenyl)[4-(4-morpholinyl)phenyl]amine (987 mg, 2.83 mmol, 52.0% yield) as a yellow solid. LCMS (m/z, ES+) = 348 (M+H).

Step C

6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine
A solution of cyanogen bromide (400 mg, 3.77 mmol) in acetonitrile (2 mL) and water (12 mL) was treated with (2-amino-5-bromophenyl)[4-(4-morpholinyl)phenyl]amine (750 mg, 2.154 mmol) as a solution in methanol/acetonitrile (12 mL). Stirring was continued for 2 hours and then the mixture was poured into ethyl acetate and diluted with saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and then triturated with DCM to afford 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (365 mg, 0.978 mmol, 45.4 % yield) as a white solid. The filtrates were collected, concentrated onto Celite®, and purified by column chromatography to afford additional 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (155 mg, 0.415 mmol, 19.28 % yield) as a white foam. LCMS (m/z, ES+) = 374 (M+H)

**Step D**

\[ \text{N-[5-\{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl\}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide} \]

A solution of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (125 mg, 0.335 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (178 mg, 0.419 mmol), potassium carbonate (139 mg, 1.005 mmol), and PdCl₂(dppf)-CH₂Cl₂ adduct (27.3 mg, 0.033 mmol) in 1,4-dioxane (8 mL)/water (8.00 mL) was maintained at 80°C for 3 hours. The solution was poured into ethyl acetate and washed with water. The suspended solids were filtered, dissolved in DMF, and purified by reverse phase hplc to afford N-[5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-2-difluorobenzenesulfonamide].
(methyloxy)-3-pyridinyl]-2,4-difluorobenzensulfonamide (18 mg, 0.030 mmol, 9.07 % yield) as a white solid. $^1$H NMR (DMSO-d$_6$) $\delta$: 10.26 (br. s., 1H), 8.10 - 8.18 (m, 1H), 7.71 (td, J = 8.5, 6.4 Hz, 1H), 7.65 (d, J = 2.3 Hz, 1H), 7.47 - 7.57 (m, 1H), 7.36 (d, J = 9.0 Hz, 2H), 7.09 - 7.30 (m, 5H), 6.84 - 6.89 (m, 1H), 6.32 (br. s., 2H), 3.72 - 3.83 (m, 4H), 3.61 (s, 3H), 3.14 - 3.27 (m, 4H).

LCMS (m/z, ES+) = 593 (M+H).

**Example 163**

N-[5-{2-amino-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzensulfonamide

\[
\begin{align*}
\text{Step A} \\
(5\text{-bromo-2-nitrophenyl})(3\text{-(4-morpholinyl)propyl})\text{amine}
\end{align*}
\]

[00410] A solution of 4-bromo-2-fluoro-1-nitrobenzene (4.00 g, 18.18 mmol) and [3-(4-morpholinyl)propyl]amine (3.00 mL, 20.00 mmol) in N,N-dimethylformamide (60 mL) was treated with [3-(4-morpholinyl)propyl]amine (3.00 mL, 20.00 mmol) and maintained with stirring at room temperature for 5 hours. The mixture was poured into water, stirred for 45 minutes, and solids were collected by vacuum filtration to afford (5-bromo-2-nitrophenyl)[3-(4-morpholinyl)propyl]amine (5.63 g, 16.36 mmol, 90 % yield) as a yellow-orange solid. $^1$H NMR (DMSO-de) $\delta$: 8.46 (t, J = 5.4 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.28 (d, J = 1.8 Hz, 1H), 6.81 (dd, J = 9.2, 2.0 Hz, 1H), 3.61 (t, J = 4.6 Hz, 4H), 3.40 (q, J = 6.4 Hz, 2H), 2.23 - 2.42 (m, 6H), 1.76 (quin, J = 6.4 Hz, 2H).
Step B
(2-amino-5-bromophenyl)[3-(4-morpholinyl)propyl]amine

[00411] A solution of (5-bromo-2-nitrophenyl)[3-(4-morpholinyl)propyl]amine (5.31 g, 15.43 mmol) in tetrahydrofuran (100 mL) was treated dropwise with a solution of sodium dithionite (21.47 g, 123 mmol) in water (100 mL). The mixture was maintained with vigorous stirring for 8 hours, diluted with ethyl acetate, and washed with water. The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by column chromatography to afford (2-amino-5-bromophenyl)[3-(4-morpholinyl)propyl]amine (2.05 g, 6.52 mmol, 42.3 % yield) as a white solid. ¹H NMR (DMSO-d₆) δ: 6.39 - 6.55 (m, 3H), 4.79 (br. s., 1H), 4.64 (br. s., 2H), 4.10 (d, J = 5.1 Hz, 2H), 3.59 (t, J = 4.6 Hz, 4H), 3.03 (br. s., 2H), 2.36 (d, J = 6.8 Hz, 4H), 1.72 (quin, J = 6.8 Hz, 2H).

Step C
6-bromo-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-2-amine

[00412] A solution of cyanogen bromide (0.911 g, 8.59 mmol) in acetonitrile (2.5 mL) and water (15 mL) was treated with (2-amino-5-bromophenyl)[3-(4-morpholinyl)propyl]amine (2 g, 6.36 mmol) as a solution in methanol (15 mL). Stirring was continued for 2 hours and then the mixture was poured into ethyl acetate and diluted with saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, filtered, and taken to a residue under reduced pressure. The solids were triturated with dichloromethane and removed via filtration. Purification of the filtrates by column chromatography afforded 6-bromo-1-[3-(4-
morpholinyl)propyl]-1H-benzimidazol-2-amine (350 mg, 1.032 mmol, 16.21 % yield) as a white foam. LCMS (m/z, ES+) = 340 (M+H).

**Step D**

N-[5-[2-amino-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

[00413] A solution of 6-bromo-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-2-amine (150 mg, 0.442 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (236 mg, 0.553 mmol), potassium carbonate (183 mg, 1.327 mmol), and PdCl₂(dpff)-CH₂Cl₂ adduct (36.1 mg, 0.044 mmol) in 1,4-dioxane (8 ml)/water (8.00 mL) was maintained with stirring at 80°C for 2 hours. The mixture was cooled, and then poured into ethyl acetate/water. The aqueous layer containing suspended solids was washed with ethyl acetate, THF/EtOAc, methylene chloride (X2) and chloroform/iPrOH (X2). All combined organic layers were concentrated and the resulting solids were triturated/sonicated with dichloromethane and collected via vacuum filtration affording analytically pure N-[5-[2-amino-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (55 mg, 0.098 mmol, 22.27 % yield) as a white solid. ¹H NMR (DMSO-de) δ: 10.32 (br. s., 1H), 8.24 (s, 1H), 7.68 - 7.84 (m, 2H), 7.48 - 7.63 (m, 1H), 7.39 (s, 1H), 7.10 - 7.27 (m, 3H), 6.67 (br. s., 2H), 4.06 (t, J = 6.2 Hz, 2H), 3.62 (s, 3H), 3.49 - 3.59 (m, 4H), 2.32 (br. s., 4H), 2.24 (t, J = 6.5 Hz, 2H), 1.75 - 1.93 (m, 2H). LCMS (m/z, ES+) = 559 (M+H).

**Example 164**

N-[5-(2-amino-1-[4-(4-morpholinyl)phenyl]methyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

294
Step A

(5-bromo-2-nitrophenyl){{4-(4-morpholinyl)phenyl}methyl}amine

A solution of 4-bromo-2-fluoro-1-nitrobenzene (3.43 g, 15.60 mmol) and {{4-(4-morpholinyl)phenyl}methyl}amine (3 g, 15.60 mmol) in N,N-dimethylformamide (35 mL) was treated with DIPEA (8.18 mL, 46.8 mmol) and maintained with stirring at room temperature for 6 hours. The solution was poured into water, stirred for 45 minutes, and solids collected via vacuum filtration to afford (5-bromo-2-nitrophenyl){{4-(4-morpholinyl)phenyl}methyl}amine (5.49 g, 14.00 mmol, 90 % yield) as an orange solid. LCMS (m/z, ES+) = 393 (M+H).

Step B

(2-amino-5-bromophenyl){{4-(4-morpholinyl)phenyl}methyl}amine

A solution of (5-bromo-2-nitrophenyl){{4-(4-morpholinyl)phenyl}methyl}amine (4.9 g, 12.49 mmol) in tetrahydrofuran (150 mL) was treated with sodium dithionite (17.39 g, 100 mmol) in water (150 mL) dropwise and maintained with stirring for 8 hours. Additional sodium
dithionite (17.39 g, 100 mmol) was added in water (150 mL) and the mixture was rapidly stirred overnight. The solution was then poured into ethyl acetate and washed with water. The organic layer were separated, dried over sodium sulfate, filtered, and then taken to a residue under reduced pressure, and the solids triturated with diethyl ether/hexanes to afford (2-amino-5-bromophenyl)[4-(4-morpholinyl)phenyl]methyl]amine (2.57 g, 7.09 mmol, 56.8 % yield) as a white solid. 

$^1$H NMR (DMSO-$d_6$) $\delta$: 7.1 - 7.30 (m, $J = 8.6$ Hz, 2H), 6.83 - 6.94 (m, $J = 8.6$ Hz, 2H), 6.42 - 6.52 (m, 2H), 6.39 (d, $J = 2.0$ Hz, 1H), 5.27 (t, $J = 5.7$ Hz, 1H), 4.73 (s, 2H), 4.17 (d, $J = 5.5$ Hz, 2H), 3.61 - 3.80 (m, 4H), 2.88 - 3.16 (m, 4H).

Step C

6-bromo-1-[4-(4-morpholinyl)phenyl]methyl]-1H-benzimidazol-2-amine

A solution of cyanogen bromide (43.9 mg, 0.414 mmol) in acetonitrile (3 mL), water (2 mL) and methanol (2 mL) was treated with solid (2-amino-5-bromophenyl)[4-(4-morpholinyl)phenyl]methyl]amine (100 mg, 0.276 mmol) in one portion and a homogenous suspension appeared to form with rapid stirring. Stirring was continued for 16 hours and then the mixture was poured into ethyl acetate and diluted with saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, filtered, and then taken to a residue under reduced pressure, and then purified by column chromatography to afford 6-bromo-1-[4-(4-morpholinyl)phenyl]methyl]-1H-benzimidazol-2-amine (33 mg, 0.085 mmol, 30.9 % yield) as a white solid. LCMS (m/z, ES$^+$) = 388 (M+H).

Step D

$N$-[5-(2-amino-1-[4-(4-morpholinyl)phenyl]methyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide
A solution of 6-bromo-1-[(4-(4-morpholinyl)phenyl)methyl]-1H-benzimidazol-2-amine (40 mg, 0.103 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (57.2 mg, 0.134 mmol), potassium carbonate (42.8 mg, 0.310 mmol), and PdCl₂(dpdpf)-CH₂Cl₂ adduct (8.43 mg, 10.33 µmol) in N,N-dimethylformamide (1 mL)/water (0.250 mL) was maintained with stirring at 90°C for 1 hour. The mixture was cooled, filtered, and injected directly onto a reverse phase hplc to afford N-[5-(2-amino-1-[(4-(4-morpholinyl)phenyl)methyl]-1H-benzimidazol-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (18 mg, 0.030 mmol, 28.7% yield) as a white solid following lyophilization. \(^1\)H NMR (DMSO-d₆) δ: 8.14 (s, 1H), 8.18 (s, 1H), 7.66 - 7.80 (m, 2H), 7.50 - 7.59 (m, 1H), 7.34 (s, 1H), 7.10 - 7.21 (m, 5H), 6.88 (d, J = 8.8 Hz, 2H), 6.69 (br. s., 2H), 5.21 (s, 2H), 3.65 - 3.73 (m, 4H), 3.61 (s, 3H), 2.97 - 3.07 (m, 4H). LCMS (m/z, ES+) = 607 (M+H)
Example 165

$N\{5\text{-}[2\text{-amino}\text{-}1\text{-}(2\text{-hydroxyethyl})\text{-}1H\text{-benzimidazol-6-yl}]\text{-}2\text{-}(methylxyloxy)\text{-}3\text{-pyridinyl}]\text{-}2,4\text{-difluorobenzene sulfonamide}$

Step A

$2\text{-}[5\text{-bromo}-2\text{-nitrophenyl}]\text{amino]ethanol}$

A solution of $4\text{-bromo-2-fluoro}-1\text{-nitrobenzene}$ (8 g, 36.4 mmol), DIPEA (12.70 mL, 72.7 mmol), and ethanolamine (3.30 mL, 54.5 mmol) in N,N-dimethylformamide (DMF) (68 mL) was maintained with stirring at room temperature for 19 hours. The mixture was poured into water and stirred vigorously. Solids were collected by vacuum filtration to afford $2\text{-}[5\text{-bromo-2-nitrophenyl}]\text{amino]ethanol}$ as a yellow solid (10.13 g, 36.5 mmol, 100% yield). $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 8.30 (t, $J=$5.2 Hz, 1 H) 7.98 (d, $J=$9.0 Hz, 1 H) 7.30 (d, $J=$2.0 Hz, 1 H) 6.83 (dd, $J=$9.0, 2.0 Hz, 1 H) 5.01 (t, $J=$5.3 Hz, 1 H) 3.62 (q, $J=$5.5 Hz, 2 H) 3.41 (q, $J=$5.5 Hz, 2 H).

Step B

$2\text{-}[2\text{-amino}-5\text{-bromophenyl}]\text{amino]ethanol}$
A solution of 2-[(5-bromo-2-nitrophenyl)amino]ethanol (4.00 g, 15.32 mmol) in THF (100mL) was stirred at room temperature as a solution of sodium hydrosulfite (26.7 g, 153 mmol) in water (100mL) was added drop wise over 30 minutes. The solution was allowed to stir at room temperature for approximately four hours before being partitioned between EtOAc and water. The organic layer was then concentrated and the residue was dissolved in 100 mL of ethanol. The solution was stirred as a solution of sodium hydrosulfite (26.7 g, 153 mmol) in water (100mL) was added drop wise. After the addition of 70 mL of the second sodium hydrosulfite solution the reaction solution became colorless. Addition was stopped at that point. The solution was concentrated to remove EtOH and the aqueous solution was diluted with water then extracted with EtOAc. The organic layer was dried with Na2SO4, filtered and concentrated to yield 2-[(2-amino-5-bromophenyl)amino]ethanol as a brown solid (2.44 g, 70%). 1H NMR (400 MHz, DMSO-d6) δ ppm 6.49 - 6.56 (m, 1 H) 6.42 - 6.49 (m, 2 H) 4.71 (t, J=5.6 Hz, 1 H) 4.62 - 4.69 (m, 3 H) 3.58 (q, J=5.9 Hz, 2 H) 3.07 (q, J=5.9 Hz, 2 H). ES-LCMS: 231.1 (M+1).

Step C
2-(2-amino-6-bromo-1H-benzimidazol-1-yl)ethanol

A solution of 2-[(2-amino-5-bromophenyl)amino]ethanol (2.43 g, 10.52 mmol) in MeOH (~40 mL) was added to a solution of cyanogen bromide in methanol (~60 mL). The resulting brown solution was allowed to stir at room temperature for 2 hours. The solution was partitioned between EtOAc and NaHCO3 solution. The aqueous partition was extracted with EtOAc then the combined organic layers were washed with NaHCO3 solution, finally washed with brine. The organic layer was dried with Na2SO4, filtered and concentrated. The residue was slurried in DCM then filtered to yield 2-(2-amino-6-bromo-1H-benzimidazol-1-yl)ethanol as a light purple solid (2.15 g, 77%). 1H NMR (400 MHz, DMSO-d6) δ ppm 7.37 (s, 1 H) 7.04 (s, 2 H) 6.50 (s, 2 H) 4.94 (t, J=5.3 Hz, 1 H) 3.82 -4.17 (m, 2 H) 3.63 (q, J=5.3 Hz, 2 H). ES-LCMS: 256.2 (M+1).
Step D

\[ \text{N-[5-[2-amino-1-(2-hydroxyethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide} \]

[00421] A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (416 mg, 0.098 mmol) and 2-(2-amino-6-bromo-1H-benzimidazol-1-yl)ethanol (200 mg, 0.781 mmol) and potassium carbonate (324 mg, 2.34 mmol) in dioxane (6.7 mL) and water (1.7 mL) was sparged with nitrogen as \( \text{PdCl}_2(\text{dppf}) \) DCM adduct (64 mg, 0.08 mmol) was added. The reaction mixture was then heated to 90°C for one hour. The solution was then partitioned between EtOAc and brine. Next, the organic layer was concentrated. DCM was added to the residual brown oil. A dark solid formed and was removed by filtration. The filtrate was concentrated to yield a sticky brown solid. The sample was slurried in EtOAc and then filtered to yield N-[5-[2-amino-1-(2-hydroxyethyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide as an off-white solid (94 mg, 25% yield). \( ^1\text{H} \) NMR (400 MHz, DMSO-\( \text{d}_6 \)) \( \delta \) ppm 10.34 (br. s., 1 H) 8.25 (s, 1 H) 7.70 - 7.87 (m, 2 H) 7.50 - 7.62 (m, 1 H) 7.41 (s, 1 H) 7.09 - 7.28 (m, 3 H) 6.50 (br. s., 2 H) 4.97 (t, \( J=4.9 \) Hz, 1 H) 4.09 (br. s., 2 H) 3.69 (d, \( J=4.9 \) Hz, 2 H) 3.62 (s, 3 H). ES-LCMS: 476.3 (M+1).

**Example 166**

\[ \text{N-[5-[2-amino-1-(3-hydroxypropyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide} \]
To a bright yellow solution of 3-[(5-bromo-2-nitrophenyl)amino]-1-propanol in EtOH (404 mL) was added a solution of sodium hydrosulfite (37.5 g, 182 mmol) in H₂O (160 mL). The mixture was allowed to stir at room temperature overnight. The resulting pale yellow slurry was filtered, and the resulting solid was washed with EtOAc. The filtrate was concentrated to about 50 mL total volume. EtOAc (400 mL) was then added and the mixture was washed with water (50 mL) and a sat. NaCl solution (50 mL). The organic layer was next concentrated to obtain 3-[(2-amino-5-bromophenyl)amino]-1-propanol as a dark oil (7.12 g, 70% as 0.4 EtOAc).

\(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \( \delta \) ppm 6.47 - 6.54 (m, 1 H) 6.41 - 6.47 (m, 2 H) 4.67 (s, 3 H) 4.50 (t, \( J=5.2 \) Hz, 1 H) 3.44 - 3.61 (m, 2 H) 2.94 - 3.1 1 (m, 2 H) 1.73 (t, \( J=6.6 \) Hz, 2 H).

Step C

3-(2-amino-6-bromo-1H-benzimidazol-1-yl)-1-propanol
A solution of 3-[(2-amino-5-bromophenyl)amino]-1-propanol (7.1 g, 25.4 mmol) in MeOH (254 ml) was treated with cyanogen bromine (5.37 g, 50.7 mmol). The reaction mixture was maintained at room temperature for 2 h. The reaction mixture was partitioned between EtOAc (100 mL) and a sat. NaHCO₃ solution (100 ml). The organic layer was washed with a sat. NaCl solution, and then concentrated. The sample was slurried in MeCN to yield 3-(2-amino-6-bromo-1H-benzimidazol-1-yl)-1-propanol as a tan solid, (3.317 g, 48%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.35 (s, 1 H) 7.05 (s, 2 H) 6.53 (s, 2 H) 4.70 (br. s., 1 H) 4.00 (t, J=6.9 Hz, 2 H) 3.36 - 3.42 (m, 2H) 1.73 - 1.81 (m, 2 H). ES-LCMS: 270.2 (M+1).

Step D

N-[5-[2-amino-1-(3-hydroxypropyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (394 mg, 0.093 mmol) and 3-(2-amino-6-bromo-1H-benzimidazol-1-yl)-1-propanol (200 mg, 0.74 mmol) and potassium carbonate (324 mg, 2.34 mmol) in dioxane (6.7 mL) and water (1.7 mL) was sparged with nitrogen as PdCl₂(dppf) DCM adduct (60 mg, 0.08 mmol) was added. The reaction mixture was then heated to 90°C for one hour. The solution was then partitioned between EtOAc and brine. The organic layer was then concentrated. DCM was then added to the residual brown oil. A solid formed and thereafter the solution was decanted. Hexane was then added to the solution and a tan solid formed. The resulting mixture was then filtered to yield N-[5-[2-amino-1-(3-hydroxypropyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide as an off-white solid (115 mg, 32% yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.33 (br. s., 1 H) 8.25 (d, J=1.9 Hz, 1 H) 7.70 - 7.85 (m, 2 H) 7.52 -7.63 (m, 1
Example 167

**N-[5-{2-amino-1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-6-yl]-2-(methylxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide**

[00425] A mixture of 2-(2-amino-6-bromo-1H-benzimidazol-1-yl)ethanol (256 mg, 1 mmol) in thionyl chloride (1 mL) was heated to reflux for 30 minutes. The resulting solution was allowed to cool before being concentrated. The residue was diluted with methanol (4 mL) and concentrated. The residue was diluted with water and K2CO3 solution was added dropwise to bring the pH to 8. The mixture was then filtered to yield 6-bromo-1-(2-chloroethyl)-1H-benzimidazol-2-amine as tan solid (240 mg, 87%). 1H NMR (400 MHz, DMSO-d6) δ ppm 7.49 (s, 1 H) 7.39 (s, 1 H) 7.11 - 7.27 (m, 3 H) 6.56 (br. s., 2 H) 4.72 (t, J=4.9 Hz, 1 H) 4.07 (t, J=6.7 Hz, 2 H) 3.62 (s, 3 H) 3.38 - 3.48 (m, 2 H) 1.82 (t, J=6.5 Hz, 2 H). ES-LCMS: 490.3 (M+1).

Step B

**6-bromo-1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-2-amine**

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[00426] A mixture of 6-bromo-1-(2-chloroethyl)-1H-benzimidazol-2-amine (100 mg, 0.36 mmol) and morpholine (0.32 ml.) was heated in a 80°C sand bath for about 20 hours. The solution was then allowed to cool before the adding EtOAc. The mixture was allowed to stir for 5 minutes then was filtered to yield an off-white solid. The sample was placed in a vial and saturated aqueous NaHCO₃ was added. The mixture was shaken, sonicated, and then filtered. The resulting white solid was washed with water to yield 6-bromo-1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-2-amine as a white solid (67 mg, 57% yield). 

$$^1H$$ NMR (400 MHz, DMSO-d$_6$) δ ppm 7.36 (s, 1H) 7.03 (s, 2H) 6.58 (s, 2H) 4.01 - 4.12 (m, 2H) 3.48 - 3.57 (m, 4H) 2.48 - 2.55 (m, 2H overlapping DMSO) 2.38 - 2.48 (m, 4H).

Step C

\[ N-[5-[2-amino-1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-
difluorobenzenesulfonamide \]

[00427] A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-
dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (84 mg, 0.197 mmol) and 6-bromo-1-[2-(4-
morpholinyl)ethyl]-1H-benzimidazol-2-amine (64 mg, 0.197 mmol) and potassium carbonate (82 mg, 0.59 mmol) in dioxane (1.7 ml.) and water (0.42 mL) was sparged with nitrogen as PdCl₂(dppf) DCM adduct (16 mg, 0.02 mmol) was added. The reaction mixture was then
heated to 90°C for one hour and a half. The solution was then partitioned between EtOAc and brine. The resulting organic layer was then concentrated. Lastly, the mixture was filtered to yield \( N-[5-{2\text{-amino-1-[2-(4-morpholinyl)ethyl]-1\text{-H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]}-2,4\text{-difluorobenzenesulfonamide} \) as an off-white solid (52 mg, 49 % yield). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) ppm 10.32 (br. s., 1 H) 8.25 (d, \( J=2.2 \) Hz, 1 H) 7.82 (d, \( J=2.3 \) Hz, 1 H) 7.75 (td, \( J=8.5, 6.3 \) Hz, 1 H) 7.51 - 7.61 (m, 1 H) 7.39 (s, 1 H) 7.11 - 7.28 (m, 3 H) 6.63 (br. s., 2 H) 4.15 (t, \( J=6.4 \) Hz, 2 H) 3.62 (s, 3 H) 3.48 - 3.59 (m, 4 H) 2.53 - 2.67 (m, 2 H) 2.44 - 2.53 (m, 2H overlapping DMSO). ES-LCMS: 545.4 (M+1).

**Example 168**

\( N-[5-{2\text{-amino-1-[2-(4-morpholinyl)ethyl]-1\text{-H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]}-2,4\text{-difluorobenzenesulfonamide} \)

![Chemical structure](image)

Step A

6-bromo-1-[2-(dimethylamino)ethyl]-1 H-benzimidazol-2-amine,

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[00428] A mixture of 6-bromo-1-(2-chloroethyl)-1 H-benzimidazol-2-amine (100 mg, 0.36 mmol) and potassium iodide (60 mg, 0.36 mmol) in a 40% solution of dimethylamine in water (3 ml) was heated overnight. The solution was then concentrated and the residue was partitioned between EtOAc and water. The organic layer was dried with Na\( _2\)SO\(_4\), filtered and concentrated to yield 6-bromo-1-[2-(dimethylamino)ethyl]-1 H-benzimidazol-2-amine (14 mg, 14
% yield). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 7.34 (s, 1 H) 7.03 (s, 2 H) 6.61 (s, 2 H) 4.04 (t, $J$=6.3 Hz, 2 H) 2.44 - 2.48 (m, 2 H) 2.19 (s, 6 H). ES-LCMS: 283.1 (M+1).

**Step B**

$N$-[5-{2-amino-1-[2-(dimethylamino)ethyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

![Chemical Structure]

A mixture of 2,4-difluoro-$N$-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (17 mg, 0.03 mmol) and 6-bromo-$1$-[2-(dimethylamino)ethyl]-1H-benzimidazol-2-amine (11 mg, 0.04 mmol) and potassium carbonate (16 mg, 0.117 mmol) in dioxane (0.33 mL) and water (0.1 mL) was sparged with nitrogen as $PdCl_2$ (dpdf) DCM adduct (3 mg, 0.004 mmol) was added. The reaction mixture was then heated to 90°C for two hours. The solution was then partitioned between EtOAc and brine. The resulting organic layer was then concentrated. The mixture was next filtered to yield $N$-[5-{2-amino-1-[2-(dimethylamino)ethyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (5.4 mg, 28 % yield) as a light brown solid. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 10.27 (br. s., 1 H) 8.23 (br. s., 1 H) 7.68 - 7.86 (m, 2 H) 7.51 - 7.60 (m, 1 H) 7.37 (s, 1 H) 7.11 - 7.27 (m, 3 H) 6.62 (br. s., 2 H) 4.05 - 4.20 (m, 2 H) 3.63 (s, 3 H) 2.55 (m, 2 H overlapping DMSO) 2.25 (s, 6 H). ES-LCMS: 503.4 (M+1).

**Example 169**

$N$-[5-{2-amino-1-[2-(1-pyrrolidinyi)ethyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide
Step A

6-bromo-1-[2-(1-pyrrolidinyl)ethyl]-1H-benzimidazol-2-amine,

[00430] A mixture of 6-bromo-1-(2-chloroethyl)-1H-benzimidazol-2-amine (100 mg, 0.36 mmol) and pyrrolidine (0.30 ml) was heated in a 80°C sand bath for ~ 18 hours. The solution was allowed to cool before the addition of EtOAc. The mixture was allowed to stir for 5 minutes and then was filtered. Next, the sample was washed with saturated aqueous NaHCO₃ and then filtered. The resulting tan solid was washed with water to yield 6-bromo-1-[2-(1-pyrrolidinyl)ethyl]-1H-benzimidazol-2-amine as a light brown solid (105 mg, 93% yield). H NMR (400 MHz, DMSO-d₆) δ ppm 7.33 (s, 1 H) 7.04 (d, J=1.0 Hz, 2 H) 6.60 (s, 2 H) 4.07 (t, J=6.5 Hz, 2H) 3.30 - 3.38 (br. s, 4H, overlapping H₂O) 2.66 (t, J=6.5 Hz, 2 H) 1.66 (dt, J=6.5, 3.2 Hz, 4 H). ES-LCMS: 309.1 (M+1).

Step B

N-[5-[2-amino-1-[2-(1-pyrrolidinyl)ethy]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2, 4-difluorobenzenesulfonamide
A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (84 mg, 0.197 mmol) and 6-bromo-1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-2-amine (64 mg, 0.197 mmol) and potassium carbonate (82 mg, 0.59 mmol) in dioxane (1.7 mL) and water (0.42 mL) was sparged with nitrogen as PdCl$_2$(dppf) DCM adduct (16 mg, 0.02 mmol) was added. The reaction mixture was then heated to 90°C for one hour and a half. The solution was then partitioned between EtOAc and brine. The organic layer was concentrated and then dissolved in DMF and filtered. The solution was then injected onto HPLC. Fractions containing the product were then combined and concentrated. The residue was then slurried in hexane/DCM to yield a white solid, which became an oil when not under reduced pressure. Finally, the residue was slurred in ether to yield N-[5-{2-amino-1-[2-(1-pyrrolidinyl)ethyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide as an-off white solid (12 mg, 6 % yield). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.09 - 8.24 (m, 1 H) 7.68 - 7.83 (m, 2 H) 7.46 - 7.59 (m, 1 H) 7.33 (s, 1 H) 7.07 - 7.26 (m, 3 H) 6.59 (br. s., 2 H) 4.16 (t, J=6.4 Hz, 2 H) 3.64 (s, 3 H) 2.75 (t, J=6.6 Hz, 2 H) 2.57 (br. s., 4 H) 1.68 (t, 4 H). ES-LCMS: 529.5 (M+1).

**Example 170**

$N$-[5-{2-amino-1-[2-(4-methyl-1-piperazinyl)ethyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide
Step A

6-bromo-1-[(4-methyl-1-piperazinyl)ethyl]-1H-benzimidazol-2-amine

[00432] A mixture of 6-bromo-1-(2-chloroethyl)-1H-benzimidazol-2-amine (100 mg, 0.36 mmol) and 1-methylpiperazine (0.40 mL) was heated in a 80°C sand bath for ~18 hours. The solution was allowed to cool before the addition of EtOAc. The mixture was allowed to stir then was sonicated before being filtered to yield a light yellow solid. The sample was washed with saturated aqueous NaHCO₃ then filtered. The resulting tan solid was washed with water to yield 6-bromo-1-[(4-methyl-1-piperazinyl)ethyl]-1H-benzimidazol-2-amine as a white solid, (29 mg, 23% yield). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 7.36 (s, 1 H) 7.03 (s, 2 H) 6.60 (s, 2 H) 4.05 (t, J=6.2 Hz, 2 H) 2.19 - 2.66 (br m, 10 H) 2.13 (s, 3 H). ES-LCMS: 338.4 (M+1).

Step B

N-[5-[(2-amino-1-[(4-methyl-1-piperazinyl)ethyl]-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide
A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-
dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (84 mg, 0.197 mmol) and 6-bromo-1-[2-(4-
morpholinyl)ethyl]-1H-benzimidazol-2-amine (64 mg, 0.197 mmol) and potassium carbonate (82 
mg, 0.59 mmol) in dioxane (1.7 mL) and water (0.42 mL) was sparged with nitrogen as 
PdCl$_2$(dppf) DCM adduct (16 mg, 0.02 mmol) was added. The reaction mixture was then 
heated to 90°C for one hour and a half. The solution was then partitioned between EtOAc and 
brine. The organic layer was concentrated. The residue was purified by reverse phase HPLC 
(10-60% MeCN / water with 0.1% formic acid) to yield N-[5-{2-amino-1-[2-(4-methyl-1-
piperazinyl)ethyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-
difluorobenzenesulfonamide as a light brown glass (11 mg, 49 % yield). $^1$H NMR (400 MHz, 
DMSO-d$_6$) δ ppm 8.05 - 8.27 (m, 2 H) 7.65 - 7.89 (m, 2 H) 7.43 - 7.63 (m, 1 H) 7.34 (s, 1 H) 7.06 
- 7.28 (m, 3 H) 6.59 (br. s., 2 H) 4.12 (t, J=6.1 Hz, 2 H) 3.64 (s, 3 H) 2.58 (t, J=6.3 Hz, 2 H) 2.25 
- 2.54 (br. m, 8 H overlapping DMSO) 2.17 (s, 3 H). ES-LCMS: 558.5 (M+1).

**Example 171**

1,1-dimethylethyl 3-{2-amino-6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-
pyridinyl]-1H-benzimidazol-1-yl}-1-pyrrolidinecarboxylate
**Step A**

1,1-dimethylethyl 3-[(5-bromo-2-nitrophenyl)amino]-1-pyrrolidinecarboxylate

An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), a 1,1-dimethylethyl 3-amino-1-pyrrolidinecarboxylate (1.693 g, 9.09 mmol) and K$_2$CO$_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated in a 90°C sand bath for 3 hours. The resulting mixture was diluted with EtOAc (200 mL) and washed with a 5% LiCl solution (3x100 mL). The organic layer was concentrated to obtain a solid. The sample was purified by silica gel chromatography (0-30% EtOAc in hexanes) to yield 1,1-dimethylethyl 3-[(5-bromo-2-nitrophenyl)amino]-1-pyrrolidinecarboxylate as a yellow solid (3.2 g, 91% yield). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 7.89 - 8.07 (m, 2 H) 7.39 (s, 1 H) 6.90 (dd, $J$=9.1, 1.9 Hz, 1 H) 4.40 (dd, $J$=14.9, 5.8 Hz, 1 H) 3.65 (dd, $J$=10.8, 6.1 Hz, 1 H) 3.36 - 3.44 (m, 1 H) 3.30 - 3.41 (m, 2 H overlapping H$_2$O) 3.22 (dd, $J$=10.9, 4.9 Hz, 1 H) 2.14 - 2.29 (m, 1 H) 1.82 - 2.05 (m, 1 H) 1.40 (s, 9 H). ES-LCMS: 286.2 (M+1-BOC).

**Step B**

1,1-dimethylethyl 3-[(2-amino-5-bromophenyl)amino]-1-pyrrolidinecarboxylate

A solution of 1,1-dimethylethyl 3-[(5-bromo-2-nitrophenyl)amino]-1-pyrrolidinecarboxylate (1.00 g, 2.59 mmol) in ethanol (60 mL) was stirred at room temperature as a solution of sodium hydrosulfite (3.60 g, 20.68 mmol) in water (12 mL) was added. The solution was allowed to stir at room temperature over night. The solution was concentrated to an off
white paste. The residue was diluted with EtOAc. Large amounts of solid present. The mixture
was filtered. The solids were washed with EtOAc. The filtrate was washed with water. The
organic layer was dried with Na₂SO₄, filtered and concentrated. The residue was purified by
silica gel chromatography (20 - 100% EtOAc in hexanes) to yield 1,1-dimethylethyl 3-[(2-amino-
5-bromophenyl)amino]-1-pyrrolidinecarboxylate as an off white solid (0.41 g, 44%). ¹H NMR
(400 MHz, DMSO-d₆) δ ppm 6.53 - 6.58 (m, 1 H) 6.50 (br. s., 1 H) 6.43 - 6.48 (m, 1 H) 4.69 -
4.85 (m, 3 H) 3.84 - 4.14 (m, 1 H) 3.47 - 3.68 (m, 1 H) 3.35 - 3.46 (m, 2 H overlapping H₂O ) 3.12
(td, J=11.3, 3.5 Hz, 1 H) 2.03 - 2.21 (m, 1 H) 1.81 (td, J=12.1 , 6.2 Hz, 1 H) 1.40 (d, J=1.8 Hz, 9

Step C

1. 1-dimethylethyl 3-(2-amino-6-bromo-1H-benzimidazol-1-yl)-1-pyrrolidinecarboxylate

![Chemical Structure](image)

[00436] A solution of 1,1-dimethylethyl 3-[(2-amino-5-bromophenyl)amino]-1-
pyrrolidinecarboxylate (0.41g, 1.15 mmol) in MeOH (22 ml) was treated with cyanogen bromine
(0.244 g, 2.302 mmol). The reaction mixture was maintained at room temperature for 3 h. LCMS
indicated complete reaction. The reaction mixture concentrated to approximately 5 mL of
volume then was partitioned between EtOAc (100 mL) and a sat. NaHC03 solution (100 mL).
The organic layer was washed with a sat. NaCl solution and concentrated. The residue was
diluted with DCM / hexanes and concentrated to obtain a 1,1-dimethylethyl 3-(2-amino-6-bromo-
1H-benzimidazol-1-yl)-1-pyrrolidinecarboxylate as an off white solid, (0.38g, 87%). ¹H NMR
(400 MHz, DMSO-d₆) δ ppm 7.40 (br. s., 1 H) 7.09 (s, 2 H) 6.67 (br. s., 2 H) 5.00 (t, J=7.6 Hz, 1
H) 3.64 (d, J=8.0 Hz, 2 H) 3.55 (br. s., 1 H) 3.25 - 3.35 (br. s., 1 H, overlapping H₂O ) 2.32 - 2.47
(m, 1 H) 2.16 (d, J=7.8 Hz, 1 H) 1.44 (br. s., 9 H). ES-LCMS: 381.8 (M+1).

