

ACYLSULFONAMIDE KAT6A INHIBITORS

CROSS-REFERENCES TO RELATED APPLICATIONS

5 **[0001]** This application claims the benefit of Indian application number 202311018002, filed on 16th March 2023; the specification of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

10 **[0002]** The present disclosure relates to an acylsulfonamide compound of Formula (J) or a pharmaceutically acceptable salt thereof, which is believed to be useful as a KAT6A inhibitor for the treatment of a disease or disorder mediated by KAT6A. The present application also describes a method of preparation of the compound and a pharmaceutical composition comprising the compound.

BACKGROUND OF THE INVENTION

15 **[0003]** The MYST family of histone acetyltransferases (HATs) is named after its four founding members MOZ, Ybf2 (Sas3), Sas2, and Tip60. Presence of zinc fingers and chromodomains is characteristic feature of these HATs. MYST acetylates lysine residues on histones H2A, H3, and H4. Several MYST family proteins contain zinc fingers as well as the highly conserved motif A found among GNATs that facilitate acetyl-CoA binding. MYST
20 HATs are involved in several key nuclear processes and play critical roles in gene-specific transcription regulation, DNA damage response, repair and replication. The anomalous activity of these HATs or their associated complexes can easily lead to severe cellular malfunction, resulting in cell death or uncontrolled growth and malignancy. Indeed, the MYST family HATs have been implicated in several forms of human cancer. (Avvakumov, N. et al. "The MYST
25 family of histone acetyltransferases and their intimate links to cancer." *Oncogene* 26.37 (2007): 5395-5407.)

30 **[0004]** MOZ (monocytic leukemia zinc finger protein) is known as oncogene in human. MOZ plays a key role as transcriptional coactivator and epigenetic regulator in the process of proliferation and the differentiation of hematopoietic progenitor and stem cells. The insights into the deregulation of these processes indicate that MOZ fusion proteins are related to the formation of leukemic stem cells and interfere with the activities of key proteins such as transcription factors, which render MOZ as a promising target for acute myeloid leukaemia

therapy. Targeting MOZ by small molecules will hold promise for acute myeloid leukaemia therapy. (Zhou C. et al. "MOZ/KAT6A: a promising target for acute myeloid leukaemia therapy." (2020): 759-761).

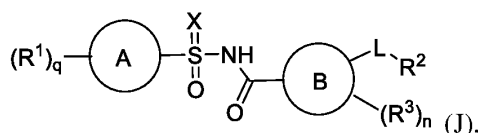
[0005] Cellular senescence plays a key role to restrict tumor growth. KAT6A has been shown to repress cellular senescence in mouse embryonic fibroblasts (MEFs) while not affecting apoptosis or DNA damage. MOZ is believed to directly bind to genes that inhibit senescence including Cdc6, E2f2, Ezh2 and Melk, and in its absence, H3K9ac and H3K27ac at the TSS of these loci is reduced. (Sheikh, B. N., et al. "MOZ (MYST3, KAT6A) inhibits senescence via the INK4A-ARF pathway." *Oncogene* 34.47 (2015): 5807-5820).

[0006] Histone acetyltransferase KAT6A-upregulated PI3K/AKT signalling through TRIM24 binding is believed critical for cell proliferation and tumor growth in gliomas. KAT6A has been shown to promote H3K23 acetylation and association with TRIM24, leading to increased PIK3CA expression and PI3K/Akt signalling activation, resulting in enhanced glioma tumorigenesis. Hence, KAT6A is believed to function as an oncogene in gliomas. (Lv, D., et al. "Histone acetyltransferase KAT6A upregulates PI3K/AKT signalling through TRIM24 binding." *Cancer research* 77.22 (2017): 6190-6201).

[0007] Many publications disclose small molecule compounds and their derivatives capable of targeting KAT target proteins. Because there are currently no FDA-approved targeted therapeutics for specific KAT6A or KAT6B target protein, there is a need for the development of compounds, compositions, and methods for treating KAT6A- or KAT6B-activated proliferative disorders and autoimmune diseases.

SUMMARY

[0008] In some embodiments, a compound of the present disclosure is represented by Formula (J):



or a pharmaceutically acceptable salt thereof,

wherein

X is O or NR⁴;

ring A is a phenyl or heteroaryl;

ring B is a phenyl or heteroaryl;

- each R^1 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, - $C(O)R^{1a}$, - $C(O)OR^{1a}$, - $OC(O)R^{1a}$, - $C(O)N(R^{1a})(R^{1b})$, - $N(R^{1a})C(O)(R^{1b})$, - $OC(O)N(R^{1a})(R^{1b})$, - $N(R^{1a})C(O)(OR^{1b})$, - $S(O)R^{1a}$, - $S(O)_2R^{1a}$, - $S(O)_2N(R^{1a})(R^{1b})$, - $S(O)(NH)R^{1a}$, - $S(O)(NH)N(R^{1a})(R^{1b})$, - $N(R^{1a})(R^{1b})$, OH, -CN, -NO₂, C_3 - C_8 cycloalkyl, (C_1 - C_3 alkyl)(C_3 - C_8 cycloalkyl), -O-(C_3 - C_8 cycloalkyl), heterocycloalkyl, (C_1 - C_3 alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C_6 - C_{10} aryl, (C_1 - C_3 alkyl)(C_6 - C_{10} aryl), -O-(C_6 - C_{10} aryl), heteroaryl, (C_1 - C_3 alkyl)(heteroaryl), or -O-(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{1c} , each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{1e} ;
- each R^{1a} and R^{1b} is independently hydrogen or C_1 - C_6 alkyl;
- each R^{1c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, - $NR^{1c1}R^{1c2}$, OH, or -CN;
- each R^{1c1} and R^{1c2} is independently hydrogen or C_1 - C_6 alkyl;
- each R^{1d} is independently deuterium, C_3 - C_8 cycloalkyl, heterocycloalkyl, C_6 - C_{10} aryl, or heteroaryl;
- each R^{1e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, or -CN;
- alternatively, two R^1 groups on adjacent carbons together with the atoms to which they are attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl substituted with 0, 1, 2, 3, 4, 5, or 6 halogen, C_1 - C_4 alkyl, OH or -CN;
- L is - C_1 - C_4 alkylene-, -(C_1 - C_4 alkylene)-O-, or -O-;
- R^2 is a heteroaryl, which is substituted with 0, 1, 2, 3, or 4 R^{2a} ;
- each R^{2a} is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, - $C(O)R^{2b}$, - $C(O)OR^{2b}$, - $OC(O)R^{2b}$, - $C(O)N(R^{2b})(R^{2c})$, - $N(R^{2b})C(O)(R^{2c})$, - $S(O)_2R^{2b}$, - $S(O)_2N(R^{2b})(R^{2c})$, - $N(R^{2b})(R^{2c})$, OH, -CN, or -NO₂;
- each R^{2b} and R^{2c} is independently hydrogen or C_1 - C_6 alkyl;
- each R^3 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, - $C(O)R^{3a}$, - $C(O)OR^{3a}$, - $OC(O)R^{3a}$, - $C(O)N(R^{3a})(R^{3b})$, - $N(R^{3a})C(O)(R^{3b})$, - $OC(O)N(R^{3a})(R^{3b})$, - $N(R^{3a})C(O)(OR^{3b})$, - $S(O)R^{3a}$, - $S(O)_2R^{3a}$, - $S(O)_2N(R^{3a})(R^{3b})$, - $S(O)(NH)R^{3a}$, - $S(O)(NH)N(R^{3a})(R^{3b})$, - $N(R^{3a})(R^{3b})$, OH, -CN, -NO₂, C_3 - C_8 cycloalkyl, (C_1 - C_3 alkyl)(C_3 - C_8 cycloalkyl), -O-(C_3 - C_8 cycloalkyl), heterocycloalkyl, (C_1 - C_3

- alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, (C₁-C₃ alkyl)(C₆-C₁₀ aryl),
-O-(C₆-C₁₀ aryl), heteroaryl, (C₁-C₃ alkyl)(heteroaryl), or -O-(heteroaryl), wherein
each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{3c}, each alkoxy is substituted with 0,
1, 2, or 3 R^{3d}, and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted
5 with 0, 1, 2, or 3 R^{3e}; or,
two R³ on the same carbon atom together represent an oxo group;
each R^{3a} and R^{3b} is independently hydrogen or C₁-C₆ alkyl;
each R^{3c} is independently C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkoxy, -NR^{3c1}R^{3c2}, OH, or -CN;
each R^{3c1} and R^{3c2} is independently hydrogen or C₁-C₆ alkyl;
10 each R^{3d} is independently C₃-C₈ cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl;
each R^{3e} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkyl, or C₁-C₆
haloalkoxy;
R⁴ is hydrogen or C₁-C₆ alkyl;
subscript n is 0, 1, 2, 3, or 4; and
15 subscript q is 0, 1, 2, 3, or 4;
wherein
each heterocycloalkyl is a 3- to 8-membered ring that includes 1 to 4 heteroatoms each
independently N, O or S; and
each heteroaryl is a 5- to 6-membered ring that includes 1 to 4 heteroatoms each independently
20 N, O or S.

- [0009]** In some embodiments, a composition of the present invention is a pharmaceutical
composition comprising a compound of the present invention, or a pharmaceutically acceptable
salt thereof and a pharmaceutically acceptable carrier or excipient. In some embodiments, a
compound of the present invention is a compound or a pharmaceutically acceptable salt thereof
25 for use as a medicament. In some embodiments, a compound of the present invention is a
compound for use in the treatment of a disease or disorder mediated by KAT6A. In some
embodiments, a method of the present invention is a method of modulating KAT6A in a subject
comprising administering to the subject in need thereof, a therapeutically effective amount of
compound of the present invention or a pharmaceutically acceptable salt thereof.
- 30 **[0010]** In some embodiments, a method of the present invention is a method of treating a
disease or disorder mediated by KAT6A in a subject comprising administering to the subject
in need thereof a therapeutically effective amount of a compound of the present invention or a
pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWING

[0011] FIG. 1 provides synergy scores of Compound 282 in combination with everolimus at various concentrations.

5 [0012] FIG. 2 provides synergy scores of Compound 282 in combination with inavolisib at various concentrations.

[0013] FIG. 3 provides synergy scores of Compound 282 in combination with alpelisib at various concentrations.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

10 I. GENERAL

[0014] The present disclosure provides, among other things, acylsulfonamide compounds represented by formula (J) and pharmaceutically acceptable salts thereof. Also described herein are pharmaceutical compositions comprising the compounds which are believed useful as KAT6A inhibitors for the treatment of diseases or disorders dependent on or mediated by
15 KAT6A. The present disclosure also includes a preparation of compound of formula (J) or a pharmaceutically acceptable salt thereof.

II. DEFINITIONS

[0015] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein
20 belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present invention.

[0016] The singular forms “a”, “an” and “the” encompass plural references unless the context clearly indicates otherwise.

25 [0017] “Alkyl” refers to monovalent saturated aliphatic groups, including but not limited to C₁-C₁₀ straight-chain alkyl groups or C₃-C₁₀ branched-chain alkyl groups. In some embodiments, an alkyl group is a C₁-C₆ straight-chain alkyl group or C₃-C₈ branched-chain alkyl group. In some embodiments, the alkyl group refers to C₁-C₄ straight-chain alkyl groups or C₃-C₆ branched-chain alkyl groups. Examples of alkyl include, but are not limited to, methyl,

ethyl, 1-propyl, 2-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl and 4-octyl. The alkyl group may be optionally substituted.

[0018] An “alkylene” refers to a divalent saturated aliphatic group, including but not limited to C₁-C₁₀ straight-chain alkylene groups or C₃-C₁₀ branched-chain alkylene groups. In some embodiments, the alkylene refers to C₁-C₆ straight-chain alkylene groups or C₃-C₈ branched-chain alkylene groups. In some embodiments, the alkylene group refers to C₁-C₄ straight-chain alkylene groups or C₃-C₆ branched-chain alkylene groups. Examples of alkylene include, but are not limited to, methylene, ethylene, 1-propylene, 2-propylene, isopropylene, n-butylene, and sec-butylene. The “alkylene” group may further be optionally substituted.

[0019] “Alkenyl” refers to a straight chain or branched hydrocarbon having at least 2 carbon atoms and at least one double bond. Alkenyl can include any number of carbons, such as C₂, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₂₋₇, C₂₋₈, C₂₋₉, C₂₋₁₀, C₃, C₃₋₄, C₃₋₅, C₃₋₆, C₄, C₄₋₅, C₄₋₆, C₅, C₅₋₆, and C₆. Alkenyl groups can have any suitable number of double bonds, including, but not limited to, 1, 2, 3, 4, 5 or more. Examples of alkenyl groups include, but are not limited to, vinyl (ethenyl), propenyl, isopropenyl, 1-butenyl, 2-butenyl, isobutenyl, butadienyl, 1-pentenyl, 2-pentenyl, isopentenyl, 1,3-pentadienyl, 1,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,5-hexadienyl, 2,4-hexadienyl, or 1,3,5-hexatrienyl. Alkenyl groups can be substituted or unsubstituted.

[0020] “Alkynyl” refers to either a straight chain or branched hydrocarbon having at least 2 carbon atoms and at least one triple bond. Alkynyl can include any number of carbons, such as C₂, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₂₋₇, C₂₋₈, C₂₋₉, C₂₋₁₀, C₃, C₃₋₄, C₃₋₅, C₃₋₆, C₄, C₄₋₅, C₄₋₆, C₅, C₅₋₆, and C₆. Examples of alkynyl groups include, but are not limited to, acetylenyl, propynyl, 1-butylnyl, 2-butylnyl, butadiynyl, 1-pentylnyl, 2-pentylnyl, isopentylnyl, 1,3-pentadiynyl, 1,4-pentadiynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 1,3-hexadiynyl, 1,4-hexadiynyl, 1,5-hexadiynyl, 2,4-hexadiynyl, or 1,3,5-hexatriynyl. Alkynyl groups can be substituted or unsubstituted.

[0021] “Alkoxy” refers to the group -O-alkyl, where alkyl groups are as defined above. In some embodiments, the alkoxy group refers to C₁-C₆ straight-chain alkoxy groups or C₃-C₈ branched-chain alkoxy groups. In some embodiments, the alkoxy group refers to C₁-C₄ straight-chain alkoxy groups or C₃-C₆ branched-chain alkoxy groups. Exemplary C₁-C₁₀ alkoxy group include but are not limited to methoxy, ethoxy, n-propoxy, n-butoxy or t-butoxy. An

alkoxy group can be optionally substituted with one or more suitable groups, as described herein.

[0022] “Alkoxyalkyl” refers to an alkyl group substituted with one or more alkoxy groups, wherein the alkyl and alkoxy groups are as defined above. In some embodiments, alkoxyalkyl represents (C₁-C₆)alkyl(C₁-C₆)alkoxy or (C₁-C₄)alkyl(C₁-C₄)alkoxy. Exemplary alkoxyalkyl group include, but are not limited to methoxymethyl, ethoxymethyl and ethoxyethyl.

[0023] The term “halo” or “halogen” alone or in combination with other term(s) means fluorine, chlorine, bromine or iodine.

[0024] “Haloalkyl” refers to alkyl substituted with one or more halogen atoms, wherein the ‘halogen’ and ‘alkyl’ groups are as defined above. Examples of haloalkyl include but are not limited to fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl and 2,2,2-trifluoroethyl.

[0025] “Haloalkoxy” refers to an alkoxy group substituted with one or more halogen atoms (i.e., haloC₁₋₈alkoxy). Examples of haloalkoxy include but are not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, pentachloroethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy and 1-bromoethoxy.

[0026] “Amino” refers to an -NH₂ group.

[0027] “Hydroxy” or “hydroxyl” alone or in combination with other term(s) means -OH.

[0028] “Hydroxyalkyl” refers to an alkyl group substituted with one or more hydroxyls.

[0029] “Cycloalkyl” refers to a single saturated or partially unsaturated all carbon ring having 3 to 20 annular carbon atoms (i.e., C₃₋₂₀ cycloalkyl), for example from 3 to 12 annular atoms, for example from 3 to 10 annular atoms, or 3 to 8 annular atoms, or 3 to 6 annular atoms, or 3 to 5 annular atoms, or 3 to 4 annular atoms. Cycloalkyl groups also include multiple condensed, saturated and partially unsaturated all carbon ring systems (e.g., ring systems comprising 2, 3 or 4 carbocyclic rings). Accordingly, cycloalkyl includes multicyclic carbocycles such as a bicyclic carbocycles (e.g., bicyclic carbocycles having about 6 to 12 annular carbon atoms such as bicyclo[3.1.0]hexane and bicyclo[2.1.1]hexane), and polycyclic carbocycles (e.g. tricyclic and tetracyclic carbocycles with up to about 20 annular carbon atoms). The rings of a multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. Non-limiting examples

of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl and 1-cyclohex-3-enyl.