Step D

1. 1-dimethylethyl 3-[2-amino-6-[5-[[2A-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-
pyridinyl]- 1H-benzimidazol- 1-yl]- 1-pyrrolidinecarboxylate

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A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (201 mg, 0.472 mmol) and 1,1-dimethylethyl 3-(2-amino-6-bromo-1H-benzimidazol-1-yl)-1-pyrrolidinecarboxylate (180 mg, 0.472 mmol) and potassium carbonate (82 mg, 0.59 mmol) in dioxane (4 mL) and water (1 mL) was sparged with nitrogen as PdC\textsuperscript{dpff} DCM adduct (39 mg, 0.047 mmol) was added. The reaction mixture was then heated to 90°C for one hour and a half. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated. The residue was slurried in DCM and filtered to yield 1,1-dimethylethyl 3-[2-amino-6-[5-\{[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl]-1-pyrrolidinecarboxylate as an off white solid (168 mg, 60 % yield). \textsuperscript{1}H NMR (400 MHz, DMSO-\textsubscript{d}\textsubscript{6}) δ ppm 10.26 (br. s., 1 H) 8.23 (br. s., 1 H) 7.79 (d, J=1.8 Hz, 1 H) 7.74 (td, J=8.5, 6.4 Hz, 1 H) 7.49 - 7.62 (m, 1 H) 7.41 (br. s., 1 H) 7.09 - 7.27 (m, 3 H) 6.57 (br. s., 2 H) 5.04 (d, J=\textbf{8.0} Hz, 1 H) 3.53 - 3.81 (m, 6 H) 3.29 - 3.43 (br. s., 1H overlapping H2O) 2.47 - 2.61 (br. s. 1H overlapping DMSO) 2.19 (br. s., 1 H) 1.39 (br. s., 9 H). ES-LCMS: 601.3 (M+1).

Example 172

\textit{N-[5-[2-amino-1-(4-methylphenyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyril]-2,4-difluorobenzenesulfonamide}
An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), 4-methylaniline (0.974 g, 9.09 mmol) and K$_2$CO$_3$ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 16 h. The resulting mixture was diluted with EtOAc (200 mL) and washed with a 5% LiCl solution (3x100 mL). The organic layer was concentrated to obtain a solid. The residue was purified by silica gel chromatography (5-13% EtOAc in hexanes) to yield 5-bromo-N-(4-methylphenyl)-2-nitroaniline (2.23 g, 80%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm: 9.47 (s, 1 H), 8.04 (d, J=9.0 Hz, 1 H), 7.20 - 7.31 (m, 4 H), 7.07 (d, J=2.0 Hz, 1 H), 6.98 (dd, J=9.1, 2.0 Hz, 1 H), 2.34 (s, 3 H).

Step B
4-bromo-N2-(4-methylphenyl)-1,2-benzenediamine
[00439] A solution of 5-bromo-N-(4-methylphenyl)-2-nitroaniline (2.23g, 7.26 mmol) in EtOH (168mL) was stirred at 60°C as a solution of sodium hydrosulfite (10.1 g, 58 mmol) in water (34mL) was added. The solution was allowed to stir for ~1 hour. LCMS shows no starting material remaining. The solution was filtered and the filtrate concentrated to an off white paste. The residue was partitioned between water and EtOAc. The aqueous layer was extracted with a second portion of EtOAc. The combined EtOAc layers were dried with Na2SO4, filtered and concentrated. The crude material was purified by silica gel chromatography to yield 4-bromo-N2-(4-methylphenyl)-1,2-benzenediamine as a light brown solid (1.19 g, 59%). 1H NMR (400 MHz, DMSO-d6) δ ppm 6.97 - 7.07 (m, 4 H) 6.86 (dd, J=8.4, 2.3 Hz, 1 H) 6.74 (d, J=8.4 Hz, 2H) 6.64 (d, J=8.4 Hz, 1 H) 4.90 (s, 2 H) 2.20 (s, 3 H).

Step C
6-bromo-1-(4-methylphenyl)-1H-benzimidazol-2-amine

[00440] A solution of 4-bromo-N2-(4-methylphenyl)-1,2-benzenediamine (1.19g, 4.29 mmol) in MeOH (86 ml) was treated with cyanogen bromine (0.910 g, 8.59 mmol). The reaction mixture was maintained at room temperature for 6 h. The reaction mixture was concentrated and the residue partitioned between EtOAc (100 mL) and a sat. NaHCO3 solution (100 ml). The organic layer was washed with a sat. NaCl solution, and then concentrated. The residue was slurried in DCM to obtain an off white solid. A second crop was obtained by filtering the filtrate. Both samples were combined to yield 6-bromo-1-(4-methylphenyl)-1H-benzimidazol-2-amine (708 mg, 51% as 0.25 DCM). 1H NMR (400 MHz, DMSO-d6) δ ppm 7.39 - 7.47 (m, 2 H) 7.31 - 7.39 (m, 2 H) 7.07 - 7.18 (m, 2 H) 6.86 (d, J=1.4 Hz, 1 H) 6.39 (s, 2 H) 2.42 (s, 3 H).

Step D
N-[5-[2-amino-1-(4-methylphenyl)-1H-benzimidazol-6-yl]-2-(methylo^difluorobenzenesulfonyl]-2,4-difluorobenzenesulfonylamine

316
A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-
dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (99 mg, 0.232 mmol) and 6-bromo-1-(4-
methyloxy)-1H-benzimidazol-2-amine (75 mg, 0.232 mmol) and potassium carbonate (96 mg, 0.7 mmol) in dioxane (2.0 ml) and water (0.50 ml) was sparged with nitrogen as 
PdCl2(dppf) DCM adduct (19 mg, 0.023 mmol) was added. The reaction mixture was then 
heated to 90°C for one hour and a half. The solution was then partitioned between EtOAc and 
brine. The organic layer was concentrated. The residue was purified by HPLC (10-70% MeCN 
water with 0.1% formic acid) to yield N-[5-[2-amino-1-(4-methylphenyl)-1H-benzimidazol-6-yl]-2-
(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide as an off-white solid (56 mg, 44 % 
yield). 1H NMR (400 MHz, DMSO-d6) δ ppm 8.14 (s, 2 H) 7.66 - 7.77 (m, 1 H) 7.63 (d, J=2.1 Hz, 
1 H) 7.37 - 7.56 (m, 5 H) 7.25 - 7.31 (m, 1 H) 7.19 - 7.25 (m, 1 H) 7.06 - 7.16 (m, 1 H) 6.89 (d, 
J=1.2 Hz, 1 H) 6.36 (s, 2 H) 3.61 (s, 3 H) 2.43 (s, 3 H). ES-LCMS: 522.3 (M+1).

**Example 173**

N-[5-[2-amino-1-(3-methylphenyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-
difluorobenzenesulfonamide

Step A
An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), 3-methylaniline (0.99 mL, 9.09 mmol) and K₂CO₃ (2.51 g, 18.18 mmol) in DMF (20 mL) was heated at 90 °C for 16 h. The resulting mixture was diluted with EtOAc (100 mL) and washed with a 5% LiCl solution (3x100 mL). The organic layer was concentrated onto Celite® and purified by silica gel chromatography (0-30% EtOAc/hexane) to obtain 5-bromo-N-(3-methylphenyl)-2-nitroaniline (1.56 g, 56% yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.45 (s, 1 H) 8.05 (d, J=9.0 Hz, 1 H) 7.26 - 7.45 (m, 1 H) 7.12 - 7.19 (m, 3 H) 7.10 (d, J=7.6 Hz, 1 H) 7.01 (dd, J=9.1, 2.1 Hz, 1 H) 2.33 (s, 3 H).

Step B

4-bromo-N2-(3-methylphenyl)-1,2-benzenediamine

A solution of 5-bromo-N-(3-methylphenyl)-2-nitroaniline (11.56 g, 5.08 mmol) in EtOH (118 mL) was stirred at room temperature as a solution of sodium hydrosulfite (7.07 g, 40.6 mmol) in water (24 mL) was added. The solution was allowed to stir at 60°C for 1 hour. The solution was filtered and the filtrate concentrated to an off white paste. The residue was partitioned between water and EtOAc. The aqueous layer was extracted with a second portion of EtOAc. The combined EtOAc layers were dried with Na₂SO₄, filtered and concentrated. The crude material was purified by silica gel chromatography (0-30% EtOAc in hexanes) to yield 4-bromo-N2-(3-methylphenyl)-1,2-benzenediamine as a dark oil (0.93 g, 53% 0.75 EtOAc). ¹H NMR (400 MHz, DMSO-c₆) δ ppm 7.15 (s, 1 H) 7.01 - 7.08 (m, 2 H) 6.92 (m, 3 H) 7.10 (d, J=7.6 Hz, 1 H) 7.01 (dd, J=9.1, 2.1 Hz, 1 H) 6.67 (d, J=8.4 Hz, 1 H) 6.53 - 6.61 (m, 3 H) 4.92 (s, 2 H) 2.20 (s, 3 H).
Step C
6-bromo-1-(3-methylphenyl)-1H-benzimidazol-2-amine

[00444] A solution of 4-bromo-N2-(3-methylphenyl)-1,2-benzenediamine (0.91 g, 2.65 mmol) in MeOH (27 ml) was treated with cyanogen bromine (0.562 g, 5.30 mmol). The reaction mixture was maintained at room temperature for 2 h. LCMS indicated complete reaction. The reaction mixture was concentrated and the residue partitioned between EtOAc (100 mL) and a sat. NaHCO3 solution (100 mL). The organic layer was washed with a sat. NaCl solution and concentrated. The residue was slurried in DCM / hexanes and filtered to obtain an off-white solid. A second crop was obtained by filtering the filtrate. Both samples were combined to yield 6-bromo-1-(3-methylphenyl)-1H-benzimidazol-2-amine as a tan solid, (560 mg, 70%) 1H NMR (400 MHz, DMSO-d6) δ ppm 7.46 - 7.54 (m, 1 H) 7.34 (d, J=7.6 Hz, 1 H) 7.23 - 7.31 (m, 2 H) 7.09 - 7.17 (m, 2 H) 6.89 (d, J=1.6 Hz, 1 H) 6.44 (s, 2 H) 2.41 (s, 3 H).

Step D
N-[5-[2-amino-1-(3-methylphenyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

[00445] A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (106 mg, 0.248 mmol) and 6-bromo-1-(3-methylphenyl)-1H-benzimidazol-2-amine (75 mg, 0.248 mmol) and potassium carbonate (82 mg, 0.59 mmol) in dioxane (2.1 mL) and water (0.53 mL) was sparged with nitrogen as
PdCl₂(clppf) DCM adduct (20 mg, 0.025 mmol) was added. The reaction mixture was then heated to 90°C for one hour and a half. The solution was then partitioned between EtOAc and brine. The organic layer was concentrated. The residue was purified by silica gel chromatography (0-5 % MeOH in DCM) to yield N-[5-[2-amino-1-(3-methylphenyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide as an-off white solid (52 mg, 49 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.27 (br. s., 1 H) 8.16 (d, J=2.0 Hz, 1 H) 7.63 - 7.76 (m, 2 H) 7.53 (t, J=8.0 Hz, 2 H) 7.26 - 7.40 (m, 4 H) 7.19 - 7.26 (m, 1 H) 7.12 (td, J=8.5, 2.0 Hz, 1 H) 6.95 (d, J=1.4 Hz, 1 H) 6.42 (br. s., 2 H) 3.61 (s, 3 H) 3.23 - 3.45 (m, 3 H) overlapping H₂O) 2.88 - 3.01 (m, 1 H) 2.21 - 2.42 (m, 1 H) 2.06 - 2.19 (m, 1 H). ES-LCMS: 522.3 (M+1).

Example 174

N-[5-[2-amino-1-(3-pyrrolidinyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

[00446] 1,1-dimethylethyl 3-[2-amino-6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-6-yl]-1-pyrrolidinocarboxylate (77 mg, 0.128 mmol) in DCM (1.2 mL) was stirred at room temperature as TFA (0.20 mL) was added. The solution was allowed to stir at room temperature for two hours. The solution was partitioned between DCM and NaHCO₃. The organic layer was dried with Na₂SO₄ filtered and concentrated to yield N-[5-[2-amino-1-[(3-pyrrolidinyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (22 mg, 34 % yield) as an-off white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.16 (d, J=2.0 Hz, 1 H) 7.67 - 7.87 (m, 2 H) 7.41 - 7.63 (m, 2 H) 7.04 - 7.31 (m, 3 H) 6.95 (br. s., 2 H) 5.04 - 5.18 (m, 1 H) 3.65 (s, 3 H) 3.23 - 3.45 (m, 3 H overlapping H₂O) 2.88 - 3.01 (m, 1 H) 2.21 - 2.42 (m, 1 H) 2.06 - 2.19 (m, 1 H). ES-LCMS: 501.4 (M+1).

Example 175

320
N-[5-{2-amino-1-[3-(1,3-oxazol-5-yl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

Step A
5-bromo-2-nitro-N-[3-(1,3-oxazol-5-yl)phenyl]aniline

An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (1.353 g, 6.15 mmol), 3-(1,3-oxazol-5-yl)aniline (0.985g, 6.15 mmol) and K$_2$CO$_3$ (1.7 g, 12.3 mmol) in DMF (13.5 mL) was heated at 90 °C for 26 h. The resulting mixture was diluted with EtOAc (100 mL) and washed with a 5% LiCl solution (3x100 mL). The organic layer was concentrated and the residue was purified by silica gel chromatography (0-40% EtOAc/hexane) to obtain 5-bromo-2-nitro-N-[3-(1,3-oxazol-5-yl)phenyl]aniline as bright red - orange solid (1.18g, 53%). $^1$H NMR (400 MHz, DMSO-c/s) δ ppm 9.54 (s, 1 H) 8.48 (s, 1 H) 8.07 (d, J=9.2 Hz, 1 H) 7.75 (s, 1 H) 7.71 (s, 1 H) 7.59 - 7.64 (m, 1 H) 7.53 - 7.58 (m, 1 H) 7.36 (d, J=8.0 Hz, 1 H) 7.23 (d, J=2.0 Hz, 1 H) 7.07 (dd, J=9.0, 2.0 Hz, 1 H). ES-LCMS: 360.0 (M+1).

Step B
4-bromo-N2-[3-(1,3-oxazol-5-yl)phenyl]-1,2-benzenediamine
A solution of 5-bromo-2-nitro-N-[3-(1,3-oxazol-5-yl)phenyl]aniline (1.17 g, 3.25 mmol) in THF (16 mL) and EtOH (16 mL) was stirred at room temperature as a solution of sodium hydrosulfite (4.52 g, 26 mmol) in water (29 mL) was added. The solution was allowed to stir at 60°C for 1 hour. The solution was filtered and the filtrate concentrated. The residue was partitioned between water and EtOAc. The aqueous layer was extracted with a second portion of EtOAc. The combined EtOAc layers were dried with Na2SO4, filtered and concentrated. The crude material was purified by silica gel chromatography (0-50% EtOAc in hexanes) to yield 4-bromo-N2-[3-(1,3-oxazol-5-yl)phenyl]-1,2-benzenediamine as a clear oil (387 mg, 29%). 1H NMR (400 MHz, DMSO-d6) δ ppm 8.40 (s, 1 H) 7.43 - 7.64 (m, 2 H) 7.22 - 7.29 (m, 1 H) 7.07 - 7.12 (m, 2 H) 7.05 (d, J=1.8 Hz, 1 H) 7.00 (dd, J=8.5, 2.2 Hz, 1 H) 6.63 - 6.77 (m, 2 H) 5.00 (s, 2 H). ES-LCMS: 330.3 (M+1).

Step C

6-bromo-1-[3-(1,3-oxazol-5-yl)phenyl]-1H-benzimidazol-2-amine

A solution of 4-bromo-N2-[3-(1,3-oxazol-5-yl)phenyl]-1,2-benzenediamine (385 mg, 1.166 mmol) in MeOH (1.17E+04 µl) was treated with cyanogen bromine (247 mg, 2.332 mmol). The reaction mixture was maintained at room temperature for 2 hours. Additional 124 mg of CNBr (124 mg, 1.17 mmol) was added. The reaction mixture was allowed to stir for another 2 hours then was concentrated and the residue partitioned between EtOAc (100 mL) and a sat. NaHC03 solution (100 mL). The organic layer was washed with a sat. NaCl solution and then concentrated. The residue was slurried in DCM to obtain 6-bromo-1-[3-(1,3-oxazol-5-yl)phenyl]-1H-benzimidazol-2-amine as an off white solid (197 mg, 48%), 1H NMR (400 MHz,
**DMSO-de** δ ppm 8.51 (s, 1 H) 7.80 - 7.93 (m, 3 H) 7.72 (t, J=7.8 Hz, 1 H) 7.42 - 7.53 (m, 1 H) 7.10 - 7.21 (m, 2 H) 6.94 (d, J=1.4 Hz, 1 H) 6.54 (s, 2 H). ES-LCMS: 354.9 (M+1).

**Step D**

\[
N-[5-\{2-amino-1-[3-(1,3-oxazol-5-yl)phenyl]-1H-benzimidazol-6-yl\}-2-(methylxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide
\]

[00450] A mixture of 2,4-difluoro-N-[2-(methylxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (60 mg, 0.141 mmol) and 6-bromo-1-[3-(1,3-oxazol-5-yl)phenyl]-1 H-benzimidazol-2-amine (50 mg, 0.141 mmol) and potassium carbonate (58 mg, 0.42 mmol) in dioxane (4 ml) and water (1 ml) was sparged with nitrogen as PdCl\(_2\) (dppf) DCM adduct (11.5 mg, 0.014 mmol) was added. The reaction mixture was then heated to 90°C for one hour and a half. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na\(_2\)SO\(_4\), filtered and the filtrate concentrated. The residue was purified by silica gel chromatography (0-10% MeOH in DCM) to yield N-[5-\{2-amino-1-[3-(1,3-oxazol-5-yl)phenyl]-1 H-benzimidazol-6-yl\}-2-(methylxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide as an-off white solid (41 mg, 51 % yield). ¹H NMR (400 MHz, DMSO-de) δ ppm 10.22 (br. s., 1 H) 8.51 (s, 1 H) 8.17 (s, 1 H) 7.83 - 7.95 (m, 3 H) 7.62 - 7.81 (m, 3 H) 7.44 - 7.61 (m, 3 H) 7.28 - 7.35 (m, 1 H) 7.20 - 7.28 (m, 1 H) 7.07 - 7.16 (m, 1 H) 7.00 (s, 1 H) 6.52 (br. s., 2 H) 3.60 (s, 3 H) ES-LCMS: 575.4 (M+1).

**Example 176**

\[
1,1-dimethylethyl\ (2S)-2-\{2-amino-6-[5-\{[(2,4-difluorophenyl)sulfonyl]amino\}-6-(methylxy)-3-pyridinyl\}-1H-benzimidazol-1-yl\}-3-methylbutanoate
\]
Step A

1, 1-dimethylethyl N-(5-bromo-2-nitrophenyl)-L-valinate

An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), 1,1-dimethylethyl L-valinate (0.68 g, 3.24 mmol) and Hunigs base (1.13 mL, 6.48 mmol) in DMF (2.28 mL) was allowed to stir at room temperature overnight. The resulting mixture was diluted with EtOAc (100 mL) and washed with a 5% LiCl solution (3x100 mL). The organic layer was concentrated onto Celite® and purified by silica gel chromatography (0-30% EtOAc/hexane) to obtain 1,1-dimethylethyl N-(5-bromo-2-nitrophenyl)-L-valinate as a yellow oil, (1.122 g, 93%) 1H NMR (400 MHz, DMSO-d6) δ ppm 8.30 (d, J=8.2 Hz, 1 H) 8.03 (d, J=9.2 Hz, 1 H) 7.27 (d, J=2.0 Hz, 1 H) 6.92 (dd, J=9.1, 2.0 Hz, 1 H) 4.44 (dd, J=8.1, 5.0 Hz, 1 H) 2.22 (dq, J=1.9, 6.8 Hz, 1 H) 1.43 (s, 9 H) 0.85 - 1.11 (m, 6 H). ES-LCMS: 373.3 (M+1).

Step B

1, 1-dimethylethyl N-(2-amino-5-bromophenyl)-L-valinate
A solution of 1,1-dimethylethyl N-(5-bromo-2-nitrophenyl)-L-valinate (1.11 g, 2.97 mmol) in ethanol (33 mL) was stirred at room temperature as a solution of sodium hydrosulfite (4.14 g, 20.71 mmol) in water (26 mL) was added. The solution was allowed to stir at room temperature overnight. The solution was concentrated to an off white paste. The residue was diluted with EtOAc. Large amounts of solid present. The mixture was filtered. The solids were washed with EtOAc. The filtrate was washed with water. The organic layer was dried with Na$_2$SO$_4$, filtered and concentrated. The residue was purified by silica gel chromatography (0-30% EtOAc in hexane) to yield 1,1-dimethylethyl N-(2-amino-5-bromophenyl)-L-valinate as a clear oil (0.575 g, 56%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 6.53 - 6.59 (m, 1 H) 6.42 - 6.49 (m, 2 H) 4.87 (s, 2 H) 4.79 (d, $J$=9.2 Hz, 1 H) 3.44 (t, $J$=8.4 Hz, 1 H) 1.90 - 2.12 (m, 1 H) 1.41 (s, 9 H) 0.93 - 1.08 (m, 6 H). ES-LCMS: 343.3 (M+1).

**Step C**

1,1-dimethylethyl (2S)-2-(2-amino-6-bromo-1H-benzimidazol-1-yl)-3-methylbutanoate

A solution of 1,1-dimethylethyl 3-[(2-amino-5-bromophenyl)amino]-1-pyrrolidinecarboxylate (0.41 g, 1.15 mmol) in MeOH (32 mL) was treated with cyanogen bromine (350 mg, 3.30 mmol). The reaction mixture was maintained at room temperature for 3 h. LCMS indicated complete reaction. The reaction mixture concentrated to approximately 5 mL of volume then was partitioned between EtOAc (100 mL) and a sat. NaHCO$_3$ solution (100 mL). The organic layer was washed with a sat. NaCl solution and then concentrated. The residue was purified by silica gel chromatography (20-100% EtOAc in hexanes) to obtain 1,1-dimethylethyl (2S)-2-(2-amino-6-bromo-1 H-benzimidazol-1-yl)-3-methylbutanoate as a clear
glass, (0.095g, 15%), 1H NMR (400 MHz, DMSO-d$_6$) δ ppm 7.36 (s, 1 H) 6.89 - 7.15 (m, 2 H) 6.66 (s, 2 H) 4.65 (d, J=10.7 Hz, 1 H) 2.64 (dt, J=10.8, 6.6 Hz, 1 H) 1.36 (s, 9 H) 1.09 (d, J=6.4 Hz, 3 H) 0.59 (d, J=6.6 Hz, 3 H). ES-LCMS: 368.2 (M+1).

**Step D**

1. 1-dimethylethyl (2S)-2-{2-amino-6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxyl)-3-pyridinyl]-1H-benzimidazol-1-yl]-3-methylbutanoate

![Chemical Structure](image)

[00454] A mixture of 2,4-difluoro-N-[2-(methyloxyl)-5-[[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]-3-pyridinyl]benzenesulfonamide (86 mg, 0.201 mmol) and 1,1-dimethylethyl (2S)-2-{2-amino-6-bromo-1 H-benzimidazol-1-yl]-3-methylbutanoate (74 mg, 0.201 mmol) and potassium carbonate (83 mg, 0.603 mmol) in dioxane (1.7 mL) and water (0.43 mL) was sparged with nitrogen as PdC^dppf) DCM adduct (16 mg, 0.02 mmol) was added. The reaction mixture was then heated to 90°C for one hour and a half. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na$_2$SO$_4$, filtered and the filtrate concentrated. The residue was purified by silica gel chromatography (0-10% MeOH in DCM) Fractions containing the product were combined and concentrated to and the residue was slurried in hexane - ether and the solution was decanted and then concentrated to yield 1,1-dimethylethyl (2S)-2-{2-amino-6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxyl)-3-pyridinyl]-1 H-benzimidazol-1-yl]-3-methylbutanoate (36 mg, 30 % yield) as tan solid 1H NMR (400 MHz, DMSO-d$_6$) δ ppm 10.27 (br. s., 1 H) 8.19 (d, J=1.2 Hz, 1 H) 7.69 - 7.82 (m, 2 H) 7.52 - 7.64 (m, 1 H) 7.34 (s, 1 H) 7.15 - 7.26 (m, 3 H) 6.65 (br. s., 2 H) 4.71 (d, J=10.5 Hz, 1 H) 3.64 (s, 3 H) 2.73 (dt, J=10.7, 6.5 Hz, 1 H) 1.34 (s, 9 H) 1.12 (d, J=6.4 Hz, 3 H) 0.62 (d, J=6.6 Hz, 3 H). ES-LCMS: 588.5 (M+1).

**Example 177**
1,1-dimethylethyl 2-{2-amino-6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl}propanoate

Step A

1,1-dimethylethyl N-(5-bromo-2-nitrophenyl)alaninate

[00455] An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (2 g, 9.09 mmol), 1,1-dimethylethyl alaninate (1.65 g, 9.09 mmol) and Hunigs base (3.18 mL, 18.18 mmol) in DMF (6.4 mL) was allowed to stir at room temperature overnight. The resulting mixture was diluted with EtOAc (100 mL) and washed with a 5% LiCl solution (3x100 mL). The organic layer was concentrated purified by silica gel chromatography (0-30% EtOAc/hexane) to obtain 1,1-dimethylethyl N-(5-bromo-2-nitrophenyl)alaninate as a yellow oil, (2.88g, 92%) 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.38 (d, J=6.4 Hz, 1 H) 8.05 (d, J=9.2 Hz, 1 H) 6.89 (d, J=1.8Hz, 1 H) 6.80 (dd, J=9.1, 1.9 Hz, 1 H) 3.99 - 4.25 (m, 1 H) 1.56 (d, J=6.8 Hz, 3 H) 1.49 (s, 9 H).

Step B

1,1-dimethylethyl N-(2-amino-5-bromophenyl)alaninate
A solution of 1,1-dimethylethyl N-(5-bromo-2-nitrophenyl)alaninate (1.00g, 2.59 mmol) in ethanol (92 mL) was stirred at room temperature as a solution of sodium hydrosulfite (3.60 g, 20.71 mmol) in water (74mL) was added. The solution was allowed to stir at room temperature for ~one hour. LCMS shows no starting material remaining. The solution was filtered and the filtrate concentrated to ~30 mL of volume. The residue was extracted with EtOAc. The organic layer was dried with Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (20 - 100% EtOAc in hexanes) to yield 1,1-dimethylethyl N-(2-amino-5-bromophenyl)alaninate as an off white solid (0.55 g, 19%).

\[ \text{1H NMR (400 MHz, DMSO-d₆) } \delta \text{ ppm } 6.56 \text{ (dd, } J=8.2, 2.1 \text{ Hz, 1 H) } 6.46 \text{ (d, } J=8.2 \text{ Hz, 1 H) } 6.34 \text{ (d, } J=2A \text{ Hz, 1 H) } 5.00 \text{ (d, } J=8.2 \text{ Hz, 1 H) } 4.82 \text{ (s, 2 H) } 3.82 \text{ (quin, } J=7.2 \text{ Hz, 1 H) } 1.31 - 1.49 \text{ (m, 12 H).} \]

Step C

1,1-dimethylethyl 2-(2-amino-6-bromo-1H-benzimidazol-1-yl)propanoate

A solution of 1,1-dimethylethyl N-(2-amino-5-bromophenyl)alaninate (0.55g, 1.745 mmol) in MeOH (10 ml) was treated with cyanogen bromine (0.370 g, 3.49 mmol). The reaction mixture was maintained at room temperature for 3 h. LCMS indicated complete reaction. The reaction mixture concentrated to approximately 5 mL of volume then was partitioned between EtOAc (100 mL) and a sat. NaHCO₃ solution (100 mL). The organic layer was washed with a sat. NaCl solution and then concentrated. The residue was purified by silica gel chromatography (20-100 % EtOAc in hexanes). Two major peaks observed. Like fractions combined and concentrated, diluted with DCM / hexanes and concentrated to obtain a dark solid. The sample was purified by silica gel chromatography (0-10% MeOH in EtOAc) to yield
1,1-dimethylethyl 2-(2-amino-6-bromo-1H-benzimidazol-1-yl)propanoate as an off white solid (0.231 g, 38%). 1H NMR (400 MHz, DMSO-d$_6$) δ ppm 6.91 - 7.23 (m, 3 H) 6.58 (s, 2 H) 5.22 (q, J=7 Hz, 1 H) 1.56 (d, J=7.2 Hz, 3 H) 1.36 (s, 9 H).

Step D

1. 1-dimethylethyl 2-{2-amino-6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl}propanoate

A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl]benzenesulfonylamide (272 mg, 0.638 mmol) and 1,1-dimethylethyl 2-(2-amino-6-bromo-1H-benzimidazol-1-yl)propanoate (217 mg, 0.638 mmol) and potassium carbonate (264 mg, 1.913 mmol) in dioxane (5.4 mL) and water (1.3 mL) was sparged with nitrogen as PdC$^{dpf}$ DCM adduct (52 mg, 0.064 mmol) was added. The reaction mixture was then heated to 90°C for two hours. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na$_2$S$_2$O$_4$, filtered and the filtrate concentrated. The residue was purified by silica gel chromatography (0-10% MeOH in DCM) to yield 1,1-dimethylethyl 2-{2-amino-6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl}propanoate as tan solid (256 mg, 72 % yield). 1H NMR (400 MHz, DMSO-d$_6$) δ ppm 10.28 (br. s., 1 H) 8.19 (d, J=2.1 Hz, 1 H) 7.67 - 7.82 (m, 2 H) 7.48 - 7.64 (m, 1 H) 7.13 - 7.33 (m, 3 H) 7.09 (s, 1 H) 6.58 (br. s., 2 H) 5.28 (q, J=7.2 Hz, 1 H) 3.64 (s, 3 H) 1.61 (d, J=7.2 Hz, 3 H) 1.35 (s, 9 H). ES-LCMS: 560.3 (M+1).

Example 178

(2S)-2-{2-amino-6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl]-3-methylbutanoic acid
(2S)-2-{2-amino-6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl]-3-methylbutanoic acid

[TFA (0.27 mL, 3.51 mmol) was added slowly to a solution of 1,1-dimethylethyl (2S)-2-[2-amino-6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl]-3-methylbutanoate (103 mg, 0.175 mmol) in DCM (1.5 mL). After 2.25 hours additional TFA (1.2 mL) was added and the solution was allowed to stir for another 2.5 hours. The solution was then concentrated and allowed to stand overnight. The residue was then diluted in DCM (1.5 mL) before the addition of TFA (1.5 mL). The solution was allowed to stir at room temperature for three hours. The solution was concentrated and the residue dissolved in DCM and washed with NaHCO₃ solution. The organic layer was dried with Na₂SO₄, filtered and concentrated. The residue was slurried in DCM - hexanes and filtered to yield (2S)-2-[2-amino-6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl]-3-methylbutanoic acid as an off white solid (79 mg, 82% yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.26 (br. s., 1 H) 10.31 (br. s., 1 H) 8.22 (d, J=1.2 Hz, 1 H) 7.70 - 7.85 (m, 2 H) 7.52 - 7.65 (m, 1 H) 7.42 (br. s., 1 H) 7.13 - 7.28 (m, 3 H) 4.70 (d, J=10.7 Hz, 1 H) 3.64 (s, 3 H) 2.59 - 2.84 (m, 1 H) 1.13 (d, J=6A Hz, 3 H) 0.61 (d, J=6.6 Hz, 3 H). ES-LCMS: 532.3 (M+1).

**Example 179**

N-{6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1-methyl-1H-benzimidazol-2-yl}acetamide
[00460] Acetic anhydride (2.5 mL) was added slowly to a flask containing 6-bromo-1-methyl-1H-benzimidazol-2-amine (400 mg, 1.769 mmol) at 0°C. The resulting mixture was allowed to stir in the ice bath for 30 minutes before being allowed to warm to room temperature. The mixture was too thick to stir. The flask was returned to the ice bath an additional 2.5 mL of acetic anhydride was added. The mixture was then allowed to stir overnight. The mixture was diluted with water and allowed to stir for 20 minutes. The resulting brown solution was extracted with DCM. The organic layer was then washed with saturated NaHCO₃ solution twice then dried with Na₂SO₄, filtered and concentrated to yield a dark solid. The residue was slurried with DCM and filtered to yield N-(6-bromo-1-methyl-1H-benzimidazol-2-yl)acetamide as an off white solid, (177 mg, 37% yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.67 (br. s., 1 H) 7.79 (s, 1 H) 7.48 (d, J=8.4 Hz, 1 H) 7.31 (dd, J=8.5, 1.9 Hz, 1 H) 3.58 (s, 3 H) 2.15 (s, 3 H). ES-LCMS: 268.0 (M+1).

Step B
N-{6-[5-[[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyri^n inyl]-1-methyl-1H-benzimidazol-2-yl}acetamide
A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (79 mg, 0.186 mmol) and N-(6-bromo-1-methyl-1H-benzimidazol-2-yl)acetamide (50 mg, 0.186 mmol) and potassium carbonate (77 mg, 0.559 mmol) in dioxane (1.6 mL) and water (0.40 mL) was sparged with nitrogen as PdC\(^{dpf}\) DCM adduct (15 mg, 0.02 mmol) was added. The reaction mixture was then heated to 90°C for one hour and a half. LCMS shows partial conversion. Additional 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (28 mg, 0.066 mmol) and PdCl\(_2\)(dpf) DCM adduct (15 mg, 0.02 mmol) was added. The mixture was then heated to 90°C for another 2 hours. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na\(_2\)SO\(_4\), filtered and the filtrate concentrated. The residue was purified by HPLC (10-70% MeCN / water with 0.1% formic acid). Fractions containing the product were combined and concentrated. The residue was slurried in hexane - ether and the solution was decanted and then concentrated to yield N-[6-[5-\{[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1-methyl-1H-benzimidazol-2-yl]acetamide as tan solid (22 mg, 24 % yield). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) ppm 10.65 (br. s., 1 H) 10.3 (br. s., 1 H) 8.33 (br. s., 1 H) 7.90 (d, \(J=1.6\) Hz, 1H) 7.68 - 7.82 (m, 2 H) 7.48 - 7.65 (m, 2 H) 7.41 (dd, \(J=8.3, 1.5\) Hz, 1 H) 7.20 (td, \(J=8.5, 2.1\) Hz, 1 H) 3.64 (s, 6 H) 2.15 (br. s., 3 H). ES-LCMS: 488.2 (M+1).
A mixture of piperdine (13 uL, 0.132 mmol), triethylamine (18 uL, 132 mmol), and (2S)-2-{2-amino-6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-1H-benzimidazol-1-yl}-3-methylbutanoic acid (35 mg, 0.66 mmol) in DMF (0.14 mL) was stirred at room temperature as T3P (18.4 uL, 0.132 mmol) was added drop wise. The solution was concentrated and the residue diluted with water and filtered to yield an off white solid. The solid purified by HPLC (10-70% MeCN water with 0.1% formic acid) to yield 2,4-difluoro-N-[5-[(3S)-3-(1-methylethyl)-2-oxo-2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]benzenesulfonamide (7.0 mg, 20% yield). 1H NMR (400 MHz, DMSO-cf) δ ppm 12.1 (br. s., 1 H) 10.29 (br. s., 1 H) 8.32 (br. s., 1 H) 7.87 (s, 1 H) 7.69 - 7.80 (m, 1 H) 7.45 - 7.68 (m, 3 H) 7.36 (d, J=8.4 Hz, 1 H) 7.08 - 7.29 (m, 1 H) 4.87 (br. s., 1 H) 3.63 (s, 3 H) 2.69 (td, J=6.8, 3.0 Hz, 1 H) 1.07 (d, J=6.8 Hz, 3 H) 0.87 (d, J=6.8 Hz, 3 H). ES-LCMS: 514.2 (M+1).