[0030] “Heteroatom” as used herein designates a sulfur, nitrogen or oxygen atom.

- 5 **[0031]** “Heterocycloalkyl” refers to a non-aromatic, saturated or partially saturated, bridged bicyclic, monocyclic or polycyclic ring system of 3- to 15-member, unless the ring size is specifically mentioned, having at least one heteroatom or hetero group selected from O, N, S, S(O), S(O)₂, NH or C(O) with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen and sulfur. Heterocycloalkyl also refers to the
- 10 bridged bicyclic ring system having at least one heteroatom or hetero group selected from O, N, S, S(O), S(O)₂, NH or C(O). Examples of heterocycloalkyl include, but not limited to, aziridinyl, oxiranyl, thiranyl, azetidiny, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, dihydropyridinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl, dioxidothiomorpholinyl,
- 15 oxopiperazinyl, oxopiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl, indolinyl, indolinylmethyl, isoindolinyl, oxoisoindolinyl, dioxoisoindolinyl, aza-bicyclooctanyl, diazabicyclooctanyl, azocinyl, chromanyl, isochromanyl and xanthenyl. Attachment of a heterocycloalkyl substituent can occur via either a carbon atom or a heteroatom. A heterocycloalkyl group can be optionally substituted with one or more suitable
- 20 groups. In some embodiments, heterocycloalkyl refers to 4- to 6-membered ring (unless the ring size is specifically mentioned) selected from the group consisting of azetidiny, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl and thiomorpholinyl. Heterocycloalkyl groups are optionally substituted by one or more groups described herein.
- 25 **[0032]** “Aryl” is an optionally substituted monocyclic, bicyclic or polycyclic aromatic hydrocarbon ring system of about 6 to 14 carbon atoms. In some embodiments, aryl includes 6- to 10-membered aromatic hydrocarbon ring systems. Examples of a C₆-C₁₄ aryl groups include, but are not limited to phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, fluorenyl, indanyl, biphenylenyl and acenaphthyl. Aryl group can be optionally substituted
- 30 with one or more suitable groups, described herein.

[0033] “Heteroaryl” refers to a completely unsaturated and aromatic ring system containing a total of 5 to 14 ring atoms, unless the ring size is specifically mentioned. At least one of the

ring atoms is a heteroatom (i.e., O, N or S), with the remaining ring atoms/groups being independently selected from C, N, O or S. A heteroaryl may be a single-ring (monocyclic) or multiple rings (bicyclic, tricyclic or polycyclic) fused together or linked covalently. In some embodiments, the heteroaryl is a 5- to 6-membered ring. The rings may contain from 1 to 4
5 heteroatoms selected from N, O and S, wherein the N atom is optionally quarternized. Any suitable ring position of the heteroaryl moiety may be covalently linked to the defined chemical structure. Examples of heteroaryls include but are not limited to furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, cinnolynyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl (pyridinyl), pyrimidinyl, pyrazinyl, pyridazinyl, benzoxazolyl,
10 benzisoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, benzotriazinyl, phthalazinyl, thianthrene, dibenzofuranyl, dibenzothienyl, benzimidazolyl, indolyl, isoindolyl, indazolyl, quinolynyl, isoquinolynyl, quinazolynyl, quinoxalynyl, purinyl, pteridinyl, 9H-carbazolyl, α -carbolynyl, indolizynyl, benzoisothiazolyl, benzoxazolyl, pyrrolopyridyl, purinyl, benzothiadiazolyl, benzooxadiazolyl, benzotriazolyl, benzotriadiazolyl, carbazolyl,
15 dibenzothienyl, acridinyl and the like. A heteroaryl can be further substituted.

[0034] “Pharmaceutically acceptable” means that, which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

20 **[0035]** “Pharmaceutically acceptable salt” refers to a product obtained by reaction of the compound of the present invention with a suitable acid or a base. In some cases, a medicament can be present in the form of a pharmaceutically acceptable salt. In some instances, a pharmaceutically acceptable salt can be a salt described in Berge et al, J. Pharm. Sci, 1977. In some instances, a pharmaceutically acceptable salts can include those salts derived from a
25 mineral, organic acid or inorganic base. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non- toxic salts of the parent compound formed, e.g., from non-toxic inorganic or organic acids.

30 **[0036]** The pharmaceutically acceptable salts of the present invention can be prepared from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the

appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in “Remington's Pharmaceutical Sciences”, 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in “Handbook of Pharmaceutical Salts: Properties, Selection and Use” by Stahl and Wermuth (Wiley- VCH, Weinheim, Germany, 2002).

10 [0037] “Composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By “pharmaceutically acceptable” it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

15 [0038] “Pharmaceutically acceptable carrier” includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, surfactant or emulsifier that has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

20 [0039] “Administer,” “administering,” and/or “administration” as used in this disclosure refer to either directly administering one or more disclosed compounds or a pharmaceutically acceptable salt of one or more disclosed compounds or a composition comprising one or more disclosed compounds to a subject or analog of the compound or a pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject's body.

25 [0040] “Carrier” encompasses carriers, excipients and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ or portion of the body to another organ or portion of the body of a subject.

30 [0041] “Treat”, “treating”, and/or “treatment” refer to a method of alleviating or abrogating a disease and/or one or more symptoms associated with the disease.

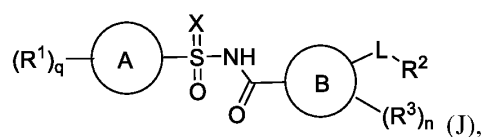
[0042] “Prevent”, “preventing”, and/or “prevention” refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from acquiring a disease. Prevent, preventing, and/or prevention also include delaying the onset of a disease and/or one or more symptoms associated with the disease and reducing a subject’s risk of acquiring a disease.

[0043] “Subject” or “patient” refers to an animal, such as a mammal, for instance, a human. In some embodiments, the subject is a mammal, such as a mouse, a rat, a dog, a cat, another veterinary animal, such as a goat, a pig, a horse, a cow, or a donkey; or a primate, such as a non-human primate, e.g., a cynomolgous monkey, rhesus monkey, or chimpanzee, or a human.

[0044] “Therapeutically effective amount” refers to an amount of a compound of formula (J) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; or a composition comprising the compound of formula (J) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, effective in producing the desired therapeutic response in a particular patient suffering from a diseases or disorder, in particular their use in diseases or disorder associated with cancer. A therapeutically effective amount includes the amount of the compound of formula (J) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, when administered, that induces a positive modification in the disease or disorder to be treated or is sufficient to prevent development of or alleviate to some extent, one or more of the symptoms of the disease or disorder being treated in a subject. In respect of the therapeutic amount of the compound, the amount of the compound used for the treatment of a subject is low enough to avoid undue or severe side effects, within the scope of sound medical judgment can also be considered. The therapeutically effective amount of the compound or composition will be varied with the particular condition being treated, the severity of the condition being treated or prevented, the duration of the treatment, the nature of concurrent therapy, the age and physical condition of the end user, the specific compound or composition employed the particular pharmaceutically acceptable carrier utilized.

III. COMPOUNDS

[0045] In some embodiments, a compound of the present disclosure is represented by Formula (J):



or a pharmaceutically acceptable salt thereof,

wherein

X is O or NR⁴;

5 ring A is a phenyl or heteroaryl;

ring B is a phenyl or heteroaryl;

each R¹ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -C(O)R^{1a}, -C(O)OR^{1a}, -OC(O)R^{1a}, -C(O)N(R^{1a})(R^{1b}), -N(R^{1a})C(O)(R^{1b}),
 10 -OC(O)N(R^{1a})(R^{1b}), -N(R^{1a})C(O)(OR^{1b}), -S(O)R^{1a}, -S(O)₂R^{1a}, -S(O)₂N(R^{1a})(R^{1b}), -S(O)(NH)R^{1a}, -S(O)(NH)N(R^{1a})(R^{1b}), -N(R^{1a})(R^{1b}), OH, -CN, -NO₂, C₃-C₈ cycloalkyl, (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), heterocycloalkyl, (C₁-C₃ alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, (C₁-C₃ alkyl)(C₆-C₁₀ aryl), -O-(C₆-C₁₀ aryl), heteroaryl, (C₁-C₃ alkyl)(heteroaryl), or -O-(heteroaryl), wherein
 15 each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{1c}, each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d}, and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{1e};

each R^{1a} and R^{1b} is independently hydrogen or C₁-C₆ alkyl;

each R^{1c} is independently C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkoxy, -NR^{1c1}R^{1c2}, OH, or -CN;

20 each R^{1c1} and R^{1c2} is independently hydrogen or C₁-C₆ alkyl;

each R^{1d} is independently deuterium, C₃-C₈ cycloalkyl, heterocycloalkyl, C₆-C₁₀ aryl, or heteroaryl;

each R^{1e} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, OH, or -CN;

25 alternatively, two R¹ groups on adjacent carbons together with the atoms to which they are attached combine to form a C₅-C₈ cycloalkyl or a heterocycloalkyl substituted with 0, 1, 2, 3, 4, 5, or 6 halogen, C₁-C₄ alkyl, OH or -CN;

L is -C₁-C₄ alkylene-, -(C₁-C₄ alkylene)-O-, or -O-;

R² is a heteroaryl, which is substituted with 0, 1, 2, 3, or 4 R^{2a};

30 each R^{2a} is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -

$C(O)R^{2b}$, $-C(O)OR^{2b}$, $-OC(O)R^{2b}$, $-C(O)N(R^{2b})(R^{2c})$, $-N(R^{2b})C(O)(R^{2c})$, $-S(O)_2R^{2b}$, $-S(O)_2N(R^{2b})(R^{2c})$, $-N(R^{2b})(R^{2c})$, OH, -CN, or $-NO_2$;

each R^{2b} and R^{2c} is independently hydrogen or C₁-C₆ alkyl;

each R^3 is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆

5 hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{3a}$, $-OC(O)R^{3a}$, $-C(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(R^{3b})$, $-OC(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(OR^{3b})$, $-S(O)R^{3a}$, $-S(O)_2R^{3a}$, $-S(O)_2N(R^{3a})(R^{3b})$, $-S(O)(NH)R^{3a}$, $-S(O)(NH)N(R^{3a})(R^{3b})$, $-N(R^{3a})(R^{3b})$, OH, -CN, -NO₂, C₃-C₈ cycloalkyl, (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), heterocycloalkyl, (C₁-C₃ alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, (C₁-C₃ alkyl)(C₆-C₁₀ aryl), -O-(C₆-C₁₀ aryl), heteroaryl, (C₁-C₃ alkyl)(heteroaryl), or -O-(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{3c} , each alkoxy is substituted with 0, 1, 2, or 3 R^{3d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{3e} ; or,

15 two R^3 on the same carbon atom together represent an oxo group;

each R^{3a} and R^{3b} is independently hydrogen or C₁-C₆ alkyl;

each R^{3c} is independently C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkoxy, $-NR^{3c1}R^{3c2}$, OH, or -CN;

each R^{3c1} and R^{3c2} is independently hydrogen or C₁-C₆ alkyl;

each R^{3d} is independently C₃-C₈ cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl;

20 each R^{3e} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy;

R^4 is hydrogen or C₁-C₆ alkyl;

subscript n is 0, 1, 2, 3, or 4; and

subscript q is 0, 1, 2, 3, or 4;

25 wherein

each heterocycloalkyl is a 3- to 8-membered ring that includes 1 to 4 heteroatoms each independently N, O or S; and

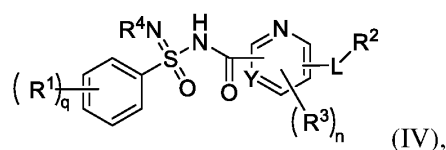
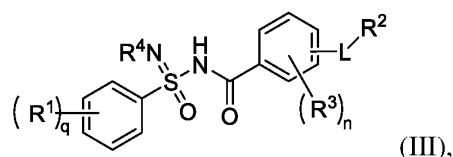
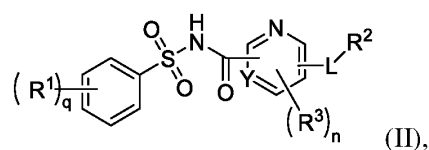
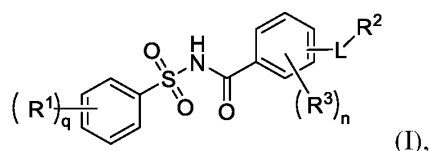
each heteroaryl is a 5- to 6-membered ring that includes 1 to 4 heteroatoms each independently N, O or S.

30 **[0046]** In some embodiments, X is O. In some embodiments, X is NH.

[0047] In some embodiments, ring B is heteroaryl. In some embodiments, ring B is a pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidyl, or pyrazinyl. In some embodiments,

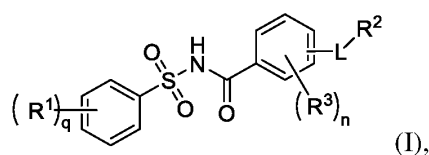
ring B is a pyridyl, pyridazinyl, pyrimidyl, or pyrazinyl. In some embodiments, ring B is pyridyl or pyrimidinyl. In some embodiments, ring B is phenyl.

[0048] In some embodiments, a compound of Formula (J), or pharmaceutically acceptable salt thereof, is a compound of Formula (I), Formula (II), Formula (III), or Formula (IV):



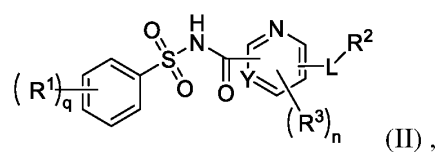
10 or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , R^3 , R^4 , and n are as described in classes and subclasses herein, both singly and in combination, and Y is N , CH , or CR^3 .

[0049] In some embodiments, a compound of Formula (J), or pharmaceutically acceptable salt thereof, is a compound of Formula (I):



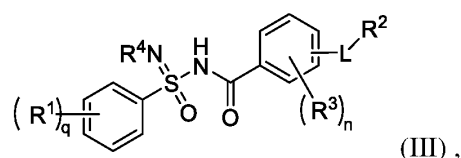
or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , R^3 , and n are as described in classes and subclasses herein, both singly and in combination.

[0050] In some embodiments, a compound of Formula (J), or pharmaceutically acceptable salt thereof, is a compound of Formula (II):



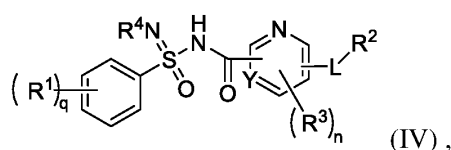
Or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , R^3 , and n are as described in classes and subclasses herein, both singly and in combination, and Y is N , CH , or CR^3 .

[0051] In some embodiments, a compound of Formula (J), or pharmaceutically acceptable salt thereof, is a compound of Formula (III):



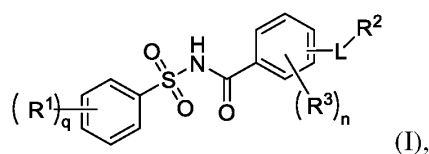
or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , R^3 , R^4 , and n are as described in classes and subclasses herein, both singly and in combination.

[0052] In some embodiments, a compound of Formula (J), or pharmaceutically acceptable salt thereof, is a compound of Formula (IV):



Or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , R^3 , R^4 , and n are as described in classes and subclasses herein, both singly and in combination, and Y is N , CH , or CR^3 .