**Example 181**

N-[5-(2-amino-1-{[2-(4-morpholinyl)cyclohexyl]methyl}-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

[Image of molecule]

**Step A**

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An orange mixture of 4-bromo-2-fluoro-1-nitrobenzene (1 g, 9.09 mmol), ([2-(4-morpholiny)l]cyclohexyl)methyl]amine (0.901 g, 4.55 mmol) and Hunigs base (3.18 mL, 9.09 mmol) in DMF (3.2 mL) was allowed to stir at room temperature overnight. The resulting mixture was diluted with EtOAc (100 mL) and washed with a 5% LiCl solution (3x100 mL). The organic layer was concentrated and purified by silica gel chromatography (0-30% EtOAc/hexane). There were two bands of fractions which contained a product with the same mass. Spectra appear to show diastereomers. Fractions containing the first peak were combined and concentrated to obtain 5-bromo-N-[2-(4-morpholiny)l]cyclohexyl)methyl]-2-nitroaniline as a yellow oil, (0.65 g, 36%). Fractions containing the second peak were combined and concentrated to obtain (0.91g, 50%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.38 (t, $J$=5.3 Hz, 1 H) 7.98 (d, $J$=9.2 Hz, 1 H) 7.18 - 7.36 (m, 1 H) 6.70 - 6.88 (m, 1 H) 3.48 - 3.76 (m, 5 H) 3.25 - 3.42 (m, 1 H overlapping H$_2$0) 2.76 - 2.57 (m, 2 H) 2.27 - 2.43 (m, 2 H) 2.07 - 2.26 (m, 1 H) 1.49 - 1.95 (m, 5H) 1.09 - 1.31 (m, 4 H) ES-LCMS: 398.0 (M+1).

Step B

6-bromo-1-[(2-(4-morpholiny)l]cyclohexyl)methyl]-1H-benzimidazol-2-amine

A solution of 5-bromo-A-[(2-(4-morpholiny)l]cyclohexyl)methyl]-2-nitroaniline (0.91 g, 2.28 mmol) in EtOH (15 mL) and THF (15 mL) was stirred at room temperature as a solution of sodium hydrosulfite (3.18 g, 18.28 mmol) in water (15mL) was added. The solution was allowed to stir at RT for 18 hours. The solution was filtered and the filtrate concentrated to an off
white paste. The residue was partitioned between water and EtOAc. The aqueous layer was extracted with a second portion of EtOAc. The combined organic layers were dried with Na₂SO₄, filtered and concentrated to yield the crude product (0.698 g). The mixture was then carried forward without purification. A solution of this mixture in MeOH (4.75 mL) was treated with cyanogen bromine (475 mg, 4.48 mmol). The reaction mixture was maintained at room temperature for 2 hours, and then an additional CNBr (270 mg, 2.55 mmol) was added. The reaction mixture was allowed to stir for another 16 hours. The solution was concentrated and the residue partitioned between EtOAc (100 mL) and a sat. NaHCC⁺ solution (100 mL). The organic layer was washed with a sat. NaCl solution and then concentrated. The residue was slurried in DCM to obtain 6-bromo-1-([2-(4-morpholinyl)cyclohexyl]methyl)-1H-benzimidazol-2-amine (92 mg, 10%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.23 (s, 1 H) 6.94 - 7.13 (m, 2 H) 6.43 (s, 2 H) 4.07 - 4.21 (m, 1 H) 3.94 - 4.06 (m, 1 H) 3.48 (br. s., 4 H) 3.30 - 3.38 (br, m, 1 H overlapping H₂O) 2.38 (br. s., 4 H) 2.08 - 2.19 (m, 1 H) 1.77 (br. s., 2 H) 1.07 - 1.63 (m, 6 H) ES- LCMS: 393.0 (M+1).

Step C

N-[5-(2-amino-1-([2-(4-morpholinyl)cyclohexyl]methyl)-1H-benzimidazol-2-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

[00465] A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (54 mg, 0.127 mmol), 6-bromo-1-[[2-(4-morpholinyl)cyclohexyl]methyl]-1 H-benzimidazol-2-amine (50 mg, 0.127 mmol), and potassium carbonate (53 mg, 0.381 mmol) in dioxane (1.1 mL) and water (0.27 mL) was sparged with nitrogen as PdCl₂(dppe) DCM adduct (10 mg, 0.01 mmol) was added. The reaction mixture was then heated to 90°C for three hours. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na₂SO₄, filtered and the filtrate concentrated.

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residue was purified by HPLC (10-60% MeCN in water). Fractions containing the product were combined and concentrated and the residue was slurried in hexane - DCM then concentrated to yield N-[5-(2-amino-1-[(2-(4-morpholinyl)cyclohexyl)methyl]-1H-benzimidazol-6-yl)-2-(methylxoy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide as an off-white solid (10 mg, 13% yield) as an off-white solid, 1H NMR (400 MHz, DMSO-d6) δ ppm 8.15 (s, 1 H) 7.96 - 8.13 (m, 1 H) 7.62 - 7.82 (m, 2 H) 7.47 (br. s., 1 H) 7.01 - 7.26 (m, 4 H) 6.40 (br. s., 2 H) 3.97 - 4.28 (m, 2 H) 3.65 (s, 3 H) 3.48 (br. s., 4 H) 2.45 (dd, J=3.6, 1.9 Hz, 4 H) 2.10 - 2.21 (m, 1 H) 1.80 (br. s., 2 H) 1.14 - 1.65 (m, 8 H). ES-LCMS: 613.3 (M+1).

Example 182
(R)-tert-butyl 2-(2-amino-6-(5-(2,4-difluorophenylsulfonamido)-6-methoxypyridin-3-yl)-1H-benzo[d]imidazol-1-yl)-3-methylbutanoate

![Chemical Structure](image)

Step A

1. 1-dimethylethyl N-(5-bromo-2-nitrophenyl)-D-valinate

[00466] A mixture of 4-bromo-2-fluoro-1-nitrobenzene (4 g, 18.18 mmol), 1,1-dimethylethyl D-valinate (3.81 g, 18.18 mmol) and Hunigs base (9.53 mL, 54.5 mmol) in DMF (12.8 mL) was allowed to stir at room temperature for 8 hours. Additional 1,1-dimethylethyl D-valinate (0.76 g, 3.64 mmol) an Hunig’s base (1.9 mL, 10.9 mmol) was added and the mixture was allowed to stir at room temperature over the weekend. The resulting mixture was diluted
with EtOAc (200 mL) and washed with a 5% LiCl solution (3x100 mL). The organic layer was dried with Na$_2$SO$_4$, filtered then concentrated to yield yellow oil. The residue was purified by silica gel chromatography (0-30 % EtOAc in hexanes) to yield 1,1-dimethylethyl N-(5-bromo-2-nitrophenyl)-D-valinate (5.92 g, 87%) as a yellow oil. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.30 (d, J=8.0 Hz, 1 H) 8.03 (d, J=9.2 Hz, 1 H) 7.27 (d, J=2.0 Hz, 1 H) 6.92 (dd, J=9.0, 2.0 Hz, 1 H) 4.44 (dd, J=8.2, 4.9 Hz, 1 H) 2.22 (td, J=6.8, 5.1 Hz, 1 H) 1.43 (s, 9 H) 0.85 - 1.13 (m, 6 H). ES-LCMS: 373.3 (M+1).

**Step B**

(R)-tert-butyl 2-((2-amino-5-bromophenyl)amino)-3-methylbutanoate

![Chemical structure of (R)-tert-butyl 2-((2-amino-5-bromophenyl)amino)-3-methylbutanoate](image)

**[00467]** A solution of 1,1-dimethylethyl N-(5-bromo-2-nitrophenyl)-D-valinate (5.92 g, 15.86 mmol) in EtOH (103 mL) was stirred as a solution of sodium hydrosulfite (22.08 g, 127 mol) in water (103 mL) was added. The solution was allowed to stir at room temperature overnight. The resulting mixture was filtered and the solid was washed with EtOAc. The filtrate was concentrated and the residue partitioned between water and EtOAc. The organic layer was dried with Na$_2$SO$_4$, filtered and concentrated to yield (R)-tert-butyl 2-((2-amino-5-bromophenyl)amino)-3-methylbutanoate (4.92 g, 82% as 0.4 EtOAc). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 6.52 - 6.64 (m, 1 H) 6.41 - 6.51 (m, 2 H) 4.87 (br. s., 2 H) 4.79 (d, J = 9.0 Hz, 1 H) 3.36 - 3.53 (m, 1 H) 1.88 - 2.14 (m, 1 H) 1.28 - 1.51 (m, 9 H) 0.86 - 1.11 (m, 6 H).

**Step C**

1,1-dimethylethyl (2R)-2-((2-amino-6-bromo-1H-benzimidazol-1-yl)-3-methylbutanoate

![Chemical structure of 1,1-dimethylethyl (2R)-2-((2-amino-6-bromo-1H-benzimidazol-1-yl)-3-methylbutanoate](image)
A solution of 1,1-dimethylethyl N-(2-amino-5-bromophenyl)-D-valinate (4.46 g, 13 mmol) in MeOH (26 mL) was stirred as CNBr (2.75 g, 26 mmol) was added. The solution turned black and was allowed to stir at room temperature overnight. The solution was concentrated and the residue was partitioned between EtOAc and NaHCO₃ solution. The organic layer was dried with Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (20-100% EtOAc in hexanes) to yield 1,1-dimethylethyl (2R)-2-(2-amino-6-bromo-1H-benzimidazol-1-yl)-3-methylbutanoate as an orange brown solid (2.30 g, 44% as 0.40 EtOAc). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.36 (s, 1 H) 6.96 - 7.13 (m, 2 H) 6.67 (s, 2 H) 4.65 (d, J=10.7 Hz, 1 H) 2.64 (dt, J=10.8, 6.6 Hz, 1 H) 1.35 (s, 9 H) 1.08 (d, J=6.4 Hz, 3 H) 0.59 (d, J=6.6 Hz, 3 H). ES-LCMS: 368.2 (M+1).

Step D

(R)-tert-butyl 2-(2-amino-6-(5-(2,4-difluorophenylsulfonamido)-6-methoxypyridin-3-yl)-1H-benzo[d]imidazole-1-yl)-3-methylbutanoate

A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (87 mg, 0.204 mmol) and (R)-tert-butyl 2-(2-amino-6-bromo-1H-benzo[d]imidazole-1-yl)-3-methylbutanoate (75 mg, 0.204 mmol) and potassium carbonate (84 mg, 0.61 mmol) in dioxane (1.7 mL) and water (0.44 mL) was sparged with nitrogen as PdC^dppe DCM adduct (17 mg, 0.020 mmol) was added. The reaction mixture was then heated to 90°C for one hour and a half. The solution was then partitioned between EtOAc and brine. The organic layer was dried with Na₂SO₄, filtered and the filtrate concentrated. The residue was purified by silica gel chromatography (0-10% MeOH in DCM). The sample was further purified by reverse phase HPLC (10-70% MeCN-Water with 0.1 % Formic acid). Fractions containing product were combined and concentrated. The residue
was slurried in a solution of hexane and ether and then concentrated to yield (R)-tert-butyl 2-(2-amino-6-(5-(2,4-difluorophenylsulfonamido)-6-methoxypyridin-3-yl)-1H-benzo[d]imidazol-1-yl)-3-methylbutanoate as an off-white solid (28 mg, 23 % yield). $^1$H NMR (400 MHz, DMSO-cf$_e$) δ ppm 8.17 (d, J=1.4 Hz 1 H) 7.66 - 7.83 (m, 2 H) 7.51 - 7.63 (m, 1 H) 7.33 (s, 1H) 7.13 - 7.25 (m, 3 H) 6.63 (br. s., 2H) 4.70 (d, J=10.5 Hz, 1H) 3.64 (s, 3H) 2.73 (dt, J=10.6, 6.6 Hz, 1H) 1.34 (s, 9H) 1.12 (d, J=6.4 Hz, 3H) 0.62 (d, J=6.6 Hz, 3H) ES-LCMS: 588.5 (M+1).

**Example 183**

$N$-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide

![Chemical structure](image)

[00470] A mixture of $N$-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)cyclopropanesulfonamide (50 mg, 0.141 mmol), 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (52.7 mg, 0.141 mmol) and PdCl$_2$(dpff)-CH$_2$Cl$_2$ adduct (1.153 mg, 0.014 mmol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat. aq. 2 mL) was heated with a microwave irradiation for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product $N$-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide as a yellow solid (3.8 mg, 7.30 μmol, 5.17 % yield). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.16 (s, 1H), 7.72 (d, J = 2.35 Hz, 1H), 7.35 (d, J = 8.99 Hz, 2H), 7.21 - 7.31 (m, 2H), 7.15 (d, J = 8.99 Hz, 2H), 6.91 (d, J = 1.17 Hz, 1H), 6.26 (s, 2H), 4.10 (d, J = 5.28 Hz, 1H), 3.92 (s, 3H), 3.69 - 3.82 (m, 4H, 3.69 - 3.82 (m, 4H), 3.21 - 3.23 (m, 4H), 0.80 - 1.07 (m, 4H); ES-LCMS: 521.3 (M+1).

**Example 184**

$N$-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methylxy)-3-
A mixture of N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]-8-quinolinesulfonamide (50 mg, 0.113 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (42.3 mg, 0.113 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (9.25 mg, 0.011 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat. aq. 2 mL) was heated with a microwave irradiation for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give N-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-8-quinolinesulfonamide as a white solid (5.6 mg, 7.89%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.12 (dd, J = 4.30, 1.56 Hz, 2 H), 8.56 (dd, J = 8.31, 1.47 Hz, 1 H), 8.22 - 8.33 (m, 2 H), 7.92 - 8.01 (m, 1 H), 7.71 - 7.81 (m, 2 H), 7.61 (t, J = 7.82 Hz, 1 H), 7.34 (m, J = 8.99 Hz, 2 H), 7.24 (d, J = 8.21 Hz, 1 H), 7.18 (m, J = 8.99 Hz, 2 H), 7.13 (dd, J = 8.11, 1.66 Hz, 1 H), 6.77 (d, J = 1.37 Hz, 1 H), 6.26 (s, 2 H), 3.74 - 3.83 (m, 4 H), 3.41 (s, 3 H), 3.20 - 3.28 (m, 4 H); ES-LCMS: 608.3 (M+1).

**Example 185**

N-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-1-phenylmethanesulfonamide
A mixture of N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-1-phenylmethanesulfonamide (50 mg, 0.124 mmol), 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (46.2 mg, 0.124 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (10.10 mg, 0.012 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat. aq. 2 mL) was heated with a microwave irradiation for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-(methyloxy)-3-pyridinyl)-1-phenylmethanesulfonamide (5.0 mg, 8.32 μmol, 6.73 % yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.21 (s, 1 H), 8.05 (br. s., 1 H), 7.30 - 7.38 (m, 5 H), 7.10 - 7.29 (m, 7 H), 6.69 - 6.79 (m, 1 H), 6.24 (s, 2 H), 4.50 (s, 2 H), 3.93 (s, 3 H), 3.71 - 3.81 (m, 4 H), 3.19 - 3.28 (m, 4 H); ES-LCMS: 571.3 (M+1).

Example 186

N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-3,4-dimethoxybenzenesulfonamide

[00473] A mixture of 3,4-dimethoxy-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (50 mg, 0.11 mmol), 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (41.4 mg, 0.11 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (9.07 mg, 0.011 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat. aq. 2 mL) was heated with a microwave irradiation for 10 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-...
methoxypyridin-3-yl)-3,4-dimethoxybenzenesulfonamide (5.4 mg, 8.49 µmol, 7.65 % yield) as a yellow solid. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 9.73 (s, 1 H), 8.06 - 8.31 (m, 2 H), 7.65 (d, $J = 2.15$ Hz, 1 H), 7.39 (d, $J = 8.79$ Hz, 2 H), 7.13 - 7.34 (m, 4 H), 6.95 (d, $J = 8.60$ Hz, 1 H), 6.54 (s, 1 H), 6.54 (s, 1 H), 6.37 - 3.76 (m, 4H), 3.71 (s, 3 H), 3.69 (s, 3 H), 3.69 (s, 3 H), 3.20 - 3.28 (m, 4 H); ES-LCMS: 617.3 (M+1).

**Example 187**

$N$-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-1, 1, 1-trifluoromethanesulfonamide

![Chemical Structure](image)

[00474] A mixture of 1,1,1-trifluoro-$N$-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanesulfonamide (50 mg, 0.131 mmol), 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (48.8 mg, 0.131 mmol) and PdCl$_2$(dpdf)-CH$_2$Cl$_2$ adduct (10.68 mg, 0.013 mmol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat. aq. 2 mL) was heated with a microwave irradiation for 10 minutes at 130 °C. The reaction was cooled, diluted with ETOAc (20 mL), washed with water, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give $N$-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-1, 1, 1-trifluoromethanesulfonamide as a yellow solid (21.3 mg, 29.7%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.35 (br. s., 2 H), 7.75 (br. s., 1 H), 7.40 - 7.60 (m, 5 H), 7.21 (d, $J = 8.99$ Hz, 2 H), 6.93 (s, 1 H), 3.71 - 3.84 (m, 4 H), 3.77 (s, 3 H), 3.12 - 3.29 (m, 4 H); ES-LCMS: 549.4 (M+1).

**Example 188**

$N$-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-methyl-3-pyridinyl]-2,4-difluorobenzenesulfonamide
A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (45.5 mg, 0.122 mmol), 2,4-difluoro-N-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (50 mg, 0.122 mmol) and PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (9.95 mg, 0.012 mmol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat. aq. 2 mL) was heated with a microwave irradiation for 10 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give N-(5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-methyl-3-pyridinyl)-2,4-difluorobenzenesulfonamide (9.7 mg, 0.016 mmol, 13.1 % yield) as a white solid. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.43 (br. s., 1 H), 7.59 - 7.84 (m, 1 H), 7.47 (br. s., 2 H), 7.35 (d, J = 8.99 Hz, 2 H), 7.23 - 7.31 (m, 1 H), 7.03 - 7.23 (m, 4 H), 6.84 (s, 1 H), 6.35 (br. s., 2 H), 3.66 - 3.84 (m, 4 H), 3.21 - 3.28 (m, 4 H), 2.27 (s, 3 H); ES-MS: 577.4 (M+1).

Example 189
N-{5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-{[(1-methylethyl)oxy]-3-pyridinyl}benzenesulfonamide
A mixture of N-[2-[(1-methylethyl)oxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (50 mg, 0.120 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (44.6 mg, 0.120 mmol) and PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (9.95 mg, 0.012 mmol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat. aq. 2 mL) was heated with a microwave irradiation for 10 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give N-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]benzenesulfonamide (8.9 mg, 0.014 mmol, 12.10 % yield) as a yellow solid. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 9.76 (br. s., 1 H), 8.07 (s, 1 H), 7.66 - 7.90 (m, 2 H), 7.52 - 7.66 (m, 2 H), 7.41 - 7.52 (m, 2 H), 7.35 (d, $J$ = 8.99 Hz, 2 H), 7.22 - 7.30 (m, 1 H), 7.18 (d, $J$ = 8.99 Hz, 2 H), 6.80 (d, $J$ = 1.37 Hz, 1 H), 6.25 (s, 2 H), 4.98 - 5.12 (m, 1 H), 3.69 - 3.86 (m, 4 H), 3.12 - 3.29 (m, 4 H), 0.98 - 1.17 (m, 6 H); ES-LCMS: 585.4 (M+1).

**Example 190**

$N$-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-4-cyanobenzesulfonamide
cyanobenzenesulfonamide (17.8 mg, 0.028 mmol, 23.64 % yield) as a yellow solid. 1H NMR (400 MHz, DMSO-d₆) δ ppm 8.14 (s, 1 H), 8.00 (d, J = 8.21 Hz, 2 H), 7.86 (d, J = 8.40 Hz, 2 H), 7.65 (d, J = 1.95 Hz, 1 H), 7.37 (d, J = 8.79 Hz, 2 H), 7.15 - 7.30 (m, 4 H), 6.87 (s, 1 H), 6.34 (br. s., 2 H), 3.70 - 3.87 (m, 4 H), 3.56 (s, 3 H), 3.21 - 3.28 (m, 4 H); ES-LCMS: 582.2 (M+1).

Example 191

N-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2-methyl-1-propanesulfonamide

[00478] A mixture of 2-methyl-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]-1-propanesulfonamide (50 mg, 0.135 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (50.4 mg, 0.135 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (9.95 mg, 0.012 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat. aq. 2 mL) was heated with a microwave irradiation for 10 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and finally concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/0.05% H₂O + formic acid) to give the product N-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2-methyl-1-propanesulfonamide (4.1 mg, 7.26 μmol, 5.37 % yield) as a yellow solid. 1H NMR (400 MHz, DMSO-dce) δ ppm 9.29 (s, 1 H), 8.16 (d, J = 2.15 Hz, 1 H), 7.71 (d, J = 2.15 Hz, 2 H), 7.35 (d, J = 8.99 Hz, 2 H), 7.21 - 7.30 (m, 2 H), 7.14 (d, J = 8.99 Hz, 2 H), 6.91 (m, 1 H), 6.28 (br. s., 1 H), 3.91 (s, 3 H), 3.63 - 3.81 (m, 4 H), 3.14 - 3.27 (m, 4 H), 3.00 (d, J = 6.45 Hz, 2 H), 2.17 (m, 1 H), 0.96 - 1.15 (m, 6 H); ES-LCMS: 537.5 (M+1).

Example 192

N-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-
A mixture of N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (50 mg, 0.128 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (47.8 mg, 0.128 mmol) and PdCl$_2$(dpdf)-CH$_2$Cl$_2$ adduct (9.95 mg, 0.012 mmol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat. aq. 2 mL) was heated with a microwave irradiation for 10 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product N-[5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]benzenesulfonamide as a yellow solid (3.0 mg, 4.12% yield). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 9.93 (s, 1 H), 7.71 (d, $J$ = 7.42 Hz, 2 H), 7.37-7.60 (m, 5 H), 7.35 (d, $J$ = 8.79 Hz, 2 H), 7.22-7.30 (m, 2 H) 7.19 (d, $J$ = 8.98 Hz, 2 H), 6.75 (s, 1 H) 6.27 (br. s., 2 H), 3.75 - 3.81 (m, 4 H), 3.64 (s, 3 H), 3.20 - 3.30 (m, 4 H); ES-LCMS: 557.4 (M+1).
A mixture of 6-bromo-1-[3-(4-thiomorpholinyl)propyl]-1H-benzimidazol-2-amine (synthesized analogously as described in Example 207 Step A and Step B, 22 mg, 0.062 mmol), 2,4-difluoro-N-[2- (methylxylo)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (26.4 mg, 0.062 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (5.06 mg, 6.19 umol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat. aq. 2 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product N-[5-{2-amino-1-[3-(4-thiomorpholinyl)propyl]-1H-benzimidazol-6-yl}-2-(methylxylo)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (7.8 mg, 0.013 mmol, 20.82% yield) as a white solid. ¹H NMR (400 MHz, Methol-d₄) δ ppm: 10.29 (br. s., 1 H), 8.25 (s., 1 H), 7.71 - 7.92 (m, 2 H), 7.50 - 7.61 (m, 1 H), 7.37 (s, 1 H) 7.18 (t, J = 7.62 Hz, 3 H), 6.63 (br. s., 2 H), 4.03 (t, J = 6.25 Hz, 2 H), 3.62 (s, 3 H), 2.57 (s, 8 H), 2.28 (t, J = 6.55 Hz, 2 H) 1.86 (t, J = 6.55 Hz, 2 H); ES-LCMS: 575.4 (M+1).

**Example 194**

N-[5-{2-amino-1-[3-(tetrahydro-1,4-oxazepin-4(5H)-yl)propyl]-1H-benzimidazol-6-yl}-2-(methylxylo)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

A mixture of 6-bromo-1-[3-(tetrahydro-1,4-oxazepin-4(5H)-yl)propyl]-1H-benzimidazol-2-amine (synthesized analogously as described in Example 207 Step A and Step B, 18.5 mg, 0.052 mmol), 2,4-difluoro-N-[2- (methylxylo)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (22.32 mg, 0.052 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (5.06 mg, 6.19 umol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat. aq. 2 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid)
to give the product N-[5-{2-amino-1-[3-(tetrahydro-1,4-oxazepin-4(5H)-yl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (9.6 mg, 0.016 mmol, 30.7% yield) as a white solid. $^1$H NMR (400 MHz, Methanol-d$_4$) δ ppm 8.28 (br. s., 3H), 8.22 (br. s., 2H), 8.01 (br. s., 1H), 7.73 - 7.90 (m, 1H), 7.66 (br. s., 1H), 7.44 (br. s., 2H), 7.21 (t, J = 8.78 Hz, 1H), 7.00 - 7.10 (m, 1H), 4.27 (br. s., 2H), 3.82 (br. s., 2H), 3.77 (s, 2H), 3.25 (br. s., 2H), 3.19 (br. s., 2H), 3.12 (br. s., 2H), 2.65 (s, 2H), 2.24 (br. s., 2H), 2.06 (br. s., 2H); ES-LCMS: 573.3 (M+1).

Example 195

$N$-[5-{2-amino-1-[3-(4-hydroxy-1-piperidinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

A mixture of 1-[3-(2-amino-6-bromo-1H-benzimidazol-1-yl)propyl]-4-piperidinol (synthesized analogously as described in Example 207 Step A and Step B, 25.3 mg, 0.072 mmol), 2,4-difluoro-$N$-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (30.5 mg, 0.072 mmol) and PdCl$_2$(dpdf)-CH$_2$Cl$_2$ adduct (5.06 mg, 6.19 umol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat. aq. 2 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and finally concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product N-[5-{2-amino-1-[3-(4-hydroxy-1-piperidinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide as a white solid (9.6 mg, 23.41%). $^1$H NMR (400 MHz, Methanol-d$_4$) δ ppm 7.82 - 8.04 (m, 2H), 7.67 - 7.81 (m, 1H), 7.21 - 7.38 (m, 2H), 7.05 - 7.19 (m, 2H), 6.96 - 7.05 (m, 1H), 3.99 - 4.16 (m, 2H), 3.82 (m, 3H), 3.63 (s, 1H), 2.79 (br. s., 2H), 2.33 (t, J = 6.64 Hz, 2H), 2.13 (br. s., 2H), 1.96 - 2.08 (m, 2H), 1.78 - 1.95 (m, 2H), 1.42 - 1.63 (m, 2H); ES-LCMS: 573.5 (M+1).
Example 196

*\text{N-[5-\{2-amino-1-\{3-(1,1-dioxido-4-thiomorpholinyl)propyl\}-1H-benzimidazol-6-yl\}-2-(methyloxy)-3-pyridinyl\]-2,4-difluorobenzenesulfonamide}*

[00483] A mixture of 6-bromo-1-[3-(1,1-dioxido-4-thiomorpholinyl)propyl]-1H-benzimidazol-2-amine (synthesized analogously as described in Example 207 Step A and Step B, 36.2 mg, 0.093 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (39.8 mg, 0.093 mmol) and \( \text{PdCl}_2(\text{dpff}) \)-\( \text{CH}_2\text{Cl}_2 \) adduct (5.06 mg, 6.19 umol) in 1,4-dioxane (3 mL) and \( \text{NaHCO}_3 \) (sat. aq. 2 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over \( \text{Na}_2\text{SO}_4 \), filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H\(_2\)O + formic acid) to give the product \( \text{N-[5-\{2-amino-1-\{3-(1,1-dioxido-4-thiomorpholinyl)propyl\}-1H-benzimidazol-6-yl\}-2-(methyloxy)-3-pyridinyl\]-2,4-difluorobenzenesulfonamide} \) as a white solid (17.8 mg, 31.1%). \(^1\text{H NMR} (400 \text{ MHz}, \text{Methanol-d},) \delta \text{ ppm} 8.24 (s, 1 H), 7.66 - 7.89 (m, 2 H), 7.50 (br. s., 1 H), 7.30 (br. s., 1 H), 7.07 - 7.21 (m, 3 H), 7.01 (d, \text{J} = 8.01 \text{ Hz}, 1 H), 6.45 (s, 2 H), 3.98 - 4.13 (m, 4 H), 3.71 (s, 3 H), 2.93 - 3.07 (m, 4 H), 2.72 - 2.84 (m, 4 H), 2.43 (t, \text{J} = 6.55 \text{ Hz}, 2 H), 1.84 (t, \text{J} = 6.45 \text{ Hz}, 2H); \text{ES-LCMS}: 607.2 \text{ (M+1).} \)

Example 197

*\text{N-[5-\{2-amino-1-[3-\{4-fluoro-1-piperidinyl\}propyl\}-1H-benzimidazo^\text{^\text{a}}\text{yl}-2-(methyloxy)-3-pyridinyl\]-2,4-difluorobenzenesulfonamide}*

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A mixture of 6-bromo-1-[3-(4-fluoro-1-piperidinyl)propyl]-1H-benzimidazol-2-amine (synthesized analogously as described in Example 207 Step A and Step B, 14 mg, 0.039 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-3-pyridinyl]benzenesulfonamide (16.88 mg, 0.039 mmol) and PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (5.06 mg, 6.19 umol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat. aq. 2 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product N-[5-{2-amino-1-[3-(4-fluoro-1-piperidinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide as a white solid (3.0 mg, 13.25%). $^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$ ppm 8.19 (s, 1 H), 7.70 - 7.85 (m, 2 H), 7.45-7.59 (m, 1 H), 7.34 (br. s., 1 H), 7.07 - 7.21 (m, 3 H), 6.65 (s, 2 H), 4.01-4.10 (m, 2 H), 3.61 (s, 3 H), 3.50 (s, 2 H), 2.21-2.36 (m, 4 H), 1.76-1.89 (m, 4 H), 1.68 (br. s., 2 H), 1.28 (s, 1 H); ES-LCMS: 575.2 (M+1).

Example 198

N-[5-{2-amino-1-[3-(1-piperidinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide
A mixture of 6-bromo-1-[3-{1-piperidinyl}propyl]-1H-benzimidazol-2-amine (synthesized analogously as described in Example 207 Step A and Step B, 21 mg, 0.062 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (26.5 mg, 0.062 mmol) and PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (5.06 mg, 6.19 μmol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat. aq. 2 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, dried over Na$_2$SO$_4$, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product N-[5-{2-amino-1-[3-(1-piperidinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide as a white solid (6.1 mg, 17.42%). $^1$H NMR (400 MHz, Methanol-d$_4$) δ ppm 7.95 (br. s., 1 H), 7.78 (d, J = 7.23 Hz, 1 H), 7.61 (br. s., 1 H), 7.49 (br. s., 1 H), 7.22 (br. s., 1 H), 7.16 (d, J = 7.62 Hz, 2 H), 7.07 (d, J = 7.43 Hz, 1 H), 6.66 (br. s., 2 H), 4.01 (br. s., 2 H), 3.68 (br. s., 3 H), 2.33 (br. s., 4 H), 2.22 (br. s., 2 H), 1.79 - 2.06 (m, 2 H), 1.51 (br. s., 4 H), 1.39 (br. s., 2 H); ES-LCMS: 557.3 (M+1).

**Example 199**

\[
N-[5-{2-amino-1-[3-{(tetrahydro-2-furanyl)methyl}amino]propyl}-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide
\]

A mixture of 6-bromo-1-{3-[(tetrahydro-2-furanyl)methyl]amino}propyl)-1H-benzimidazol-2-amine (synthesized analogously as described in Example 207 Step A and Step B, 20.2 mg, 0.057 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (24.37 mg, 0.057 mmol) and PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (5.06 mg, 6.19 μmol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat. aq. 2 mL) was
heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product N-[5-{2-amino-1-[3-[(tetrahydro-2-furanylmethyl)amino]propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (9.5 mg, 0.017 mmol, 29.0 % yield) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ ppm 7.83 - 7.96 (m, 2 H), 7.79 (s, 1 H), 7.21 - 7.32 (m, 2 H), 7.06 - 7.21 (m, 2 H), 6.96 - 7.06 (m, 1 H), 4.15 (t, J = 6.45 Hz, 2 H), 3.98 (dd, J = 7.04, 4.49 Hz, 1 H), 3.81 (s, 3 H), 3.68 - 3.77 (m, 1 H), 2.54 - 2.77 (m, 4 H), 1.82 - 2.07 (m, 4 H), 1.52 (dd, J = 11.82, 8.1 Hz, 1 H); ES-MS: 573.3 (M+1).

**Example 200**

N-[5-{2-amino-1-[3-(2,6-dimethyl-4-morpholinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

[00487] A mixture of 6-bromo-1-[3-(2,6-dimethyl-4-morpholinyl)propyl]-1H-benzimidazol-2-amine (synthesized analogously as described in Example 207 Step A and StepB, 21.5 mg, 0.059 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (24.95 mg, 0.059 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (5.06 mg, 6.19 µmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat. aq. 2 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product N-[5-{2-amino-1-[3-(2,6-dimethyl-4-morpholinyl)propyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide as a white solid (15.2 mg, 44.3%). ¹H NMR (400 MHz, CDCl₃)
δ ppm 8.04 - 8.31 (m, 1 H), 7.98 (s, 1 H), 7.76-7.92 (m, 1 H), 7.46 (d, J = 8.19 Hz, 1 H), 7.20 - 7.28 (m, 1 H), 7.14 (s, 1 H), 6.85-7.02 (m, 2 H), 5.94 (br. s., 2 H), 4.09 (br. s., 2 H), 3.93 (s, 3 H), 3.70 (m, 2 H), 2.77 (d, J = 10.93 Hz, 2 H), 2.20 - 2.38 (m, 2 H), 2.07 (br. s., 2 H). 1.78 (t, J = 10.83 Hz, 2 H), 1.19 - 1.37 (m, 6 H); ES-LCMS: 587.3 (M+1).

**Example 201**

2-amino-6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridiny l-N,N-dimethyl-1H-benzimidazole-1-sulfonamide

![Chemical Structure](image)

To a solution of 2-amino-6-iodo-N,N-dimethyl-1H-benzimidazole-1-sulfonamide (36.3 mg, 0.099 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (42.2 mg, 0.099 mmol) and PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (5.06 mg, 6.19 umol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat. aq. 2 mL) was heated with a microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$S$_2$O$_4$, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 2-amino-6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridiny l-N,N-dimethyl-1 H-benzimidazole-1 -sulfonamide (12.1 mg, 0.022 mmol, 22.01 % yield) as a white solid. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 10.30 (s, 1 H), 8.19 (br. s., 1 H), 7.66 - 7.82 (m, 2 H), 7.49 - 7.66 (m, 2 H), 7.36 (d, J = 8.21 Hz, 1 H), 7.29 (d, J = 8.21 Hz, 1 H), 7.20 (m, 1 H), 6.99 (s, 2 H), 3.67 (s, 3 H), 2.92 (s, 6 H); ES-LCMS: 539.0 (M+1).

**Example 202**

N-[5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridiny l]-2,4-difluorobenzenesulfonamide

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To a solution of 1-(cyclopropylsulfonyl)-6-iodo-1H-benzimidazol-2-amine (34.1 mg, 0.094 mmol), potassium acetate (92 mg, 0.938 mmol) and PdCl$_2$(dpdf)-CH$_2$Cl$_2$ adduct (5.06 mg, 6.19 umol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat. aq. 2 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product N-[5-[2-amino-1-(cyclopropylsulfonyl)-1H-benzimidazol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (7.5 mg, 0.014 mmol, 14.92 % yield) as a white solid. $^1$H NMR (400 MHz, DMSO-de) $\delta$ 8.05 (br. s., 1 H), 7.78 (br. s., 1H), 7.43-7.72 (m, 3 H), 7.22-7.42 (m, 2H) 7.16 (br. s., 1H), 7.03 (br. s., 2 H), 3.67 (br. s., 3 H), 2.66 (br. s., 1 H), 1.33 (br. s., 2 H) 1.14 (br. s., 2 H); ES-LCMS: 536.2 (M+1).