[0053] In some embodiments, a compound of Formula (J) or pharmaceutically acceptable salt thereof is represented by Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, -

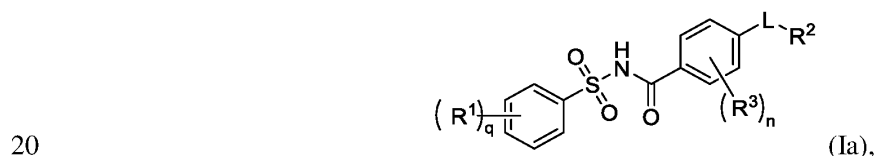
- $C(O)R^{1a}$, $-C(O)OR^{1a}$, $-OC(O)R^{1a}$, $-C(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(R^{1b})$,
 $-OC(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(OR^{1b})$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)_2N(R^{1a})(R^{1b})$,
 $-S(O)(NH)R^{1a}$, $-S(O)(NH)N(R^{1a})(R^{1b})$, $-N(R^{1a})(R^{1b})$, OH, -CN, -NO₂, C₃-C₈ cycloalkyl,
 5 (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), heterocycloalkyl, (C₁-C₃
 alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, (C₁-C₃ alkyl)(C₆-C₁₀ aryl),
 -O-(C₆-C₁₀ aryl), heteroaryl, (C₁-C₃ alkyl)(heteroaryl), or -O-(heteroaryl), wherein
 each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{1c}, each alkoxy and alkynyl is
 substituted with 0, 1, 2, or 3 R^{1d}, and each cycloalkyl, heterocycloalkyl, aryl, and
 heteroaryl is substituted with 0, 1, 2, or 3 R^{1e};
- 10 each R^{1a} and R^{1b} is independently hydrogen or C₁-C₆ alkyl;
 each R^{1c} is independently C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkoxy, -NR^{1c1}R^{1c2}, OH, or -CN;
 each R^{1c1} and R^{1c2} is independently hydrogen or C₁-C₆ alkyl;
 each R^{1d} is independently deuterium, C₃-C₈ cycloalkyl, heterocycloalkyl, C₆-C₁₀ aryl, or
 heteroaryl;
- 15 each R^{1e} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkyl, C₁-C₆
 haloalkoxy, OH, or -CN;
 alternatively, two R¹ groups on adjacent carbons together with the atoms to which they are
 attached combine to form a C₅-C₈ cycloalkyl or a heterocycloalkyl substituted with 0,
 1, 2, 3, 4, 5, or 6 halogen, C₁-C₄ alkyl, OH or -CN;
- 20 L is -C₁-C₄ alkylene-, -(C₁-C₄ alkylene)-O-, or -O-;
 R² is a heteroaryl, which is substituted with 0, 1, 2, 3, or 4 R^{2a};
 each R^{2a} is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆
 hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -
 $C(O)R^{2b}$, $-C(O)OR^{2b}$, $-OC(O)R^{2b}$, $-C(O)N(R^{2b})(R^{2c})$, $-N(R^{2b})C(O)(R^{2c})$, $-S(O)_2R^{2b}$,
 25 $-S(O)_2N(R^{2b})(R^{2c})$, $-N(R^{2b})(R^{2c})$, OH, -CN, or -NO₂;
 each R^{2b} and R^{2c} is independently hydrogen or C₁-C₆ alkyl;
 each R³ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆
 hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -
 $C(O)R^{3a}$, $-C(O)OR^{3a}$, $-OC(O)R^{3a}$, $-C(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(R^{3b})$,
 30 $-OC(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(OR^{3b})$, $-S(O)R^{3a}$, $-S(O)_2R^{3a}$, $-S(O)_2N(R^{3a})(R^{3b})$,
 $-S(O)(NH)R^{3a}$, $-S(O)(NH)N(R^{3a})(R^{3b})$, $-N(R^{3a})(R^{3b})$, OH, -CN, -NO₂, C₃-C₈ cycloalkyl,
 (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), heterocycloalkyl, (C₁-C₃
 alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, (C₁-C₃ alkyl)(C₆-C₁₀ aryl),
 -O-(C₆-C₁₀ aryl), heteroaryl, (C₁-C₃ alkyl)(heteroaryl), or -O-(heteroaryl), wherein

each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{3c} , each alkoxy is substituted with 0, 1, 2, or 3 R^{3d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{3e} ; or,

two R^3 on the same carbon atom together represent an oxo group;

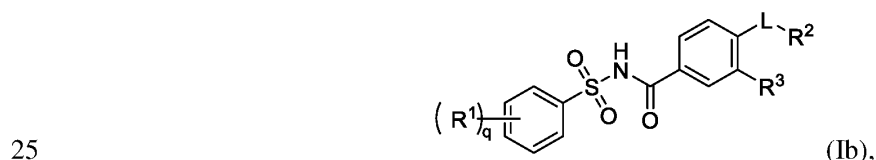
- 5 each R^{3a} and R^{3b} is independently hydrogen or C_1 - C_6 alkyl;
 each R^{3c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, $-NR^{3c1}R^{3c2}$, OH, or -CN;
 each R^{3c1} and R^{3c2} is independently hydrogen or C_1 - C_6 alkyl;
 each R^{3d} is independently C_3 - C_8 cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl;
 each R^{3e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, or C_1 - C_6
 10 haloalkoxy;
 subscript n is 0, 1, 2, 3, or 4; and
 subscript q is 0, 1, 2, 3, or 4;
 wherein
 each heterocycloalkyl is a 3- to 8-membered ring that includes 1 to 4 heteroatoms each
 15 independently N, O or S; and
 each heteroaryl is a 5- to 6-membered ring that includes 1 to 4 heteroatoms each independently
 N, O or S.

[0054] In some embodiments, a compound of Formula (J), Formula (I), or pharmaceutically acceptable salt thereof is represented by Formula (Ia):



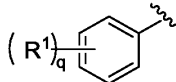
or a pharmaceutically acceptable salt thereof, wherein R^1 , q, R^2 , L, R^3 , and n are as described in classes and subclasses herein, both singly and in combination.

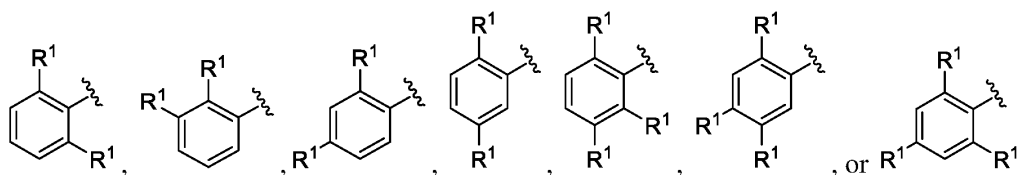
[0055] In some embodiments, a compound of Formula (J), (I), and/or (Ia), or pharmaceutically acceptable salt thereof, is represented by Formula (Ib):



or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , and R^3 are as described in classes and subclasses herein, both singly and in combination.

- [0056]** In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein

the group  has the structure:



wherein R^1 is as described in classes and subclasses herein, wherein R^1 is as described in classes and subclasses herein.

- [0057]** In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^1 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, -CN, C_3 - C_8 cycloalkyl, (C_1 - C_3 alkyl)(C_3 - C_8 cycloalkyl), -O-(C_3 - C_8 cycloalkyl), heterocycloalkyl, (C_1 - C_3 alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C_6 - C_{10} aryl, or heteroaryl, wherein each alkyl is substituted with 0, 1, 2, or 3 R^{1c} , and each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d} , or alternatively, two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl.

- [0058]** In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^1 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, C_3 - C_8 cycloalkyl, (C_1 - C_3 alkyl)(C_3 - C_8 cycloalkyl), -O-(C_3 - C_8 cycloalkyl), C_6 - C_{10} aryl, or heteroaryl, wherein each alkyl is substituted with 0 or 1 R^{1c} , and each alkoxy and alkynyl is substituted with 0 or 1 R^{1d} , or alternatively, two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl.

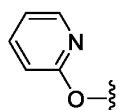
[0059] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{1a} and R^{1b} is independently hydrogen or C_1 - C_4 alkyl.

[0060] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound wherein each R^{1c} is halogen, - $NR^{1c1}R^{1c2}$, OH, or -CN.

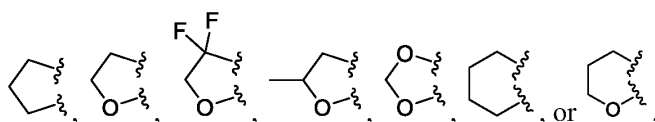
[0061] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{1d} is independently heteroaryl.

[0062] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{1e} is independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, C_1 - C_4 haloalkyl, or -CN.

[0063] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^1 is independently CH_3 , CH_2CH_3 , $-C(CH_3)_3$, OCH_3 , CH_2CH_3 , $-OCH(CH_3)_2$, OCH_2 -pyridyl, $C(CH_3)_2OH$, F, Cl, Br, CF_3 , $OCHF_2$, OCF_3 , OCH_2CF_3 , OH, cyclopropyl, cyclopropyloxy, cyclobutyloxy, phenyl, pyrazolyl, or



; or alternatively, two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a cyclopentyl, cyclohexyl, dihydrofuran, tetrahydrofuran, methyltetrahydrofuran, 1,3-dioxole, dihydro-1,3-oxazine, difluorodihydrofuran, or methylidihydrofuran. In some embodiments, two R^1 on adjacent carbon atoms combine to form:



[0064] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof,

thereof, wherein L is $-\text{CH}_2-$, $-\text{O}-$, or $-\text{CH}_2\text{O}-$.

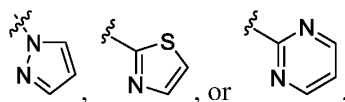
[0065] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein L is $-\text{CH}_2-$.

[0066] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein R^2 is pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidyl, or pyrazinyl, which are each substituted by 0, 1, or 2 R^{2a} .

[0067] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{2a} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, or $-\text{CN}$.

[0068] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{2b} and R^{2c} is independently hydrogen or C_1 - C_4 alkyl.

[0069] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein R^2 is



[0070] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein R^2 is



[0071] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof,

thereof, wherein each R^3 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{3a}$, $-OC(O)R^{3a}$, $-C(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(R^{3b})$, $-S(O)_2R^{3a}$, $-S(O)_2N(R^{3a})(R^{3b})$, OH, -CN, C_3 - C_8 cycloalkyl, or heterocycloalkyl.

5 **[0072]** In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein two R^3 on the same carbon atom together represent an oxo group.

[0073] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{3a} and R^{3b} is independently hydrogen or C_1 - C_4 alkyl.

[0074] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{3c} is halogen, $-NR^{3c1}R^{3c2}$, OH, or -CN.

15 **[0075]** In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{3d} is independently heteroaryl.

[0076] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{3e} is independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, or C_1 - C_4 haloalkyl.

[0077] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^3 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, -CN, or C_3 - C_8 cycloalkyl.

25 **[0078]** In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^3 is independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, -CN, or C_3 - C_6 cycloalkyl.

[0079] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt

thereof, wherein each R³ is independently Me, OMe, OEt, CHF₂, CF₃, OCHF₂, OCF₃, F, Br, CN, or cyclopropyl.

[0080] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein subscript q is 1, 2, or 3.

[0081] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein subscript n is 1 or 2.

[0082] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound having the structure of a compound shown in Table 1, or pharmaceutically acceptable salt thereof.

Table 1. Compounds

No.	Structure	Name
1		4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-2-methoxybenzamide
2		4-((1H-pyrazol-1-yl)methyl)-2-methoxy-N-((2-methoxyphenyl)sulfonyl)benzamide
3		4-((1H-pyrazol-1-yl)methyl)-N-((5-ethyl-2-methoxyphenyl)sulfonyl)-2-methoxybenzamide
4		4-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-2-methoxybenzamide
5		4-((1H-pyrazol-1-yl)methyl)-2-methoxy-N-((6-methoxy-2,3-dihydro-1H-inden-5-yl)sulfonyl)benzamide
6		3-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-5-methoxybenzamide

No.	Structure	Name
7		4-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-2-fluorobenzamide
8		4-((1H-pyrazol-1-yl)methyl)-N-((4-(tert-butyl)-2-methoxyphenyl)sulfonyl)-3-methoxybenzamide
9		5-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-2-methoxybenzamide
10		4-((1H-pyrazol-1-yl)methyl)-2-methoxy-N-((2-methoxy-4-(1H-pyrazol-1-yl)phenyl)sulfonyl)benzamide
11		4-((1H-pyrazol-1-yl)methyl)-N-((4-(tert-butyl)-2-methoxyphenyl)sulfonyl)-2-methoxybenzamide
12		4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-3-fluorobenzamide
13		4-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-3-fluorobenzamide
14		4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide
15		4-((1H-pyrazol-1-yl)methyl)-2-methoxy-N-((3-methoxy-5,6,7,8-tetrahydronaphthalen-2-yl)sulfonyl)benzamide
16		4-((1H-pyrazol-1-yl)methyl)-3-bromo-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)benzamide
17		4-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-3-cyclopropylbenzamide
18		4-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-3-cyanobenzamide

No.	Structure	Name
19		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methoxy-5-(1H-pyrazol-1-yl)phenyl)sulfonyl)benzamide
20		4-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-3-methylbenzamide
21		4-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-3-ethoxybenzamide
22		4-((1H-pyrazol-1-yl)methyl)-N-([1,1'-biphenyl]-2-ylsulfonyl)-3-methoxybenzamide
23		4-((1H-pyrazol-1-yl)methyl)-N-((3-hydroxyphenyl)sulfonyl)-3-methoxybenzamide
24		4-((1H-pyrazol-1-yl)methyl)-N-((5-bromo-2-methoxyphenyl)sulfonyl)-3-methoxybenzamide
25		4-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-3-(trifluoromethyl)benzamide
26		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methoxyphenyl)sulfonyl)benzamide
27		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((6-methoxy-2,3-dihydro-1H-inden-5-yl)sulfonyl)benzamide
28		4-((1H-pyrazol-1-yl)methyl)-3-cyclopropyl-N-((2,6-dimethoxyphenyl)sulfonyl)benzamide
29		4-((1H-pyrazol-1-yl)methyl)-N-((5-cyclopropyl-2-methoxyphenyl)sulfonyl)-3-methoxybenzamide

No.	Structure	Name
30		4-((1H-pyrazol-1-yl)methyl)-N-((5-ethyl-2-methoxyphenyl)sulfonyl)-3-methoxybenzamide
31		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methoxy-4-(trifluoromethyl)phenyl)sulfonyl)benzamide
32		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methoxy-5-(trifluoromethyl)phenyl)sulfonyl)benzamide
33		4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-3-(trifluoromethoxy)benzamide
34		4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-3-methylbenzamide
35		4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-3-(trifluoromethyl)benzamide
36		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methoxy-6-(1H-pyrazol-1-yl)phenyl)sulfonyl)benzamide
37		4-((1H-pyrazol-1-yl)methyl)-3-(difluoromethoxy)-N-((2,6-dimethoxyphenyl)sulfonyl)benzamide
38		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((6-methoxy-2,3-dihydrobenzofuran-7-yl)sulfonyl)benzamide
39		4-((1H-pyrazol-1-yl)methyl)-N-((5-hydroxy-2-methoxyphenyl)sulfonyl)-3-methoxybenzamide

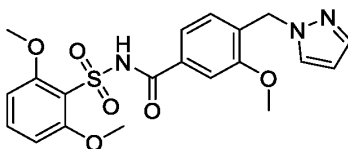
No.	Structure	Name
40		4-((1H-pyrazol-1-yl)methyl)-3-cyclopropyl-N-((2,6-dimethoxyphenyl)sulfonyl)-2-fluorobenzamide
41		4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-2,3-dimethoxybenzamide
42		4-((1H-pyrazol-1-yl)methyl)-N-((2,4-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide
43		4-((1H-pyrazol-1-yl)methyl)-N-((5-fluoro-2,4-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide
44		4-((1H-pyrazol-1-yl)methyl)-N-((5-chloro-2,4-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide
45		4-((1H-pyrazol-1-yl)methyl)-N-((5-bromo-2,4-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide
46		4-((1H-pyrazol-1-yl)methyl)-N-((3-chloro-2,6-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide
47		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)benzamide
48		4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-2,5-dimethoxybenzamide
49		4-((1H-pyrazol-1-yl)methyl)-3-bromo-N-((2,6-dimethoxyphenyl)sulfonyl)-2-fluorobenzamide

No.	Structure	Name
50		N-((2,6-dimethoxyphenyl)sulfonyl)-3-methoxy-4-((pyrimidin-2-yloxy)methyl)benzamide
51		4-((1H-pyrazol-1-yl)methyl)-N-((2-(difluoromethoxy)phenyl)sulfonyl)-3-methoxybenzamide
52		4-((1H-pyrazol-1-yl)methyl)-N-((2-cyclopropoxy-6-methoxyphenyl)sulfonyl)-3-methoxybenzamide
53		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-(pyridin-2-ylmethoxy)phenyl)sulfonyl)benzamide
54		4-((1H-pyrazol-1-yl)methyl)-N-((5-(2-hydroxypropan-2-yl)-2-methoxyphenyl)sulfonyl)-3-methoxybenzamide
55		4-((1H-pyrazol-1-yl)methyl)-N-((2-isopropoxy-6-methoxyphenyl)sulfonyl)-3-methoxybenzamide
56		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((5-methoxy-2,3-dihydro-1H-inden-4-yl)sulfonyl)benzamide
57		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl)sulfonyl)benzamide
58		N-((2,6-dimethoxyphenyl)sulfonyl)-3-methoxy-4-((thiazol-2-yloxy)methyl)benzamide

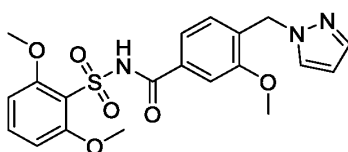
No.	Structure	Name
59		N-((2,6-dimethoxyphenyl)sulfonyl)-3-methoxy-4-(thiazol-2-yl)benzamide
60		4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxy-3-methylphenyl)sulfonyl)-3-methoxybenzamide
61		4-((1H-pyrazol-1-yl)methyl)-N-((3-cyclopropyl-2,6-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide
62		4-((1H-pyrazol-1-yl)methyl)-N-((2-cyclopropoxyphenyl)sulfonyl)-3-methoxybenzamide
63		4-((1H-pyrazol-1-yl)methyl)-N-((5-chloro-2,3-dihydrobenzofuran-7-yl)sulfonyl)-3-methoxybenzamide
64		4-((1H-pyrazol-1-yl)methyl)-N-((2,3-dihydrobenzofuran-5-yl)sulfonyl)-3-methoxybenzamide
65		4-((1H-pyrazol-1-yl)methyl)-N-((3-chloro-4-methoxyphenyl)sulfonyl)-3-methoxybenzamide
66		4-((1H-pyrazol-1-yl)methyl)-N-((3-ethyl-2,6-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide
67		4-((1H-pyrazol-1-yl)methyl)-N-((2-ethoxy-6-methoxyphenyl)sulfonyl)-3-methoxybenzamide
68		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methoxy-6-(2,2,2-trifluoroethoxy)phenyl)sulfonyl)benzamide

No.	Structure	Name
69		4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-2-fluoro-3-methoxybenzamide
70		4-((1H-pyrazol-1-yl)methyl)-N-((2,3-dihydrobenzofuran-7-yl)sulfonyl)-3-methoxybenzamide
309		4-((1H-pyrazol-1-yl)methyl)-N-((5-chloro-2,3-dihydrobenzofuran-7-yl)sulfonyl)-3-methoxybenzamide
310		4-((1H-pyrazol-1-yl)methyl)-N-((2,3-dihydrobenzofuran-5-yl)sulfonyl)-3-methoxybenzamide
311		4-((1H-pyrazol-1-yl)methyl)-N-((3-chloro-4-methoxyphenyl)sulfonyl)-3-methoxybenzamide
312		4-((1H-pyrazol-1-yl)methyl)-N-((6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-3-yl)sulfonyl)-3-methoxybenzamide
314		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methyl-2,3-dihydrobenzofuran-7-yl)sulfonyl)benzamide
315		4-((1H-pyrazol-1-yl)methyl)-N-((2,3-dihydrobenzofuran-7-yl)sulfonyl)-3-methoxybenzamide

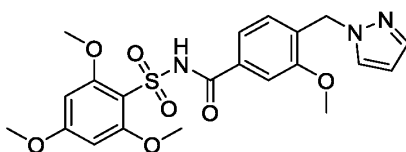
[0083] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound wherein the compound has the structure:



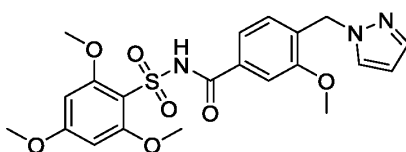
- 5 [0084] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), is a compound wherein the compound has the structure:



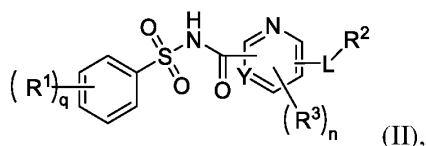
- [0085] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), or pharmaceutically acceptable salt thereof, is a compound wherein the compound has the structure:
- 10



- [0086] In some embodiments, a compound of Formula (J), (I), (Ia), and/or (Ib), is a compound wherein the compound has the structure:



- 15 [0087] In some embodiments, a compound of Formula (J) is represented by Formula (II):



or a pharmaceutically acceptable salt thereof, wherein

- each R^1 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, - $C(O)R^{1a}$, - $C(O)OR^{1a}$, - $OC(O)R^{1a}$, - $C(O)N(R^{1a})(R^{1b})$, - $N(R^{1a})C(O)(R^{1b})$, - $OC(O)N(R^{1a})(R^{1b})$, - $N(R^{1a})C(O)(OR^{1b})$, - $S(O)R^{1a}$, - $S(O)_2R^{1a}$, - $S(O)_2N(R^{1a})(R^{1b})$, - $S(O)(NH)R^{1a}$, - $S(O)(NH)N(R^{1a})(R^{1b})$, - $N(R^{1a})(R^{1b})$, OH, -CN, -NO₂, C_3 - C_8 cycloalkyl, (C_1 - C_3 alkyl)(C_3 - C_8 cycloalkyl), -O-(C_3 - C_8 cycloalkyl), heterocycloalkyl, (C_1 - C_3 alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C_6 - C_{10} aryl, (C_1 - C_3 alkyl)(C_6 - C_{10} aryl), -O-(C_6 - C_{10} aryl), heteroaryl, (C_1 - C_3 alkyl)(heteroaryl), or -O-(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{1c} , each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{1e} ;
- each R^{1a} and R^{1b} is independently hydrogen or C_1 - C_6 alkyl;
- each R^{1c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, - $NR^{1c1}R^{1c2}$, OH, or -CN;
- each R^{1c1} and R^{1c2} is independently hydrogen or C_1 - C_6 alkyl;
- each R^{1d} is independently deuterium, C_3 - C_8 cycloalkyl, heterocycloalkyl, C_6 - C_{10} aryl, or heteroaryl;
- each R^{1e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, or -CN;
- alternatively, two R^1 groups on adjacent carbons together with the atoms to which they are attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl substituted with 0, 1, 2, 3, 4, 5, or 6 halogen, C_1 - C_4 alkyl, OH or -CN;
- L is - C_1 - C_4 alkylene-, -(C_1 - C_4 alkylene)-O-, or -O-;
- R^2 is a heteroaryl, which is substituted with 0, 1, 2, 3, or 4 R^{2a} ;
- each R^{2a} is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, - $C(O)R^{2b}$, - $C(O)OR^{2b}$, - $OC(O)R^{2b}$, - $C(O)N(R^{2b})(R^{2c})$, - $N(R^{2b})C(O)(R^{2c})$, - $S(O)_2R^{2b}$, - $S(O)_2N(R^{2b})(R^{2c})$, - $N(R^{2b})(R^{2c})$, OH, -CN, or -NO₂;
- each R^{2b} and R^{2c} is independently hydrogen or C_1 - C_6 alkyl;
- Y is CH, CR^3 , or N;
- each R^3 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, - $C(O)R^{3a}$, - $C(O)OR^{3a}$, - $OC(O)R^{3a}$, - $C(O)N(R^{3a})(R^{3b})$, - $N(R^{3a})C(O)(R^{3b})$, - $OC(O)N(R^{3a})(R^{3b})$, - $N(R^{3a})C(O)(OR^{3b})$, - $S(O)R^{3a}$, - $S(O)_2R^{3a}$, - $S(O)_2N(R^{3a})(R^{3b})$, - $S(O)(NH)R^{3a}$, - $S(O)(NH)N(R^{3a})(R^{3b})$, - $N(R^{3a})(R^{3b})$, OH, -CN, -NO₂, C_3 - C_8 cycloalkyl,

(C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), heterocycloalkyl, (C₁-C₃ alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, (C₁-C₃ alkyl)(C₆-C₁₀ aryl), -O-(C₆-C₁₀ aryl), heteroaryl, (C₁-C₃ alkyl)(heteroaryl), or -O-(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{3c}, each alkoxy is substituted with 0, 1, 2, or 3 R^{3d}, and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{3e}; or,

two R³ on the same carbon atom together represent an oxo group;

each R^{3a} and R^{3b} is independently hydrogen or C₁-C₆ alkyl;

each R^{3c} is independently C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkoxy, -NR^{3c1}R^{3c2}, OH, or -CN;

each R^{3c1} and R^{3c2} is independently hydrogen or C₁-C₆ alkyl;

each R^{3d} is independently C₃-C₈ cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl;

each R^{3e} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy;

subscript n is 0, 1, 2, 3, or 4; and

subscript q is 0, 1, 2, 3, or 4;

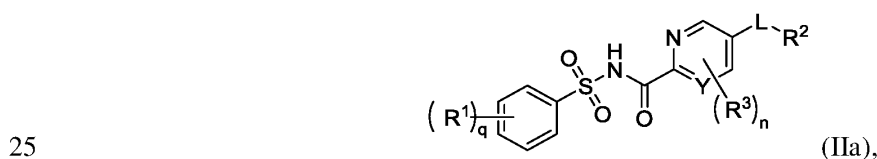
wherein

each heterocycloalkyl is a 3- to 8-membered ring that includes 1 to 4 heteroatoms each independently N, O or S; and

each heteroaryl is a 5- to 6-membered ring that includes 1 to 4 heteroatoms each independently N, O or S.

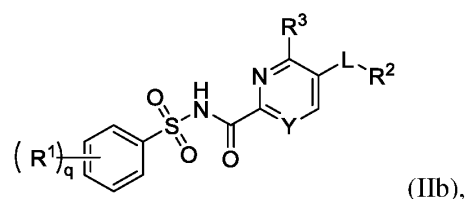
[0088] In some embodiments of Formula (II), Y is N. In some embodiments, Y is CR³. In some embodiments, Y is CH.

[0089] In some embodiments, a compound of Formula (J), Formula (II), or pharmaceutically acceptable salt thereof, is represented by Formula (IIa):



or a pharmaceutically acceptable salt thereof, wherein R¹, q, R², L, R³, and n are as described in classes and subclasses herein, both singly and in combination, and Y is N, CH, or CR³.

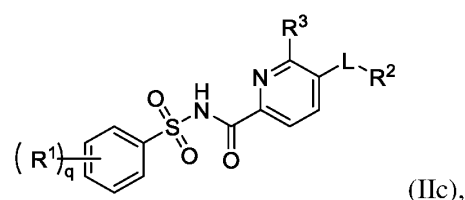
[0090] In some embodiments, a compound of Formula (J), (II), and/or (IIa), or pharmaceutically acceptable salt thereof, is represented by Formula (IIb):



or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , and R^3 are as described in classes and subclasses herein, both singly and in combination, and Y is N , CH , or CR^3 .

[0091] In some embodiments, a compound of Formula (J), (II), (IIa), and/or (IIb), or
 5 pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein Y is N . In some embodiments, Y is CR^3 . In some embodiments, Y is CH .

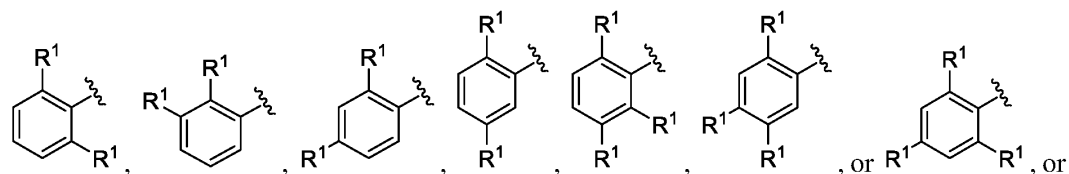
[0092] In some embodiments, a compound of Formula (J), (II), (IIa), and/or (IIb), or pharmaceutically acceptable salt thereof, is represented by Formula (IIc):



10 or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , and R^3 are as described in classes and subclasses herein, both singly and in combination.

[0093] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein

15 the group has the structure:



a pharmaceutically acceptable salt thereof, wherein R^1 is as described in classes and subclasses herein.

[0094] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a
 20 pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt

thereof, wherein each R^1 is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, OH, -CN, C₃-C₈ cycloalkyl, (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), heterocycloalkyl, (C₁-C₃ alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, or heteroaryl, wherein each alkyl is substituted with 0, 1, 2, or 3 R^{1c} , and each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d} ; or alternatively, two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a C₅-C₈ cycloalkyl or a heterocycloalkyl.

[0095] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^1 is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, OH, C₃-C₈ cycloalkyl, (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), C₆-C₁₀ aryl, or heteroaryl, wherein each alkyl is substituted with 0 or 1 R^{1c} , and each alkoxy and alkynyl is substituted with 0 or 1 R^{1d} ; or alternatively, two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a C₅-C₈ cycloalkyl or a heterocycloalkyl.

[0096] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{1a} and R^{1b} is independently hydrogen or C₁-C₃ alkyl.

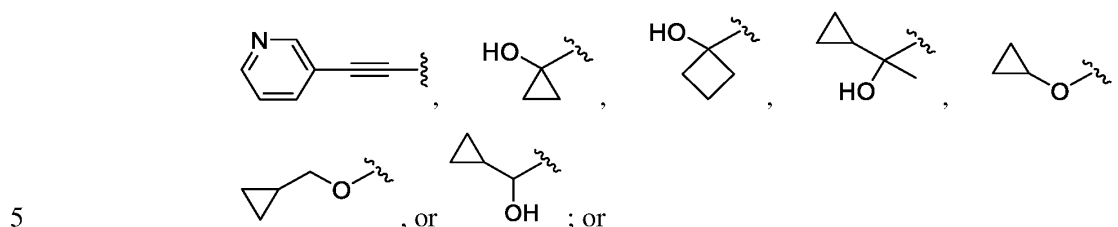
[0097] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{1c} is halogen, -NR^{1c1}R^{1c2}, OH, or -CN.

[0098] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{1d} is independently heteroaryl.

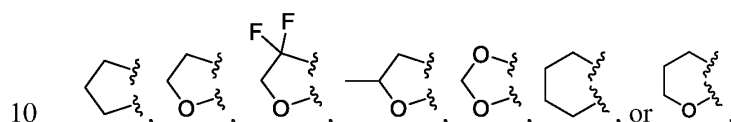
[0099] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{1e} is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, or -CN.

[0100] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^1 is

independently $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{C}(\text{CH}_3)_3$, $-\text{OCH}_3$, $-\text{OCD}_3$, $-\text{C}(\text{CH}_3)_2\text{OCH}_3$, $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_3)\text{OH}$, F, Cl, Br, CF_3 , OCHF_2 , OCF_3 , OCH_2CF_3 , cyclopropyl, cyclopropyloxy, cyclobutyloxy,



two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a cyclopentyl, cyclohexyl, dihydrofuran, tetrahydrofuran, methyltetrahydrofuran, 1,3-dioxole, dihydro-1,3-oxazine, or methyldihydrofuran. In some embodiments, two R^1 on adjacent carbon atoms combine to form:



[0101] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein L is $-\text{CH}_2-$, $-\text{CH}_2\text{O}-$, or $-\text{O}-$.

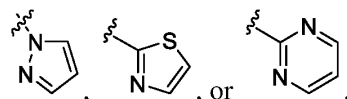
15 **[0102]** In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein L is $-\text{CH}_2-$.

20 **[0103]** In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein R^2 is pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidyl, or pyrazinyl, which are each substituted by 0, 1, or 2 R^{2a} .

25 **[0104]** In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{2a} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, or $-\text{CN}$.

[0105] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound wherein each R^{2b} and R^{2c} is independently hydrogen or C_1 - C_4 alkyl, or a pharmaceutically acceptable salt thereof.

[0106] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or
5 pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein R^2 is



[0107] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt
10 thereof, wherein R^2 is



[0108] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^3 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 -
15 C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{3a}$, $-OC(O)R^{3a}$, $-C(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(R^{3b})$, $-S(O)_2R^{3a}$, $-S(O)_2N(R^{3a})(R^{3b})$, OH, -CN, C_3 - C_8 cycloalkyl, or heterocycloalkyl.

[0109] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt
20 thereof, wherein two R^3 on the same carbon atom together represent an oxo group.

[0110] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{3a} and R^{3b} is independently hydrogen or C_1 - C_4 alkyl.

[0111] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a
25 pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{3c} is halogen, $-NR^{3c1}R^{3c2}$, OH, or -CN.

[0112] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{3d} is independently heteroaryl.

5 [0113] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R^{3e} is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₁-C₄ haloalkyl.

10 [0114] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R³ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -CN, or C₃-C₈ cycloalkyl.

15 [0115] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R³ is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, -CN, or C₃-C₆ cycloalkyl.

[0116] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein each R³ is independently Me, Ome, CHF₂, CF₃, OCHF₂, OCF₃, or cyclopropyl.

20 [0117] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound wherein subscript q is 1, 2, or 3, or a pharmaceutically acceptable salt thereof.

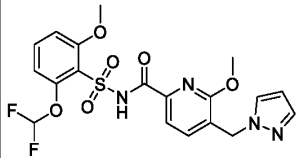
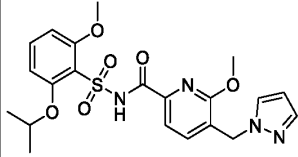
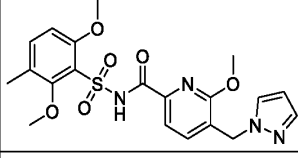
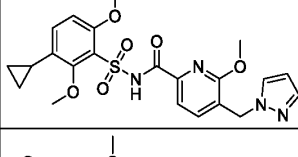
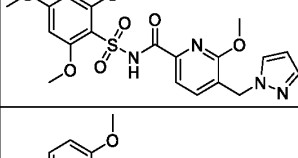
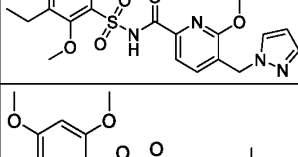
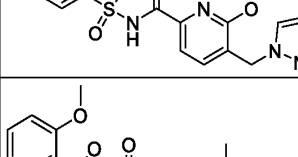
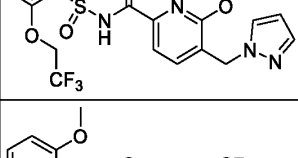
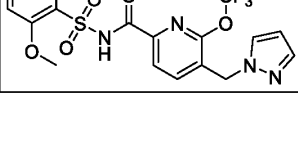
25 [0118] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein subscript n is 0 or 1.