**Example 203**

$N$-[5-[2-amino-1-[1-(4-morpholinylmethyl)cyclopropyl]methyl]-1H-benzimida^zol-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

A mixture of 6-bromo-1-[1-(4-morpholinylmethyl)cyclopropyl]methyl]-1 H-benzimidazol-2-amine (synthesized analogously as described in Example 161 Step A, Step B and Step C, 25.7 mg, 0.070 mmol)and 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-
A mixture of 6-bromo-1-[3-(4-morpholinyl)butyl]-1H-benzimidazol-2-amine (synthesized analogously as described in Example 161 Step A, Step B and Step C, 37.1 mg, 0.105 mmol), 2,4-difluoro-N-[2-(methylxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (44.8 mg, 0.105 mmol), potassium acetate (69.1 mg, 0.704 mmol) and PdCl2(dppf)-CH2Cl2 adduct (8.62 mg, 10.56 µmol) in 1,4-dioxane (3 mL) and H2O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na2SO4, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H2O + formic acid) to give the product N-[5-{2-amino-1-[3-(4-morpholinyl)butyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (15.5 mg, 0.025 mmol, 35.8 % yield) as a brown solid.

1H NMR (400 MHz, DMSO-c/e) δ 8.26 (br. s., 1 H), 8.15 (br. s., 1 H), 7.95 (br. s., 1 H), 7.82 (br. s., 1 H), 7.69-7.80 (m, 1 H), 7.51-7.62 (m, 1 H), 7.49 (br. s., 1 H), 7.20 (br. s., 2 H), 3.99 (br. s., 4 H), 3.62 (s, 3 H), 2.89 (br. s., 4H), 2.45 (br. s., 2H), 2.09 (br. s., 2H), 0.84 (br. s., 2H), 0.40 (br. s., 2 H); ES-LCMS: 585.4 (M+1).

Example 204

N-[5-{2-amino-1-[3-(4-morpholinyl)butyl]-1H-benzimidazol-6-yl}-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

[00491] A mixture of 1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (30 mg, 0.070 mmol), potassium acetate (69.1 mg, 0.704 mmol) and PdCl2(dppf)-CH2Cl2 adduct (8.62 mg, 10.56 µmol) in 1,4-dioxane (3 mL) and H2O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na2SO4, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H2O + formic acid) to give the product N-[5-{2-amino-1-[3-(4-morpholinyl)butyl]-1H-benzimidazol-6-yl}-2-
(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (18.4 mg, 0.032 mmol, 30.3 % yield) as a white solid. 1H NMR (400 MHz, DMSO-d6) δ 8.24 (br. s., 1 H), 8.13 (s, 1 H), 7.79 (br. s., 1 H), 7.70-7.78 (m, 1H), 7.50-7.62 (m, 1H), 7.34 (br. s., 1H), 7.12-7.24 (m, 2H), 6.67 (br. s., 2H), 4.02-4.12 (m, 2H), 3.62 (s, 3H), 3.50-3.59 (m, 4H), 2.22-2.28 (m, 2H), 1.80-1.92 (m, 2H), 1.64-1.77 (m, 2H); ES-LCMS: 573.3 (M+1).

Example 205

N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)thiophene-2-sulfonamide

Thiophene-2-sulfonyl chloride (15.79 mg, 0.086 mmol) was added to 6-(5-amino-6-methoxypyridin-3-yl)-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (30 mg, 0.072 mmol) in Pyridine (1 mL) and the solution was stirred at room temperature for 60 minutes. All the solvents were removed and the crude residue was purified by reverse phase chromatography (0-60% ACN/H2O + formic acid) to give the product N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)thiophene-2-sulfonamide (14.6 mg, 0.026 mmol, 35.7 % yield) as a white solid. 1H NMR (400 MHz, DMSO-d6) δ ppm 8.15 - 8.28 (m, 1H), 7.84 (dd, J = 4.98, 1.27 Hz, 1H), 7.61 (d, J = 2.35 Hz, 1H), 7.47 (dd, J = 4.98, 1.27 Hz, 1H), 7.36 - 7.45 (m, 3H), 7.33 (d, J = 6.64 Hz, 2H), 7.21 (d, J = 8.99 Hz, 2H), 6.99 - 7.15 (m, 1H), 6.75 - 6.98 (m, 2H), 3.74 - 3.88 (m, 4H), 3.71 (s, 3H), 3.12 - 3.29 (m, 4H); ES-LCMS: 563.2 (M+1).

Example 206

N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazoL6-y0-2-methoxypyridin-3-yl)-1-methyl-1H-indole-7-sulfonamide
1-methyl-1H-indole-7-sulfonyl chloride (19.85 mg, 0.086 mmol) was added to the solution of 6-(5-amino-6-methoxypyridin-3-yl)-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (30 mg, 0.072 mmol) in pyridine (1 mL). The solution was stirred at room temperature for 60 minutes. All the solvents were removed and the crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-1-methyl-1H-indole-7-sulfonamide (12.8 mg, 0.021 mmol, 28.9 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.02 (br. s., 1 H), 7.75 (d, J = 7.65 Hz, 1 H), 7.62 (d, J = 7.61 Hz, 1 H), 7.40 - 7.54 (m, 2 H), 7.32 (d, J = 8.98 Hz, 2 H), 7.18 (d, J = 8.98 Hz, 2 H), 7.22 (d, J = 8.19 Hz, 1 H), 7.05 - 7.12 (m, 1 H), 6.87 (m, 1 H), 6.69 (s, 2 H), 6.61 (d, J = 2.93 Hz, 2 H), 6.31 (br. s., 4 H), 4.23 (s, 3 H), 3.75 - 3.84 (m, 4 H), 3.72 (s, 3 H), 3.22 - 3.29 (m, 4 H); ES-LCMS: 610.3 (M+1).

**Example 207**

N-(5-(2-amino-1-(3-cyanopropyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

Step A

6-bromo-1-(3-chloropropyl)-1H-benzimidazol-2-amine
A mixture of 3-(2-amino-6-bromo-1H-benzimidazol-1-yl)-1-propanol (3.312 g, 12.3 mmol) in thionyl chloride (12.3 mL) was stirred at RT for 10 minutes then heated to reflux for 30 minutes. The resulting solution was allowed to cool before being concentrated. The residue was diluted with methanol (25 mL) and concentrated. The residue was diluted with water and K$_2$CO$_3$ solution was added drop wise to bring the pH to 8. The mixture was then filtered to yield 6-bromo-1-(3-chloropropyl)-1H-benzimidazol-2-amine as a tan solid (3.67 g,>100%). The crude solid was used without purification assuming theoretical yield. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 8.66 (br. s., 2 H) 7.76 (s, 1 H) 7.12 - 7.47 (m, 2 H) 4.23 (t, J=6.7 Hz, 2 H) 3.71 (t, J=6.7 Hz, 2 H) 2.03 - 2.21 (m, 2 H). LCMS: m/z 288.1 (MH$^+$).

Step B

4-(2-amino-6-bromo-1H-benzo[d]imidazol-1-yl)butanenitrile

A solution of 6-bromo-1-(3-chloropropyl)-1H-benzo[d]imidazol-2-amine (50 mg, 0.173 mmol) and sodium cyanide (8.49 mg, 0.173 mmol) with Nal (2 mg) in N,N-dimethylformamide (DMF) (3 mL) was stirred at 65 °C. After 16 hours, the reaction was diluted with EtOAc, washed with water, dried (brine, Na$_2$SO$_4$) and used directly in the subsequent reaction. ES-LCMS: 279.1, 281.1 (M+1).

Step C

$N$-(5-(2-amino-1-(3-cyanopropyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide
A degassed solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (73.7 mg, 0.173 mmol) and 4-(2-amino-6-bromo-1H-benzo[d]imidazol-1-yl)butanenitrile (48.3 mg, 0.173 mmol) with PdCl₂(dppf)-CH₂Cl₂ adduct (14.13 mg, 0.017 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat aq, 1 mL) was degassed, then heated with microwave irradiation to 120 °C. After cooling to room temperature, the reaction was diluted with EtOAc and water. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (10-90% ACN/ H₂O + formic acid). Isolation and lyophilization of the fractions gave the desired product as an off white solid. ¹H NMR (400 MHz, DMSO-δ6) δ ppm 8.35 (m, 1 H); 8.14 (s, 1 H), 7.90 (m, 1 H), 7.75 (m, 1 H), 7.62 (br. s., 1 H), 7.58 (m, 1 H), 7.42 (br. s., 1 H), 7.30 (m, 2 H), 7.20 (m, 1 H), 7.16 - 7.29 (m, 4 H), 4.11 (m, 2 H), 3.61 (s, 3H), 2.58 (m, 2 H), 2.02 (m, 2 H); ES+ LCMS: 499.3 (M+1).

Example 208

N-(5-(2-amino-1-(2-thiomorpholinoethyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyrindin-3-yl)-2,4-difluorobenzenesulfonamide

Step A

6-bromo-1-(2-thiomorpholinoethyl)-1H-benzo[d]imidazol-2-amine
A solution of 6-bromo-1-(2-chloroethyl)-1H-benzo[d]imidazol-2-amine (65 mg, 0.237 mmol) in thiomorpholine (1221 mg, 11.84 mmol) with NaI (2 mg) was stirred at 105 °C. After 3 hrs the reaction was diluted with EtOAc, washed with water, dried (brine, Na2SO4) and used directly in the subsequent reaction! ES-LCMS: 341.3, 343.3 (M+1).

**Step B**

N-(5-(2-amino-1-(2-thiomorpholinoethyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

A degassed solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (73.7 mg, 0.173 mmol) and 6-bromo-1-(2-thiomorpholinoethyl)-1H-benzo[d]imidazol-2-amine (59.2 mg, 0.173 mmol) with PdCl2(dppf)-CH2Cl2 adduct (14.13 mg, 0.017 mmol) in 1,4-dioxane (3 mL) and NaHCO3 (sat aq, 1 mL) was degassed, then heated with microwave irradiation to 120 °C. After cooling to room temperature, the reaction was diluted with EtOAc and water. The combined organics were washed with brine, dried over Na2SO4, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (10-90% ACN/ H2O + formic acid). Isolation and lyophilization of the fractions gave the desired product as an off white solid. 1H NMR (400 MHz, DMSO-d6) δ ppm 8.7 (br. s., 2H) 8.37 (m, 1 H), 8.14 (s, 1 H), 7.95 (m, 1 H), 7.82 (br. s., 1 H), 7.77 (m, 1 H), 7.58 (m, 1 H), 7.49 (m, 1 H), 7.45 (m, 1 H), 7.20 (m, 1 H), 4.29 (m, 2 H), 3.61 (s, 3H), 3.35 (br. s., 6 H), 2.73 (br. s., 4 H); ES+ LCMS: 561.3 (M+1).

**Example 209**

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Step A

4-(2-(2-amino-6-bromo-1H-benzo[d]imidazol-1-yl)ethyl)thiomorpholine 1,1-dioxide

[00499] A solution of chloride (65 mg, 0.237 mmol) with thiomorpholine dioxide (1600 mg, 11.84 mmol) in N,N-dimethylformamide (DMF) (3 mL) with NaI (2 mg) was stirred at 105 °C. After 3 hrs the reaction was diluted with EtOAc, washed with water, dried (brine, Na₂SO₄), and used directly in the subsequent reaction. ES-LCMS: 373.3, 375.3 (M+1).

Step B

N-(5-(2-amino-1-(2-(1,1-dioxidothiomorpholino)ethyl)-1H-benz[b]thiophen-2-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

[00500] A degassed solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.101 g, 0.237 mmol) and 4-(2-(2-amino-6-bromo-1H-benzo[d]imidazol-1-yl)ethyl)thiomorpholine 1,1-dioxide (0.088 g, 0.237 mmol) with
PdCl₂(dppf)-CH₂Cl₂ adduct (19 mg, 0.024 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat aq, 1 mL) was degassed, then heated with microwave irradiation to 120 °C. After cooling to room temperature, the reaction was diluted with EtOAc and water. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (10-90% ACN/H₂O + formic acid). Isolation and lyophilization of the fractions gave the desired product as an off white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.37 (m, 1 H), 7.90 (m, 1 H), 7.75 (m, 1 H), 7.59 (m, 2 H), 7.30 (m, 2 H), 7.21 (m, 1 H), 7.49 (m, 1 H), 7.45 (m, 1 H), 7.20 (m, 1 H), 4.23 (m, 2 H), 3.63 (s, 3 H), 3.30 (br. s., 8 H), 2.83 (m, 2 H); ES-LCMS: 593.3 (M+1).

**Example 210**

*N-(5-(2-amino-1H-phenyl-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide*

![Chemical Structure](image)

**Step A**

*4-bromo-2-nitro-N-phenylaniline*

![Chemical Structure](image)

[00501] A solution of 4-bromo-1-fluoro-2-nitrobenzene (1.8 g, 8.18 mmol), aniline (0.896 mL, 9.82 mmol) and DIEA (2.144 mL, 12.27 mmol) in N,N-dimethylformamide (DMF) (10 mL) was heated in a microwave to 120 °C for 20 minutes. The reaction was then poured onto ice and filtered to give the product which was used directly. ES-LCMS: 293.0, 295.0 (M+1).

**Step B**

*4-bromo-N1-phenylbenzene-1,2-diamine*
A solution of 4-bromo-2-nitro-N-phenylaniline (2.4 g, 8.2 mmol) in ethanol (100 mL) was treated with a solution of sodium dithionite (13 g, 65 mmol) in water (100 mL) and the mixture was heated in to 50 °C for 16 hrs. Diluted with EtOAc, dried with brine Na₂SO₄ and concentrated to an oil which was used directly. ES-LCMS: 263.0, 265.0 (M+1).

Step C

5-bromo-1-phenyl-1H-benzo[d]imidazol-2-amine

A solution of 4-bromo-N1-phenylbenzene-1,2-diamine (2.16 g, 8.2 mmol) in methanol (30 mL) was treated with cyanogen bromide (1.65 g, 16.4 mmol) and the mixture stirred for 3 hours. The reaction was partitioned between NaHCO₃ (aq.) and EtOAc and the organic layer dried (brine, Na₂SO₄), concentrated and triturated with DCM to give the product. ES-LCMS: 288.0, 288.0 (M+1).

Step D

N-(5-(2-amino-1-phenyl-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

A degassed solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.148 g, 0.347 mmol) 6-bromo-1-phenyl-1H-benzo[d]imidazol-2-amine (0.1 g, 0.237 mmol) with PdCl₂(dppf)-CH₂Cl₂ adduct (28 mg, 0.035 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat aq, 1 mL) was degassed, then heated with
microwave irradiation to 120 °C. After cooling to room temperature, the reaction was diluted with EtOAc and water. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (10-90% ACN/ H₂O + formic acid). Isolation and lyophilization of the fractions gave the desired product as an off white solid. 1H NMR (400 MHz, DMSO-d₆) δ ppm 8.17 (m, 1 H), 7.70-7.5 (m, 8 H), 7.29 (m, 1 H), 7.26 (m, 1 H), 7.13 (m, 1 H), 6.95 (m, 1 H), 6.45 (br. s., 2 H), 3.61 (s, 3 H); ES-LCMS: 508.3 (M+1).

Example 211

N-(5-(2-amino-1-(tert-butyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

Step A

4-bromo-N-(tert-butyl)-2-nitroaniline

[00505] A solution of 4-bromo-1-fluoro-2-nitrobenzene (2 g, 9.09 mmol), tert-butyl amine (0.997 g, 13.64 mmol) and DIEA (2.382 mL, 13.64 mmol) in N,N-dimethylformamide (DMF) (10 mL) was heated to 40 °C for 16 hrs. The reaction mixture was poured onto ice and the resulting precipitate filtered and used directly in the subsequent reaction. ES-LCMS: 273.0, 275.0 (M+1).

Step B

4-bromo-N1-(tert-butyl)benzene-1,2-diamine
A solution of 4-bromo-N-(tert-butyl)-2-nitroaniline compound (2.483 g, 9.09 mmol) in ethanol (100 mL) was treated with a solution of sodium dithionate (14.99 g, 72.7 mmol) in water (100 mL) and the mixture was heated in to 50 °C for 16 hrs. Diluted with EtOAc, dried with brine Na$_2$SO$_4$ and concentrated to an oil which was used directly. ES-LCMS: 243.0, 245.0 (M+1).

**Step C**

5-bromo-1-(tert-butyl)-1H-benz[d]imidazol-2-amine

A solution of 4-bromo-N1-(tert-butyl)benzene-1,2-diamine (2.210 g, 9.09 mmol) in methanol (30 mL) was treated with cyanogen bromide (1.926 g, 18.18 mmol) and the mixture stirred for 16 hours. Added an additional 2 g of cyanogen bromide and heated to 50 °C for 12 hours. Purified on silica gel eluting the desired product with 10% NH$_4$OH : 90% MeOH as a brown solid. ES-LCMS: 268.0, 270.0 (M+1).

**Step D**

N-(5-(2-amino-1-(tert-butyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

A degassed solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.127 g, 0.298 mmol) 6-bromo-1-(tert-butyl)-1 H-benzo[d]imidazol-2-amine (0.08 g, 0.298 mmol) with PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (25 mg, 0.03 mmol) in 1,4-dioxane (3 mL) and NaHCO$_3$ (sat aq. 1 mL) was degassed, then heated with microwave irradiation to 120 °C. After cooling to room temperature, the reaction was diluted with EtOAc and water. The combined organics were washed with brine, dried over
Na$_2$SO$_4$, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (10-90% ACN/ H$_2$O + formic acid). Isolation and lyophilization of the fractions gave the desired product as an off white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 8.27 (m, 1 H), 7.76 (m, 2 H), 7.59 (m, 2 H), 7.22 (m, 3 H), 6.55 (br. s., 2 H), 3.36 (s, 3 H), 1.79 (s, 9 H); ES-LCMS: 488.3 (M+1).

**Example 212**

$N$-(5-(2-amino-1-(2-phenylpropan-2-yl)-1H-benzo[d]imidazol-6-yl)-2-methoxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide

![Chemical Structure]

**Step A**

4-bromo-2-nitro-$N$-(2-phenylpropan-2-yl)aniline

![Chemical Structure]

**[00509]** A solution of 4-bromo-1-fluoro-2-nitrobenzene (2 g, 9.09 mmol), cumyl amine (1.475 g, 11 mmol) and DIEA (2.382 mL, 13.64 mmol) in N,N-dimethylformamide (DMF) (10 mL) was heated to 60 °C for 16 hrs. The reaction mixture was poured onto ice and the resulting precipitate filtered and used directly in the subsequent reaction. ES-LCMS: 335.0, 337.0 (M+1).

**Step B**

4-bromo-$N$1-(2-phenylpropan-2-yl)benzene-1,2-diamine

![Chemical Structure]
A solution of 4-bromo-2-nitro-N-(2-phenylpropan-2-yl)aniline (3.05 g, 9.09 mmol) in ethanol (100 mL) was treated with a solution of sodium dithionate (18.7 g, 91 mmol) in water (100 mL) and the mixture was heated in to 50 °C for 16 hrs. Then DCM (50 mL) was added and another 4 eq of dithionite in water (50 mL). After 30 minutes, the reaction was partitioned between DCM and water and the organic layer dried (brine, Na₂SO₄) and concentrated to give the crude product. ES-LCMS: 305.0, 307.0 (M+1).

**Step C**

5-bromo-1-(2-phenylpropan-2-yl)-1H-benzo[d]imidazol-2-amine

A solution of 4-bromo-N1-(tert-butyl)benzene-1,2-diamine (2.78 g, 9.09 mmol) in methanol (50 mL) was treated with cyanogen bromide (1.926 g, 18.18 mmol) and the mixture stirred for 16 hours at 50 °C. The mixture was next purified on silica gel, which eluted with the desired product in 10% NH₄OH : 90% MeOH as a light brown solid. ES-LCMS: 330.0, 332.0 (M+1).

**Step D**

N-(5-(2-amino-1-(2-phenylpropan-2-yl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzesulfonamide

A degassed solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.129 g, 0.3 mmol) 5-bromo-1-(2-phenylpropan-2-yl)-1H-benzo[d]imidazol-2-amine (0.1 g, 0.3 mmol) with PdCl₂(dpff)-CH₂Cl₂ adduct (25 mg, 0.03 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat aq, 1 mL) was degassed, then heated with microwave irradiation to 120 °C. After cooling to room temperature, the
reaction was diluted with EtOAc and water. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (10-90% ACN/ H₂O + formic acid). Isolation and lyophilization of the fractions gave the desired product as an off white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.91 (m, 1 H), 7.71 (m, 1 H), 7.59-7.50 (m, 2 H), 7.45-7.15 (m, 9 H), 6.75 (br. s., 2 H), 3.61 (s, 3 H), 2.08 (s, 6 H); ES-LCMS: 550.5 (M+1).

Example 213

*N-(5-(2-amino-1-((tetrahydro-2H-pyran-4-yl)methyl)O-1H-benzo[d]imidazol^\textregistered^yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide*

![Chemical Structure](image)

Step A

4-bromo-2-nitro-N-((tetrahydro-2H-pyran-4-yl)methyl)aniline

[00513] A solution of 4-bromo-1-fluoro-2-nitrobenzene (2 g, 9.09 mmol), (tetrahydro-2H-pyran-4-yl)methanamine(1 g, 10 mmol) and DIEA (2.382 mL, 13.64 mmol) in N,N-dimethylformamide (DMF) (10 mL) was heated to 60 °C for 16 hrs. The reaction mixture was poured onto ice and the resulting precipitate filtered and used directly in the subsequent reaction.ES-LCMS: 315.0, 317.0 (M+1).

Step B

4-bromo-N1-((tetrahydro-2H-pyran-4-yl)methyl)benzene-1,2-diamine
A solution of 4-bromo-2-nitro-N-((tetrahydro-2H-pyran-4-yl)methyl)aniline (2.87 g, 9.09 mmol) in ethanol (100 mL) was treated with a solution of sodium dithionate (15 g, 72 mmol) in water (100 mL) and the mixture was stirred for 30 minutes. Then DCM (50 mL) was added and the reaction was partitioned between DCM and water and the organic layer dried (brine, Na2S04) and concentrated to give the crude product. ES-LCMS: 285.0, 287.0 (M+1).

Step C
5-bromo-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-2-amine

A solution of 4-bromo-N1-((tetrahydro-2H-pyran-4-yl)methyl)benzene-1,2-diamine (2.6 g, 9.09 mmol) in methanol (50 mL) was treated with cyanogen bromide (1.56 g, 14.58 mmol) and the mixture stirred for 45 minutes. Purified on silica gel eluting the desired product with 10% NH4OH: 90% MeOH as a light brown solid. ES-LCMS: 310.0, 312.0 (M+1).

Step D
N-(5-(2-amino-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidaol-2-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

A degassed solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.137 g, 0.3 mmol) 5-bromo-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-2-amine (0.1 g, 0.3 mmol) with PdCl2(dppf)-CH2Cl2 adduct (26 mg, 0.03 mmol) in 1,4-dioxane (3 mL) and NaHCO3 (sat aq, 1 mL) was degassed,
then heated with microwave irradiation to 120 °C. After cooling to room temperature, the reaction was diluted with EtOAc and water. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (10-90% ACN/ H₂O + formic acid). Isolation and lyophilization of the fractions gave the desired product as an off white solid. ¹H NMR (400 MHz, DMSO-cf) δ ppm 8.28 (m, 1 H), 7.81 (m, 1 H), 7.75 (m, 1 H), 7.58 (m, 1 H), 7.48 (m, 1 H), 7.21-7.15 (m, 3H), 6.65 (br. s., 2 H), 3.94 (m, 2 H), 3.82 (m, 2H), 3.61 (s, 3 H), 3.20 (m, 2H), 1.38 (s, 5 H); ES-LCMS: 530.5 (M+1).

**Example 214**

\[
N-(5-(2-amino-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-benzo[d]imidazo[6-yl]-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide
\]

![Example 214](image)

**Step A**

4-bromo-2-nitro-N-((tetrahydro-2H-pyran-4-yl)ethyl)aniline

![Step A](image)

[00517] A solution of 4-bromo-1-fluoro-2-nitrobenzene (1.55 g, 7.05 mmol), (tetrahydro-2H-pyran-4-yl)ethanamine (1 g, 7.75 mmol) and DIEA (1.6 mL, 9.16 mmol) in N,N-dimethylformamide (DMF) (10 mL) was stirred at RT for 16 hrs. The reaction mixture was poured onto ice and the resulting precipitate filtered and used directly in the subsequent reaction. ES-LCMS: 329.0, 331.0 (M+1).

**Step B**

4-bromo-N1-((tetrahydro-2H-pyran-4-yl)ethyl)benzene-1,2-diamine

370
A solution of 4-bromo-2-nitro-N-((tetrahydro-2H-pyran-4-yl)ethyl)aniline (2.33g, 7.09 mmol) in ethanol (100 mL) was treated with a solution of sodium dithionate (11.6 g, 56.6 mmol) in water (100 mL) and the mixture was stirred for 30 minutes. Then DCM (50 mL) was added and the reaction was partitioned between DCM and water and the organic layer then dried (brine, Na2S04) and concentrated to give the crude product. ES-LCMS: 299.0, 301.0 (M+1).

Step C

5-bromo-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-benzo[d]imidazol-2-amine

A solution of 4-bromo-N1-((tetrahydro-2H-pyran-4-yl)ethyl)benzene-1,2-diamine (2.1 g, 7.08 mmol) in methanol (20 mL) was treated with cyanogen bromide (1.2 g, 11.3 mmol) and the mixture stirred for 45 minutes. Purified on silica gel eluting the the desired product with 10% NH4OH : 90% MeOH as a light brown solid. ES-LCMS: 324.0, 326.0 (M+1).

Step D

N-(5-(2-amino-1-(2-(tetrahydro-2H^-yran-4-yl)ethyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide
A degassed solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.131 g, 0.3 mmol) 5-bromo-1-((tetrahydro-2H-pyran-4-yl)ethyl)-1 H-benzo[d]imidazol-2-amine (0.1 g, 0.3 mmol) with PdCl₂(dppf)-CH₂Cl₂ adduct (26 mg, 0.03 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat aq, 1 mL) was degassed, then heated with microwave irradiation to 120 °C. After cooling to room temperature, the reaction was diluted with EtOAc and water. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (10-90% ACN/H₂O + formic acid). Isolation and lyophilization of the fractions gave the desired product as an off white solid. ¹H NMR (400 MHz, DMSO-cf) δ ppm 8.28 (m, 1 H), 7.81 (m, 1 H), 7.75 (m, 1 H), 7.58 (m, 1 H), 7.48 (m, 1 H), 7.21-7.15 (m, 3H), 6.65 (br. s., 2 H), 3.94 (m, 2 H), 3.76 (m, 2H), 3.61 (s, 3 H), 3.15 (m, 4H), 1.34 (s, 5 H); ES-LCMS: 544.5 (M+1).

Example 215

N-(5-(2-amino-1-(pyridin-2-ylmethanamine)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

![Chemical Structure]

Step A

4-bromo-2-nitro-N-(pyridin-2-ylmethaniline)

[00521] A solution of 4-bromo-1-fluoro-2-nitrobenzene (2 g, 9.09 mmol), (pyridin-2-ylmethanamine (1.18 g, 10.9 mmol) and DIEA (2.382 mL, 13.64 mmol) in N,N-dimethylformamide (DMF) (10 mL) was heated to 60 °C for 16 hrs. The reaction mixture was
poured onto ice and the resulting precipitate filtered and used directly in the subsequent reaction. ES-LCMS: 308.0, 310.0 (M+1).

**Step B**

4-bromo-N 1-(pyridin-2-ylmethyl)benzene-1,2-diamine

[00522] A solution of 4-bromo-2-nitro-N-(pyridin-2-ylmethyl)aniline (9.09 mmol) in ethanol (100 mL) was treated with a solution of sodium dithionate (15 g, 72 mmol) in water (100 mL) and the mixture was stirred for 30 minutes. Then DCM (50 mL) was added and the reaction was partitioned between DCM and water and the organic layer was then dried (brine, Na2SO4) and concentrated to give the crude product. ES-LCMS: 278.0, 280.0 (M+1).

**Step C**

5-bromo- 1-(pyridin-2-ylmethyl)- 1H-benzo[d]imidazol-2-amine

[00523] A solution of 4-bromo-N 1-(pyridin-2-ylmethyl)benzene-1,2-diamine (9.09 mmol) in methanol (50 mL) was treated with cyanogen bromide (1.56 g, 14.58 mmol) and the mixture stirred for 45 minutes. The mixture was then purified on silica gel, and the desired product was eluted with 10% NH2OH : 90% MeOH as a light brown solid. ES-LCMS: 303.0, 305.0 (M+1).

**Step D**

N-(5-(2-amino-1-(pyridin-2-ylmethyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide
A degassed solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.137 g, 0.3 mmol) 5-bromo-1-(pyridin-2-ylmethyl)-1H-benzo[d]imidazol-2-amine (0.1 g, 0.3 mmol) with PdCl₂(dpff)-CH₂Cl₂ adduct (26 mg, 0.03 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat aq, 1 mL) was degassed, then heated with microwave irradiation to 120 °C. After cooling to room temperature, the reaction was diluted with EtOAc and water. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (10-90% ACN/ H₂O + formic acid). Isolation and lyophilization of the fractions gave the desired product as an off white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.53 (m, 1 H), 8.22 (m, 1 H), 7.75-7.66 (m, 3 H), 7.55 (m, 1 H), 7.42 (m, 1 H), 7.31-7.11 (m, 7H), 5.46 (s, 2 H), 3.94 (m, 2 H), 3.59 (s, 3 H); ES-LCMS: 523.5 (M+1).

Example 216

N-(5-(2-amino-1-(2-morpholino-1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

Step A

4-bromo-N-(2-morpholino-1-phenylethyl)-2-nitroaniline

A solution of 4-bromo-1-fluoro-2-nitrobenzene (1 g, 4.55 mmol), 2-morpholino-1-phenylethanamine (0.94 g, 4.55 mmol) and DIEA (0.9 mL, 5.45 mmol) in N,N-dimethylformamide (DMF) (10 mL) was heated to 60 °C for 16 hrs. The reaction mixture was
poured onto ice and the resulting precipitate filtered and used directly in the subsequent reaction. ES-LCMS: 406.0, 408.0 (M+1).

Step B
4-bromo-N1-(2-morpholino-1-phenylethyl)benzene-1,2-diamine

[00526] A solution of 4-bromo-N-(2-morpholino-1-phenylethyl)-2-nitroaniline (4.55 mmol) in ethanol (100 mL) was treated with a solution of sodium dithionite (8 g, 38 mmol) in water (100 mL) and the mixture was stirred for 30 minutes. Next, DCM (50 mL) was added and the reaction was partitioned between DCM and water and the organic layer dried (brine, Na2SO4) and then concentrated to give the crude product. ES-LCMS: 376.0, 378.0 (M+1).

Step C
5-bromo-1-(2-morpholino-1-phenylethyl)-1H-benzo[d]imidazol-2-amine

[00527] A solution of 4-bromo-N1-(2-morpholino-1-phenylethyl)benzene-1, 2-diamine (4.55 mmol) in methanol (20 mL) was treated with cyanogen bromide (0.78 g, 7 mmol) and the mixture stirred for 45 minutes. The resulting mixture was then purified on silica gel and the desired product was eluted with 10% NH40H : 90% MeOH as a light brown solid. ES-LCMS: 401.0, 403.0 (M+1).

Step D
N-(5-(2-amino-1-(2-morpholino-1-phenylethyl)-1H-benzo[d]imidazol-6-yl)-2-m ethoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide
A degassed solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.137 g, 0.3 mmol) 5-bromo-1-(2-morpholino-1-phenylethyl)-1H-benzo[d]imidazol-2-amine (0.1 g, 0.3 mmol) with PdCl₂(dppf)-CH₂Cl₂ adduct (26 mg, 0.03 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat aq, 1 mL) was degassed, then heated with microwave irradiation to 120 °C. After cooling to room temperature, the reaction was diluted with EtOAc and water. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (10-90% ACN/ H₂O + formic acid). Isolation and lyophilization of the fractions gave the desired product as an off white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.09 (m, 1 H), 7.69 (m, 2 H), 7.55 (m, 2 H), 7.45 (m, 5 H), 7.32 (m, 2 H), 7.28-7.11 (m, 3H), 5.89 (m, 1 H), 3.94 (m, 2 H), 3.61 (s, 3 H), 2.63 (m, 2H), 2.35 (m, 2H) ; ES-LCMS: 621.5 (M+1).

**Example 217**

N-(5-(2-amino-1-(2-morpholino-2-phenylethyl)-1H-benzo[d]imidazol-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

Step A

4-bromo-N-(2-morpholino-2-phenylethyl)-2-nitroaniline
A solution of 4-bromo-1-fluoro-2-nitrobenzene (1 g, 4.55 mmol), 2-morpholino-2-phenylethanamine (0.94 g, 4.55 mmol) and DIPEA (0.9 mL, 5.45 mmol) in N,N-dimethylformamide (DMF) (10 mL) was heated to 60 °C for 16 hrs. The reaction mixture was poured onto ice and the resulting precipitate filtered and used directly in the subsequent reaction. ES-LCMS: 406.0, 408.0 (M+1).

Step B

4-bromo-N1-(2-morpholino-2-phenylethyl)benzene-1,2-diamine

A solution of 4-bromo-N-(2-morpholino-1-phenylethyl)-2-nitroaniline (4.55 mmol) in ethanol (100 mL) was treated with a solution of sodium dithionate (8 g, 38 mmol) in water (100 mL) and the mixture was stirred for 30 minutes. Next, DCM (50 mL) was added and the reaction was partitioned between DCM and water and the organic layer dried (brine, Na₂SO₄) and concentrated to give the crude product. ES-LCMS: 376.0, 378.0 (M+1).

Step C

5-bromo-1-(2-morpholino-2-phenylethyl)-1H-benz[d]imidazol-2-amine

A solution of 4-bromo-N1-(2-morpholino-2-phenylethyl)benzene-1,2-diamine (4.55 mmol) in methanol (20 mL) was treated with cyanogen bromide (0.78 g, 7 mmol) and the mixture stirred for 45 minutes. The resulting mixture was then purified on silica gel and the
desired product was eluted with 10% NH₄OH : 90% MeOH as a light brown solid. ES-LCMS:
401.0, 403.0 (M+1).

Step D

\[ N-(5\text{-}(2\text{-amino}-1\text{-}(2\text{-morpholino}-2\text{-phenylethyl})-1H\text{-benzo}[d]\text{imidazo}-6\text{-yl})-2\text{-methoxypyridin}-3\text{-yl})-2,4\text{-difluorobenzenesulfonamide} \]

[00532] A degassed solution of 2,4-difluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (0.137 g, 0.3 mmol) 5-bromo-1-(2-morpholino-2-phenylethyl)-1 H-benzo[d]imidazol-2-amine (0.1 g, 0.3 mmol) with PdCl₂(dppf)-CH₂Cl₂ adduct (26 mg, 0.03 mmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat aq, 1 mL) was degassed, then heated with microwave irradiation to 120 °C. After cooling to room temperature, the reaction was diluted with EtOAc and water. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by reverse phase chromatography (10-90% ACN/ H₂O + formic acid). Isolation and lyophilization of the fractions gave the desired product as an off white solid. \(^1\)H NMR (400 MHz, DMSO-cf) \( \delta \) ppm 8.27 (m, 1 H), 7.83 (m, 1 H), 7.75 (m, 1 H), 7.57 (m, 1 H), 744 (m, 1 H), 7.33-7.17 (m, 8H), 6.94 (br. s., 2 H), 4.77 (m, 1 H), 4.30 (m, 1 H), 4.00 (m, 1H) 3.61 (s, 3H), 2.57 (m, 2H), 2.20 (m, 2H); ES-LCMS: 621.5 (M+1).