[0119] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound wherein the compound has the structure of a compound shown in Table 2, or a pharmaceutically acceptable salt thereof.

Table 2. Compounds

No.	Structure	Name
201		5-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)picolinamide
202		6-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-5-methoxynicotinamide
203		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
204		5-((1H-pyrazol-1-yl)methyl)-N-((5-ethyl-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
205		5-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
206		5-((1H-pyrazol-1-yl)methyl)-N-((5-cyclopropyl-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
207		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2-methoxy-5-(trifluoromethyl)phenyl)sulfonyl)picolinamide
208		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2-methoxyphenyl)sulfonyl)picolinamide
209		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-methylpicolinamide

No.	Structure	Name
210		5-((1H-pyrazol-1-yl)methyl)-N-((5-ethyl-2-methoxyphenyl)sulfonyl)-4-methoxypicolinamide
211		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((6-methoxy-2,3-dihydrobenzofuran-7-yl)sulfonyl)picolinamide
212		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-4-methoxypicolinamide
213		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((6-methoxy-2,3-dihydro-1H-inden-5-yl)sulfonyl)picolinamide
214		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2-methoxy-5-methylphenyl)sulfonyl)picolinamide
215		5-((1H-pyrazol-1-yl)methyl)-6-(difluoromethoxy)-N-((2,6-dimethoxyphenyl)sulfonyl)picolinamide
216		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((5-methoxy-2,3-dihydro-1H-inden-4-yl)sulfonyl)picolinamide
217		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl)sulfonyl)picolinamide
218		5-((1H-pyrazol-1-yl)methyl)-N-((2-ethoxy-6-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
219		5-((1H-pyrazol-1-yl)methyl)-N-((2-cyclobutoxy-6-methoxyphenyl)sulfonyl)-6-methoxypicolinamide

No.	Structure	Name
220		5-((1H-pyrazol-1-yl)methyl)-N-((2-(difluoromethoxy)-6-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
221		5-((1H-pyrazol-1-yl)methyl)-N-((2-isopropoxy-6-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
222		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxy-3-methylphenyl)sulfonyl)-6-methoxypicolinamide
223		5-((1H-pyrazol-1-yl)methyl)-N-((3-cyclopropyl-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
224		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)picolinamide
225		5-((1H-pyrazol-1-yl)methyl)-N-((3-ethyl-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
226		5-((1H-pyrazol-1-yl)methyl)-N-((2,4-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
227		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2-methoxy-6-(2,2,2-trifluoroethoxy)phenyl)sulfonyl)picolinamide
228		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-(trifluoromethoxy)picolinamide

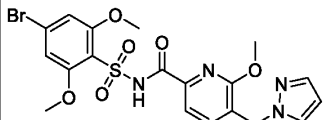
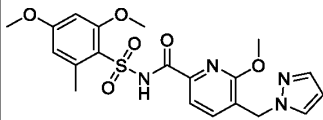
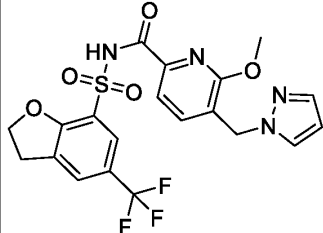
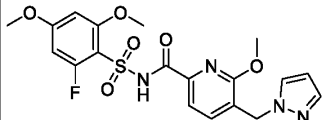
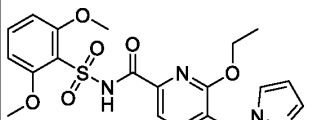
No.	Structure	Name
229		5-((1H-pyrazol-1-yl)methyl)-6-cyclopropyl-N-((2,6-dimethoxyphenyl)sulfonyl)picolinamide
230		5-((1H-pyrazol-1-yl)methyl)-N-((5-(2-hydroxypropan-2-yl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
231		5-((1H-pyrazol-1-yl)methyl)-6-(difluoromethyl)-N-((2,6-dimethoxyphenyl)sulfonyl)picolinamide
233		5-((1H-pyrazol-1-yl)methyl)-N-((2,3-dihydro-1H-inden-4-yl)sulfonyl)-6-methoxypicolinamide
234		5-((1H-pyrazol-1-yl)methyl)-N-((2,3-dihydro-1H-inden-5-yl)sulfonyl)-6-methoxypicolinamide
235		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2-methoxy-6-(trifluoromethoxy)phenyl)sulfonyl)picolinamide
236		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-(trifluoromethyl)picolinamide
237		5-((1H-pyrazol-1-yl)methyl)-N-((3-(2-hydroxypropan-2-yl)phenyl)sulfonyl)-6-methoxypicolinamide
238		5-((1H-pyrazol-1-yl)methyl)-N-((5-chloro-2,4-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
239		5-((1H-pyrazol-1-yl)methyl)-N-((5-(2-hydroxybutan-2-yl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide

No.	Structure	Name
240		5-((1H-pyrazol-1-yl)methyl)-N-((5-(1-cyclopropyl-1-hydroxyethyl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
241		5-((1H-pyrazol-1-yl)methyl)-N-((3-chloro-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
242		5-((1H-pyrazol-1-yl)methyl)-N-((5-bromo-2,4-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
244		5-((1H-pyrazol-1-yl)methyl)-N-((5-fluoro-2,4-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
245		5-((1H-pyrazol-1-yl)methyl)-N-((2-(cyclopropylmethoxy)-6-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
246		5-((1H-pyrazol-1-yl)methyl)-N-((2,3-dihydrobenzofuran-7-yl)sulfonyl)-6-methoxypicolinamide
247		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-ethylpicolinamide
248		5-((1H-pyrazol-1-yl)methyl)-N-((2-cyclopropoxy-6-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
249		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((7-methoxychroman-8-yl)sulfonyl)picolinamide
250		5-((1H-pyrazol-1-yl)methyl)-N-((3-ethyl-2,4,6-trimethoxyphenyl)sulfonyl)-6-methoxypicolinamide

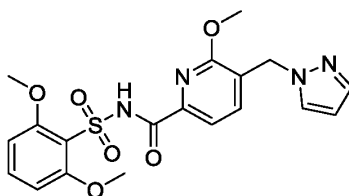
No.	Structure	Name
251		5-((1H-pyrazol-1-yl)methyl)-N-((6-ethoxy-3-ethyl-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
252		5-((1H-pyrazol-1-yl)methyl)-N-((3-ethyl-2-methoxy-6-(2,2,2-trifluoroethoxy)phenyl)sulfonyl)-6-methoxypicolinamide
253		5-((1H-pyrazol-1-yl)methyl)-N-((4,6-dimethoxy-2,3-dihydrobenzofuran-7-yl)sulfonyl)-6-methoxypicolinamide
254		5-((1H-pyrazol-1-yl)methyl)-N-((3,3-difluoro-6-methoxy-2,3-dihydrobenzofuran-7-yl)sulfonyl)-6-methoxypicolinamide
255		5-((1H-pyrazol-1-yl)methyl)-N-((5-(1-hydroxycyclopropyl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
256		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2-methoxy-5-(2-methoxypropan-2-yl)phenyl)sulfonyl)picolinamide
257		5-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2,3-dihydrobenzofuran-7-yl)sulfonyl)-6-methoxypicolinamide
258		5-((1H-pyrazol-1-yl)methyl)-N-((5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
259		5-((1H-pyrazol-1-yl)methyl)-N-((5-(1-hydroxycyclobutyl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
264		5-((1H-pyrazol-1-yl)methyl)-N-((4-(tert-butyl)-2-methoxyphenyl)sulfonyl)-4-methoxypyrimidine-2-carboxamide

No.	Structure	Name
265		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-ethylpicolinamide
266		5-((1H-pyrazol-1-yl)methyl)-N-((5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
267		6-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide
268		5-((1H-pyrazol-1-yl)methyl)-N-((3-ethyl-2,4,6-trimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
269		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxy-4-(pyridin-3-ylethynyl)phenyl)sulfonyl)-6-methoxypicolinamide
270		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2,4,6-tris(methoxy-d3)phenyl)sulfonyl)picolinamide
271		5-((1H-pyrazol-1-yl)methyl)-N-((5-ethyl-2-methoxyphenyl)sulfonyl)-4-methoxypyrimidine-2-carboxamide
272		5-((1H-pyrazol-1-yl)methyl)-4-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)pyrimidine-2-carboxamide
273		5-((1H-pyrazol-1-yl)methyl)-N-((5-cyclopropyl-2-methoxyphenyl)sulfonyl)-4-methoxypyrimidine-2-carboxamide
274		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-4-methoxypyrimidine-2-carboxamide

No.	Structure	Name
275		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxy-4-methylphenyl)sulfonyl)-6-methoxypicolinamide
276		5-((1H-pyrazol-1-yl)methyl)-N-((5-bromo-2,4-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
277		5-((1H-pyrazol-1-yl)methyl)-N-((5-fluoro-2,4-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
278		5-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-1-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide
279		5-((1H-pyrazol-1-yl)methyl)-N-((2-cyclopropoxy-6-methoxyphenyl)sulfonyl)-6-methoxypicolinamide
280		5-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2,3-dihydrobenzofuran-7-yl)sulfonyl)-6-methoxypicolinamide
281		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((5-methoxybenzo[d][1,3]dioxol-4-yl)sulfonyl)picolinamide
282		5-((1H-pyrazol-1-yl)methyl)-N-((4-fluoro-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
283		5-((1H-pyrazol-1-yl)methyl)-N-((4-chloro-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
284		5-((1H-pyrazol-1-yl)methyl)-N-((6-ethoxy-3-ethyl-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide

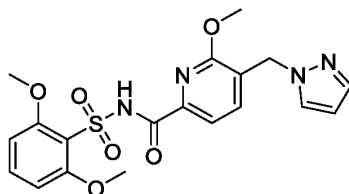
No.	Structure	Name
285		5-((1H-pyrazol-1-yl)methyl)-N-((4-bromo-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
286		5-((1H-pyrazol-1-yl)methyl)-N-((2,4-dimethoxy-6-methylphenyl)sulfonyl)-6-methoxypicolinamide
287		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((5-(trifluoromethyl)-2,3-dihydrobenzofuran-7-yl)sulfonyl)picolinamide
288		5-((1H-pyrazol-1-yl)methyl)-N-((2-fluoro-4,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide
289		5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-ethoxypicolinamide

[0120] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound wherein the compound has the structure:

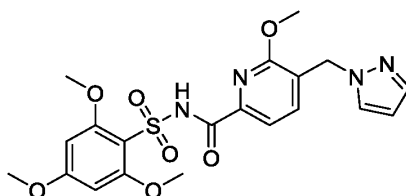


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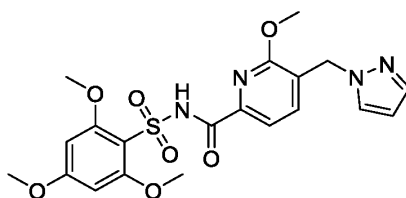
[0121] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), is a compound wherein the compound has the structure:



[0122] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound wherein the compound has the structure:

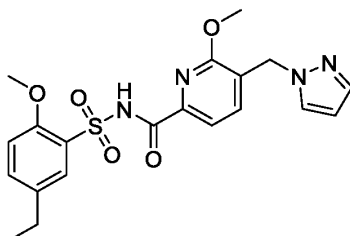


5 [0123] In some embodiments of a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), is a compound wherein the compound has the structure:

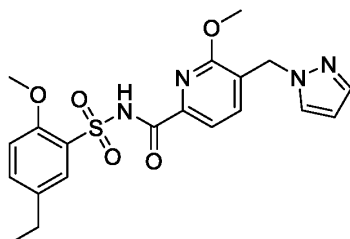


[0124] In some embodiments, a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), or a pharmaceutically acceptable salt thereof, is a compound wherein the compound has the structure:

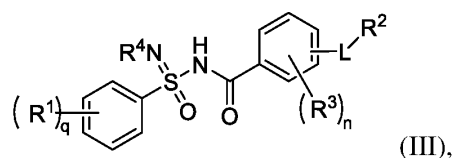
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[0125] In some embodiments of a compound of Formula (J), (II), (IIa), (IIb), and/or (IIc), is a compound wherein the compound has the structure:



15 [0126] In some embodiments, a compound of Formula (J) or pharmaceutically acceptable salt thereof is represented by Formula (III):

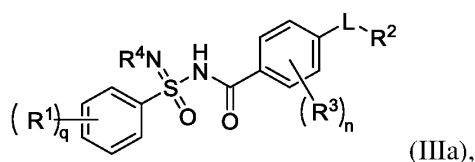


or a pharmaceutically acceptable salt thereof, wherein

- each R^1 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, -
 5 $C(O)R^{1a}$, $-C(O)OR^{1a}$, $-OC(O)R^{1a}$, $-C(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(R^{1b})$,
 $-OC(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(OR^{1b})$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)_2N(R^{1a})(R^{1b})$,
 $-S(O)(NH)R^{1a}$, $-S(O)(NH)N(R^{1a})(R^{1b})$, $-N(R^{1a})(R^{1b})$, OH, -CN, -NO₂, C_3 - C_8 cycloalkyl,
 $(C_1$ - C_3 alkyl)(C_3 - C_8 cycloalkyl), $-O$ -(C_3 - C_8 cycloalkyl), heterocycloalkyl, $(C_1$ - C_3
 alkyl)(heterocycloalkyl), $-O$ -(heterocycloalkyl), C_6 - C_{10} aryl, $(C_1$ - C_3 alkyl)(C_6 - C_{10} aryl),
 10 $-O$ -(C_6 - C_{10} aryl), heteroaryl, $(C_1$ - C_3 alkyl)(heteroaryl), or $-O$ -(heteroaryl), wherein
 each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{1c} , each alkoxy and alkynyl is
 substituted with 0, 1, 2, or 3 R^{1d} , and each cycloalkyl, heterocycloalkyl, aryl, and
 heteroaryl is substituted with 0, 1, 2, or 3 R^{1e} ;
 each R^{1a} and R^{1b} is independently hydrogen or C_1 - C_6 alkyl;
 15 each R^{1c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, $-NR^{1c1}R^{1c2}$, OH, or -CN;
 each R^{1c1} and R^{1c2} is independently hydrogen or C_1 - C_6 alkyl;
 each R^{1d} is independently deuterium, C_3 - C_8 cycloalkyl, heterocycloalkyl, C_6 - C_{10} aryl, or
 heteroaryl;
 each R^{1e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, C_1 - C_6
 20 haloalkoxy, OH, or -CN;
 alternatively, two R^1 groups on adjacent carbons together with the atoms to which they are
 attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl substituted with 0,
 1, 2, 3, 4, 5, or 6 halogen, C_1 - C_4 alkyl, OH or -CN;
 L is $-C_1$ - C_4 alkylene-, $-(C_1$ - C_4 alkylene)-O-, or -O-;
 25 R^2 is a heteroaryl, which is substituted with 0, 1, 2, 3, or 4 R^{2a} ;
 each R^{2a} is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6
 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, -
 $C(O)R^{2b}$, $-C(O)OR^{2b}$, $-OC(O)R^{2b}$, $-C(O)N(R^{2b})(R^{2c})$, $-N(R^{2b})C(O)(R^{2c})$, $-S(O)_2R^{2b}$,
 $-S(O)_2N(R^{2b})(R^{2c})$, $-N(R^{2b})(R^{2c})$, OH, -CN, or -NO₂;
 30 each R^{2b} and R^{2c} is independently hydrogen or C_1 - C_6 alkyl;

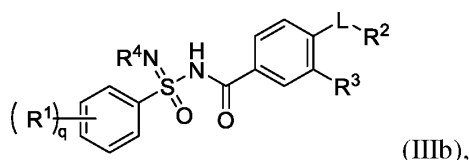
- each R^3 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{3a}$, $-OC(O)R^{3a}$, $-C(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(R^{3b})$, $-OC(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(OR^{3b})$, $-S(O)R^{3a}$, $-S(O)_2R^{3a}$, $-S(O)_2N(R^{3a})(R^{3b})$, $-S(O)(NH)R^{3a}$, $-S(O)(NH)N(R^{3a})(R^{3b})$, $-N(R^{3a})(R^{3b})$, OH, $-CN$, $-NO_2$, C_3 - C_8 cycloalkyl, $(C_1$ - C_3 alkyl)(C_3 - C_8 cycloalkyl), $-O$ -(C_3 - C_8 cycloalkyl), heterocycloalkyl, $(C_1$ - C_3 alkyl)(heterocycloalkyl), $-O$ -(heterocycloalkyl), C_6 - C_{10} aryl, $(C_1$ - C_3 alkyl)(C_6 - C_{10} aryl), $-O$ -(C_6 - C_{10} aryl), heteroaryl, $(C_1$ - C_3 alkyl)(heteroaryl), or $-O$ -(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{3c} , each alkoxy is substituted with 0, 1, 2, or 3 R^{3d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{3e} ; or,
- two R^3 on the same carbon atom together represent an oxo group;
- each R^{3a} and R^{3b} is independently hydrogen or C_1 - C_6 alkyl;
- each R^{3c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, $-NR^{3c1}R^{3c2}$, OH, or $-CN$;
- each R^{3c1} and R^{3c2} is independently hydrogen or C_1 - C_6 alkyl;
- each R^{3d} is independently C_3 - C_8 cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl;
- each R^{3e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, or C_1 - C_6 haloalkoxy;
- R^4 is hydrogen or C_1 - C_6 alkyl;
- subscript n is 0, 1, 2, 3, or 4; and
- subscript q is 0, 1, 2, 3, or 4;
- wherein
- each heterocycloalkyl is a 3- to 8-membered ring that includes 1 to 4 heteroatoms each independently N, O or S; and
- each heteroaryl is a 5- to 6-membered ring that includes 1 to 4 heteroatoms each independently N, O or S.

[0127] In some embodiments, a compound of Formula (J) or Formula (III) is represented by Formula (IIIa):



or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , R^3 , n , and R^4 are as described in classes and subclasses herein, both singly and in combination.

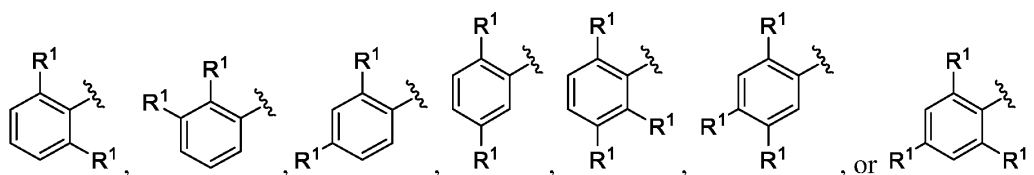
[0128] In some embodiments, a compound of Formula (J), (III), and/or (IIIa), or pharmaceutically acceptable salt thereof, is represented by Formula (IIIb):



or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , R^3 , and R^4 are as described in classes and subclasses herein, both singly and in combination.

[0129] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof,

10 the group has the structure:



[0130] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^1 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, -CN, C_3 - C_8 cycloalkyl, $(C_1$ - C_3 alkyl)(C_3 - C_8 cycloalkyl), -O-(C_3 - C_8 cycloalkyl), heterocycloalkyl, $(C_1$ - C_3 alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C_6 - C_{10} aryl, or heteroaryl, wherein each alkyl is substituted with 0, 1, 2, or 3 R^{1c} , and each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d} ; or alternatively, two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl.

[0131] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^1 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, C_3 - C_8 cycloalkyl, $(C_1$ -

C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), C₆-C₁₀ aryl, or heteroaryl, wherein each alkyl is substituted with 0 or 1 R^{1c}, and each alkoxy and alkynyl is substituted with 0 or 1 R^{1d}; or alternatively, two R¹ on adjacent carbons together with the atoms to which they are attached combine to form a C₅-C₈ cycloalkyl or a heterocycloalkyl.

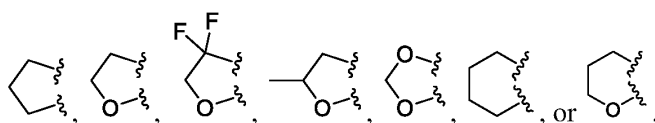
- 5 **[0132]** In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^{1a} and R^{1b} is independently hydrogen or C₁-C₄ alkyl.

[0133] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^{1c} is halogen, -NR^{1c1}R^{1c2}, OH, or -CN.

- 10 **[0134]** In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^{1d} is independently heteroaryl.

[0135] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^{1e} is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, or -CN.

- 15 **[0136]** In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R¹ is independently -CH₃, -CH₂CH₃, -C(CH₃)₃, -OCH₃, -CH₂CH₃, -OCH(CH₃)₂, -OCH₂-pyridyl, -C(CH₃)₂OH, F, Cl, Br, -CF₃, -OCHF₂, -OCF₃, -OCH₂CF₃, -C(CH₃)₂CH₂OH, -OH, cyclopropyl, cyclopropyloxy, cyclobutyloxy, phenyl, or pyrazolyl; or alternatively, two R¹ on adjacent carbons together with the atoms to which they are attached combine to form a cyclopentyl, cyclohexyl, dihydrofuran, tetrahydrofuran, methyltetrahydrofuran, 1,3-dioxole, dihydro-1,3-oxazine, or methyldihydrofuran. In some embodiments, two R¹ on adjacent carbon atoms combine to form:
- 20



- 25 **[0137]** In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, L is -CH₂-, -CH₂O-, or -O-.

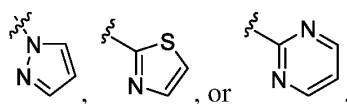
[0138] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, L is -CH₂-.

[0139] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, R^2 is pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidyl, or pyrazinyl, which are each substituted by 0, 1, or 2 R^{2a} .

- 5 [0140] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^{2a} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, or -CN.

- [0141] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or
10 pharmaceutically acceptable salt thereof, each R^{2b} and R^{2c} is independently hydrogen or C_1 - C_4 alkyl.

[0142] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, R^2 is



- 15 [0143] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, R^2 is



- [0144] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^3 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy,
20 C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{3a}$, $-OC(O)R^{3a}$, $-C(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(R^{3b})$, $-S(O)_2R^{3a}$, $-S(O)_2N(R^{3a})(R^{3b})$, OH, -CN, C_3 - C_8 cycloalkyl, or heterocycloalkyl.

- [0145] In some embodiments, a compound of Formula (J), (III), (IIIa), and/or (IIIb), or
25 pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein two R^3 on the same carbon atom together represent an oxo group.

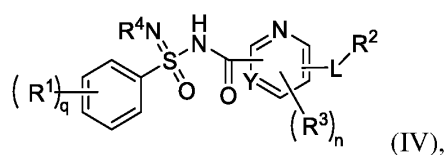
- [0146] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^{3a} and R^{3b} is independently hydrogen or C₁-C₄ alkyl.
- 5 [0147] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^{3c} is halogen, $-NR^{3c1}R^{3c2}$, OH, or -CN.
- [0148] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^{3d} is independently heteroaryl.
- [0149] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^{3e} is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, 10 halogen, or C₁-C₄ haloalkyl.
- [0150] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^3 is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -CN, or C₃-C₈ cycloalkyl.
- [0151] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or 15 pharmaceutically acceptable salt thereof, each R^3 is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, -CN, or C₃-C₆ cycloalkyl.
- [0152] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, each R^3 is independently Me, OMe, OEt, CHF₂, CF₃, OCHF₂, OCF₃, F, Br, CN, or cyclopropyl.
- 20 [0153] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, R^4 is hydrogen or C₁-C₄ alkyl. In some embodiments, R^4 is Me, Et, or iPr. In some embodiments, R^4 is hydrogen.
- [0154] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, subscript q is 1, 2, or 3.
- 25 [0155] In some embodiments of a compound of Formula (J), (III), (IIIa), and/or (IIIb), or pharmaceutically acceptable salt thereof, subscript n is 1 or 2.
- [0156] In some embodiments, a compound of Formula (J), (III), (IIIa), and/or (IIIb), or a pharmaceutically acceptable salt thereof, is a compound wherein the compound has the structure of a compound shown in Table 3, or a pharmaceutically acceptable salt thereof.

Table 3. Compounds

No.	Structure	Name
71		4-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxyphenylsulfonimidoyl)-3-methoxybenzamide
72		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-(2-methoxyphenylsulfonimidoyl)benzamide
73		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-(2-methoxy-6-(2,2,2-trifluoroethoxy)phenylsulfonimidoyl)benzamide
74		4-((1H-pyrazol-1-yl)methyl)-N-(2-cyclobutoxy-6-methoxyphenylsulfonimidoyl)-3-methoxybenzamide
75		4-((1H-pyrazol-1-yl)methyl)-N-(2,4-dimethoxyphenylsulfonimidoyl)-3-methoxybenzamide
76		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-(2,4,6-trimethoxyphenylsulfonimidoyl)benzamide
291a		(R)-4-((1H-pyrazol-1-yl)methyl)-N-(5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenylsulfonimidoyl)-3-methoxybenzamide
291b		(S)-4-((1H-pyrazol-1-yl)methyl)-N-(5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenylsulfonimidoyl)-3-methoxybenzamide
292		4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)(methylamino)(oxo)-l6-sulfaneylidene)-3-methoxybenzamide
295a		(R)-4-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxyphenylsulfonimidoyl)-3-methoxybenzamide

No.	Structure	Name
295b		(S)-4-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxyphenylsulfonimidoyl)-3-methoxybenzamide
299		4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-(2,4,6-trimethoxyphenylsulfonimidoyl)benzamide
299a		(R)-4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-(2,4,6-trimethoxyphenylsulfonimidoyl)benzamide
299b		(S)-4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-(2,4,6-trimethoxyphenylsulfonimidoyl)benzamide
300a		(R)-4-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxyphenylsulfonimidoyl)-3-(trifluoromethoxy)benzamide
300b		(S)-4-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxyphenylsulfonimidoyl)-3-(trifluoromethoxy)benzamide
302a		(R)-4-((1H-pyrazol-1-yl)methyl)-N-(3-chloro-2,6-dimethoxyphenylsulfonimidoyl)-3-methoxybenzamide
302b		(S)-4-((1H-pyrazol-1-yl)methyl)-N-(3-chloro-2,6-dimethoxyphenylsulfonimidoyl)-3-methoxybenzamide
304a		(R)-4-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxy-3-methylphenylsulfonimidoyl)-3-methoxybenzamide
304b		(S)-4-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxy-3-methylphenylsulfonimidoyl)-3-methoxybenzamide

[0157] In some embodiments, a compound of Formula (J) is represented by Formula (IV):

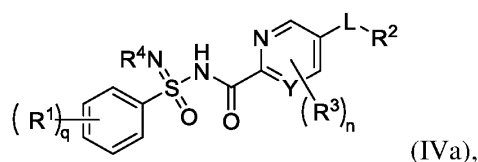


or a pharmaceutically acceptable salt thereof, wherein

- each R^1 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, -
 5 $C(O)R^{1a}$, $-C(O)OR^{1a}$, $-OC(O)R^{1a}$, $-C(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(R^{1b})$,
 $-OC(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(OR^{1b})$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)_2N(R^{1a})(R^{1b})$,
 $-S(O)(NH)R^{1a}$, $-S(O)(NH)N(R^{1a})(R^{1b})$, $-N(R^{1a})(R^{1b})$, OH, -CN, -NO₂, C_3 - C_8 cycloalkyl,
 $(C_1$ - C_3 alkyl)(C_3 - C_8 cycloalkyl), $-O$ -(C_3 - C_8 cycloalkyl), heterocycloalkyl, $(C_1$ - C_3
 alkyl)(heterocycloalkyl), $-O$ -(heterocycloalkyl), C_6 - C_{10} aryl, $(C_1$ - C_3 alkyl)(C_6 - C_{10} aryl),
 10 $-O$ -(C_6 - C_{10} aryl), heteroaryl, $(C_1$ - C_3 alkyl)(heteroaryl), or $-O$ -(heteroaryl), wherein
 each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{1c} , each alkoxy and alkynyl is
 substituted with 0, 1, 2, or 3 R^{1d} , and each cycloalkyl, heterocycloalkyl, aryl, and
 heteroaryl is substituted with 0, 1, 2, or 3 R^{1e} ;
 each R^{1a} and R^{1b} is independently hydrogen or C_1 - C_6 alkyl;
 15 each R^{1c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, $-NR^{1c1}R^{1c2}$, OH, or -CN;
 each R^{1c1} and R^{1c2} is independently hydrogen or C_1 - C_6 alkyl;
 each R^{1d} is independently deuterium, C_3 - C_8 cycloalkyl, heterocycloalkyl, C_6 - C_{10} aryl, or
 heteroaryl;
 each R^{1e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, C_1 - C_6
 20 haloalkoxy, OH, or -CN;
 alternatively, two R^1 groups on adjacent carbons together with the atoms to which they are
 attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl substituted with 0,
 1, 2, 3, 4, 5, or 6 halogen, C_1 - C_4 alkyl, OH or -CN;
 L is $-C_1$ - C_4 alkylene-, $-(C_1$ - C_4 alkylene)-O-, or -O-;
 25 R^2 is a heteroaryl, which is substituted with 0, 1, 2, 3, or 4 R^{2a} ;
 each R^{2a} is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6
 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, -
 $C(O)R^{2b}$, $-C(O)OR^{2b}$, $-OC(O)R^{2b}$, $-C(O)N(R^{2b})(R^{2c})$, $-N(R^{2b})C(O)(R^{2c})$, $-S(O)_2R^{2b}$,
 $-S(O)_2N(R^{2b})(R^{2c})$, $-N(R^{2b})(R^{2c})$, OH, -CN, or -NO₂;
 30 each R^{2b} and R^{2c} is independently hydrogen or C_1 - C_6 alkyl;
 Y is CH, CR^3 , or N;

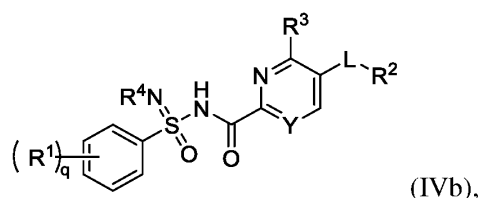
- each R^3 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{3a}$, $-OC(O)R^{3a}$, $-C(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(R^{3b})$, $-OC(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(OR^{3b})$, $-S(O)R^{3a}$, $-S(O)_2R^{3a}$, $-S(O)_2N(R^{3a})(R^{3b})$, $-S(O)(NH)R^{3a}$, $-S(O)(NH)N(R^{3a})(R^{3b})$, $-N(R^{3a})(R^{3b})$, OH, -CN, -NO₂, C_3 - C_8 cycloalkyl, $(C_1$ - C_3 alkyl)(C_3 - C_8 cycloalkyl), $-O$ -(C_3 - C_8 cycloalkyl), heterocycloalkyl, $(C_1$ - C_3 alkyl)(heterocycloalkyl), $-O$ -(heterocycloalkyl), C_6 - C_{10} aryl, $(C_1$ - C_3 alkyl)(C_6 - C_{10} aryl), $-O$ -(C_6 - C_{10} aryl), heteroaryl, $(C_1$ - C_3 alkyl)(heteroaryl), or $-O$ -(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{3c} , each alkoxy is substituted with 0, 1, 2, or 3 R^{3d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{3e} ; or,
- two R^3 on the same carbon atom together represent an oxo group;
- each R^{3a} and R^{3b} is independently hydrogen or C_1 - C_6 alkyl;
- each R^{3c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, $-NR^{3c1}R^{3c2}$, OH, or -CN;
- each R^{3c1} and R^{3c2} is independently hydrogen or C_1 - C_6 alkyl;
- each R^{3d} is independently C_3 - C_8 cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl;
- each R^{3e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, or C_1 - C_6 haloalkoxy;
- R^4 is hydrogen or C_1 - C_6 alkyl;
- subscript n is 0, 1, 2, 3, or 4; and
- subscript q is 0, 1, 2, 3, or 4;
- wherein
- each heterocycloalkyl is a 3- to 8-membered ring that includes 1 to 4 heteroatoms each independently N, O or S; and
- each heteroaryl is a 5- to 6-membered ring that includes 1 to 4 heteroatoms each independently N, O or S.

[0158] In some embodiments, a compound of Formula (J), Formula (IV), or a pharmaceutically acceptable salt thereof is represented by Formula (IVa):



or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , R^3 , n , and R^4 are as described in classes and subclasses herein, both singly and in combination, and Y is N, CH, or CR^3 .

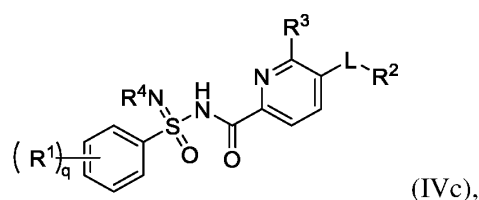
[0159] In some embodiments, a compound of Formula (J), (IV), and/or (IVa), or a
5 pharmaceutically acceptable salt thereof is represented by Formula (IVb):



or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , R^3 , and R^4 are as described in classes and subclasses herein, both singly and in combination, and Y is N, CH, or CR^3 .