**Example 218**

1-cyclopentyl-6-[5-(methylsulfonyl)-3-pyridinyl]-1H-benzimidazol-2-amine

![Chemical structure of the desired product as described in Example 218]
A degassed mixture of [5-(methylsulfonyl)-3-pyridinyl]boronic acid (38 mg, 0.189 mmol), 6-bromo-1-cyclopentyl-1H-benzo[d]imidazol-2-amine (53.0 mg, 0.189 mmol), Pd(dppf)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (15.44 mg, 0.019 mmol), potassium acetate (55.7 mg, 0.567 mmol) and 6-bromo-1-cyclopentyl-1H-benzimidazol-2-amine (53.0 mg, 0.189 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain 1-cyclopentyl-6-[5-(methylsulfonyl)-3-pyridinyl]-1H-benzo[d]imidazol-2-amine (15 mg, 0.040 mmol, 21.15% yield): $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.70 (br. s., 2 H) 1.98 (br. s., 4 H) 2.16 (br. s., 2 H) 3.41 (s, 3 H) 4.79 (quin, J=8.70 Hz, 1 H) 6.56 (s, 2 H) 7.28 (d, J=8.1 Hz, 1 H) 7.41 (d, J=8.21 Hz, 1 H) 7.52 (s, 1 H) 8.45 (s, 1 H) 8.95 (s, 1 H) 9.21 (s, 1 H); ES LC-MS m/z =357.5 (M+H)$^+$.

Example 219
6-[5-(methylsulfonyl)-3-pyridinyl]-1-[3-(4-morpholinyl)propyl]-1H-benzo[d]imidazol-2-amine

A degassed mixture of 3-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (52.6 mg, 0.186 mmol), 6-bromo-1-[3-(4-morpholinyl)propyl]-1H-benzo[d]imidazol-2-amine (63 mg, 0.186 mmol), Pd(dppf)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (15.17 mg, 0.019 mmol) and potassium acetate (54.7 mg, 0.557 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/EtOAc) to obtain 6-[5-(methylsulfonyl)-3-pyridinyl]-1-[3-(4-morpholinyl)propyl]-1H-benzo[d]imidazol-2-amine (15 mg, 0.034 mmol, 18.47% yield): $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.89 (quin, J=6.47 Hz, 2 H) 2.25 (t, J=6.60 Hz, 2 H) 2.32 (br.
Example 220

6-[5-(methylsulfonyl)-3-pyridinyl]-1-[(1S)-1-phenylethyl]-1H-benzimidazol-2-amine

[00535] A degassed mixture of [5-(methylsulfonyl)-3-pyridinyl]boronic acid (38.1 mg, 0.190 mmol), 6-bromo-1-[(1S)-1-phenylethyl]-1H-benzimidazol-2-amine (60 mg, 0.190 mmol), Pd(dppe)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (15.50 mg, 0.019 mmol) and potassium acetate (55.9 mg, 0.569 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated onto silica gel and purified by column chromatography (silica gel, 0-20% MeOH/ EtOAc) to obtain 6-[5-(methylsulfonyl)-3-pyridinyl]-1-[(1S)-1-phenylethyl]-1H-benzimidazol-2-amine (25 mg, 0.061 mmol, 31.9% yield) as a white solid: $^1$H NMR (400 MHz, DMSO-de) δ ppm 1.91 (d, J=7.02 Hz, 3 H) 3.36 (s, 3 H) 5.86 (q, J=6.99 Hz, 1 H) 6.71 (s, 2 H) 7.09 (s, 1 H) 7.22 - 7.33 (m, 2 H) 7.33 - 7.43 (m, 5 H) 8.24 (s, 1 H) 8.90 (d, J=1.66 Hz, 1 H) 8.96 (d, J=1.66 Hz, 1 H); ES LC-MS m/z =393.5 (M+H)$^+$.  

Example 221

1-(1,1-dimethylethyl)-6-[5-(methylsulfonyl)-3-pyridinyl]-1H-benzimidazol-2-amine

[00536] A degassed mixture of [5-(methylsulfonyl)-3-pyridinyl]boronic acid (45.0 mg, 0.224 mmol), 6-bromo-1-[(1,1-dimethylethyl)-1H-benzimidazol-2-amine (60 mg, 0.224 mmol),
Pd(dppf)$_2$Cl$_2$ CH$_2$Cl$_2$ adduct (18.27 mg, 0.022 mmol) and potassium acetate (65.9 mg, 0.671 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The resulting mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in CH$_2$Cl$_2$ and a small amount of MeOH, and filtered through a plug of Celite®. The filtrate was concentrated. The residue was dissolved in DMF, filtered and purified by HPLC (10-60% CH$_3$CN/H$_2$O), both containing 0.1% formic acid) to obtain 1-(1,1-dimethylethyl)-6-[5-(methylsulfonyl)-3-pyridinyl]-1H-benzimidazol-2-amine (47 mg, 0.14 mmol, 51.1 % yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 1.75 - 1.85 (m, 9 H) 3.40 (s, 3 H) 6.20 (br. s., 2 H) 7.25 (d, J=8.10 Hz, 1 H) 7.39 (dd, J=8.19, 1.37 Hz, 1 H) 7.80 (d, J=0.88 Hz, 1 H) 8.09 - 8.21 (m, 1 H) 8.43 (apparent t, J=2.05 Hz, 1 H) 8.95 (d, J=2.05 Hz, 1 H) 9.18 (d, J=2.05 Hz, 1 H); ES LC-MS $m/z$ =345.4 (M+H)$^+$. 

**Example 222**

6-[5-(methylsulfonyl)-3-pyridinyl]-1-(phenylsulfonyl)-1H-benzimidazol-2-amine

A degassed mixture of [5-(methylsulfonyl)-3-pyridinyl]boronic acid (35.2 mg, 0.175 mmol), 6-iodo-1-(phenylsulfonyl)-1H-benzimidazol-2-amine (70 mg, 0.175 mmol), Pd(dppf)$_2$Cl$_2$ CH$_2$Cl$_2$ adduct (14.32 mg, 0.018 mmol) and potassium acetate (51.6 mg, 0.526 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 50 °C overnight. The reaction mixture was allowed to cool to room temperature, then diluted with EtOAc (50 mL) and water (50 mL). The aq. layer was washed with CH$_2$Cl$_2$ (50 mL). The organic layers were combined, dried (Na$_2$SO$_4$), filtered and then concentrated. The residue was taken up into DMF and purified by HPLC (0-100% CH$_3$CN/H$_2$O), both containing 0.1% formic acid) to obtain 6-[5-(methylsulfonyl)-3-pyridinyl]-1-(phenylsulfonyl)-1H-benzimidazol-2-amine (18 mg, 0.040 mmol, 23.00 % yield) as a white solid: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 3.43 (s, 3 H) 7.30 (d, J=8.19 Hz, 1 H) 7.41 (s, 2 H) 7.59 - 7.70 (m, 3 H) 7.75 - 7.81 (m, 1 H) 8.02 (d, J=1.56 Hz, 1 H) 8.16 (d, J=1.17 Hz, 1 H) 8.18 (s, 1 H) 8.47 (J=2.15 Hz, 1 H) 9.03 (d, J=2.15 Hz, 1 H) 9.23 (d, J=2.15 Hz, 1 H); ES LC-MS $m/z$ =429.3 (M+H)$^+$. 

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Example 223
6-[6-(methyloxy)-5-(methylsulfonyl)-3-yl]pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

A degassed mixture of 2-(methyloxy)-3-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (88 mg, 0.281 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (70 mg, 0.188 mmol), Pd(dpdpf)$_2$Cl$_2$CH$_2$Cl$_2$ adduct (15.32 mg, 0.019 mmol) and potassium acetate (55.2 mg, 0.563 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C for 3 h. The reaction mixture was allowed to cool to room temperature then was diluted with EtOAc (50 mL) and H$_2$O (25 mL). The organic layer was dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated. The residue was taken up into DMF. The resulting slurry was filtered, solid washed with EtOAc and water to obtain 6-[6-(methyloxy)-5-(methylsulfonyl)-3-yl]pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (45 mg, 0.088 mmol, 47.0 % yield) as a grey solid: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 3.19 - 3.27 (m, 4 H) 3.31 (s, 3 H) 3.73 - 3.81 (m, 4 H) 4.05 (s, 3 H) 6.32 (s, 2 H) 6.97 (s, 1 H) 7.08 - 7.22 (m, 2 H) 7.24 - 7.39 (m, 4 H) 8.16 (d, J=2.54 Hz, 1 H) 8.69 (d, J=2.44 Hz, 1 H); ES LC-MS m/z =480.5 (M+H)$^+$. 

Example 224
N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)pyridin-2-yl)benzenesulfonamide
A degassed mixture of N-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)benzenesulfonamide (140 mg, 0.389 mmol), 6-bromo-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-2-amine (145 mg, 0.389 mmol), Pd(dppf)₂Cl₂·CH₂Cl₂ adduct (349 mg, 0.427 mmol) and potassium acetate (114 mg, 1.166 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a microwave apparatus at 130 °C for 15 min. The reaction mixture was allowed to cool to room temperature, then was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL) and CH₂Cl₂ (50 mL). The organic layers were concentrated onto Celite® and purified by HPLC to obtain N-(5-(2-amino-1-(4-morpholinophenyl)-1H-benzo[d]imidazol-6-yl)pyridin-2-yl)benzenesulfonamide (9.6 mg, 0.018 mmol, 4.69% yield) as a white solid: ¹H NMR (400 MHz, DMSO-de) δ ppm 3.17 - 3.26 (m, 4 H) 3.70 - 3.84 (m, 4 H) 6.23 (s, 2 H) 6.91 (s, 1 H) 7.13 (d, J=8.78 Hz, 3 H) 7.21 (s, 2 H) 7.32 (d, J=8.78 Hz, 2 H) 7.51 (d, J=7.61 Hz, 3 H) 7.86 (d, J=6.83 Hz, 3 H) 8.19 (br. s., 1 H); ES LC-MS m/z =527.3 (M+H)+.

Example 225

6-[5-(methylsulfonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), [5-(methylsulfonyl)-3-pyridinyl]boronic acid (20.09 mg, 0.100 mmol) and PdCl₂(dppf)·CH₂Cl₂ adduct (8.16 mg, 9.99 µmol) in 1,4-dioxane (3 mL) and NaHCO₃ (sat. aq. 2
mL) was heated with microwave irradiation for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 6-[5-(methylsulfonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine as a white solid (10.8 mg, 22.84%). ¹H NMR (400 MHz, DMSO-d6) δ ppm 9.12 (br. s., 1 H), 8.92 (br. s., 1 H), 8.36 (br. s., 1 H), 7.47 (d, J=8.01 Hz, 1 H), 7.31 - 7.41 (m, 3 H), 7.08 - 7.24 (m, 3 H), 6.37 (br. s., 2 H), 3.77 (m, 4 H), 3.37 (s, 3 H), 3.23 (m, 4 H); ES-LCMS: 450.4 (M+1).

Example 227

5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}^-N-(1,1-dimethylethyl)-3-pyridinecarboxamide

[00541] A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), (5-[(1,1-dimethylethyl)amino]carbonyl)-3-pyridinyl)boronic acid (22.19 mg, 0.100 mmol), PdCl₂(dppt)-CH₂Cl₂ adduct (8.16 mg, 9.99 umol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-N-(1,1-dimethylethyl)-3-pyridinecarboxamide (5.5 mg, 0.011 mmol, 11.46 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d6) δ ppm 8.84 - 8.89 (m, 1 H), 8.78 - 8.83 (m, 1 H), 8.20 (s, 1 H), 8.07 (s, 1 H), 7.29 - 7.44 (m, 4 H), 7.16 (d, J = 8.79 Hz, 2 H), 7.08 (s, 1 H), 6.33 (br. s., 2 H), 3.69 - 3.84 (m, 4 H), 3.18 - 3.26 (m, 4 H), 1.39 (s, 9 H); LCMS: 471.4 (M+1).
5-[2-aminophenyl]-1H-benzimidazol-6-yl]-N-methyl-2-pyridinecarboxamide

A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridinecarboxamide (26.2 mg, 0.100 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (8.16 mg, 9.99 µmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-[2-aminophenyl]-1H-benzimidazol-6-yl]-N-methyl-2-pyridinecarboxamide (6.1 mg, 0.014 mmol, 13.96 % yield) as a white solid.¹ NMR (400 MHz, DMSO-de) δ ppm 8.81 (d, J = 1.76 Hz, 1 H), 8.65 - 8.73 (m, 1 H), 8.11 (dd, J = 8.21, 2.15 Hz, 1 H), 7.99 (d, J = 8.21 Hz, 1 H), 7.44 (dd, J = 8.21, 1.56 Hz, 1 H), 7.30 - 7.39 (m, 3 H), 7.15 (d, J = 8.79 Hz, 2 H), 7.05 - 7.11 (m, 1 H), 6.35 (s, 2 H), 3.73 - 3.82 (m, 4 H), 3.19 - 3.27 (m, 4 H), 2.82 (d, J = 4.89 Hz, 3 H); LCMS: 429.4 (M+1).

Example 228

5-[2-aminophenyl]-1H-benzimidazol-L6-yl]-3-pyridinecarbonitrile

A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinecarbonitrile (22.99...
mg, 0.100 mmol), PdCl₂(dpff)-CH₂Cl₂ adduct (8.16 mg, 9.99 umol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-[2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl]-3-pyridinecarbonitrile (3.8 mg, 9.39 µmol, 9.40 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.08 (d, J = 2.35 Hz, 1 H), 8.86 (d, J = 1.95 Hz, 1 H), 8.53 (t, J = 2.05 Hz, 1 H), 7.44 (dd, J = 8.21, 1.76 Hz, 1 H), 7.35 (d, J = 8.99 Hz, 2 H), 7.31 (d, J = 8.21 Hz, 1 H), 7.15 - 7.19 (m, 2 H), 7.14 (s, 1 H), 6.36 (s, 2 H), 3.74 - 3.83 (m, 4 H), 3.20 - 3.27 (m, 4 H); LCMS: 397.3 (M+1).

Example 229

6-[5-(methyloxy)-3^yridinyl]-1-[4-(4-morphoUnyl)phenyl]-1H-benzimidazol-2-amine

[00544] A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (85 mg, 0.229 mmol), [5-(methyloxy)-3-pyridinyl]boronic acid (35 mg, 0.229 mmol), PdCl₂(dpff)-CH₂Cl₂ adduct (8.16 mg, 9.99 umol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 6-[5-(methyloxy)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1 H-benzimidazol-2-amine (28.3 mg, 0.069 mmol, 30.2 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.36 (br. s., 1 H), 8.20 (br. s., 1 H), 7.32 - 7.55 (m, 5 H), 7.17 (d, J = 8.01 Hz, 2 H), 7.09 (br. s., 1 H), 6.95 (br. s., 2 H), 3.87 (br. s., 3 H) 3.72-3.83 (m, 4 H), 3.21-3.29 (m, 4 H); LCMS: 402.4 (M+1).

Example 230
5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-3-pyridinecarboxamide

[00545] A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (73 mg, 0.196 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinecarboxamide (48.5 mg, 0.196 mmol), PdCl₂(dpff)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 5-{2-amino-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-6-yl}-3-pyridinecarboxamide (54.1 mg, 0.128 mmol, 65.4 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.90 (dd, J = 5.76, 2.05 Hz, 2 H), 8.31 (t, J = 2.15 Hz, 1 H), 8.25 (s, 1 H), 7.64 (s, 1 H), 7.43 - 7.49 (m, 1 H), 7.32 - 7.40 (m, 3 H), 7.17 (d, J = 8.98 Hz, 2 H), 7.08 - 7.14 (m, 1 H), 6.68 (br. s., 2 H), 3.73 - 3.80 (m, 4 H), 3.20 - 3.27 (m, 4 H); LCMS: 415.4 (M+1).

Example 231

6-[5-(4-morpholinylcarbonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

[00546] A mixture of 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), 4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinecarboxamide (48.5 mg, 0.196 mmol), PdCl₂(dpff)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 6-[5-(4-morpholinylcarbonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (55.4 mg, 0.128 mmol, 65.4 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.90 (dd, J = 5.76, 2.05 Hz, 2 H), 8.31 (t, J = 2.15 Hz, 1 H), 8.25 (s, 1 H), 7.64 (s, 1 H), 7.43 - 7.49 (m, 1 H), 7.32 - 7.40 (m, 3 H), 7.17 (d, J = 8.98 Hz, 2 H), 7.08 - 7.14 (m, 1 H), 6.68 (br. s., 2 H), 3.73 - 3.80 (m, 4 H), 3.20 - 3.27 (m, 4 H); LCMS: 415.4 (M+1).
Example 232

6-[(5,6-bis(methyloxy)-3-pyridinyl)-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

[00547] A mixture of 2-(methylsulfonfyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (56.6 mg, 0.200 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (74.6 mg, 0.200 mmol), PdCl2(dppf)-CH2Cl2 adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H2O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na2SO4, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H2O + formic acid) to give the product 6-[5-(4-morpholinylcarbonyl)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (12 mg, 0.023 mmol, 22.80 % yield) as a white solid. 1H NMR (400 MHz, DMSO-d6) δ ppm 8.85 (d, J = 2.15 Hz, 1 H), 8.48 (d, J = 1.76 Hz, 1 H), 7.95 (t, J = 2.05 Hz, 1 H), 7.34 - 7.42 (m, 3 H), 7.29 - 7.33 (m, 1 H), 7.12 - 7.18 (m, 2 H), 7.07 (d, J = 1.37 Hz, 1 H), 6.33 (br s., 2 H), 3.73 - 3.81 (m, 4 H), 3.61-3.67 (m., 4 H), 3.53-3.60 (m, 3 H), 3.20 - 3.26 (m, 4 H); LCMS: 485.3 (M+1).

Example 233

6-[5,6-bis(methyloxy)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

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A mixture of 2,3-bis(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (26.5 mg, 0.100 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (37.3 mg, 0.100 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (8.16 mg, 9.99 umol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product as a white solid (6.6mg, 14.7%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 7.81 (d, J = 1.95 Hz, 1 H), 7.38 (d, J = 1.76 Hz, 1 H), 7.36 (s, 1 H), 7.34 (s, 1 H), 7.27 (s, 2 H), 7.15 (d, J = 8.98 Hz, 2 H), 6.98 (s, 1 H), 6.22 (s, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.75 - 3.79 (m, 4 H), 3.19 - 3.24 (m, 4 H); LCMS: 432.3 (M+1).

Example 234

1-[4-(4-morpholinyl)phenyl]-6-[2-(trifluoromethyl)-3^yridinyl]-1H-benzimidazol-2-amine

A mixture of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (53.4 mg, 0.196 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (73.0 mg, 0.196 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product as a white solid (6.6mg, 14.7%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 7.81 (d, J = 1.95 Hz, 1 H), 7.38 (d, J = 1.76 Hz, 1 H), 7.36 (s, 1 H), 7.34 (s, 1 H), 7.27 (s, 2 H), 7.15 (d, J = 8.98 Hz, 2 H), 6.98 (s, 1 H), 6.22 (s, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.75 - 3.79 (m, 4 H), 3.19 - 3.24 (m, 4 H); LCMS: 432.3 (M+1).
acid) to give the product 1-[4-(4-morpholinyl)phenyl]-6-[2-(trifluoromethyl)-3-pyridinyl]-1H-benzimidazol-2-amine (14.1 mg, 0.031 mmol, 15.91 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-δ₆) δ ppm 8.68 (d, J = 3.51 Hz, 1 H), 7.89 (d, J = 7.22 Hz, 1 H), 7.69 (dd, J = 7.80, 4.68 Hz, 1 H), 7.31 (d, J = 8.78 Hz, 2 H), 7.26 (d, J = 8.19 Hz, 1 H), 7.12 (d, J = 8.98 Hz, 2 H), 6.95 - 7.01 (m, 1 H), 6.73 (s, 1 H), 6.32 (s, 2 H), 3.72 - 3.79 (m, 4 H); LCMS: 440.5 (M+1).

Example 235
6-[2-(methyloxy)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine

[00550] A mixture of [2-(methyloxy)-3-pyridinyl]boronic acid (31.1 mg, 0.204 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (76 mg, 0.204 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H₂O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/H₂O + formic acid) to give the product 6-[2-(methyloxy)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (31.7 mg, 0.076 mmol, 37.2 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-δ₆) δ ppm 8.08 (dd, J = 4.88, 1.76 Hz, 1 H), 7.64 (dd, J = 7.41, 1.76 Hz, 1 H), 7.33 (m, J = 8.78 Hz, 2 H), 7.17 - 7.27 (m, 2 H), 7.14 (m, J = 8.78 Hz, 2 H), 7.01 (dd, J = 7.32, 4.98 Hz, 1 H), 6.93 (s, 1 H), 6.32 (br. s., 2 H), 3.81 (s, 3 H), 3.73 - 3.79 (m, 4 H), 3.18 - 3.24 (m, 4 H); LCMS: 402.4 (M+1).

Example 236
6-[4-(methyloxy)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine
A mixture of 4-(methyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (47.9 mg, 0.204 mmol), 6-bromo-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (76 mg, 0.204 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H$_2$O + formic acid) to give the product 6-[4-(methyloxy)-3-pyridinyl]-1-[4-(4-morpholinyl)phenyl]-1H-benzimidazol-2-amine (12.0 mg, 0.029 mmol, 14.24 % yield) as a white solid. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.36 (d, J = 5.66 Hz, 1 H), 8.28 (s, 1 H), 7.33 (d, J = 8.78 Hz, 2 H), 7.24 (d, J = 8.00 Hz, 1 H), 7.10 - 7.17 (m, 3 H), 7.08 (d, J = 5.66 Hz, 1 H), 6.87 (d, J = 1.37 Hz, 1 H), 6.23 (s, 2 H), 3.79 (s, 3 H), 3.73 - 3.78 (m, 4 H), 3.17 - 3.24 (m, 4 H); LCMS: 402.4 (M+1).

**Example 237**

1-(cyclopropylsulfonyl)-6-[5-(methylsulfonyl)-3-pyridinyl]-1H-benzimidazol-2-amine

A mixture of 1-(cyclopropylsulfonyl)-6-iodo-1H-benzimidazol-2-amine (27.1 mg, 0.075 mmol), [5-(methylsulfonyl)-3-pyridinyl]boronic acid (15 mg, 0.075 mmol), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 mL) and H$_2$O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na$_2$SO$_4$, filtered, and then concentrated. The crude residue was purified by reverse phase
chromatography (0-60% ACN/ H₂O + formic acid) to give the product 1-(cyclopropylsulfonyl)-6-
[5-(methylsulfonyl)-3-pyridinyl]-1H-benzimidazol-2-amine (8.9 mg, 0.022 mmol, 29.8 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.21 (br. s., 1 H), 9.01 (br. s., 1 H), 8.48 (br. s., 1 H), 7.87 (br. s., 1 H), 7.60 - 7.75 (m, 1 H), 7.40 (br. s., 1 H), 7.15 (br. s., 2 H), 4.11 (br. s., 1 H), 3.41 (br. s., 3 H), 1.37 (br. s., 2 H), 1.16 (br. s., 2 H); LCMS: 393.2 (M+1).

Example 238

2-amino-N,N-dimethyl-6-[5-(methylsulfonyl)-3-pyridinyl]-1H-benzimidazole-1-sulfonamide

[00553] A mixture of 2-amino-6-iodo-N,N-dimethyl-1H-benzimidazole-1-sulfonamide (27.3 mg, 0.075 mmol), [5-(methylsulfonyl)-3-pyridinyl]boronic acid (15 mg, 0.075 mmol), PdCl₂(dpff)-CH₂Cl₂ adduct (14.91 mg, 0.018 mmol) and potassium acetate (98 mg, 0.999 mmol) in 1,4-dioxane (3.0 ml.) and H₂O (0.75 mL) was heated with microwave for 15 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (20 mL), washed with water, filtered, dried over Na₂SO₄, filtered, and then concentrated. The crude residue was purified by reverse phase chromatography (0-60% ACN/ H₂O + formic acid) to give the product 2-amino-N,N-dimethyl-6-
[5-(methylsulfonyl)-3-pyridinyl]-1H-benzimidazole-1-sulfonamide (8.3 mg, 0.021 mmol, 27.6 % yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 9.09 (s, 2 H), 8.37 (s, 1 H), 7.86 (s, 1 H), 7.49 (m, 2 H), 5.77 (br. s., 2 H), 3.18 (s, 3 H), 3.00 (s, 6 H); LCMS: 396.2 (M+1).
General Scheme 9

1. Suzuki Rxn #1
2. NBS
3. Suzuki Rxn #2
4. HCl, Dioxane
Example 239

N-[5-{2-amino-3-[4-(4-morpholinyl)phenyl]imidazo[1,2-a]pyridin-6-yl}-2-(meth yloxy)-3- pyridinyl]-2,4-difluorobenzencesulfonamide

Step A

*Methyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate*

[00554] A solution of 5-bromo-2-pyridinamine (7 g, 40.5 mmol) and methyl 3-bromo-2- oxopropanoate (9.52 g, 52.6 mmol) in ethanol (75 mL) was maintained at reflux for 16 hours. The solution was concentrated under reduced pressure and triturated from diethyl ether to afford methyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate (5.35 g, 20.97 mmol, 51.8 % yield) as a yellow solid. LCMS (m/z, ES+) = 256 (M+H).

Step B

6-bromoimidazo[1,2-a]pyridine-2-carboxylic acid

[00555] A solution of methyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate (1500 mg, 5.88 mmol) in tetrahydrofuran (25 mL) was treated with 1.0N NaOH (aq) (6.47 mL, 6.47 mmol) and maintained with rapid stirring for 3 hours. The mixture was acidified by dropwise addition of 5.0N HCl as to adjust the pH to about 2, and then stirring was stopped and a steady stream of air was maintained over the reaction for 3-4 hours so as to concentrate by roughly 1/2 (most THF evaporated).
The thick slurry was filtered and the solids dried under vacuum to afford 6-bromoimidazo[1,2-a]pyridine-2-carboxylic acid (1250 mg, 5.19 mmol, 88 % yield) as a yellow solid. LCMS (m/z, ES+) = 242 (M+H).

Step C
1. 1-dimethylethyl (6-bromoimidazo[1,2-a]pyridin-2-yl)carbamate

A solution of 6-bromoimidazo[1,2-a]pyridine-2-carboxylic acid (1.25 g, 5.19 mmol), triethylamine (2.168 mL, 15.56 mmol), and diphenylphosphorylazide (2.80 mL, 12.96 mmol) in tert-butanol (30 mL) was maintained at reflux for 3 hours. The solution was concentrated under reduced pressure, redissolved in ethyl acetate, and then washed with saturated sodium bicarbonate (aq). The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and finally purified by column chromatography to afford 1,1-dimethylethyl (6-bromoimidazo[1,2-a]pyridin-2-yl)carbamate (640 mg, 2.050 mmol, 39.5 % yield) as a yellow solid. LCMS (m/z, ES+) = 313 (M+H).

Step D
1. 1-dimethylethyl [6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl)carbamate

A solution of 1,1-dimethylethyl (6-bromoimidazo[1,2-a]pyridin-2-yl)carbamate (625 mg, 2.002 mmol), potassium carbonate (553 mg, 4.00 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (1067 mg, 2.503 mmol), and PdCl2(dppf)-CH2Cl2 adduct (164 mg, 0.200 mmol) in 1,4-dioxane
(12 ml_/water (3 mL) was maintained with stirring at 80°C for 2 hours. The solution was cooled, poured into ethyl acetate, and washed with water. The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and purified by silica gel chromatography (EtOAc/Hex). The fractions containing product were re-purified by silica gel chromatography (MeOH/CH₂Cl₂) to afford 1,1-dimethylethyl [6-[5-[[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]carbamate (880 mg, 1.656 mmol, 83 % yield) contaminated with roughly 2/3 mol% pinacol. LCMS (m/z, ES+) = 532 (M+H).

Step E

1. 1-dimethylethyl [3-bromo-6-[5-[[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]carbamate

A solution of 1,1-dimethylethyl [6-[5-[[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]carbamate (260 mg, 0.489 mmol) in N,N-dimethylformamide (5 mL) was maintained at 0°C and treated with NBS (91 mg, 0.514 mmol) in one portion. The mixture was maintained with stirring for 1 hour during which it was allowed to warm to room temperature. The solution was poured into ethyl acetate and washed with 5% LiCl (aq). The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and then purified by column chromatography to afford 1,1-dimethylethyl [3-bromo-6-[5-[[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]carbamate (200 mg, 0.328 mmol, 67.0 % yield) as a white solid. LCMS (m/z, ES+) = 611 (M+H).

Step F

1. 1-dimethylethyl [6-[5-[[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-yridinyl]-3-[4-(4-morpholiny1)phenyl]imidazo[1,2-a]pyridin-2-yl]carbamate
A solution of 1,1-dimethylethyl (3-bromo-6-[5-((2,4-difluorophenyl)sulfonyl)amino]-6-(methyloxy)-3-pyridinyl)imidazo[1,2-a]pyridin-2-yl)carbamate (200 mg, 0.328 mmol), [4-(4-morpholinyl)phenyl]boronic acid (119 mg, 0.573 mmol), potassium carbonate (136 mg, 0.983 mmol), and \( \text{PdCl}_2(\text{dppf})-\text{CH}_2\text{Cl}_2 \) adduct (40.1 mg, 0.049 mmol) in 1,4-dioxane (5 ml)/water (1 mL) was maintained at 80°C for 2 hours. The mixture was cooled to room temperature, poured into ethyl acetate, and washed with water. The organic layer was separated, dried over sodium sulfate, filtered, stripped onto Celite®, and then purified by column chromatography (0-75% EtOAc/CH₂Cl₂) to afford 1,1-dimethylethyl (6-[5-((2,4-difluorophenyl)sulfonyl)amino]-6-(methyloxy)-3-pyridinyl)-3-[4-(4-morpholinyl)phenyl]imidazo[1,2-a]pyridin-2-yl)carbamate (65 mg, 0.094 mmol, 28.6 % yield) as a white solid. LCMS (m/z, ES+) = 693 (M+H).

**Step G**

\[ \text{N-[5-(2-amino-3-[4-(4-morpholinyl)phenyl]imidazo[1,2-a]pyridin-6-yl]-2-(^\text{\textdegree} \text{ethyloxy})-3-pyridinyl]-2,4-difluorobenzenesulfonamide} \]

A solution of 1,1-dimethylethyl (6-[5-((2,4-difluorophenyl)sulfonyl)amino]-6-(methyloxy)-3-pyridinyl)-3-[4-(4-morpholinyl)phenyl]imidazo[1,2-a]pyridin-2-yl)carbamate (65 mg, 0.094 mmol) in 4.0M HCl in dioxane (4692 µl, 18.77 mmol) was maintained with stirring for 25 minutes. The solution was concentrated under reduced pressure, re-dissolved in a minimum (1 mL) of DMF, and purified by reverse phase hplc to afford N-[5-[2-amino-3-[4-(4-morpholinyl)phenyl]imidazo[1,2-a]pyridin-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (28 mg, 0.047 mmol, 50.4 % yield) as a yellow solid following lyophilization. ¹H NMR (DMSO-d₆) δ: 10.30 (br. s., 1H), 8.25 (s, 2H), 7.67 - 7.83 (m, 2H), 7.50 (d, J = 8.8 Hz, 3H), 7.26 - 7.40 (m, 2H), 6.97 - 7.21 (m, 3H), 5.10 (br. s., 2H), 3.69 - 3.85 (m, 4H), 3.62 (s, 3H), 3.1 1 - 3.23 (m, 4H). LCMS (m/z, ES+) = 593 (M+H).
Example 240
1,1-dimethylethyl {3-bromo-6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl}carbamate

[00562] A solution of 1,1-dimethylethyl {6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl}carbamate (540 mg, 1.016 mmol) in N,N-dimethylformamide (12 mL) was maintained at 0°C and treated with NBS (181 mg, 1.016 mmol) in one portion. The mixture was maintained with stirring for 1 hour during which it was allowed to warm to room temperature. The solution was poured into ethyl acetate and washed with 5% LiCl (aq). The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and then purified by column chromatography to afford 1,1-dimethylethyl {3-bromo-6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl}carbamate (626 mg, 1.026 mmol, 101% yield) as a white solid. 1H NMR (DMSO-d6) δ: 10.35 (s, 1H), 9.24 (s, 1H), 8.30 - 8.46 (m, 2H), 7.98 (d, J = 2.3 Hz, 1H), 7.77 (td, J = 8.5, 6.3 Hz, 1H), 7.51 - 7.70 (m, 3H), 7.22 (td, J = 8.5, 2.1 Hz, 1H), 3.66 (s, 3H), 1.46 (s, 9H). LCMS (m/z, ES+) = 611 (M+H).

Example 241
(1,1-dimethylethyl {6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl}carbamate
A solution of 1,1-dimethylethyl {3-bromo-6-[[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl}carbamate (200 mg, 0.328 mmol), [3-(4-morpholinyl)phenyl]boronic acid (170 mg, 0.819 mmol), potassium carbonate (136 mg, 0.983 mmol), and PdCl\(_2\)(dpdf)-CH\(_2\)Cl\(_2\) adduct (26.8 mg, 0.033 mmol) in 1,4-dioxane (5 ml)/water (1 mL) was maintained with stirring at 80°C for 3 hours. The mixture was cooled, poured into ethyl acetate, and washed with water. The aqueous layer was washed with DCM and the combined organic layers were dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and then purified by column chromatography to afford (1,1-dimethylethyl {6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl}carbamate (43 mg, 0.081 mmol, 24.69% yield, which was further purified by reverse phase hplc) and a lower spot (1,1-dimethylethyl {6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-3-[3-(4-morpholinyl)phenyl]imidazo[1,2-a]pyridin-2-yl}carbamate (93 mg, 0.134 mmol, 41.0% yield, which was used in a subsequent transformation) as yellow solids.

\(^1\)H NMR (DMSO-\(d_6\)) \(\delta\): 10.33 (br. s., 1H), 9.97 (br. s., 1H), 8.84 (s, 1H), 8.32 (d, \(J = 2.1\) Hz, 1H), 7.90 (d, \(J = 2.3\) Hz, 2H), 7.76 (td, \(J = 8.5, 6.3\) Hz, 1H), 7.53 - 7.64 (m, 1H), 7.46 (s, 2H), 7.20 (td, \(J = 8.4, 2.2\) Hz, 1H), 3.63 (s, 3H), 1.49 (s, 9H). LCMS (m/z, ES+) = 532 (M+H).

**Example 242**

N-[5-{2-amino-3-[3-(4-morpholinyl)phenyl]imidazo[1,2-a]pyridin-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

![Chemical Structure](image)

A solution of 1,1-dimethylethyl {6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-3-[3-(4-morpholinyl)phenyl]imidazo[1,2-a]pyridin-2-yl}carbamate (93 mg, 0.134 mmol) in 4.0N HCl in dioxanes (336 µL, 1.343 mmol) was maintained with stirring for 4 hours. A thick slurry was formed. The mixture was concentrated and the solids were triturated with diethyl ether and collected via vacuum filtration. The filtrated solids were extremely hydroscopic after 5 minutes. The filter apparatus was rinsed with methanol, and methanol...
filtrates were concentrated and the resulting residue was purified by reverse phase HPLC and lyophilized affording N-[5-[2-amino-3-[3-(4-morpholyl)phenyl]imidazo[1,2-a]pyridin-6-yl]-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (43 mg, 0.073 mmol, 54.0 % yield) as a yellow. \(^1\)H NMR (DMSO-d\(_6\)) \(\delta\): 10.29 (br. s., 1H), 8.37 (s, 1H), 8.22 - 8.29 (m, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.72 (td, J = 8.5, 6.4 Hz, 1H), 7.48 - 7.60 (m, 1H), 7.31 - 7.45 (m, 3H), 7.03 - 7.17 (m, 3H), 6.96 (dd, J = 8.3, 2.1 Hz, 1H), 5.22 (br. s., 2H), 3.69 - 3.81 (m, 4H), 3.10 - 3.25 (m, 4H).

LCMS (\(m/z\), ES+) = 593 (M+H).