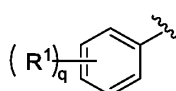
[0160] In some embodiments, a compound of Formula (J), (IV), (IVa), and/or (IVb), or
10 pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein Y is N. In some embodiments, Y is CR^3 . In some embodiments, Y is CH.

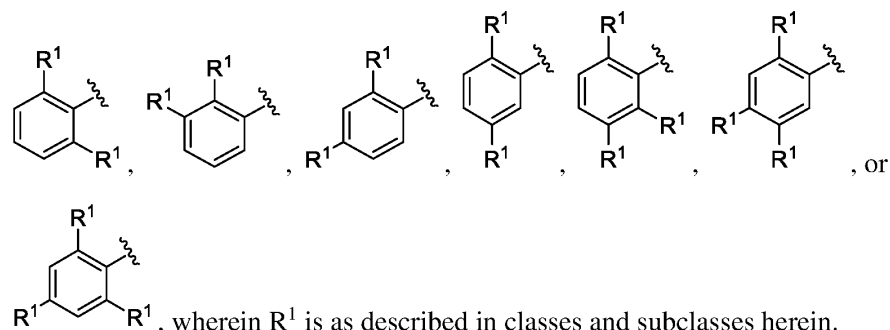
[0161] In some embodiments, a compound of (J), (IV), (IVa), and/or (IVb) is represented by Formula (IVc):



15 or a pharmaceutically acceptable salt thereof, wherein R^1 , q , R^2 , L , R^3 , and R^4 are as described in classes and subclasses herein, both singly and in combination.

[0162] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof,

the group $(R^1)_q$  has the structure:



[0163] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc),
 5 or a pharmaceutically acceptable salt thereof, each R^1 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, -CN, C_3 - C_8 cycloalkyl, (C_1 - C_3 alkyl)(C_3 - C_8 cycloalkyl), -O-(C_3 - C_8 cycloalkyl), heterocycloalkyl, (C_1 - C_3 alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C_6 - C_{10} aryl, or heteroaryl, wherein each alkyl is substituted with 0, 1, 2, or 3 R^{1c} , and each alkoxy and alkynyl
 10 is substituted with 0, 1, 2, or 3 R^{1d} ; or alternatively, two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl.

[0164] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc),
 or a pharmaceutically acceptable salt thereof, each R^1 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, C_3 - C_8
 15 cycloalkyl, (C_1 - C_3 alkyl)(C_3 - C_8 cycloalkyl), -O-(C_3 - C_8 cycloalkyl), C_6 - C_{10} aryl, or heteroaryl, wherein each alkyl is substituted with 0 or 1 R^{1c} , and each alkoxy and alkynyl is substituted with 0 or 1 R^{1d} ; or alternatively, two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl.

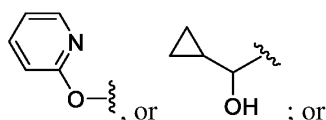
[0165] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc),
 20 or a pharmaceutically acceptable salt thereof, each R^{1a} and R^{1b} is independently hydrogen or C_1 - C_3 alkyl.

[0166] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc),
 or a pharmaceutically acceptable salt thereof, each R^{1c} is halogen, $-NR^{1c1}R^{1c2}$, OH, or -CN.

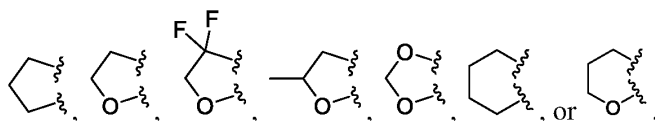
[0167] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc),
 25 or a pharmaceutically acceptable salt thereof, each R^{1d} is independently heteroaryl.

[0168] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, each R^{1e} is independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, C_1 - C_4 haloalkyl, or $-CN$.

[0169] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc),
 5 or a pharmaceutically acceptable salt thereof, each R^1 is independently $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-OCH_3$, $-CH_2CH_3$, $-OCH(CH_3)_2$, $-C(CH_3)_2OH$, $-C(CH_3)_2CH_2OH$, $-C(CH_3)(CH_2CH_3)OH$, F, Cl, Br, $-CF_3$, $-OCHF_2$, $-OCF_3$, $-OCH_2CF_3$, cyclopropyl, cyclopropyloxy, cyclobutyloxy,



10 two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a cyclopentyl, cyclohexyl, dihydrofuran, tetrahydrofuran, methyltetrahydrofuran, 1,3-dioxole, dihydro-1,3-oxazine, or methyldihydrofuran. In some embodiments, two R^1 on adjacent carbon atoms combine to form:



15 **[0170]** In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, L is $-CH_2-$, $-CH_2O-$, or $-O-$.

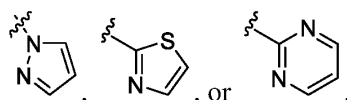
[0171] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, L is $-CH_2-$.

[0172] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc),
 20 or a pharmaceutically acceptable salt thereof, R^2 is pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidyl, or pyrazinyl, which are each substituted by 0, 1, or 2 R^{2a} .

[0173] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc),
 25 or a pharmaceutically acceptable salt thereof, each R^{2a} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, or $-CN$.

[0174] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, each R^{2b} and R^{2c} is independently hydrogen or C₁-C₄ alkyl.

[0175] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc),
5 or pharmaceutically acceptable salt thereof, R^2 is



[0176] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, R^2 is



10 [0177] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, each R^3 is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -C(O) R^{3a} , -C(O)OR^{3a}, -OC(O) R^{3a} , -C(O)N(R^{3a})(R^{3b}), -N(R^{3a})C(O)(R^{3b}), -S(O)₂ R^{3a} , -S(O)₂N(R^{3a})(R^{3b}), OH, -CN, C₃-C₈ cycloalkyl, or heterocycloalkyl.

15 [0178] In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is a compound, or pharmaceutically acceptable salt thereof, wherein two R^3 on the same carbon atom together represent an oxo group.

[0179] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, each R^{3a} and R^{3b} is independently hydrogen or
20 C₁-C₄ alkyl.

[0180] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, each R^{3c} is halogen, -NR^{3c1} R^{3c2} , OH, or -CN.

[0181] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, each R^{3d} is independently heteroaryl.

25 [0182] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, each R^{3e} is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₁-C₄ haloalkyl.

[0183] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, each R^3 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, -CN, or C_3 - C_8 cycloalkyl.

[0184] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc),
5 or a pharmaceutically acceptable salt thereof, each R^3 is independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, -CN, or C_3 - C_6 cycloalkyl.

[0185] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, each R^3 is independently Me, Ome, CHF_2 , CF_3 , $OCHF_2$, OCF_3 , or cyclopropyl.

10 **[0186]** In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), pharmaceutically acceptable salt thereof, R^4 is hydrogen or C_1 - C_4 alkyl. In some embodiments, R^4 is Me, Et, or iPr. In some embodiments, R^4 is hydrogen.

[0187] In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, subscript q is 1, 2, or 3.

15 **[0188]** In some embodiments of a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, subscript n is 0 or 1.

[0189] In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, is a compound wherein the compound has the structure of a compound shown in Table 4, or a pharmaceutically acceptable salt thereof.

20 **Table 4. Compounds**

No.	Structure	Name
232		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-(2-methoxyphenylsulfonimidoyl)picolinamide
243		5-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxyphenylsulfonimidoyl)-6-methoxypicolinamide
260		5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-(2-methoxy-6-(2,2,2-trifluoroethoxy)phenylsulfonimidoyl)picolinamide

No.	Structure	Name
261		5-((1H-pyrazol-1-yl)methyl)-N-(2-cyclobutoxy-6-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide
262		5-((1H-pyrazol-1-yl)methyl)-N-(2,4-dimethoxyphenylsulfonimidoyl)-6-methoxypicolinamide
263		5-((1H-pyrazol-1-yl)methyl)-N-(2,4,6-trimethoxyphenylsulfonimidoyl)picolinamide
290a		(R)-5-((1H-pyrazol-1-yl)methyl)-N-(5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide
290b		(S)-5-((1H-pyrazol-1-yl)methyl)-N-(5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide
293a		(R)-5-((1H-pyrazol-1-yl)methyl)-N-(3-chloro-2,6-dimethoxyphenylsulfonimidoyl)-6-methoxypicolinamide
293b		(S)-5-((1H-pyrazol-1-yl)methyl)-N-(3-chloro-2,6-dimethoxyphenylsulfonimidoyl)-6-methoxypicolinamide
294		5-((1H-pyrazol-1-yl)methyl)-N-(2-ethoxy-6-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide
294a		(R)-5-((1H-pyrazol-1-yl)methyl)-N-(2-ethoxy-6-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide
294b		(S)-5-((1H-pyrazol-1-yl)methyl)-N-(2-ethoxy-6-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide

No.	Structure	Name
296a		(R)-5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-(2,4,6-trimethoxyphenylsulfonimidoyl)picolinamide
296b		(S)-5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-(2,4,6-trimethoxyphenylsulfonimidoyl)picolinamide
297		5-((1H-pyrazol-1-yl)methyl)-N-(5-(2-hydroxypropan-2-yl)-2-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide
298a		(R)-5-((1H-pyrazol-1-yl)methyl)-N-(2-cyclobutoxy-6-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide
298b		(S)-5-((1H-pyrazol-1-yl)methyl)-N-(2-cyclobutoxy-6-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide
301a		(R)-5-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxy-3-methylphenylsulfonimidoyl)-6-methoxypicolinamide
301b		(S)-5-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxy-3-methylphenylsulfonimidoyl)-6-methoxypicolinamide
303a		(R)-5-((1H-pyrazol-1-yl)methyl)-N-(2,3-dihydrobenzofuran-7-sulfonimidoyl)-6-methoxypicolinamide
303b		(S)-5-((1H-pyrazol-1-yl)methyl)-N-(2,3-dihydrobenzofuran-7-sulfonimidoyl)-6-methoxypicolinamide
305a		(R)-5-((1H-pyrazol-1-yl)methyl)-N-(2-fluoro-6-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide

No.	Structure	Name
305b		(S)-5-((1H-pyrazol-1-yl)methyl)-N-(2-fluoro-6-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide
306a		(R)-5-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxy-4-methylphenylsulfonimidoyl)-6-methoxypicolinamide
306b		(S)-5-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxy-4-methylphenylsulfonimidoyl)-6-methoxypicolinamide
307a		(R)-5-((1H-pyrazol-1-yl)methyl)-N-(2-fluorophenylsulfonimidoyl)-6-methoxypicolinamide
307b		(S)-5-((1H-pyrazol-1-yl)methyl)-N-(2-fluorophenylsulfonimidoyl)-6-methoxypicolinamide
308a		(R)-5-((1H-pyrazol-1-yl)methyl)-N-(2,6-difluorophenylsulfonimidoyl)-6-methoxypicolinamide
308b		(S)-5-((1H-pyrazol-1-yl)methyl)-N-(2,6-difluorophenylsulfonimidoyl)-6-methoxypicolinamide

[0190] In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is selected from the group consisting of:

- 5 4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide (14)e
- 4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)benzamide
- 4-((1H-pyrazol-1-yl)methyl)-N-((2-ethoxy-6-methoxyphenyl)sulfonyl)-3-methoxybenzamide (67),
- 10 5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide (203),

- 5-((1H-pyrazol-1-yl)methyl)-N-((5-ethyl-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide (204),
5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)picolinamide (224),
5-((1H-pyrazol-1-yl)methyl)-6-cyclopropyl-N-((2,6-dimethoxyphenyl)sulfonyl)picolinamide (229),
5-((1H-pyrazol-1-yl)methyl)-N-((3-chloro-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide (241),
5-((1H-pyrazol-1-yl)methyl)-N-((4-bromo-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide (285),
4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methyl-2,3-dihydrobenzofuran-7-yl)sulfonyl)benzamide (314),

and pharmaceutically acceptable salts thereof.

- [0191]** In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is 4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide, or a pharmaceutically acceptable salt thereof. In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is 4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)benzamide, or a pharmaceutically acceptable salt thereof.
- In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is 4-((1H-pyrazol-1-yl)methyl)-N-((2-ethoxy-6-methoxyphenyl)sulfonyl)-3-methoxybenzamide, or a pharmaceutically acceptable salt thereof. In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is 5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide, or a pharmaceutically acceptable salt thereof. In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is 5-((1H-pyrazol-1-yl)methyl)-N-((5-ethyl-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide, or a pharmaceutically acceptable salt thereof. In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is 5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)picolinamide, or a pharmaceutically acceptable salt thereof. In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is 5-((1H-pyrazol-1-yl)methyl)-6-cyclopropyl-N-

((2,6-dimethoxyphenyl)sulfonyl)picolinamide, or a pharmaceutically acceptable salt thereof. In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is 5-((1H-pyrazol-1-yl)methyl)-N-((3-chloro-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide, or a pharmaceutically acceptable salt thereof. In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is 5-((1H-pyrazol-1-yl)methyl)-N-((4-bromo-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide, or a pharmaceutically acceptable salt thereof. In some embodiments, a compound of Formula (J), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, is 4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methyl-2,3-dihydrobenzofuran-7-yl)sulfonyl)benzamide, or a pharmaceutically acceptable salt thereof.

IV. COMPOSITIONS

[0192] In some embodiments, the pharmaceutical composition of the present invention comprises a compound of the present invention, such as a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0193] The compounds of the present invention may be used as single drug or as a pharmaceutical composition in which the compound is mixed with various pharmacologically acceptable excipients.

[0194] The compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the invention. The pharmaceutical composition of the present patent application comprises one or more compounds described herein and one or more pharmaceutically acceptable excipients. Typically, the pharmaceutically acceptable excipients are approved by regulatory authorities or are generally regarded as safe for human or animal use. The pharmaceutically acceptable excipients include, but are not limited to, carriers, diluents, glidants and lubricants, preservatives, buffering agents, chelating agents, polymers, gelling agents, viscosifying agents and solvents.

[0195] The pharmaceutical composition can be administered by oral, parenteral or inhalation routes. Examples of the parenteral administration include administration by injection, percutaneous, transmucosal, transnasal and transpulmonary administrations.

5 [0196] Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid, lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, fatty acid esters and polyoxyethylene.

10 [0197] The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, suspending agents, preserving agents, buffers, sweetening agents, flavoring agents, colorants or any combination of the foregoing.

[0198] The pharmaceutical compositions may be in conventional forms, for example, tablets, capsules, solutions, suspensions, injectables or products for topical application. Further, the pharmaceutical composition of the present invention may be formulated so as to provide a
15 desired release profile.

[0199] Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted routes of administration of pharmaceutical compositions. The route of administration may be any route which effectively transports the active compound of the patent application to the appropriate
20 or desired site of action. Suitable routes of administration include, but are not limited to oral, nasal, buccal, dermal, intradermal, transdermal, parenteral, rectal, subcutaneous, intravenous, intraurethral, intramuscular or topical.

[0200] Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and
25 lozenges.

[0201] Liquid formulations include, but are not limited to, syrups, emulsions and sterile injectable liquids, such as suspensions or solutions.

[0202] Topical dosage forms of the compounds include ointments, pastes, creams, lotions, powders, solutions, eye or ear drops, impregnated dressings and may contain appropriate
30 conventional additives such as preservatives, solvents to assist drug penetration.

[0203] The pharmaceutical compositions of the present patent application may be prepared by conventional techniques known in literature.

[0204] Suitable doses of the compounds for use in treating the diseases or disorders described herein can be determined by those skilled in the relevant art. Therapeutic doses are generally identified through a dose ranging study in humans based on preliminary evidence derived from the animal studies. Doses must be sufficient to result in a desired therapeutic benefit without causing unwanted side effects. Mode of administration, dosage forms and suitable pharmaceutical excipients can also be well used and adjusted by those skilled in the art. All changes and modifications are envisioned within the scope of the present patent application.

[0205] In some embodiments, a pharmaceutical composition of the present invention is a pharmaceutical composition comprising a compound of Formula (J) or a pharmaceutically acceptable salt thereof as described herein and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of at least one compound described herein. The composition described herein the present invention may be associated with a pharmaceutically acceptable excipient (such as a carrier or a diluent) or be diluted by a carrier or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container.

[0206] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (for example, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

[0207] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for

example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0208] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0209] Compositions for rectal or vaginal administration can be suppositories which can be prepared by mixing the compounds of this application with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0210] Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0211] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, including but not limited to tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

[0212] Dosage forms for topical or transdermal administration of a compound of this application include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be

required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this application.

5 **[0213]** The ointments, pastes, creams and gels may contain, in addition to an active compound of this application, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures thereof.

10 **[0214]** Powders and sprays can contain, in addition to the compounds of this application, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

15 **[0215]** Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0216] Administration of the disclosed compounds and pharmaceutical compositions can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, intravenous, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes.