**Example 243**

N-[6-[5-[[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]acetamide

![Chemical structure](attachment:image.png)

**Step A**

6-bromoimidazo[1,2-a]pyridin-2-amine

[00565] A solution of 1,1-dimethylethyl (6-bromoimidazo[1,2-a]pyridin-2-yl)carbamate (800 mg, 2.56 mmol) in dichloromethane (25 mL) was treated with trifluoroacetic acid (8.33 mL) and maintained with stirring at room temperature for 3 hours. The mixture was concentrated under reduced pressure, azeotroped three times from dichloromethane, and the resulting residue was triturated with diethyl ether. The solids were collected via vacuum filtration to afford 6-bromoimidazo[1,2-a]pyridin-2-amine (632 mg, 1.938 mmol, 76 % yield) as a yellow solid. LCMS (\(m/z\), ES+) = 327 (M+H).

**Step B**

N-(6-bromoimidazo[1,2-a]pyridin-2-yl)acetamide
A solution of 6-bromoimidazo[1,2-a]pyridin-2-amine (100 mg, 0.307 mmol), DIPEA (0.268 mL, 1.533 mmol), and DMAP (1.873 mg, 0.015 mmol) in dichloromethane (7 mL) was treated with acetic anhydride (0.087 mL, 0.920 mmol)-total 3 equivalents in three portions over 3 hours. The mixture was poured into saturated sodium bicarbonate and diluted with dichloromethane. The organic layer was separated, dried over sodium sulfate, concentrated, and the resulting residue was triturated with diethyl ether. The resulting solids were collected by vacuum filtration to afford N-(6-bromoimidazo[1,2-a]pyridin-2-yl)acetamide (55 mg, 0.216 mmol, 70.6 % yield) as a white solid. LCMS (m/z, ES+) = 255 (M+H).

Step C

N-{6-[5-[[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3^yridinyl]imidazo[1,2-a]pyridin-2-yl]acetamide

A solution of N-(6-bromoimidazo[1,2-a]pyridin-2-yl)acetamide (50 mg, 0.197 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (109 mg, 0.256 mmol), potassium carbonate (68.0 mg, 0.492 mmol), and PdCl$_2$(dpdf)-CH$_2$Cl$_2$ adduct (16.07 mg, 0.020 mmol) in N,N-dimethylformamide (1 mL)/water (0.250 mL) was maintained at 80 °C for 2 hours, cooled, filtered, and purified by reverse phase HPLC to afford N-{6-[5-[[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]acetamide (33 mg, 0.070 mmol, 35.4 % yield) as a white solid. $^1$H NMR (DMSO-d$_6$) δ: 10.73 (s, 1H), 8.90 (s, 1H), 8.32 (d, J = 2.3 Hz, 1H), 8.13 (d, J = 5.1 Hz, 2H), 7.91 (d, J = 2.3 Hz, 1H), 7.76 (td, J = 8.5, 6.4 Hz, 1H), 7.54 - 7.63 (m, 1H), 7.39 - 7.54 (m, 2H), 7.01 - 7.29 (m, 1H), 3.63 (s, 3H), 2.08 (s, 3H). LCMS (m/z, ES+) = 474 (M+H).

Example 244

N-[5-(2-aminomidazo[1,2-a]pyridin-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide
A solution of 6-bromoimidazo[1,2-a]pyridin-2-amine (50 mg, 0.236 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (131 mg, 0.307 mmol), potassium carbonate (81 mg, 0.589 mmol), and PdCl$_2$(dpff)-CH$_2$Cl$_2$ adduct (19.26 mg, 0.024 mmol) in N,N-dimethylformamide (1 ml)_water (0.250 mL) was maintained at 80 °C for 3 hours. The mixture was cooled to room temperature, filtered, and then purified by reverse phase HPLC to afford N-[5-(2-aminoimidazo[1,2-a]pyridin-6-yl)-2-(methyloxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide (30 mg, 0.070 mmol, 29.5 % yield) as a white solid following lyophilization. $^1$H NMR (DMSO-d$_6$) δ: 10.31 (br. s., 1H), 8.65 (s, 1H), 8.29 (d, J = 2.3 Hz, 1H), 7.86 (d, J = 2.3 Hz, 1H), 7.74 (td, J = 8.4, 6.5 Hz, 1H), 7.51 - 7.66 (m, 1H), 7.14 - 7.34 (m, 3H), 7.02 (s, 1H), 5.19 (br. s., 2H), 3.61 (s, 3H). LCMS (m/z, ES+) = 432 (M+H).

Example 245
N-[6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]benzamide

Step A
N-(6-bromoimidazo[1,2-a]pyridin-2-yl)benzamide
A solution of 6-bromoimidazo[1,2-a]pyridin-2-amine (150 mg, 0.460 mmol), DMAP (2.81 mg, 0.023 mmol), DIPEA (0.562 mL, 3.22 mmol), and benzoic anhydride (416 mg, 1.840 mmol) in dichloromethane (10 mL) was maintained with stirring at room temperature for 3 hours. The mixture was poured into sodium bicarbonate and diluted with additional dichloromethane. The organic layer was separated, dried over sodium sulfate, filtered, taken to a residue under reduced pressure, and then purified by column chromatography (MeOH/DCM). The fraction containing the product was then repurified by column chromatography (EtOAc/DCM) to afford N-(6-bromoimidazo[1,2-a]pyridin-2-yl)benzamide (55 mg, 0.174 mmol, 37.8 % yield) as a white solid. LCMS (m/z, ES+) = 317 (M+H).

Step B

N-{6-[[2,4-difluorophenyl)sulfonyl]amino}-6-(methyloxy)-3-pyridinylimidazo[1,2-a]pyridin-2-yl]benzamide

A solution of N-(6-bromoimidazo[1,2-a]pyridin-2-yl)benzamide (55 mg, 0.174 mmol), 2,4-difluoro-N-[2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (96 mg, 0.226 mmol), potassium carbonate (72.1 mg, 0.522 mmol), and PdCl₂(dppf)-CH₂Cl₂ adduct (14.21 mg, 0.017 mmol) in N,N-dimethylformamide (1 mL)/water (0.250 mL) was maintained at 80 °C for 1 hour. The mixture was cooled, filtered, and afterwards, the solution was injected directly into a reverse phase HPLC to afford after lyophilization of the pure fractions: N-{6-[5-[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinylimidazo[1,2-a]pyridin-2-yl}benzamide (40 mg, 0.075 mmol, 42.9 % yield) as a white solid. ¹H NMR (DMSO-d₆) δ: 11.28 (s, 1H), 10.35 (br. s., 1H), 8.96 (s, 1H), 8.35 (s, 2H), 8.03 - 8.14 (m, 2H), 7.92 (br. s., 1H), 7.71 - 7.82 (m, 1H), 7.39 - 7.65 (m, 6H), 7.12 - 7.28 (m, 1H), 3.64 (s, 3H). LCMS (m/z, ES+) = 536 (M+H).

Example 246

5-(2-aminoimidazo[1,2-a]pyridin-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide
Step A

*Methyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate*

A solution of 5-bromo-2-pyridinamine (7.0 g, 40.5 mmol) and methyl 3-bromo-2-oxopropanoate (9.52 g, 52.7 mmol) in ethanol was stirred at 100 °C. After 3 hrs, the reaction was cooled to room temperature and all the solvent was removed. The residue was used directly in the subsequent reaction. ES-LCMS: 257.3, 255.3 (M+1).

Step B

6-bromoimidazo [1,2-a]pyridine-2-carboxylic acid

A solution of methyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate (9.75 g, 38.2 mmol) in THF was treated with NaOH solution (5.0 N, 15 mL). The mixture was stirred at room temperature for 3 hrs and then HCl solution was added until the pH=5. The solution was washed with water for 3 times and dried over Na₂SO₄, filtered and concentrated to white solid which was used directly. ES-LCMS: 241.2, 243.2 (M+1).

Step C

1-dimethylethyl (6-bromoimidazo[1,2-a]pyridin-2-yl)carbamate
A mixture of 6-bromoimidazo[1,2-a]pyridine-2-carboxylic acid (7.2 g, 30 mmol), diphenyl azidophosphate (16.5 g, 60 mmol) and Et$_3$N (6.1 g, 60 mol) in 150 mL t-Butyl alcohol was stirred at 100 °C overnight. All the solvent was removed and the residue was purified on silica gel column to give the product 1,1-dimethylethyl (6-bromoimidazo[1,2-a]pyridin-2-yl)carbamate as a white solid (4.56 g, 14.6 mmol). ES-LCMS: 312.4, 314.4 (M+1).

**Step D**

1, 1-dimethylethyl {6-[5-[(1,1-dimethylethyl)amino]sulfonyl]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl}carbamate

A mixture of N-(1,1-dimethylethyl)-2-(methyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinesulfonamide (3.7 g, 10 mmol), 1-dimethylethyl (6-bromoimidazo[1,2-a]pyridin-2-yl)carbamate (3.12 g, 10 mmol), (dppf)-CH$_2$Cl$_2$ adduct (0.83 g, 1 mmol) and potassium phosphate (5.76 g, 60 mmol) in 1,4-dioxane (8 mL) and H$_2$O (2 mL) was heated by microwave irradiation for 30 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (100 mL), washed with water, dried over Na$_2$SO$_4$, filtered, and then concentrated. The crude residue was purified by silica gel column to give the product 1,1-dimethylethyl {6-[5-[(1,1-dimethylethyl)amino]sulfonyl]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl}carbamate as a white solid (2.66 g, 5.6 mmol). ES-LCMS: 476.2 (M+1).

**Step E**

5-(2-aminoimidazo[1,2-a]pyridin-6-yl)-N-(1,1-dimethylethyl)-2-(methyloxy)-3-pyridinesulfonamide
1,1-dimethylethyl \{6-[5-[(1,1-dimethylethyl)amino]sulfonyl]-6-(methyloxy)-3-pyridinyl\}imidazo[1,2-a]pyridin-2-yl\}carbamate was treated with 1 mL TFA at room temperature for 0.5 h, poured into 20 mL EtOAc and treated with 2 mL pyridine. The solution was washed with water 3 times and dried over Na$_2$SO$_4$, filtered and then all of the solids were removed. The residue was purified on silica gel column to give the product 5-(2-aminoimidazo[1,2-a]pyridin-6-yl)-N-(1,1-dimethylethyl)-2-(methyloxy)-3-pyridinesulfonamide as a yellow solid (75 mg, 95%). 1H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 9.09 (s, 1 H), 8.77 (d, $J = 2.54$ Hz, 1 H), 8.40 (d, $J = 2.34$ Hz, 1 H), 7.97 (dd, $J = 9.17$, 1.37 Hz, 1 H), 7.68 (d, $J = 9.17$ Hz, 1 H), 7.59 (s, 1 H), 7.23 (s, 1 H), 4.07 (s, 4 H), 1.10 (s, 9 H); ES-LCMS: 376.2 (M+1).

**Example 247**

\[ N-(6-(5-(N-(tert-butyl)sulfamoyl)-6-methoxypyridin-3-y0imidazo[1,2-a]pyridin-2-y1)acetamide \]

5-(2-aminoimidazo[1,2-a]pyridin-6-yl)-N-(tert-butyl)-2-methoxypyridine-3-sulfonamide (30 mg, 0.080 mmol) was treated with acetic anhydride (530 mg, 5.19 mmol) and the solution was stirred at room temperature for 0.5 h. The solution was poured into 20 mL of water and saturated Na$_2$CO$_3$ solution was added until the PH = 7. The solution was poured into
50 mL of EtOAc and washed with water for 3 times. The solution was dried over MgSO₄ and filtered, all the solvents were removed and the residue was purified on an ISCO silica gel column to give the product N-(6-(5-(N-(tert-butyl)sulfamoyl)-6-methoxypyridin-3-yl)imidazo[1,2-a]pyridin-2-yl)acetamide (15.5 mg, 0.036 mmol, 45.5 %, yield) as a white solid. 1H NMR (400 MHz, DMSO-d₆) δ ppm 10.75 (s, 1 H), 9.01 (s, 1 H), 8.72 (d, J = 2.34 Hz, 1 H), 8.35 (d, J = 2.54 Hz, 1 H), 8.13 (s, 1 H), 7.49 - 7.62 (m, 3 H), 4.06 (s, 3 H), 2.08 (s, 3 H), 1.11 (s, 9 H); ES-LCMS: 418.3 (M+1).

Example 248

N-(5-(2-amino-3-(4-cyanophenyl)imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

Step A

1,1-dimethylethyl [6-[5-[[2,4-difluorophenyl]sulfonyl]amino]-6-(methyloxy)-3-pyridinylimidazo[1,2-a]pyridin-2-yl]carbamate

[00577] A mixture of 2,4-difluoro-N-[2-(methyloxy)-5-(4,4',5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]benzenesulfonamide (4.26 g, 10 mmol), 1-dimethylethyl (6-bromimidazo[1,2-a]pyridin-2-yl)carbamate (3.12 g, 10 mmol), (dppe)-CH₂Cl₂ adduct (0.83 g, 1 mmol) and potassium phosphate (5.76 g, 60 mmol) in 1,4-Dioxane (8 mL) and H₂O (2 mL) was heated with microwave for 30 minutes at 130 °C. The reaction was cooled, diluted with EtOAc (100 mL), washed with water, dried over Na₂SO₄, filtered, and then concentrated. The crude
residue was purified by silica gel column to give the product 1,1-dimethylethyl (6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]carbamate as a white solid (3.40 g, 6.4 mmol). ES-LCMS: 532.2 (M+1).

Step B
1. 1-dimethylethyl {6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]-3-iodoimidazo[1,2-a]pyridin-2-yl]carbamate

[00578] 1,1-dimethylethyl {6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]carbamate (1.06 g, 20 mmol) in 5 mL DMF was treated with NIS (0.495 g, 22.0 mmol) at room temperature for 1 h. The solution was poured into 200 mL EtOAc and washed with water, dried over Na₂SO₄, filtered, and then concentrated to give the product as a brown solid which was used directly. ES-LCMS: 658.3 (M+1).

Step C
1. 1-dimethylethyl {3-(4-cyanophenyl)-6-[5-[(2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinyl]imidazo[1,2-a]pyridin-2-yl]carbamate

[00579] A mixture of PdCl₂(dppf)-CH₂Cl₂ adduct (8.20 mg, 10.04 pmol), potassium phosphate (213 mg, 1.004 mmol), 2-(4-isocyanophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (23.00 mg, 0.100 mmol), tert-butyl (6-(5-(2,4-difluorophenylsulfonyl)-6-methoxypyridin-3-yl)-
3-iodoimidazo[1,2-a]pyridin-2-yl)carbamate (66 mg, 0.100 mmol) in 1,4-Dioxane (3 mL) and water (0.75 ml) was heated to 100 °C by microwave for 15 mins. The reaction was cooled, diluted with EtOAc (100 mL), washed with water, dried over Na₂SO₄, filtered, and then concentrated. The residue was purified on silica gel column to give the product 1,1-dimethylthyl 3-(4-cyanophenyl)-6-[5-[[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinylimidazo[1,2-a]pyridin-2-yl)carbamate as a white solid (24.7 mg, 0.040 mmol, 40% yield). ES-LCMS: 618.4 (M+1).

Step D

N-[5-[2-amino-3-(4-cyanophenyl)imidazo[1,2-a]pyridin-6-yl]-2-(methoxy)-3-pyridinyl]-2,4-difluorobenzenesulfonamide

[00580] 1,1-dimethylthyl 3-(4-cyanophenyl)-6-[5-[[2,4-difluorophenyl)sulfonyl]amino]-6-(methyloxy)-3-pyridinylimidazo[1,2-a]pyridin-2-yl)carbamate as a white solid (24.7 mg, 0.04 mmol) was treated with TFA (0.5 mL) at room temperature for 30 minutes. The solution was poured into 20 mL EtOAc and then treated with 1 mL Et₃N. Next, it was washed with water, dried over Na₂SO₄, filtered, and then concentrated to give the product N-(5-(2-amino-3-(4-cyanophenyl)imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (20.2 mg, 0.037 mmol, 92.5 % yield) as a yellow solid. 1 H NMR (400 MHz, DMSO-d₆) δ ppm 10.29 (br. s., 1 H), 8.51 (s, 1 H), 8.31 (br. s., 1 H), 7.81 - 7.97 (m, 5 H), 7.69 - 7.76 (m, 1 H), 7.56 (br. s., 1 H), 7.42 (s, 2 H), 7.16 (br. s., 1 H), 5.63 (s, 2 H), 3.62 (s, 3 H); ES-LCMS: 533.2 (M+1).

Example 249

N-(5-(2-amino-3-(4-(dimethylamino)phenyl)imidazo[1,2-a]pyridin-6-yl)-2-m ethoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide
A mixture of PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (8.20 mg, 10.04 µμI), potassium phosphate (213 mg, 1.004 mmol), tert-butyl (6-(5-(2,4-difluorophenylsulfonamido)-6-methoxypyridin-3-yl)-3-iodoimidazo[1,2-a]pyridin-2-yl)carbamate (66 mg, 0.100 mmol), N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (24.81 mg, 0.100 mmol) in 1,4-Dioxane (3 mL) and water (0.75 ml) was heated to 100 °C by microwave for 15 mins. The reaction was then cooled, diluted with EtOAc (100 mL), washed with water, dried over Na$_2$SO$_4$, filtered, and finally concentrated. Next, the residue was purified via silica gel column and then treated with TFA (0.25 mL, 3.24 mmol) at room temperature for 1 h. The solution was poured into 20 mL EtOAc and then treated with Et$_3$N. It was then washed with water, dried over Na$_2$SO$_4$, filtered, and concentrated to give the product N-(5-(2-amino-3-(4-(dimethylamino)phenyl)imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (10.7 mg, 0.019 mmol, 18.78 % yield) as a yellow solid.

1H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.16 (s, 1 H), 8.08 (d, J = 2.34 Hz, 1 H), 7.85 (d, J = 2.34 Hz, 1 H), 7.80 (td, J = 8.49, 6.24 Hz, 1 H), 7.39 - 7.47 (m, 4 H), 7.17 (ddd, J = 10.59, 8.73, 2.34 Hz, 1 H), 6.99 (d, J = 8.78 Hz, 2 H), 6.89 - 6.96 (m, 1 H), 3.80 (s, 3 H), 3.03 (s, 6 H); ES-LCMS: 551.2 (M+1).

**Example 250**

N-(5-(2-amino-3-(4-methoxyphenyl)imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide
A mixture of PdCl₂(dppf)-CH₂Cl₂ adduct (8.20 mg, 10.04 Mmol), potassium phosphate (213 mg, 1.004 mmol), tert-butyl (6-(5-(2,4-difluorophenylsulfonamido)-6-methoxy pyridin-3-yl)-3-iodoimidazo[1,2-a]pyridin-2-yl)carbamate (66 mg, 0.100 mmol), 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (23.50 mg, 0.100 mmol) in 1,4-Dioxane (3 mL) and water (0.75 ml) was heated to 100 °C by microwave irradiation for 15 mins. The reaction was cooled, diluted with EtOAc (100 mL), washed with water, dried over Na₂SO₄, filtered, and then concentrated. The residue was purified via silica gel column and then treated with TFA (0.25 mL, 3.24 mmol) at room temperature for 1 h. The solution was poured into 20 mL EtOAc and then treated with Et₃N. It was then washed with water, dried over Na₂SO₄, filtered, and then concentrated to give the product N-(5-(2-amino-3-(4-methoxy phenyl)imidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenz esulfonamide (24.0 mg, 0.043 mmol, 43.1 % yield) as a yellow solid. 1 H NMR (400 MHz, DMSO-d₆) δ ppm 8.38 (s, 1 H), 8.13 (d, J = 2.15 Hz, 1 H), 7.91 (d, J = 2.34 Hz, 1 H), 7.75 - 7.84 (m, 3 H), 7.67 - 7.75 (m, 2 H), 7.45 - 7.51 (m, 2 H), 7.15 - 7.24 (m, 1 H), 6.98 - 7.05 (m, 1 H), 3.77 - 3.81 (s, 3 H), 3.63 - 3.66 (s, 3 H); ES-LCMS: 538.2 (M+1).

Example 251

N-(5-(2-amino-3-phenylimidazo[1,2-a]pyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide

[00583] A mixture of PdCl₂(dppf)-CH₂Cl₂ adduct (8.20 mg, 10.04 Mmol), potassium phosphate (213 mg, 1.004 mmol), tert-butyl (6-(5-(2,4-difluorophenylsulfonamido)-6-methoxy pyridin-3-yl)-3-iodoimidazo[1,2-a]pyridin-2-yl)carbamate (66 mg, 0.100 mmol) and phenylboronic acid (12.24 mg, 0.100 mmol) in 1,4-dioxane (3 mL) and water (0.75 ml) was heated by microwave irradiation for 15 minutes. The reaction was cooled, diluted with EtOAc (100 mL), washed with water, dried over Na₂SO₄, filtered, and then concentrated. The residue was purified via a silica gel column and then treated with TFA (0.25 mL, 3.24 mmol) at room
temperature for 1 h. The solution was poured into 20 mL EtOAc and then treated with Et$_3$N. It was then washed with water, dried over Na$_2$SO$_4$, filtered, and concentrated to give the product N-(5-(2-amino-3-phenylimidazot1 ,2-alpyridin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (7.9 mg, 0.015 mmol, 15.04 % yield) as a yellow solid. 1 H NMR (400 MHz, DMSO-d$_6$) δ ppm 8.42 (s, 1 H), 8.31 (d, J = 2.34 Hz, 1 H), 8.13 (s, 1 H), 7.85 (d, J = 2.34 Hz, 1 H), 7.72 (dd, J = 8.59, 2.15 Hz, 1 H), 7.67 (d, J = 7.22 Hz, 2 H), 7.57 (t, J = 7.90 Hz, 4 H), 7.38 - 7.43 (m, 1 H), 7.13 - 7.19 (m, 1 H), 3.62 (s, 3 H); ES-LCMS: 508.2 (M+1).

Administration and Formulation

[00584] The chemical entities provided herein may inhibit viral replication by inhibiting the enzymes involved in replication, such as the non-structural proteins including RNA dependent RNA polymerase. They may also inhibit other enzymes utilized in the activity or proliferation of viruses in the Flaviviridae family, such as HCV. The chemical entities are administered at a therapeutically effective dosage, e.g., a dosage sufficient to provide treatment for the disease.

[00585] In another embodiment, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable diluent and a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[00586] The compounds of the present invention can also be supplied in the form of a pharmaceutically acceptable salt. The terms "pharmaceutically acceptable salt" refer to salts prepared from pharmaceutically acceptable inorganic and organic acids and bases.

[00587] -Pharmaceutically acceptable inorganic bases include metallic ions. More preferred metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like and in their usual valences. Exemplary salts include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts.

[00588] Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, including in part, trimethylamine, diethyamine, N, N’-dibenzylethlenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine; substituted amines including naturally occurring substituted amines; cyclic amines; quaternary ammonium cations; and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethlenediamine, diethyamine, 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.

[00589] Illustrative pharmaceutically acceptable acid addition salts of the compounds of the present invention can be prepared from the following acids, including, without limitation formic, acetic, propionic, benzoic, succinic, glycolic, gluconic, lactic, maleic, malic, tartaric, citric, nitric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, hydrochloric, hydrobromic, hydroiodic, isocitric, trifluoroacetic, pamoic, propionic, anthranilic, mesylic, oxalacetic, oleic, stearic, salicylic, p-hydroxybenzoic, nicotinic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, phosphoric, phosphonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, sulfuric, salicylic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids. Preferred pharmaceutically acceptable salts include the salts of hydrochloric acid and trifluoroacetic acid. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention. For example, the pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p.1418, the disclosure of which is hereby incorporated by reference only with regards to the lists of suitable salts.

[00590] The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water. Pharmaceutically acceptable solvates include hydrates and other solvates wherein the solvent of crystallization may be isotopically substituted, e.g. D₂O, d₆-acetone, d₆-DMSO.
Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group or a cycloalkyl group, geometric cis/trans (or Z/E) isomers are possible. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ("tautomerism") can occur. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the claimed compounds present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallisation and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on a resin with an asymmetric stationary phase and with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkyamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Mixtures of stereoisomers may be separated by conventional techniques known to those skilled in the art. [see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).]

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the
same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

[00599] Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as $^2$H and $^3$H, carbon, such as $^{13}$C, $^{13}$C and $^{14}$C, chlorine, such as $^{35}$Cl, fluorine, such as $^{18}$F, iodine, such as $^{125}$I and $^{131}$I, nitrogen, such as $^{13}$N and $^{15}$N, oxygen, such as $^{15}$O, $^{17}$O and $^{18}$O, phosphorus, such as $^{32}$P, and sulphur, such as $^{35}$S.

[00600] Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. $^3$H, and carbon-14, i.e. $^{14}$C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[00601] Substitution with heavier isotopes such as deuterium, i.e. $^2$H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

[00602] Isotopically-labelled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

[00603] The composition of the present invention may be administered as prodrugs. Thus, certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'.

[00604] Administration of the chemical entities described herein can be via any of the accepted modes of administration for agents that serve similar utilities including, but not limited to, orally, sublingually, subcutaneously, intravenously, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarily, vaginally, rectally, or intraocularly. In some embodiments, oral or parenteral administration is used.

[00605] Pharmaceutical compositions or formulations include solid, semi-solid, liquid and aerosol dosage forms, such as, e.g., tablets, capsules, powders, liquids, suspensions, suppositories, aerosols or the like. The chemical entities can also be administered in sustained or controlled release dosage forms, including depot injections, osmotic pumps, pills, transdermal (including electrottransport) patches, and the like, for prolonged and/or timed, pulsed administration at a predetermined rate. In certain embodiments, the compositions are provided in unit dosage forms suitable for single administration of a precise dose.
The chemical entities described herein can be administered either alone or more typically in combination with a conventional pharmaceutical carrier, excipient or the like (e.g., mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, sodium crosscarmellose, glucose, gelatin, sucrose, magnesium carbonate, and the like). If desired, the pharmaceutical composition can also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH buffering agents and the like (e.g., sodium acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine acetate, triethanolamine oleate, and the like). Generally, depending on the intended mode of administration, the pharmaceutical composition will contain about 0.005% to 95%; in certain embodiments, about 0.5% to 50% by weight of a chemical entity. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania.

In certain embodiments, the compositions will take the form of a pill or tablet and thus the composition will contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives or the like. In another solid dosage form, a powder, marume, solution or suspension (e.g., in propylene carbonate, vegetable oils or triglycerides) is encapsulated in a gelatin capsule.

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. at least one chemical entity and optional pharmaceutical adjuvants in a carrier (e.g., water, saline, aqueous dextrose, glycerol, glycols, ethanol or the like) to form a solution or suspension. Injectable compositions can be prepared in conventional forms, either as liquid solutions or suspensions, as emulsions, or in solid forms suitable for dissolution or suspension in liquid prior to injection. The percentage of chemical entities contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the chemical entities and the needs of the subject. However, percentages of active ingredient of 0.01% to 10% in solution are employable, and will be higher if the composition is a solid which will be subsequently diluted to the above percentages. In certain embodiments, the composition will comprise from about 0.2 to 2% of the active agent in solution.

Pharmaceutical compositions of the chemical entities described herein may also be administered to the respiratory tract as an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In
such a case, the particles of the pharmaceutical composition have diameters of less than 50 microns, in certain embodiments, less than 10 microns.

In general, the chemical entities provided will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the chemical entity, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the chemical entity used, the route and form of administration, and other factors. The drug can be administered more than once a day, such as once or twice a day.

Therapeutically effective amounts of the chemical entities described herein may range from approximately 0.01 to 200 mg per kilogram body weight of the recipient per day; such as about 0.01-100 mg/kg/day, for example, from about 0.1 to 50 mg/kg/day. Thus, for administration to a 70 kg person, the dosage range may be about 7-3500 mg per day.

In general, the chemical entities will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. In certain embodiments, oral administration with a convenient daily dosage regimen that can be adjusted according to the degree of affliction may be used. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions. Another manner for administering the provided chemical entities is inhalation.

The choice of formulation depends on various factors such as the mode of drug administration and bioavailability of the drug substance. For delivery via inhalation the chemical entity can be formulated as liquid solution, suspensions, aerosol propellants or dry powder and loaded into a suitable dispenser for administration. There are several types of pharmaceutical inhalation devices—nebulizer inhalers, metered dose inhalers (MDI) and dry powder inhalers (DPI). Nebulizer devices produce a stream of high velocity air that causes the therapeutic agents (which are formulated in a liquid form) to spray as a mist that is carried into the patient's respiratory tract. MDIs typically are formulation packaged with a compressed gas. Upon actuation, the device discharges a measured amount of therapeutic agent by compressed gas, thus affording a reliable method of administering a set amount of agent. DPI dispenses therapeutic agents in the form of a free flowing powder that can be dispersed in the patient's inspiratory air-stream during breathing by the device. In order to achieve a free flowing powder, the therapeutic agent is formulated with an excipient such as lactose. A measured amount of the therapeutic agent is stored in a capsule form and is dispensed with each actuation.
Recently, pharmaceutical compositions have been developed 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. Patent 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 cross-linked 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.

The compositions are comprised of, in general, at least one chemical entity described herein 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 at least one chemical entity described herein. 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. Liquid carriers, for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compressed gases may be used to disperse a chemical entity described herein in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc. 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 amount of the chemical entity in a composition can vary within the full range employed by those skilled in the art. Typically, the composition will contain, on a weight percent (wt%) basis, from about 0.01-99.99 wt% of at least one chemical entity described herein based on the total composition, with the balance being one or more suitable pharmaceutical excipients. In certain embodiments, the at least one chemical entity described herein is present at a level of about 1-80 wt%. Representative pharmaceutical compositions containing at least one chemical entity described herein are described below.
In another embodiment, there is provided a method for treating a viral infection in a mammal mediated at least in part by a virus in the Flaviviridae family of viruses, which method comprises administering to a mammal that has been diagnosed with said viral infection or is at risk of developing said viral infection a compound described herein. In another embodiment, the virus is hepatitis C virus.

In another embodiment, the method for treating a viral infection in a mammal mediated at least in part by a virus in the Flaviviridae family of viruses further comprises administration of a therapeutically effective amount of one or more agents active against hepatitis C virus. In another embodiment, the agent is an inhibitor of HCV protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV replicase, HCV NS5A protein, or inosine 5'-monophosphate dehydrogenase. In another embodiment, the agent is interferon. In another embodiment, the agent is ribavirin. In yet another embodiment, the agent(s) is a combination of interferon and ribavirin that is administered either simultaneously or sequentially.

In addition, the chemical entities described herein can be co-administered with, and the pharmaceutical compositions can include, other medicinal agents, pharmaceutical agents, adjuvants, and the like. Suitable medicinal and pharmaceutical agents include therapeutically effective amounts of one or more agents active against HCV. In some embodiments, the agent active against HCV is an inhibitor of HCV protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV replicase, HCV NS5A protein, or inosine 5'-monophosphate dehydrogenase.

Active agents against HCV include ribavirin, levovirin, viramidine, thymosin alpha-1, an inhibitor of NS3 serine protease, and inhibitor of inosine monophosphate dehydrogenase, interferon-alpha, either alone or in combination with ribavirin or levovirin. In some embodiments, the additional agent active against HCV is interferon-alpha or pegylated interferon-alpha alone or in combination with ribavirin or levovirin. In some embodiments, the agent active against hepatitis C virus is interferon.

The above other therapeutic agents, when employed in combination with the chemical entities described herein, may be used, for example, in those amounts indicated in the Physicians’ Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Additionally, the present specification is directed to a pharmaceutical composition comprising a therapeutically effective amount of at least one chemical entity described herein in combination with a therapeutically effective amount of another active agent against RNA-dependent RNA virus and, in particular, against HCV. Agents active against HCV include, but
are not limited to, ribavirin, levovirin, viramidine, thymosin alpha-1, an inhibitor of HCV NS3 serine protease, or an inhibitor of inosine monophosphate dehydrogenase, interferon-alpha pegylated interferon-alpha (peginterferon-alpha), a combination of interferon-alpha and ribavirin, a combination of peginterferon-alpha and ribavirin, a combination of interferon-alpha and levovirin, and a combination of peginterferon-alpha and levovirin. Interferon-alpha includes, but is not limited to, recombinant interferon-alpha2a (such as ROFERON interferon available from Hoffman-LaRoche, Nutley, NJ), interferon-alpha2b (such as Intron-A interferon available from Schering Corp., Kenilworth, New Jersey, USA), a consensus interferon, and a purified interferon-alpha product. For a discussion of ribavirin and its activity against HCV, see J.O. Saunders and S.A. Raybuck, "Inosine Monophosphate Dehydrogenase: Consideration of Structure, Kinetics and Therapeutic Potential," Ann. Rep. Med. Chem., 2:201-210 (2000).

[00625] The following examples serve to more fully describe the manner of making and using the above-described invention. It is understood that these examples in no way serve to limit the true scope of the invention, but rather are presented for illustrative purposes.

**BIOLOGICAL EXAMPLES**

**EXAMPLE 252**

ANTHI-HEPATITIS C ACTIVITY

[00626] In certain embodiments, the presently described formulas and compounds can exhibit anti-hepatitis C activity by fully or partially inhibiting the host cell's PI4Ka enzyme, which has been recently described as an important host factor for HCV replication. The presently described formulas and compounds show various potencies against PI4Ka, which correlates well with the corresponding antiviral (e.g., replicon) activities. A number of assays have been published to assess these activities. A general method that assesses the gross increase of HCV virus in culture was disclosed in U.S. Patent No. 5,738,985 to Miles et al. *In vitro* assays have been reported in Ferrari et al. *Jnl. of Vir.,* 73:1649-1654, (1999); Ishii et al., *Hepatology, 29:1227-1235, (1999); Lohmann et al., *J. Biol. Chem.,* 274:10807-10815, (1999); and Yamashita et al., *J. Biol. Chem.,* 273:15479-15486, (1998).

**EXAMPLE 253**

REPLICON ASSAY

[00627] Compounds were assayed for activity against HCV using the genotype 1a and 1b subgenomic replicon model systems. Stable cell lines bearing the genotype 1a and 1b replicons...
were used for screening of compounds. Both replicons are bicistonic and contain the firefly luciferase gene. The ET cell line is stably transfected with RNA transcripts harboring a \textit{I}_{39}\text{sucl-}
\textit{ubi-neo}/NS3-3'/ET replicon with firefly luciferase-ubiquitin-neomycin phosphotransferase fusion protein and EMCV-IRES driven NS3-5B polyprotein containing the cell culture adaptive mutations (E1202G; T1280I; K1846T) (\textit{Krieger et al}, 2001 and unpublished). The genotype 1a replicon is a stable cell line licensed from Apath LLC, modified to contain the firefly luciferase gene. The cells were grown in DMEM, supplemented with 10% fetal calf serum, 2 mM Glutamine, Penicillin (100 IU/mL)/Streptomycin (100 pg/mL), 1x nonessential amino acids, and 250-500 \textmu g/mL G418 ("Geneticin"). They were all available through Life Technologies (Bethesda, Md.). The cells were plated at 0.5 x 10^4 cells/well in 384 well plates containing the compounds. The final concentration of compounds ranged between 0.03 pM to 50 pm and the final DMSO concentration of 0.5-1%.
Luciferase activity was measured 48 hours later by adding a Steady glo (Promega, Madison, Wis.). Percent inhibition of replication data was plotted relative to no compound control. Under the same condition, cytotoxicity of the compounds was determined using cell titer glo (Promega, Madison, Wis). IC_{50} s were determined from a 10 point dose response curve using 3-4-fold serial dilution for each compound, which spans a concentration range > 1000 fold. BioAssay determines the level of inhibition for each compound by normalizing cross-talk corrected plate values against the negative (low or background, cells with no compound present) and positive (high DMSO, no cells) controls to determine Percent Inhibition:

\[
100 \times \frac{1 - (\text{Cross-talk corrected value} - \text{Compound Positive Control Mean})}{\text{DMSO Negative Control Mean} - \text{Compound Positive Control Mean}}
\]

These normalized values are exported to IC_{50} where they are plotted against the molar compound concentrations using the standard four parameter logistic equation:

\[
y = A + \frac{B-A}{1 + \left(\frac{10^X}{10^C}\right)^D}
\]

Where:
- \(A\) = minimum \(y\)
- \(B\) = maximum \(y\)
- \(D\) = slope factor
- \(x = \log_{10} \text{compound concentration} \ [M]\)
- \(C = \log_{10} \text{EC}_{50}\)

As shown below, the tested compounds were found to inhibit the activity of the replicon with \(\text{plC}_{50}\) values of about 9 or less. Preferably, the compounds will exhibit \(\text{plC}_{50}\) values of about 8 or less, in some embodiments, about 7 or less, and in some embodiments, about 6 or less. Further, compounds of the present disclosure, which were tested against more than one genotype of HCV replicon, were found to have similar inhibitory properties.

**EXAMPLE 254**

**PI4KA\text{pl} IC_{50} \text{determination}**

To determine the potency of compounds as inhibitors of PI4Kalpha protein, a microfluidics-based kinase detection platform was utilized confidentially through a contract...
research organization (Nanosyn, Inc, Research Triangle Park, North Carolina). Compounds were sent at top concentration of 10 µM and subsequently serially diluted to 10 pM. This enzymatic assay detection technology is based upon the difference between net charge of substrates and products, allowing electrophoretic separation of product from substrate. The product of PI4KAlfa kinase reactions are then quantitated using Caliper LabChip microfluidic instrumentation. IC\textsubscript{50}s are calculated as the concentration corresponding to 50% inhibition of PKKalpha product production.

[00632] When tested in biological \textit{in vitro} models, certain compounds of Table 1 were found to have plC\textsubscript{50} values listed in Table 8.

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</table>
Formulation Examples

The following are representative pharmaceutical formulations containing a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Formulation Example 1
Tablet formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound</td>
<td>400</td>
</tr>
<tr>
<td>cornstarch</td>
<td>50</td>
</tr>
<tr>
<td>croscarmellose sodium</td>
<td>25</td>
</tr>
<tr>
<td>lactose</td>
<td>120</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>5</td>
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</tbody>
</table>

Formulation Example 2
Capsule formulation.

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity per capsule (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound</td>
<td>200</td>
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</table>
Lactose, spray-dried 148
magnesium stearate 2

Formulation Example 3
Suspension formulation

[00636] The following ingredients are mixed to form a suspension for oral administration.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
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<tbody>
<tr>
<td>compound</td>
<td>1.0 g</td>
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<tr>
<td>fumaric acid</td>
<td>0.5 g</td>
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<tr>
<td>sodium chloride</td>
<td>2.0 g</td>
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<tr>
<td>methyl paraben</td>
<td>0.15 g</td>
</tr>
<tr>
<td>propyl paraben</td>
<td>0.05 g</td>
</tr>
<tr>
<td>granulated sugar</td>
<td>25.0 g</td>
</tr>
<tr>
<td>sorbitol (70% solution)</td>
<td>13.00 g</td>
</tr>
<tr>
<td>Veegum K (Vanderbilt Co.)</td>
<td>1.0 g</td>
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<tr>
<td>flavoring</td>
<td>0.035 mL</td>
</tr>
<tr>
<td>colorings</td>
<td>0.5 mg</td>
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<tr>
<td>distilled water</td>
<td>q.s. (quantity sufficient) to 100 mL</td>
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</table>

Formulation Example 4
Injectable formulation

[00637] The following ingredients are mixed to form an injectable formulation.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
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<tbody>
<tr>
<td>compound</td>
<td>0.2 mg-20 mg</td>
</tr>
<tr>
<td>sodium acetate buffer solution, HCl (1 N) or NaOH (1 N)</td>
<td>0.4 M 2.0 mL</td>
</tr>
<tr>
<td>water (distilled, sterile)</td>
<td>q.s. to suitable pH</td>
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<tr>
<td></td>
<td>q.s. to 20 mL</td>
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</tbody>
</table>

Formulation Example 5
Suppository Formulation

[00638] A suppository of total weight 2.5 g is prepared by mixing the compound with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
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</table>

430
Although the invention has been shown and described above with reference to some embodiments, those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention.

For example, for claim construction purposes, it is not intended that the claims set forth hereinafter be construed in any way narrower than the literal language thereof, and it is thus not intended that exemplary embodiments from the specification be read into the claims. Accordingly, it is to be understood that the present invention has been described by way of illustration and not limitations on the scope of the claims. Accordingly, the invention is limited only by the following claims. All publications, issued patents, patent applications, books and journal articles, cited in this application are each herein incorporated by reference in their entirety.
WHAT IS CLAIMED IS:

1. A compound comprising the structure of Formula (I):

   ![Formula Image]

   or a pharmaceutically acceptable salt thereof, wherein:

   - **Z** is selected from the group consisting of a bond and a (branched or straight chain) (C<sub>1</sub> - C<sub>6</sub>)alkylene;
   - **X** is selected from the group consisting of hydrogen, (d-C<sub>6</sub>)alkoxy, nitrile, -C(0)R<sup>12</sup>,
     -C(0)R<sup>14</sup>, -S<sub>0</sub>2R<sup>6</sup>, -SO<sub>2</sub>R<sup>12</sup>, -SO<sub>2</sub>R<sup>14</sup>, -SO<sub>2</sub>R<sup>14</sup>(R<sup>6</sup>)<sub>n</sub>, -NHSO<sub>2</sub>R<sup>10</sup>(R<sup>6</sup>)<sub>n</sub>,
     -NHSO<sub>2</sub>R<sup>6</sup>R<sup>10</sup>(R<sup>6</sup>)<sub>n</sub>, -NHSO<sub>2</sub>2R<sup>13</sup>, -NHSO<sub>2</sub>R<sup>14</sup>, -NHSO<sub>2</sub>R<sup>14</sup>(R<sup>6</sup>)<sub>n</sub>, and
     -NHSO<sub>2</sub>R<sup>14</sup>(R<sup>6</sup>)<sub>n</sub>;
   - **R<sup>1</sup>** is selected from the group consisting of hydrogen, -R<sup>6</sup>R<sup>14</sup>, -C(0)R<sup>9</sup>, -R<sup>6</sup>R<sup>10</sup>,
     -C(0)R<sup>10</sup>, and -C(0)R<sup>14</sup>;
   - **R<sup>2</sup>** is selected from the group consisting of hydrogen, nitrile, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, nitrile, oxo, hydroxyl, -NHR<sup>9</sup>R<sup>14</sup>, -OR<sup>7</sup>, -R<sup>6</sup>R<sup>14</sup>(R<sup>6</sup>)<sub>n</sub>W<sup>-</sup>-R<sup>6</sup>R<sup>14</sup>, -R<sup>12</sup>,
     -R<sup>14</sup>, -R<sup>10</sup>R<sup>6</sup>, -R<sup>10</sup>(R<sup>6</sup>)<sub>n</sub>, -S<sub>0</sub>2R<sup>15</sup>, -S<sub>0</sub>2R<sup>15</sup>, -S<sub>0</sub>2R<sup>15</sup>, -S<sub>0</sub>2R<sup>15</sup>, -R<sup>13</sup>R<sup>14</sup>, -R<sup>6</sup>R<sup>15</sup>,
     -R<sup>10</sup>R<sup>14</sup>, -(R<sup>14</sup>R<sup>12</sup>), -R<sup>13</sup>R<sup>6</sup>, -R<sup>14</sup>R<sup>6</sup>, -C<sub>0</sub>2R<sup>7</sup>, (C<sub>3</sub>C<sub>1</sub>)<sub>n</sub>cycloalkyl, and (C<sub>4</sub>C<sub>4</sub>)aryl,
   wherein **A** and **Q** are optionally chosen from -(CH<sub>2</sub>)<sub>W</sub>R<sup>10</sup> or -(CH<sub>2</sub>)<sub>W</sub>R<sup>14</sup>;
   - **R<sup>1</sup>** and **R<sup>2</sup>** taken together with any intervening atoms and when **Z** is a bond, can
     optionally form a fused (C<sub>2</sub>-C<sub>6</sub>)heterocyclic ring having 1-3 heteroatoms selected
     from S, N and O; wherein said fused heterocyclic ring can also be optionally
     substituted with one to two R<sup>6</sup> groups;
   - **R<sup>3</sup>** is selected from the group consisting of hydrogen, nitrile, halo, and (C<sub>1</sub>-C<sub>6</sub>)alkyl;
   - **R<sup>4</sup>** is selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (CrC<sub>6</sub>)alkoxy, nitrile,
     oxo, -C(0)R<sup>12</sup>, -S<sub>0</sub>2R<sup>6</sup>, -R<sup>9</sup>(R<sup>15</sup>)<sub>n</sub>W<sup>-</sup>-OR<sup>7</sup>, -R<sup>12</sup>, and halo;
   - **R<sup>5</sup>** is a branched or straight chain (CrC<sub>6</sub>)alkylene;
R^6 is independently selected from the group consisting of (CrC_6)alkyl, oxo, \( c_1 \)-C_6alkoxy, -OR^7, halo, nitrile, and -C0_\_2R^7;

R^7 is selected from the group consisting of hydrogen and (CrC_6)alkyl;

R^8 is independently selected from the group consisting of hydrogen, (d-C_\_ \_C_\_ Alkyl, -R^10, -R^13, -R^14, -R^5R^13, -R^5R^10, -R^10(R^11)_M, -R^5R^14, and -R^5R^10(R^11)_M;

R^9 is (C_1-C_7)alkyl;

R^10 is (C_4-C_14)aryl;

R^11 is selected from the group consisting of nitrile, halo, (C_1-C_6)alkyl, (CrC_6)alkoxy, and -R^14R^12;

R^12 is -N(R^6)_2, wherein each instance of R^8 may be independently and separately chosen from among the possible R^6 substituents;

R^13 is \( c_3 \)-c_4)Cycloalkyl;

R^14 is selected from (CrC_n)heterocycle or (CrC_n)heteroaryl, each having one to three heteroatoms selected from S, N and O;

R^15 is halo;

each m is independently zero or an integer from 1 to 3;

each n is independently zero or an integer from 1 to 3; and

each w is independently zero or an integer from 1 to 3.

2. The compound according claim 1, wherein Z is selected from the group consisting of a bond, methylene, ethylene, dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene, methylpropylene, methylcyclopropylmethyl, and isopropylmethylene.

3. The compound according to claim 2, wherein Z is selected from the group consisting of a bond, methylene, and ethylene.

4. The compound according to claim 3, wherein Z is selected from a bond or methylene.

5. The compound according to claim 4, wherein Z is a bond.

6. The compound according to claim 4, wherein Z is methylene.

7. The compound according to claim 1, wherein X is selected from the group consisting of -SO_2R^5, -SO_2R^12, -SO_2R^14, -SO_2R^14(R^6)_n, -NHSO_2R^10, -NHSO_2R^10(R^6)_n.
-NHSO2R13, -NHSO2R14, -NHS02R6R14, -NHS02R6(R6)n, -NHS02R9, and -NHS02R14(R6)n.

8. The compound according to claim 7, wherein X is selected from the group consisting of -SO2R6, -SO2R12, -SO2R14, and -SO2R14(R6)n.

9. The compound according to claim 8, wherein X is selected from the group consisting of -NHS02R10, -NHSO2R10(R6)n, -NHS02R13, -NHS02R6R14, -NHS02R14(R6)n, -NHS02R6(R6)n, -NHS02R9, and -NHS02R14(R6)n.

10. The compound according to claim 9, wherein X is selected from -NHSO2R10(R6)n or -SO2R12.

11. The compound according to claim 10, wherein X is -NHSO2R10(R6)n.

12. The compound according to claim 1, wherein R1 is selected from the group consisting of -R6R14, -(C0)R9, -R6R10, -(C0)R10, and -(C0)R14.

13. The compound according to claim 1, wherein R1 is hydrogen.

14. The compound according to claim 1, wherein R2 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR5R14, -OR7, -R6R10, -R10R6R14, -R12, -R14, -(R14)2, -SO2R15, -SO2R12, -SO2R13, -SO2R14, -C02R7, -R10R6, -R13R14, -R15R14, -R13R6, -R14R6, -(R14R12), (C3Cl3)cycloalkyl, and phenyl.

15. The compound according to claim 14, wherein R2 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR5R14, -OR7, -R6R10, -R10R6R14, -R12, -R14, -(R14)2, -SO2R15, -SO2R12, -SO2R13, -SO2R14, -C02R7, -R10R6, -R13R14, -R15R14, -R13R6, -R14R6, -(R14R12), cyclopentyl, dihydroindenyl, and phenyl.

16. The compound according to claim 15 wherein R2 is -R10R14.

17. The compound according to claim 16, wherein R2 is morpholinylphenyl.

18. The compound according to claim 1, wherein R3 is hydrogen.
19. The compound according to claim 1, wherein $R^4$ is selected from the group consisting of hydrogen, -C(0)R, -SO$_2$R, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, trifluoromethyl, fluoro, and iodo.

20. The compound according to claim 19, wherein $R^4$ is methoxy.

21. The compound according to claim 19, wherein $R^5$ is methylene.

22. The compound according to claim 1, wherein $R^6$ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and -CO$_2$R.

23. The compound according to claim 22, wherein $R^6$ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and t-butyl.

24. The compound according to claim 1, wherein $R^7$ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl.

25. The compound according to claim 1, wherein $R^8$ is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -R$^8$R$_{10}$, -R$^8$R$_{14}$, -R$^8$R$_{13}$, -R$^{10}$R$_{11}$, and -R$^8$R$_{10}$(R$^{11}$)$_m$.

26. The compound according to claim 25, wherein $R^8$ is independently selected from hydrogen or methyl.

27. The compound according to claim 1, wherein $R^9$ is independently selected from the group consisting of $R^9$ is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, and neopentyl.

28. The compound according to claim 1, wherein $R^{10}$ is phenyl.

29. The compound according to claim 1, wherein $R^{11}$ is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, and methoxy.

30. The compound according to claim 1, wherein $R^{13}$ is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl.
31. The compound according to claim 1, wherein R is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropryanyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidine, piperidinyl, and pyridinyl.

32. The compound according to claim 31, wherein R\textsuperscript{14} is morpholinyl.

33. The compound according to claim 1, wherein Z is selected from the group consisting of a bond, methylene, and ethylene.

34. The compound according to claim 33, wherein Z is a bond.

35. The compound according to claim 33, wherein Z is methylene.

36. The compound according to claim 1, wherein each m is independently an integer ranging from 1 to 3.

37. The compound according to claim 1, wherein each n is independently an integer from 1 to 3.

38. The compound according to claim 1, wherein each w is independently an integer from 1 to 6.

39. The compound according to claim 36, wherein m is 3.

40. The compound according to claim 37, wherein n is 2.

41. The compound according to claim 38, wherein w is 1.

42. The compound according to claim 1, having the structure of Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

- Z is selected from the group consisting of a bond, methylene, ethylene, dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene, methylpropylene, methylcyclopropylmethyl, and isopropylmethylene;
- X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R\textsuperscript{12}, -C(0)R\textsuperscript{14}, -SO\textsubscript{2}R\textsuperscript{6}, -SO\textsubscript{2}R\textsuperscript{12}, -SO\textsubscript{2}R\textsuperscript{14}, -SO\textsubscript{2}R\textsuperscript{14}(R\textsuperscript{6})\textsubscript{n}, -NHSO\textsubscript{2}R\textsuperscript{10}, -NHSO\textsubscript{2}R\textsuperscript{10}(R\textsuperscript{6})\textsubscript{n}, -NHSO\textsubscript{2}R\textsuperscript{13}, -NHSO\textsubscript{2}R\textsuperscript{14}, -NHSO\textsubscript{2}R\textsuperscript{14}R\textsuperscript{14}, -NHSO\textsubscript{2}R\textsuperscript{6}(R\textsuperscript{6})\textsubscript{n}, -NHSO\textsubscript{2}R\textsuperscript{9}, -NHSO\textsubscript{2}R\textsuperscript{14}(R\textsuperscript{6})\textsubscript{n}.
R^1 is selected from the group consisting of hydrogen, -R^6R^{14}, -R^6R^{10}, -C(0)R^10, -C(0)R^{14}, and -C(0)R^9;

R^2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR^5R^{14}, -OR^7, -R^6R^{10}, -R^6R^{14}, -R^{12}, -R^{14}, -(R^{14})_2, -S0_2R^{10}, -S0_2R^{12}, -S0_2R^{14}, -C0_2R^7, -R^{10}R^6, -R^{10}R^{14}, -R^{12}R^6, -R^{14}R^6, -(R^{14}R^{12}), cyclopentyl, dihydroindenyl, and phenyl, wherein A and Q are independently chosen from -(CH_2)_W R^10 or -(CH_2)_W R^{14};

R^1 and R^2 taken together with any intervening atoms and when Z is a bond can optionally form a fused imidazole ring that can also be optionally substituted with one to two R^6 groups;

R^3 is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;

R^4 is selected from the group consisting of hydrogen, -C(0)R^12, -S0_2R^9, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;

R^5 is selected from the group consisting of methylene, ethylene, and propylene;

R^6 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, o xo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and -C0_2R^7;

R^7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl;

R^8 is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, - R^6R^{10}, -R^6R^{13}, -R^{10}(R^{11})_M, -R^6R^{14}, and - R^8R^{10}(R^{11})_M;

R^9 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, penty l, t-pentyl, neopentyl, dimethylbutanyl, and dimethylpentanyl;

R^{10} is phenyl;

R^{11} is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and -R^{14}R^{12};

R^{12} is -N(R^8)_2, wherein each R^8 may be independently chosen from among the R^8 substituents;

R^{13} is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
R\textsuperscript{14} is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidone, piperidinyl, and pyridinyl;

R\textsuperscript{15} is selected from the group consisting of fluoro, chloro, and iodo;

each m is independently zero or an integer from 1 to 3;

each n is independently zero or an integer from 1 to 3;

and each w is independently zero or an integer from 1 to 3.

43. The compound according to claim 1, having the structure of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

Z is a bond or methylene;

X is selected from the group consisting of hydrogen, (d-C\textsubscript{6})alkoxy, nitrile, -C(0)R\textsuperscript{12}, -C(0)R\textsuperscript{14}, -S0\textsubscript{2}R\textsuperscript{6}, -S0\textsubscript{2}R\textsuperscript{12}, -S0\textsubscript{2}R\textsuperscript{14}, -S0\textsubscript{2}R\textsuperscript{14}(R\textsuperscript{6})\textsubscript{n}, -NHSO\textsubscript{2}R\textsuperscript{10}(R\textsuperscript{6})\textsubscript{n}, -NHSO\textsubscript{2}R\textsuperscript{10}(R\textsuperscript{6})\textsubscript{n}, -NHS0\textsubscript{2}R\textsuperscript{14}, -NHS0\textsubscript{2}R\textsuperscript{14}, -NHS0\textsubscript{2}R\textsuperscript{14}(R\textsuperscript{6})\textsubscript{n} and

-\textsuperscript{NHS0\textsubscript{2}} R\textsuperscript{i} (R\textsuperscript{6})\textsubscript{n};

R\textsuperscript{1} is selected from the group consisting of hydrogen, -R\textsuperscript{8}R\textsuperscript{14}, and -C(0)R\textsuperscript{8};

R\textsuperscript{2} is selected from the group consisting of hydrogen, (d-C\textsubscript{6})alkoxy, nitrile, oxo, hydroxyl, -NHR\textsuperscript{8}R\textsuperscript{14}, -OR\textsuperscript{7}, -R\textsuperscript{8}R\textsuperscript{14}(R\textsuperscript{6})\textsubscript{w}, -R\textsuperscript{10}R\textsuperscript{14}, -R\textsuperscript{12}, -R\textsuperscript{14}, -R\textsuperscript{10}R\textsuperscript{6}, -R\textsuperscript{10}(R\textsuperscript{6})\textsubscript{w}, -S0\textsubscript{2}R\textsuperscript{10}, -S0\textsubscript{2}R\textsuperscript{12}, -S0\textsubscript{2}R\textsuperscript{14}, -S0\textsubscript{2}R\textsuperscript{14}, -R\textsuperscript{13}R\textsuperscript{13}, -R\textsuperscript{13}R\textsuperscript{13}, -R\textsuperscript{8}R\textsuperscript{10}, -R\textsuperscript{10}R\textsuperscript{14}, -(R\textsuperscript{14}R\textsuperscript{12}), -R\textsuperscript{13}R\textsuperscript{8}, -R\textsuperscript{14}R\textsuperscript{6}, -C0\textsubscript{2} R\textsuperscript{7}, (C\textsubscript{3}C\textsubscript{1}C\textsubscript{1})cycloalkyl, and (C\textsubscript{4}C\textsubscript{4})aryl,

wherein A and Q are independently chosen from -(CH\textsubscript{2})\textsuperscript{w}R\textsuperscript{10} or -(CH\textsubscript{2})\textsuperscript{w}R\textsuperscript{14};

R\textsuperscript{1} and R\textsuperscript{2} taken together with any intervening atoms and when Z is a bond, can optionally form a fused (C\textsubscript{2}-C\textsubscript{6})heterocyclic ring having 1-3 heteroatoms selected from S, N and O; wherein said fused heterocyclic ring can also be optionally substituted with one to two R\textsuperscript{6} groups;

R\textsuperscript{3} is selected from the group consisting of hydrogen, halo, and (C\textsubscript{1}-C\textsubscript{6})alkyl;

R\textsuperscript{4} is selected from the group consisting of hydrogen, (C\textsubscript{1}-C\textsubscript{6})alkyl, (CrC\textsubscript{6})alkoxy, nitrile, oxo, -C(0)R\textsuperscript{12}, -S0\textsubscript{2}R\textsuperscript{6}, -R\textsuperscript{9}(R\textsuperscript{15})\textsubscript{n}, -OR\textsuperscript{7}, -R\textsuperscript{12}, and halo;

R\textsuperscript{5} is a branched or straight chain (CrC\textsubscript{6})alkylene;

R\textsuperscript{6} is independently selected from the group consisting of (CrC\textsubscript{6})alkyl, oxo, (C\textsubscript{1}-C\textsubscript{6})alkoxy, -OR\textsuperscript{7}, halo, nitrile, and -C0\textsubscript{2} R\textsuperscript{7};

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R^7 is selected from the group consisting of hydrogen and (C=C_6)alkyl;
R^8 is independently selected from the group consisting of hydrogen, (d-C_6)alkyl, -R^10,
-R^13, -R^14, -R^6R^13, -R^6R^10, -R^6(R^11)_m and -R^2R^6(R^11)_m;
R^9 is (C=C_6)alkyl;
R^10 is (C_4-C_14)aryl;
R^11 is selected from the group consisting of nitrile, halo, (C_1-C_6)alkyl, (C=C_6)alkoxy, and
-R^14R^12;
R^15 is -N(R^5)_2, wherein each instance of R^8 may be independently and separately
chosen from among the possible R^9 substituents;
R^13 is (C_3-C_12)cycloalkyl;
R^14 is selected from (C=C^r heterocycle or (C_1-C_14)heteroaryl, each having one to three
heteroatoms selected from N and O;
R^15 is halo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

44. The compound according to claim 1, having the structure of Formula (I),
or a pharmaceutically acceptable salt thereof, wherein:
Z is a bond;
X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R^12,
-C(0)R^14, -SO_2R^6, -SO_2R^13, -SO_2R^14, -SO_2R^14(R^6)_n, -NHSO_2R^10, -NHSO_2R^6(R^6)_n,
-NHSO_2R^13, -NHSO_2R^14, -NHSO_2R^14(R^6)_n, -NHSO_2R^9(R^6)_n, -NHSO_2R^9,
-NHSO_2R^14(R^6)_n;
R^1 is selected from the group consisting of hydrogen, -R^6R^14, and -C(0)R^9;
R^2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy,
propano, hydroxyl, -NHR^5R^14, -OR^7, -R^9R^10, -R^9R^6R^14, -R^16, -R^14, -R^14(R^14)_2,
-SO_2R^10, -SO_2R^13, -SO_2R^14, -C0_2R^7, -R^10R^6, -R^13R^14, -R^16R^14, -R^13R^6, -R^14R^6,
-R^14(R^14)_2, cyclopentyl, dihydroindenyl, and phenyl, wherein A and Q are
independently chosen from -(CH_2)_W^R^10 or -(CH_2)_W^R^14;
R^1 and R^2 taken together with any intervening atoms and when Z is a bond can
optionally form a fused imidazole ring that can also be optionally substituted with one to two \( R^6 \) groups;

\( R^3 \) is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;

\( R^4 \) is selected from the group consisting of hydrogen, \(-C(0)R^1\), \(-SO_2R^9\), methyl, ethyl, propyl, isopropyl, butyl, \( t \)-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;

\( R^5 \) is selected from the group consisting of methylene, ethylene, and propylene;

\( R^6 \) is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, \( t \)-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and \(-CO_2R^7\);

\( R^7 \) is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, \( t \)-butyl, and pentyl;

\( R^8 \) is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, \( t \)-butyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, \(-R^8R^{10}, -R^8R^{13}, -R^{16}(R^{11})_M\), and \(-R^8R^{16}(R^{11})_M\);

\( R^9 \) is methyl, ethyl, propyl, isopropyl, butyl, \( t \)-butyl, isopropyl, pentyl, \( t \)-pentyl, neopentyl, dimethylbutanyl, and dimethylpentanlyl;

\( R^{10} \) is phenyl;

\( R^{11} \) is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and \(-R^{14}R^{12}\);

\( R^{12} \) is \(-N(R^8)_2\), wherein each \( R^8 \) may be independently chosen from among the \( R^8 \) substituents;

\( R^{13} \) is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;

\( R^{14} \) is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrrolidinyl, pyrrolidione, piperidinyl, and pyridinyl;

\( R^{15} \) is selected from the group consisting of fluoro, chloro, and iodo;

each \( m \) is independently zero or an integer from 1 to 3;

each \( n \) is independently zero or an integer from 1 to 3; and

each \( w \) is independently zero or an integer from 1 to 3.

45. The compound according to claim 1, having the structure of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:
Z is a bond or methylene;
X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R 1₂,
-C(0)R 1₄, -S0₂R₆, -S0₂R₁₂, -S0₂R₁₄, -S0₂R₁₄(R₆)ₙ, -NHS0₂R₁₀, -NHSO₂R₁₆(R₆)ₙ,
-NHS₀₂R₁₃, -NHS₀₂R₁₄, -NHS₀₂R₁₄(R₆)ₙ, -NHS₀₂R₁₀(R₆)ₙ, -NHS₀₂R₆,
-NHS₀₂R₁₄(R₆)ₙ,
R¹ is hydrogen;
R² is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl,
butil, isobutyl, t-butil, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy,
hydroxyl, -NHR₁₄, -OR₁₇, -R₁₄R₁ₐ, -R₁₄R₁ₐR₁₄, -R₁₄, -R₁₄, -(R₁₄)₂, -S0₂R₁₀, -
S₀₂R₁₂, -S₀₂R₁₃, -S₀₂R₁₄, -C₀₂R₇, -R₁₄R₁₄, -R₁₄R₁₄, -R₁₄R₁₄, -R₁₄R₁₄, -R₁₄R₆, -R₁₄R₆,
-(R₁₄R₁₄), cyclopentyl, dihydroindenyl, and phenyl;
R³ is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;
R⁴ is selected from the group consisting of hydrogen, -C(0)R 1₂, -S0₂R₆, methyl, ethyl,
propyl, isopropyl, butyl, t-buty1, methoxy, ethoxy, amino, nitrile, oxo, methylamino,
dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;
R⁵ is selected from the group consisting of methylene, ethylene, and propylene;
R⁶ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl,
isobutyl, t-butil, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo,
nitrile, and -C0₂R₇;  
R⁷ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl,
butil, t-butil, and penty1;
R⁸ is independently selected from the group consisting of hydrogen, methyl, ethyl,
propyl, isopropyl, butyl, t-butil, phenyl, cyclopropyl, cyclobutyl, cyclopentyl,
cyclohexyl, - R₁₄R₁₄, - R₁₄R₁₃, - R₁₄(R₁₁)ₘ and - R₁₆(R₁₁)ₘ;
R⁹ is methyl, ethyl, propyl, isopropyl, butyl, t-butil, isopropyl, penty1, t-penty1, neopenty1,
dimethylbutanyl, and dimethylpentanyl;
R¹₀ is phenyl;
R¹₁ is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, and
methoxy;
R¹₂ is -N(R₈)₂, wherein each R₈ may be independently chosen from among the R₈
substituents;
R¹₃ is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
R¹₄ is selected from the group consisting of morpholyl, thiomorpholyl,
tetrahydropyranyl, imidazolyl, quinolinyl, oxazepiny1, pyrimidiny1, pyrazolyl,
R^{15} is selected from the group consisting of fluoro, chloro, and iodo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

46. The compound according to claim 1, having the structure of Formula (I) or a
pharmaceutically acceptable salt thereof, wherein:

Z is a bond;
X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R^{12},
-C(0)R^{14}, -SO_2R^8, -SO_2R^{12}, -SO_2R^{14}, -SO_2R^{14}(R^6)_n, -NHSO_2R^{10}, -NHSO_2R^{16}(R^6)_n,
-NHSO_2R^{13}, -NHSO_2R^{14}, -NHSO_2R^6R^{14}, -NHSO_2R^6(R^6)_n, -NHSO_2R^9, and
-NHSO_2R^{14}(R^6)_n;

R^1 is hydrogen;
R^2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl,
butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy,
hydroxyl, -NHR^5R^{14}, -OR^7, -R^9R^{10}, -R^{16}R^5R^{14}, -R^{12}, -R^{14}, -(R^{14})_2, -SO_2R^{10},
-SO_2R^{12}, -SO_2R^{13}, -SO_2R^{14}, -C_0_2R^7, -R^{10}R^6, -R^{13}R^{14}, -R^{10}R^{14}, -R^{13}R^6, -R^{14}R^6,
-(R^{14}R^{12}), cyclopentyl, dihydroindenyl, and phenyl;

R^3 is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;
R^4 is selected from the group consisting of hydrogen, -C(0)R^{12}, -SO_2R^8, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino,
dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;
R^5 is selected from the group consisting of methylene, ethylene, and propylene;
R^6 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl,
isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo,
nitrile, and -C_2O_2R^7;
R^7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl,
butyl, t-butyl, and pentyl;

R^8 is independently selected from the group consisting of hydrogen, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl,
cyclohexyl, -R^{10}R^{11}, -R^{16}R^{13}, -R^{16}(R^{11})_M, and -R^{16}R^{16}(R^{11})_M;
R^9 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyl,
dimethylbutanyl, and dimethylpentanyl;
R_{10} is phenyl;
R_{11} is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, and methoxy;
R_{15} is -N(R_{8})_{2}, wherein each R_{8} may be independently chosen from among the R_{8} substituents;
R_{13} is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
R_{14} is selected from the group consisting of morpholinyl, thiomorpholinyl,
tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl,
indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidone,
piperidinyl, and pyridinyl;
R_{16} is selected from the group consisting of fluoro, chloro, and iodo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

47. A compound comprising the structure of Formula (IA):

or a pharmaceutically acceptable salt thereof, wherein:
Z is selected from the group consisting of a bond and a (branched or straight chain) (C_{1}-
C_{6})alkylene;
X is selected from the group consisting of hydrogen, (C_{1}-C_{6})alkoxy, nitrile, -C(0)R_{12},
-C(0)R_{14}, -S0_{2}R_{6}, -S0_{2}R_{13}, -S0_{2}R_{14}, -S0_{2}R_{14}(R_{6})_{n}, -NHSO_{2}R_{14}(R_{6})_{n},
-NHSO_{2}R_{14}(R_{6})_{m}, -NHSO_{2}R_{14}(R_{6})_{m}, -NHSO_{2}R_{14}, -NHSO_{2}R_{14}(R_{6})_{n}, and
-NHSO_{2}R_{14}(R_{6})_{n};
R_{1} is selected from the group consisting of hydrogen, -R_{6}R_{14}, and -C(0)R_{9};
R_{2} is selected from the group consisting of hydrogen, -Q, halo, (CrC_{6})alkyl, (Cl-
C₆alkoxy, nitrile, oxo, hydroxyl, -NHR, -OR, -R₆R₄(R₅)ₓW, -R₁₀R₆R₁₄, -R₁₂-, R₁₄, -R₁₀R₆, -R₁₀(R₆)ₓₙ, -S₀₂⁻R₁₀, -S₀₂⁻R₁₂, -S₀₂⁻R₁₄, -R₁₃R₁₄, -R⁹R₁₀, -R¹₀R₁₄, -(R¹₄R¹₂), -R¹₃R₆, -R¹₄R₆, -CO₂⁻R₇, (C₉C₈Cl₂)cycloalkyl, and (C₅C₄Cl₄)aryl, wherein A and Q are independently chosen from -(CH₂)₉W⁻R¹₀ or -(CH₂)₉W⁻R¹₄;
R¹ and R² taken together with any intervening atoms and when Z is a bond, can optionally form a fused (C₂-C₆)heterocyclic ring having 1-3 heteroatoms selected from S, N and O; wherein said fused heterocyclic ring can also be optionally substituted with one to two R₆ groups;
R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (CrC₆)alkoxy, nitrile, oxo, -C(0)R₁², -S₀₂⁻R₉, -R⁹(R₁₅)ₓₙ, -OR₇, -R₇², and halo;
R⁵ is a branched or straight chain (C₁-C₆)alkylene;
R⁶ is independently selected from the group consisting of (C₁-C₆)alkyl, oxo, (C₁-C₆)alkoxy, -OR₇, halo, nitrile, and -CO₂⁻R₇;
R⁷ is selected from the group consisting of hydrogen and (CrC₆)alkyl;
R⁸ is independently selected from the group consisting of hydrogen, (CrC₆)alkyl, -R¹₀, -R¹₃, -R¹₄, -R⁶R¹₃, -R⁶R¹₀, -R¹₃(R¹₁)ₓₚ and -R⁶R¹₀(R¹₁)ₓₚ;
R⁹ is (Ci-C₆)alkyl;
R¹₀ is (C₅-C₄Cl₄)aryl;
R¹¹ is selected from the group consisting of nitrile, halo, (Ci-C₆)alkyl, (CrC₆)alkoxy, and -R¹₄R₁₂;
R¹₂ is -N(R⁸)₂, wherein each instance of R⁸ may be independently and separately chosen from among the possible R⁸ substituents;
R¹₃ is (C₃-C₂Cl₂)cycloalkyl;
R¹₄ is selected from (CrCₙ) heterocycle or (CrCₙ) heteroaryl, each having one to three heteroatoms selected from N and O;
R¹₅ is halo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

48. The compound according to claim 47, having the structure of Formula (IA), or a pharmaceutically acceptable salt thereof, wherein:
Z is selected from the group consisting of a bond, methylene, ethylene, dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene,
methylpropylene, methylcyclopropylmethyl, and isopropylmethylene;

X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R 9, -C(0)R 14, -S0 2 R 8, -SO 2 R 12, -SO 2 R 14, -SO 2 R 14( R 6 ), -NHS0 2 R 10, -NHSO 2 R 16( R 6 ) n,

-NHS0 2 R 13, -NHS0 2 R 14, -NHS0 2 R 6 R 14, -NHS0 2 R 6( R 6 ) n, -NHS0 2 R 8, -NHS0 2 R 14( R 6 ) n,

R 1 is selected from the group consisting of hydrogen, -R 6 R 14, and -C(0)R 9;

R 2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR 5 R 14, -OR 7, -R 6 R 10, -R 6 R 16 R 14, -R 12, -R 14, -(R 14 ) 2, -SO 2 R 10, -SO 2 R 13, -SO 2 R 14, -SO 2 R 2, -C0 2 R 7, -R 10 R 6, -R 13 R 14, -R 16 R 14, -R 13 R 6, -R 14 R 6, -(R 14 R 13), cyclopentyl, dihydroindenyl and phenyl, wherein A and Q are independently chosen from -CH 2 W R 16 or -CH 2 W R 14;

R 1 and R 2 taken together with any intervening atoms and when Z is a bond can optionally form a fused imidazole ring that can also be optionally substituted with one to two R 6 groups;

R 4 is selected from the group consisting of hydrogen, -C(0)R 9, -SO 2 R 8, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;

R 5 is selected from the group consisting of methylene, ethylene, and propylene;

R 6 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and -C0 2 R 7;

R 7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl;

R 8 is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, - R 5 R 10, - R 6 R 13, -R 16( R 11 ) M and - R 6 R 16( R 11 ) M;

R 9 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyl, dimethylbutanyl, and dimethylpentanyl;

R 10 is phenyl;

R 11 is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and -R 14 R 12;
\( R^{12} \) is \(-N(R^8)_2\), wherein each \( R^8 \) may be independently chosen from among the \( R^8 \) substituents;

\( R^1 \) is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;

\( R^{14} \) is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidone, piperidinyl, and pyridinyl;

\( R^{15} \) is selected from the group consisting of fluoro, chloro, and iodo;

each \( m \) is independently zero or an integer from 1 to 3;

each \( n \) is independently zero or an integer from 1 to 3; and

each \( w \) is independently zero or an integer from 1 to 3.

49. A compound comprising the structure of Formula (IB):

\[
\text{(IB)}
\]

or a pharmaceutically acceptable salt thereof, wherein:

\( Z \) is selected from the group consisting of a bond and a (branched or straight chain) \((d-C_6)\)alkylene;

\( X \) is selected from the group consisting of hydrogen, \([(CrC_6)\)alkoxy, nitrile, \(-C(0)R^{12}\), \(-C(0)R^{14}\), \(-S_02R^6\), \(-S_02R^{12}\), \(-S_02R^{14}\), \(-S_02R^{14}(R^6)_n\), \(-NHSO_2R^{10}(R^6)_n\), \(-NHSO_2R^5R^{10}(R^6)_n\), \(-NHSO_2R^{13}\), \(-NHSO_2R^{14}\), \(-NHSO_2R^5(R^6)_n\), and \(-NHSO_2R^{14}(R^6)_n\);

\( R^1 \) is selected from the group consisting of hydrogen, \(-R^6R^{14}\), and \(-C(0)R^9\);

\( R^2 \) is selected from the group consisting of hydrogen, \(\text{halo, (CrC_6)alkyl, (C-C_6)alkoxy, nitrile, oxo, hydroxyl, -NHR}^3R^{14}, -OR^7, -R^6R^{14}(R^6)_n, -R^{10}R^6R^{14}, -R^{12}, -R^{14}, -R^{10}R^6, -R^{10}(R^6)_n, -S_02R^{10}, -S_02R^{12}, -S_02R^{14}, -S_02R^{14}, -R^{13}R^{14}, -R^6R^{10}, -R^{10}R^{14}, -(R^{14}R^{12}), -R^{13}R^6, -R^{14}R^6, -C_02R^7, (C_3-Ci_2)cycloalkyl, and (C_4-Ci_4)aryl, \)

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wherein A and Q are independently chosen from -(CH₂)₆R₁ or -(CH₂)₄R₁;
R₁ and R₂ taken together with any intervening atoms and when Z is a bond, can
optionally form a fused (C₆-C₆) heterocyclic ring having 1-3 heteroatoms selected
from S, N and O; wherein said fused heterocyclic ring can also be optionally
substituted with one to two R₆ groups;
R₃ is selected from the group consisting of hydrogen, halo, and (CrC₆)alkyl;
R₄ is selected from the group consisting of hydrogen, (Ci-C₆)alkyl, (CrC₆)alkoxy, nitrile,
oxo, -C(0)R₁₂, -S0₂R₉, -R₉(R₁₅), -OR₇, and -R₁₂;
R₅ is a branched or straight chain (CrC₆)alkylene;
R₆ is independently selected from the group consisting of (C₁-C₆)alkyl, oxo, (C₁-
C₆)alkoxy, -OR₇, halo, nitrile, and -C0₂R₇;
R₇ is selected from the group consisting of hydrogen and (C₁-C₆)alkyl;
R₈ is independently selected from the group consisting of hydrogen, (CrC₆)alkyl, -R₁₀,
-R₁₃, -R₁₄, -R₅R₁₃, -R₅R₁₀, -R₉(R₁₅), and -R₅R₁₀(R₁₅);
R₉ is (Cl-C₆)alkyl;
R₁₀ is (Cr₄-C₄₄)aryl;
R₁₁ is selected from the group consisting of nitrile, halo, (Cl-C₆)alkyl, (CrC₆)alkoxy, and
-R₁₄R₁₂;
R₁₂ is -N(R₆)₂, wherein each instance of R₈ may be independently and separately
chosen from among the possible R₈ substituents;
R₁₃ is (C₃-C₃)cycloalkyl;
R₁₄ is selected from (CrCn) heterocycle or (CrCn) heteroaryl, each having one to three
heteroatoms selected from N and O;
R₁₅ is halo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

50. The compound according to claim 49, having the structure of Formula (IB),
or a pharmaceutically acceptable salt thereof, wherein:
Z is selected from the group consisting of a bond, methylene, ethylene,
dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene,
methylpropylene, methylcyclopropylmethyl, and isopropylmethylene;
X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R², -C(0)R¹°₄, -S0²R₆, -S0₂R¹², -S0₂R¹⁴, -S0₂R¹⁴(R⁰)ₙ, -NH50₂R¹⁰, -NH50₂R¹⁵(R⁶)ₙ, -NH50₂R¹₃, -NH50₂R¹⁴, -NH50₂R⁵R¹⁴, -NH50₂R⁶(R⁰)ₙ, -NH50₂R⁶, -NH50₂R¹⁵(R⁰)ₙ.

R¹ is selected from the group consisting of hydrogen, -R⁵R¹₄, and -C(0)R⁹;

R² is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxy, -NH5R⁵R¹₄, -OR⁷, -R⁰R¹⁰, -R¹⁰R⁵R¹₄, -R¹₂, -R¹₄, -(R¹₄)₂, -S0₂R¹₉, -S0₂R¹₂, -S0₂R¹₄, -S0₂R¹₄, -C0₂R⁷, -R¹⁰R⁶, -R¹₃R¹₄, -R¹₄R¹₄, -R¹₃R⁶, -R¹₄R⁶, -(R¹₄R¹₄), cyclopentyl, dihydroindenyl, and phenyl, wherein A and Q are independently chosen from -(CH₂)ₙR₁₀ or -(CH₂)ₙR¹₄;

R¹ and R² taken together with any intervening atoms and when Z is a bond can optionally form a fused imidazole ring that can also be optionally substituted with one to two R⁶ groups;

R³ is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;

R⁴ is selected from the group consisting of hydrogen, -C(0)R¹°₄, -S0₂R⁶, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, and trifluoromethyl;

R⁵ is selected from the group consisting of methylene, ethylene, and propylene;

R⁶ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and -C0₂R⁷;

R⁷ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl;

R⁸ is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -R⁵R¹₀, -R⁶R¹₃, -R¹₀(R¹¹)ₘ, and -R⁶R¹₀(R¹¹)ₘ;

R⁹ is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyl, dimethylbutanyl, and dimethylpentanyl;

R¹₀ is phenyl;

R¹¹ is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and -R¹₄R¹₂;
\( R^{12} \) is \(-N(R^8)_2\), wherein each \( R^8 \) may be independently chosen from among the \( R^8 \) substituents;
\( R^{13} \) is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;
\( R^{14} \) is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidione, piperidinyl, and pyridinyl;
\( R^{15} \) is selected from the group consisting of fluoro, chloro, and iodo;
each \( m \) is independently zero or an integer from 1 to 3;
each \( n \) is independently zero or an integer from 1 to 3; and
each \( w \) is independently zero or an integer from 1 to 3.

51. A compound comprising the structure of Formula (II):

\[
\text{(II)}
\]

or a pharmaceutically acceptable salt thereof, wherein:
\( Z \) is selected from the group consisting of a bond and a (branched or straight chain) \((\text{C}_1-\text{C}_6)\)alkylene;
\( X \) is selected from the group consisting of \(-R^{10}, -R^{10}(R^8)_n, -R^{13}, -R^{14}, -R^6R^{14}, -R^9(R^8)_n, -R^9, \) and \(-R^{12}(R^8)_n\);
\( R^1 \) is selected from the group consisting of hydrogen, \(-R^6R^{14}, \) and \(-\text{(C}(0)R)^9;\)
\( R^2 \) is selected from the group consisting of hydrogen, halo, \((\text{CrC}_6)\)alkyl, \((\text{Ci-})\)alkyl,...
C_{6}\text{alkoxy}, nitrile, oxo, hydroxyl, -NHR^{5}R^{14}, -OR^{7}, -R^{5}R^{14}(R^{6})_{n}, -R^{10}R^{5}R^{14}, -R^{12}, -R^{13}, -R^{10}R^{6}, -R^{10}(R^{6})_{n}, -S_{0}^{2}R^{10}, -S_{0}^{2}R^{12}, -S_{0}^{2}R^{13}, -S_{0}^{2}R^{14}, -R^{13}R^{14}, -R^{9}R^{10}, -R^{10}R^{14}, -(R^{14}R^{12}), -R^{13}R^{6}, -R^{14}R^{6}, -C_{0}^{2}R^{7}, (C_{6}^{2}Cl_{2})\text{cycloalkyl}, and (C_{6}^{2}Cl_{4})\text{aryl},

wherein A and Q are independently chosen from -(CH_{2})_{W}R^{10} or -(CH_{2})_{W}R^{14};

R^{3} is selected from the group consisting of hydrogen, halo, and (CrC_{6})alkyl;

R^{4} is selected from the group consisting of hydrogen, (C_{1}-C_{6})alkyl, (CrC_{6})alkoxy, nitrile, oxo, -C(0)R^{12}, -S_{0}^{2}R^{9}, -R^{9}(R^{15})_{n}, -OR^{7}, -R^{12}, and halo;

R^{5} is a branched or straight chain (C_{1}-C_{6})alkylene;

R^{6} is independently selected from the group consisting of (C_{1}-C_{6})alkyl, oxo, (C_{1}-C_{6})alkoxy, -OR^{7}, halo, nitrile, and -C_{0}^{2}R^{7};

R^{7} is selected from the group consisting of hydrogen and (C_{1}-C_{6})alkyl;

R^{8} is independently selected from the group consisting of hydrogen, (C_{1}-C_{6})alkyl, -R^{10}, -R^{13}, -R^{14}, -R^{5}R^{13}, -R^{5}R^{10}, -R^{10}(R^{11})_{M}, and -R^{5}R^{10}(R^{11})_{M};

R^{9} is (CrC_{6})alkyl;

R^{10} is (C_{4}-C_{14})aryl;

R^{11} is selected from the group consisting of nitrile, halo, (Ci-C_{6})alkyl, (CrC_{6})alkoxy, and -R^{14}R^{12};

R^{12} is -N(R^{8})_{2}, wherein each instance of R^{8} may be independently and separately chosen from among the possible R^{8} substituents;

R^{13} is (C_{3}-Cl_{2})\text{cycloalkyl};

R^{14} is selected from (CrCn) heterocycle or (CrCn) heteroaryl, each having one to three heteroatoms selected from N and O;

R^{15} is halo;

each m is independently zero or an integer from 1 to 3;

each n is independently zero or an integer from 1 to 3; and

each w is independently zero or an integer from 1 to 3.

52. The compound according to claim 51, having the structure of Formula (II), or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from the group consisting of a bond, methylene, ethylene,

dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene,
methylpropylene, methylcyclopropylmethyl, and isopropylmethylene;

X is selected from the group consisting of X is selected from the group consisting of -R^{10}, -R^{10}(R^{6})_{n}, -R^{13}, -R^{14}, -R^{6}R^{14}, -R^{9}(R^{6})_{n}, -R^{9}, and -R^{14}(R^{6})_{n};
R is selected from the group consisting of hydrogen, -R'R_4, and -C(0)R; R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy, propoxy, hydroxyl, -NHR_5R_14, -OR_7, -R_8R_14, -R_8R_5R_14, -R_14, -R_14, -(R_14)_2, -SO_2R_10, -SO_2R_12, -SO_2R_13, -SO_2R_14, -CO_2R_7, -R_10R_6, -R_13R_14, -R_16R_14, -R_13R_6, -R_16R_6, -(R_14R_12), cyclopentyl, and phenyl, wherein A and Q are independently chosen from -(CH_2)_WR_10 or -(CH_2)_WR_14; R_3 is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl; R_4 is selected from the group consisting of hydrogen, -C(0)R_12, -SO_2R_6, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino, dimethylamino, trifluoromethyl, fluoro, iodo, and chloro; R_5 is selected from the group consisting of methylene, ethylene, and propylene; R_6 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and -CO_2R_7; R_7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl; R_8 is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -R_8R_10, -R_8R_13, -R_10(R_11)_M, and -R_8R_15(R_11)_M; R_9 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyl, dimethylbutanyl, and dimethylpentanyl; R_{10} is phenyl; R_{11} is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and -R_14R_12; R_{12} is -N(R_8)_2, wherein each R_8 may be independently chosen from among the R_8 substituents; R_{13} is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl; R_{14} is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidione, piperidinyl, and pyridinyl;
R¹⁵ is selected from the group consisting of fluoro, chloro, and iodo; each m is independently zero or an integer from 1 to 3; each n is independently zero or an integer from 1 to 3; and each w is independently zero or an integer from 1 to 3.

53. A compound comprising the structure of Formula (III):

![Structure](image)

or a pharmaceutically acceptable salt thereof, wherein:

- Z is selected from the group consisting of a bond and a (branched or straight chain) (d-C₆)alkylene;
- X is selected from the group consisting of -R⁶, -R¹², -R¹⁴, and -R¹⁴(R⁶)ₙ;
- R¹ is selected from the group consisting of hydrogen, -R⁶R¹⁴, and -C(0)R ⁰,
- R² is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, nitrile, oxo, hydroxyl, -NHR⁵R¹⁴, -OR⁷, -R⁵R¹⁴(R⁶)ₙ, -R⁰R⁵R¹⁴, -R¹⁴, -R¹⁰R⁶, -R¹⁰(R⁶)ₙ, -S₀₂R¹⁰, -S₀₂R¹², -S₀₂R¹³, -S₀₂R¹⁴, -R³R¹⁴, -R⁹R¹⁰, -R¹⁰R¹⁴, -(R¹⁴R¹²), -R¹³R⁶, -R¹⁴R⁶, -C₀₂R⁷, (C₅-C₂)cycloalkyl, and (C₄-C₁)aryl, wherein A and Q are independently chosen from -(CH₂)ₙR¹⁰ or -(CH₂)ₙR¹⁴;
- R³ is selected from the group consisting of hydrogen, halo, and (C₁-C₆)alkyl;
- R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (CrC₆)alkoxy, nitrile, oxo, -C(0)R ¹², -S₀₂R⁹, -R³(R¹⁵)ₙ, -OR⁷, -R¹², and halo;
- R⁵ is a branched or straight chain (C₁-C₆)alkylene;
- R⁶ is independently selected from the group consisting of (CrC₆)alkyl, oxo, (C₁-C₆)alkoxy, -OR⁷, halo, nitrile, and -C₀₂R⁷;
- R⁷ is selected from the group consisting of hydrogen and (CrC₆)alkyl;
- R⁸ is independently selected from the group consisting of hydrogen, (CrC₆)alkyl, -R¹⁰,
R₉ is \((\text{Ci-C}_6)\)alkyl;
R₁₀ is \((\text{C}_4-\text{C}_{14})\)aryl;
R¹¹ is selected from the group consisting of nitrile, halo, \((\text{Ci-C}_6)\)alkyl, \((\text{CrC}_6)\)alkoxy, and -R₁⁴ R¹₂;
R₁₂ is -N(R₈)₂, wherein each instance of R₈ may be independently and separately chosen from among the possible R₈ substituents;
R¹₃ is \((\text{C}_3-\text{C}_{13})\)cycloalkyl;
R¹₄ is selected from \((\text{CrC}^\ast\text{heterocycle})\) or \((\text{C}_r-\text{C}_{11})\)heteroaryl, each having one to three heteroatoms selected from N and O;
R¹₅ is halo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

54. The compound according to claim 53, having the structure of Formula (III),
or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from the group consisting of a bond, methylene, ethylene,
dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene,
methylpropylene, methycyclopropylmethyl, and isopropylmethylene;
X is selected from the group consisting of -R⁶, -R¹₂, -R¹₄, and -R¹₄(R₆)ₙ, -C(0)R¹₂, and -C(0)R¹₄;
R¹ is selected from the group consisting of hydrogen, -R⁶ R¹₄, and -C(0)R⁹;

R² is selected from the group consisting of hydrogen, methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy,
propoxy, hydroxyl, -NHR⁵ R¹₄, -OR⁷, -R⁹ R¹₀, -R¹₀ R⁶ R¹₄, -R¹₂, -R¹₄, -(R¹₄)₂, -
S₀₂ R¹₀, -S₀₂ R¹₂, -S₀₂ R¹₃, -S₀₂ R¹₄, -C₀₂ R⁷, -R¹₀ R⁶, -R¹₃ R¹₄, -R¹₆ R¹₄, -R¹₃ R⁶, -
R¹₄ R⁶, -(R¹₄ R¹₅), cyclopentyl, dihydroindenyl, and phenyl, wherein A and Q are
independently chosen from -(CH₂)w R¹₀ or -(CH₂)w R¹₄;
R³ is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;
R⁴ is selected from the group consisting of hydrogen, -C(0)R¹₂, -S₀₂ R⁶, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino,
dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;

$R^5$ is selected from the group consisting of methylene, ethylene, and propylene;

$R^6$ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo, nitrile, and $-CO_2R^7$;

$R^7$ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and pentyl;

$R^8$ is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-R^{5}R^{10}$, $-R^{6}R^{13}$, $-R^{15}(R^{11})_M$, and $-R^{5}R^{15}(R^{11})_M$;

$R^9$ is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyl, dimethylbutanyl, and dimethylpentanyl;

$R^{10}$ is phenyl;

$R^{11}$ is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and $-R^{14}R^{15}$;

$R^{12}$ is $-N(R^{8})_2$, wherein each $R^8$ may be independently chosen from among the $R^8$ substituents;

$R^{13}$ is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;

$R^{14}$ is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, piperidinyl, and pyridinyl;

$R^{15}$ is selected from the group consisting of fluoro, chloro, and iodo;

each $m$ is independently zero or an integer from 1 to 3;

each $n$ is independently zero or an integer from 1 to 3; and

each $w$ is independently zero or an integer from 1 to 3.

55. A compound comprising the structure of Formula (I):

(I)
or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from the group consisting of a bond and a (branched or straight chain) (d-C₆)alkylene;

X is selected from the group consisting of hydrogen, (C₁-C₆)alkoxy, nitrile, -C(0)R₁₂, and -C(0)R₁₄;

R¹ is selected from the group consisting of hydrogen, -R⁶R¹₄, -C(0)R⁹,

R² is selected from the group consisting of hydrogen, (Br-C₆)alkoxy, nitrile, oxo, hydroxyl, -NHR⁶R¹₄, -OR⁷, -R⁶R¹₄(R⁶)₊, -R¹₀R⁶, -R¹₀(R⁶)₊, -S₀₂R₁₀, -SO₂R₁₂, -SO₂R¹₄, -R¹₃R¹₄, -R⁹R¹₀, -R¹₀R¹₄, -(R¹₄R¹₄), -R¹₃R⁶, -R¹₄R⁶, -C₀₂R⁹, (C₅-C₆)cycloalkyl, and (C₄-C₆)aryl,

wherein A and Q are independently chosen from -(CH₂)₆₋₇ or -(CH₂)₆₋₇;

R³ is selected from the group consisting of hydrogen, halo, and (CrC₆)alkyl;

R⁴ is selected from the group consisting of hydrogen, (Ci-C₆)alkyl, (CrC₆)alkoxy, nitrile, oxo, -C(0)R₁₂, -SO₂R⁹, -OR⁷, -R₁₄, and halo;

R⁵ is a branched or straight chain (CrC₆)alkylene;

R⁶ is independently selected from the group consisting of (CrC₆)alkyl, oxo, (C₁-C₆)alkoxy, -OR⁷, halo, nitrile, and -C₀₂R⁷;

R⁷ is selected from the group consisting of hydrogen and (CrC₆)alkyl;

R⁸ is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, -R¹₀, -R¹₃, -R¹₄, -R⁶R¹₃, -R⁶R¹₀, -R¹₀(R¹₁)₉, and -R⁶R¹₀(R¹₁)₉;

R⁹ is (C₁-C₆)alkyl;

R¹₀ is (C₄-C₆)aryl;

R¹₁ is selected from the group consisting of nitrile, halo, (C₁-C₆)alkyl, (CrC₆)alkoxy, and -R₁₄R¹₂;

R¹₂ is -N(R⁸)₂, wherein each instance of R⁸ may be independently and separately chosen from among the possible R⁸ substituents;
R^{13} is (C_3-C_2)cycloalkyl;
R^{14} is selected from (CrC_n)heterocycle or (CrC_n)heteroaryl, each having one to three heteroatoms selected from N and O;
R^{15} is halo;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

56. The compound according to claim 55, having the structure of Formula (I) or a pharmaceutically acceptable salt thereof, wherein:
Z is selected from the group consisting of a bond, methylene, ethylene,
dimethylmethylene, dimethylmethylene, ethylmethylene, propylmethylene,
methylpropylene, methylcyclopropylmethyl, and isopropylmethylene;
X is selected from the group consisting of hydrogen, (CrC_6)alkoxy, nitrile, -C(0)R^{12}, and -C(0)R^{14};
R^1 is selected from the group consisting of hydrogen, -R^6R^{14}, and -C(0)R^{15};

R^2 is selected from the group consisting of hydrogen,

isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy,
propoxy, hydroxyl, -NHR^5R^{14}, -OR^7, -R^9R^{10}, -R^{10}R^{14}, -R^{14}, -R^{15}, -(R^{14})_2,-
S_2R^{10}, -S_2R^{12}, -S_2R^{13}, -S_2R^{14}, -C_2R^7, -R^6R^{12}, -R^{12}R^{14}, -R^{14}R^{15}, -R^{15}R^{16}, -R^{16}R^{14}, -R^{16}R^{15},
-R^6, -(R^{14}R^{15}), cyclopentyl, and phenyl, wherein A and Q are independently chosen from -(CH_2)_W^10 or -(CH_2)_W^{14};
R^3 is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;
R^4 is selected from the group consisting of hydrogen, -C(0)R^{12}, -S_2R^6, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino,
dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;
R^5 is selected from the group consisting of methylene, ethylene, and propylene;
R^6 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl,
isobutyl, t-butyl, oxo, methoxy, ethoxy, propoxy, hydroxy, fluoro, chloro, iodo,
nitrile, and -C_2R^7;
R^7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl,
butyl, t-butyl, and pentyl;
R\(^8\) is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -R\(^8\)R\(^{10}\), -R\(^8\)R\(^{13}\), -R\(^8\)R\(^{10}\)(R\(^{11}\))\(_M\), and -R\(^8\)R\(^{15}\)(R\(^{11}\))\(_M\); 

R\(^9\) is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyl, dimethylbutanyl, and dimethylpentanyl; 

R\(^{10}\) is phenyl; 

R\(^{11}\) is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and -R\(^{14}\)R\(^{12}\); 

R\(^{12}\) is -N(R\(^8\))\(_2\), wherein each R\(^8\) may be independently chosen from among the R\(^8\) substituents; 

R\(^{13}\) is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl; 

R\(^{14}\) is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, piperidinyl, and pyridinyl; 

R\(^{15}\) is selected from the group consisting of fluoro, chloro, and iodo; each m is independently zero or an integer from 1 to 3; each n is independently zero or an integer from 1 to 3; and each w is independently zero or an integer from 1 to 3.

57. A compound comprising the structure of Formula (IV):

\[
\text{(IV)}
\]

or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from the group consisting of a bond and a (branched or straight chain) (d-C\(_6\))alkylene;

X is selected from the group consisting of hydrogen, (CrC\(_6\))alkoxy, nitrile, -C(0)R\(^{12}\),
R is halo;

R is halo;

R is halo;

R \text{ is selected from the group consisting of hydrogen, } -R^5 R^{14}, \text{ and } -C(0)R^{10} ;

C(0)R^{14}, -S0_2 R^6, -S0_2 R^{12}, -S0_2 R^{14}, -S0_2 R^{14}(R^6)_n, -NHSO_2 R^{10}(R^6)_n, -NHSO_2 R^6 R^{10}(R^6)_n, -NHSO_2 R^6 R^{14}(R^6)_n, and -NHSO_2 R^6 (R^6)_n ;

R^1 \text{ is selected from the group consisting of hydrogen, } -R^5 R^{14}, \text{ and } -C(0)R^{10} ;

R^2 \text{ is selected from the group consisting of hydrogen, } -R^5 R^{14}, \text{ and } -C(0)R^{10} ;

R^3 \text{ is selected from the group consisting of hydrogen, halo, and } (CrC_6)\text{alkyl} ;

R^4 \text{ is selected from the group consisting of hydrogen, } (CrC_6)\text{alkyl, } (CrC_6)\text{alkoxy, nitrile, oxo, hydroxyl, } -NHR^{15} R^{14}, -OR^7, -R^5 R^{14}(R^6)_n, -R^{16} R^6 R^{14}, -R^{12}, -R^{14}, -R^{10} R^6, -R^6 (R^6)_n, -S0_2 R^{10}, -S0_2 R^{12}, -S0_2 R^{14}, -R^{13} R^{14}, -R^{10} R^{10}, -R^{14} R^{12}, -R^{13} R^6, -R^{14} R^6, -C0_2 R^7, (C_3-C_{12})\text{cycloalkyl}, \text{ and } (C_4-C_{14})\text{aryl}, \text{ wherein } A \text{ and } Q \text{ are independently chosen from } -(CH_2)_W R^{10} \text{ or } -(CH_2)_W R^{14} ;

R^1 \text{ and } R^2 \text{ taken together with any intervening atoms and when } Z \text{ is a bond, can optionally form a fused } (C_2-C_6)\text{heterocyclic ring having } 1 \text{ to } 3 \text{ heteroatoms selected from } S, N \text{ and } O \text{ where said fused heterocyclic ring can also be optionally substituted with one to two } R^6 \text{ groups} ;

R^3 \text{ is selected from the group consisting of hydrogen, halo, and } (CrC_6)\text{alkyl} ;

R^4 \text{ is selected from the group consisting of hydrogen, } (CrC_6)\text{alkyl, } (CrC_6)\text{alkoxy, nitrile, oxo, } -C(0)R^{12}, -S0_2 R^6, -R^{10} (R^{15})_n, -OR^7, -R^{12}, \text{ and halo} ;

R^5 \text{ is a branched or straight chain } (CrC_6)\text{alkylene} ;

R^6 \text{ is independently selected from the group consisting of } (CrC_6)\text{alkyl, oxo, } (C_1-C_6)\text{alkoxy}, -OR^7, \text{ halo, nitrile, and } -C0_2 R^7 ;

R^7 \text{ is selected from the group consisting of hydrogen and } (CrC_6)\text{alkyl} ;

R^8 \text{ is independently selected from the group consisting of hydrogen, } (CrC_6)\text{alkyl, } -R^{10}, -R^{13}, -R^{14}, -R^5 R^{13}, -R^6 R^{10}, -R^{10} (R^{11})_M, \text{ and } -R^6 R^{10} (R^{11})_M ;

R^9 \text{ is } (Ci-C_6)\text{alkyl} ;

R^{10} \text{ is } (C_4-C_{14})\text{aryl} ;

R^{11} \text{ is selected from the group consisting of nitrile, halo, } (C_1-C_6)\text{alkyl, } (CrC_6)\text{alkoxy, and } -R^{14} R^{12} ;

R^{12} \text{ is } -N(R^6)_2, \text{ wherein each instance of } R^6 \text{ may be independently and separately chosen from among the possible } R^6 \text{ substituents} ;

R^{13} \text{ is } (C_3-C_{12})\text{cycloalkyl} ;

R^{14} \text{ is selected from } (CrCn)\text{heterocycle or } (CrCn)\text{heteroaryl}, \text{ each having one to three heteroatoms selected from } N \text{ and } O ;

R^{15} \text{ is halo} ;
each m is independently zero or an integer from 1 to 3;
each n is independently zero or an integer from 1 to 3; and
each w is independently zero or an integer from 1 to 3.

58. The compound according to claim 57, having the structure of Formula (IV):
or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from the group consisting of a bond, methane, ethylene,
dimethylmethylene, methylmethylene, ethylmethylene, propylmethylene,
methylpropylene, methylvicyclopentylmethylene, and isopropylmethylene;
X is selected from the group consisting of hydrogen, methoxy, nitrile, -C(0)R 12,
-C(0)R 14, -SO 2R 6, -SO 2R 12, -SO 2R 14, -SO 2R 14(R 6)n, -NHSO 2R 10, -NHSO 2R 14(R 6)n,
-NHSO 2R 14, -NHSO 2R 14, -NHSO 2R 4R 14, -NHSO 2R 2R 6(R 6)n, -NHSO 2R 8,
-NHSO 2R 14(R 6)n;
R 1 is selected from the group consisting of hydrogen, -R 5R 14, and -C(0)R 9;

R 2 is selected from the group consisting of hydrogen,

\[
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\end{array}
\]

methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, t-butyl, nitrile, fluoro, chloro, iodo, methoxy, ethoxy,
prophox, hydroxyl, -NHR 5R 14, -OR 7, -R 8R 10, -R 9R 14, -R 12, -R 14, -(R 14) 2, -
-SO 2R 10, -SO 2R 12, -SO 2R 14, -SO 2R 14, -SO 2R 14, -SO 2R 14, -SO 2R 7, -R 10R 6, -R 12R 14, -R 14R 14, -R 13R 6, -
R 14R 6, -(R 14R 14), cyclopentyl, dihydroindenyl, and phenyl, wherein A and Q are
independently chosen from -(CH 2) 2W R 10 or -(CH 2) 2W R 14;
R 1 and R 2 taken together with any intervening atoms and when Z is a bond can
optionally form a fused imidazole ring that can also be optionally substituted with
one to two R 6 groups;
R 3 is selected from the group consisting of hydrogen, chloro, iodo, fluoro, and methyl;
R 4 is selected from the group consisting of hydrogen, -C(0)R 12, -SO 2R 6, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, methoxy, ethoxy, amino, nitrile, oxo, methylamino,
dimethylamino, trifluoromethyl, fluoro, iodo, and chloro;
R 5 is selected from the group consisting of methylene, ethylene, and propylene;
R 6 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl,
isobutyl, t-butyl, oxo, methoxy, ethoxy, proprvxy, hydroxyl, fluoro, chloro, iodo,
nitrile, and -C0 2R 7;
R 7 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl,
butyl, t-butyl, and pentyl;

R^8 is independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -R^6R^10, -R^6R^12, -R^10(R^11)_M, and -R^6R^12(R^11)_M;

R^9 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isopropyl, pentyl, t-pentyl, neopentyl, dimethylbutanyl, and dimethylpentanyl;

R^10 is phenyl;

R^11 is selected from the group consisting of methyl, nitrile, fluoro, iodo, chloro, methoxy, and -R^14R^12;

R^12 is -N(R^6)_2, wherein each R^8 may be independently chosen from among the R^8 substituents;

R^13 is selected from the group consisting of cyclopropyl, cyclobutyl, and cyclohexyl;

R^14 is selected from the group consisting of morpholinyl, thiomorpholinyl, tetrahydropyranyl, imidazolyl, quinolinyl, oxazepinyl, pyrimidinyl, pyrazolyl, indolyl, thiophenyl, tetrahydrofuranyl, piperazinyl, pyrrolidinyl, pyrrolidione, piperidinyl, and pyridinyl;

R^15 is selected from the group consisting of fluoro, chloro, and iodo;

each m is independently zero or an integer from 1 to 3;

each n is independently zero or an integer from 1 to 3; and

each w is independently zero or an integer from 1 to 3.

59. A compound comprising the structure of Formula (V):

(V)

or a pharmaceutically acceptable salt thereof, wherein:

X is selected from -NHSO_2R^10(R^6)_n or -SO_2R^12;

R^1 is selected from the group consisting of hydrogen, -C0_2R^7, -C(0)R^10, and -C(0)R^9;

R^2 is selected from the group consisting of hydrogen, -R^10R^12, -R^10R^14, -R^10, -R^15, and -R^10R^6,
**R**^4^ is selected from hydrogen or (C\textsubscript{1}-C\textsubscript{6})alkoxy;

**R**^6^ is independently selected from the group consisting of (CrC\textsubscript{6})alkyl, oxo, (C\textsubscript{1}-C\textsubscript{6})alkoxy, -OR\textsuperscript{7}, halo, nitrile, and -CO\textsubscript{2}R\textsuperscript{7};

**R**\textsuperscript{7} is selected from hydrogen or (Ci-C\textsubscript{6})alkyl;

**R**\textsuperscript{8} is selected from hydrogen or (Ci-C\textsubscript{6})alkyl;

**R**\textsuperscript{9} is (Ci-C\textsubscript{6})alkyl;

**R**\textsuperscript{10} is (C\textsubscript{4}-C\textsubscript{14})aryl;

**R**\textsuperscript{12} is -N(R\textsuperscript{8})\textsubscript{2}, wherein each instance of **R**\textsuperscript{8} may be independently and separately chosen from among the possible **R**\textsuperscript{8} substituents;

**R**\textsuperscript{14} is selected from (CrC\textsuperscript{\textalpha}heterocycle or (CrCn)heteroaryl, each having one to three heteroatoms selected from N and O;

**R**\textsuperscript{15} is halo; and

each n is independently zero or an integer from 1 to 3.

60. The compound according to claim 59, having the structure of Formula (V) or a pharmaceutically acceptable salt thereof, wherein:

X is selected from -NHSO\textsubscript{2}R\textsuperscript{10}(R\textsuperscript{8})\textsubscript{2} or -SO\textsubscript{2}R\textsuperscript{12};

**R**\textsuperscript{1} is selected from the group consisting of hydrogen, -C0\textsubscript{2}R\textsuperscript{7}, -C(0)R\textsuperscript{10}, and -C(0)R\textsuperscript{9};

**R**\textsuperscript{2} is selected from the group consisting of hydrogen, -R\textsuperscript{10}R\textsuperscript{12}, -R\textsuperscript{10}R\textsuperscript{14}, -R\textsuperscript{10}, -R\textsuperscript{15}, and -R\textsuperscript{10}R\textsuperscript{6};

**R**\textsuperscript{10} is selected from hydrogen or methoxy;

**R**\textsuperscript{10} is independently selected from the group consisting of methyl, oxo, methoxy, fluoro, bromo, nitrile, and -C0\textsubscript{2}R\textsuperscript{7};

**R**\textsuperscript{7} is selected from the group consisting of hydrogen, methyl, ethyl, propyl, and butyl;

**R**\textsuperscript{8} is selected from the group consisting of hydrogen, methyl, ethyl, propyl, and butyl;

**R**\textsuperscript{9} is selected from the group consisting of methyl, ethyl, propyl, and butyl;

**R**\textsuperscript{10} is phenyl;

**R**\textsuperscript{12} is -N(R\textsuperscript{8})\textsubscript{2}, wherein each instance of **R**\textsuperscript{8} may be independently and separately chosen from among the possible **R**\textsuperscript{8} substituents;

**R**\textsuperscript{14} is morpholinyl; and

**R**\textsuperscript{15} is selected fluoro or bromo.

61. A compound selected from the group consisting of those compounds in Table 1.
62. The use of a compound or salt as defined in any of the preceding claims in the manufacture of a medicament for use in the treatment of a viral infection in a human.

63. A pharmaceutical composition comprising a pharmaceutically acceptable diluent and a therapeutically effective amount of a compound as defined in any of the preceding claims.

64. A method for treating a viral infection in a mammal mediated at least in part by a virus in the *Flaviviridae* family of viruses which method comprises administering to a mammal, that has been diagnosed with said viral infection or is at risk of developing said viral infection, a compound of any one of claims 1 to 61.

65. The method of claim 64, wherein said virus is hepatitis C virus.

66. The method of claim 64, further comprising administration of a therapeutically effective amount of one or more agents active against hepatitis C virus.

67. The method of claim 66, wherein said agent active against hepatitis C virus is an inhibitor of HCV protease, HCV polymerase, HCV helicase, HCV entry, HCV assembly, HCV egress, HCV replicase, HCV NS5A protein, or inosine 5’-monophosphate dehydrogenase.

68. The method of claim 66, wherein said agent active against hepatitis C virus is interferon.

69. The method of claim 66, wherein said agent active against hepatitis C virus is ribavirin.

70. The method of claim 66, wherein said agent active against hepatitis C virus is interferon in combination with ribavirin.