20 **[0217]** Depending on the intended mode of administration, the disclosed compounds or pharmaceutical compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions or the like, sometimes in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered
25 in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form and all using forms well known to those skilled in the pharmaceutical arts.

30 **[0218]** Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising one or more compounds of the present disclosure and a pharmaceutically acceptable carrier, such as, but not limited to, a) a diluent, e.g., purified water, triglyceride oils, such as hydrogenated or partially hydrogenated vegetable oil or mixtures thereof, corn oil, olive oil, sunflower oil, safflower oil, fish oils, such as EPA or DHA or their esters or triglycerides or

mixtures thereof, omega-3 fatty acids or derivatives thereof, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, sodium, saccharin, glucose and/or glycine; b) a lubricant, e.g., silica, talcum, stearic acid, its magnesium or calcium salt, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and/or polyethylene glycol; for tablets also; c) a binder, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, magnesium carbonate, natural sugars such as glucose or beta- lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, waxes and/or polyvinylpyrrolidone, if desired; d) a disintegrant, e.g., starches, agar, methyl cellulose, bentonite, xanthan gum, alginic acid or its sodium salt or effervescent mixtures; e) absorbent, colorant, flavorant and sweetener; f) an emulsifier or dispersing agent, such as Tween 80, Labrasol, HPMC, DOSS, caproyl 909, labrafac, labrafil, peceol, transcutool, capmul MCM, capmul PG-12, captex 355, gelucire, vitamin E TGPS or other acceptable emulsifier; and/or g) an agent that enhances absorption of the compound such as cyclodextrin, hydroxypropyl-cyclodextrin, PEG400, PEG200.

15 **[0219]** Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, etc. For example, one or more disclosed compound is dissolved in or mixed with a pharmaceutically acceptable solvent such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form an injectable isotonic solution or suspension. Proteins such as albumin, chylomicron particles or serum proteins can be used to
20 solubilize the disclosed compounds.

[0220] One or more disclosed compounds or compositions can be delivered by parental administration. The parental injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for
25 dissolving in liquid prior to injection.

[0221] In some embodiments, a pharmaceutical composition of the present invention comprises a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or
30 diluent).

[0222] In some embodiments, a pharmaceutical composition of the present invention comprising a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb),

(IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof is for use as a medicament.

[0223] In some embodiments, a pharmaceutical composition of the present invention comprising a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb),
5 (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof is for treating a disease or disorder that is dependent on or mediated by KAT6A.

V. ADMINISTRATION

[0224] The compound of the present disclosure may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as
10 at least about one week, at least about two weeks, at least about three weeks, one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer. In one variation, the compound is administered on a daily or intermittent schedule for the required duration, up to the individual's life.

[0225] The dosage or dosing frequency of the compound of the present disclosure may be
15 adjusted over the course of the treatment, based on the judgment of the administering physician.

[0226] The compound may be administered to an individual, such as a human in an effective amount.

[0227] The compound of the present invention can be administered by any useful route and means, such as by oral or parenteral (e.g., intravenous) administration. Therapeutically
20 effective amounts of the compound of the present invention are from about 0.00001 mg/kg body weight per day to about 10 mg/kg body weight per day, such as from about 0.0001 mg/kg body weight per day to about 10 mg/kg body weight per day, or such as from about 0.001 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0.01 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0.05
25 mg/kg body weight per day to about 0.5 mg/kg body weight per day.

[0228] Therapeutically effective amounts of the compound of the present invention, are from about 0.01 mg per dose to about 1000 mg per dose, such as from about 0.01 mg per dose to about 100 mg per dose, or such as from about 0.1 mg per dose to about 100 mg per dose, or such as from about 1 mg per dose to about 100 mg per dose, or such as from about 1 mg per
30 dose to about 10 mg per dose. Other therapeutically effective amounts of the compound of the present invention are about 1 mg per dose, or about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35,

40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or about 100 mg per dose. Other therapeutically effective amounts of the compound of the present invention are about 100 mg per dose, or about 125, 150, 175, 200, 225, 250, 275, 300, 350, 400, 450, or about 500 mg per dose. A single dose can be administered hourly, daily, or weekly. For example, a single dose can be administered once every 1 hour, 2, 3, 4, 6, 8, 12, 16 or once every 24 hours. A single dose can also be administered once every 1 day, 2, 3, 4, 5, 6, or once every 7 days. A single dose can also be administered once every 1 week, 2, 3, or once every 4 weeks. In certain embodiments, a single dose can be administered once every week. A single dose can also be administered once every month.

10 VI. METHODS AND/OR USES

[0229] In some embodiments, a method of the present invention is a method of treating a disease or a disorder comprising administering a therapeutically effective amount of a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof to a subject, e.g., a human, in need thereof.

[0230] In some embodiments, a use of the present invention is a use of a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a disease or condition, e.g., cancer.

20 [0231] In some embodiments, a compound for use of the present invention is a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, for use in the treatment of diseases or disorders mediated by KAT6A.

25 [0232] In some embodiments, a method of the present invention is a method of inhibiting KAT6A in a subject comprising administering to the subject in need thereof, a therapeutically effective amount of a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof.

30 [0233] In some embodiments, a method of the present invention is a method for treating a disease or disorder mediated by KAT6A, in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound of Formula ((J), (I), (Ia), (Ib),

(II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof.

[0234] In some embodiments, a compound for use of the present invention is a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, for use as a medicament.

[0235] In some embodiments, a method of the present invention is a method of modulating KAT6A in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof.

[0236] In some embodiments, a use of the present invention is a use of a pharmaceutical composition comprising a compound of Formula(J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder mediated by KAT6A. In some embodiments, the use of a pharmaceutical composition comprises a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer that is mediated by KAT6A.

[0237] In some embodiments, a use of the present invention is a use of compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing a disease or disorder mediated by KAT6A.

[0238] In some embodiments, the disease or disorder is dependent upon or mediated by KAT6A is cancer.

[0239] In some embodiments, the cancer is selected from brain gliomas, glioblastomas, astrocytomas, multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, colon cancer, head and neck cancer, kidney, liver, lung cancer, bone cancer, colorectal cancer, germ cell cancer, melanoma, ovarian cancer, pancreatic cancer, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma and thyroid cancer, lymphoblastic T cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia,

- acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, mantle cell leukemia, megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, erythroleukemia, malignant lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, uterine cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor (GIST), neuroendocrine cancers, testicular cancer, and virus-related cancer.
- 10 **[0240]** In some embodiments, a use of the present invention is a use of compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer selected from brain gliomas, glioblastomas, astrocytomas, multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, colon cancer, head and neck cancer, kidney, liver, lung cancer, bone cancer, colorectal cancer, germ cell cancer, melanoma, ovarian cancer, pancreatic cancer, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma and thyroid cancer, lymphoblastic T cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, mantle cell leukemia, megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, erythroleukemia, malignant lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, uterine cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor (GIST), neuroendocrine cancers, testicular cancer, and virus-related cancer.
- 20
- 25
- 30 **[0241]** In some embodiments, a compound for use of the present invention is a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, for use in treating of a disease or disorder mediated by KAT6A.

[0242] In some embodiments, a compound for use of the present invention is a compound of Formula (J), (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), and/or (IVc), or a pharmaceutically acceptable salt thereof, for use in treating or preventing cancer selected from brain gliomas, glioblastomas, astrocytomas, multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, colon cancer, head and neck cancer, kidney, liver, lung cancer, bone cancer, colorectal cancer, germ cell cancer, melanoma, ovarian cancer, pancreatic cancer, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma and thyroid cancer, lymphoblastic T cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, mantle cell leukemia, megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, erythroleukemia, malignant lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, uterine cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor (GIST), neuroendocrine cancers, testicular cancer, and virus-related cancer.

[0243] In some embodiments, the present disclosure provides compounds for use in combination with other compounds or biologic entities for treatment of disease or disorder. Suitable combinations and doses of compounds for combination therapy used in treating the diseases or disorders described herein can be determined by those skilled in the relevant art. Combination therapies for compounds of the present disclosure can be used for treatment of disease or disorder. In some embodiments, the disease or disorder is cancer.

[0244] In some embodiments, the present disclosure provides compounds for use in a method of treating a disease or disorder in a subject that comprises administering to the subject the compound in combination or alternation with an estrogen receptor antagonist or a estrogen receptor partial antagonist. As described herein, an estrogen receptor "partial" antagonist refers to an estrogen receptor antagonist that exhibits antagonist activity in estrogen receptor antagonist assays, but also exhibits detectable estrogen receptor agonist activity in estrogen receptor agonist assays.

[0245] In some embodiments, the present disclosure provides compounds for use in a method of treating a disease or disorder in a subject that comprises administering to the subject the compound in combination or alternation with a Selective Estrogen Receptor Modulator (SERM). In some embodiments, the SERM is tamoxifen, endoxifene, raloxifene, toremifene, 5 lasofoxifene, ospemifene, elacestrant or bazedoxifene.

[0246] In some embodiments, the present disclosure provides compounds for use in a method of treating a disease or disorder in a subject that comprises administering to the subject the compound in combination or alternation with a Selective Estrogen Receptor Degradar. In some 10 embodiments, the SERD is fulvestrant, camizestrant, palazestrant, imlunestrant, elacestrant, or giredestrant.

[0247] In some embodiments, the present disclosure provides compounds for use in a method of treating a disease or disorder in a subject that comprises administering to the subject the compound in combination or alternation with a Complete Estrogen Receptor Antagonist (CERAN). In some embodiments, the CERAN is fulvestrant or palazestrant. In some 15 embodiments, the CERAN is fulvestrant. In some embodiments, the CERAN is palazestrant.

[0248] In some embodiments, the present disclosure provides compounds for use in a method of treating a disease or disorder in a subject that comprises administering to the subject the compound in combination or alternation with an additional anti-cancer agent. In some 20 embodiments, an additional anti-cancer agent is selected from a HER2 inhibitor, an mTOR inhibitor, a CDK4/6 inhibitor, a CDK2-selective inhibitor, a CDK4-selective inhibitor, a PI3 kinase inhibitor, a PIK3CA inhibitor, an aromatase inhibitor, an antibody to or inhibitor of PD-1, PD-L1 or CTLA-4, an antibody to or inhibitor of EGFR, PGFR, or IGFR, a USP1 inhibitor or an AKT inhibitor.

[0249] In some embodiments, an additional anti-cancer agent is a CDK2 inhibitor. In some 25 embodiments, a CDK2 inhibitor is PF-07104091 (tagtociclib).

[0249] In some embodiments, an additional anti-cancer agent is a HER2 inhibitor. In some 30 embodiments, a HER2 inhibitor is selected from tucatinib, trastuzumab, pertuzumab, ado-trastuzumab, trastuzumab emtansine, ado-trastuzumab emtansine, trastuzumab deruxtecan, pertuzumab, lapatinib, and neratinib.

[0250] In some embodiments, an additional anti-cancer agent is an mTOR inhibitor. In some embodiments, an mTOR inhibitor is selected from everolimus, sirolimus, temsirolimus, and LY3023414.

[0251] In some embodiments, an additional anti-cancer agent is a CDK4/6 inhibitor. In some embodiments, a CDK4/6 inhibitor is selected from palbociclib, abemaciclib, ribociclib, lerociclib, trilaciclib, and SHR6390.

5 [0252] In some embodiments, an additional anti-cancer agent is a CDK4-selective inhibitor. In some embodiments, a CDK-4 selective inhibitor is PF-07220060 (atirmociclib).

[0253] In some embodiments, an additional anti-cancer agent is a PI3 kinase inhibitor. In some embodiments, a PI3 kinase inhibitor is selected from perifosine, CAL101, BEZ235, XL147, XL765, GDC-0941, and IPI-145.

10 [0254] In some embodiments, a PI3 kinase inhibitor is a PIK3CA inhibitor. In some embodiments, a PIK3CA inhibitor is selected from alpelisib, taselisib, LY3023414, Inavolisib, STX-478, RLY-2608, LOXO-783, OKI-219, and TOS-358.

15 [0255] In some embodiments, an additional anti-cancer agent is an aromatase inhibitor. In some embodiments, an aromatase inhibitor is selected from aminoglutethimide, testolactone, anastrozole, letrozole, exemestane, vorozole, formestane, fadrozole, 4-hydroxyandrostenedione, 1,4,6-androstatrien-3,17-dione, and 4-androstene-3,6,17-trione.

[0256] In some embodiments, an additional anti-cancer agent is an antibody to or inhibitor of PD-1, PD-L1 or CTLA-4.

[0257] In some embodiments, an additional anti-cancer agent is an antibody to or inhibitor of EGFR, PGFR, or IGFR. In some embodiments, an anti-cancer agent is erlotinib or gefitinib.

20 [0258] In some embodiments, an additional anti-cancer agent is a USP1 inhibitor.

[0259] In some embodiments, an additional anti cancer agent is an AKT inhibitor. In some embodiments, an additional anti cancer agent is capivasertib.

VII. EXAMPLES

25 [0260] While specific embodiments of the subject invention have been discussed, the specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

30 [0261] The following abbreviations refer respectively to the definitions below:

DMSO – dimethylsulfoxide;

THF – tetrahydrofuran;

- DCM – dichloromethane;
LiHMDS -lithium bis(trimethylsilyl)amide;
Pd(Amphos)Cl₂ – bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II);
NH₄Cl – ammonium chloride;
- 5 Na₂SO₄ – sodium sulfate;
BPO – benzoyl peroxide;
br – broad;
°C – degree Celsius;
DMSO-d₆ – deuterated dimethylsulfoxide;
- 10 DMF- N, N-dimethylformamide;
Et – ethyl;
g- gram;
h – hours;
¹H – proton;
- 15 iPr – isopropyl;
LC–MS – liquid chromatography-mass spectroscopy;
Me – methyl;
MHz – megahertz (frequency);
MS – mass spectroscopy;
- 20 Ms – methanesulfonyl;
M – molar;
mmol – millimole;
mL – millilitre;
min – minutes;
- 25 mol – moles;
M^{+/-} - molecular ion;m/z-mass to charge ratio;
NBS – N-bromosuccinimide;
NMR – nuclear magnetic resonance;
ppm – parts per million;
- 30 rt or RT – room temperature;
RM – reaction mixture;
br – broad;
s – singlet;
d – doublet;

t – triplet;

q – quartet;

m – multiplet;

dd – doublet of doublets;

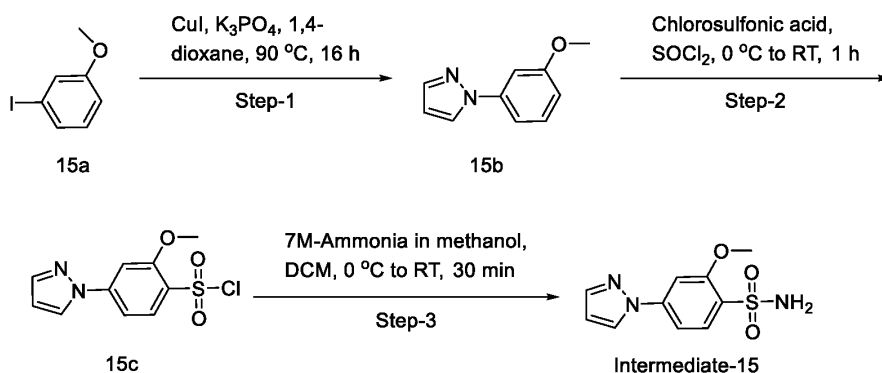
5 TLC – thin layer chromatography;

% – percentage; and

δ – delta.

a) Sulfonamide Intermediates

10 **Intermediate 15: 2-Methoxy-4-(1H-pyrazol-1-yl)benzenesulfonamide**



[0262] Step 1: 1-(3-Methoxyphenyl)-1H-pyrazole

[0263] To a degassed solution of 1-iodo-3-methoxybenzene (10 g, 42.7 mmol) in 1,4-dioxane (100 mL) were added 1H-pyrazole (3.49 g, 51.2 mmol), CuI (0.81 g, 4.2 mmol) and

15 **K₃PO₄** (18.1 g, 85.4 mmol) at RT. Then the reaction mixture was heated to 90 °C for 16 h. The reaction mixture was cooled to RT and was added water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated to get crude compound. The crude compound was purified by combi flash chromatography using 20% ethyl acetate in hexane to afford the title compound (6.5 g, 87.3%). LC-MS: 175.1 [M+H]⁺.

20 **[0264]** Step 2: 2-Methoxy-4-(1H-pyrazol-1-yl)benzenesulfonyl chloride

[0265] To a solution of 1-(3-methoxyphenyl)-1H-pyrazole (2 g, 11.4 mmol) in chlorosulfonic acid (13.3 g, 114.8 mmol) was added thionyl chloride (1.6 g, 13.7 mmol) dropwise at 0 °C. Reaction mixture was brought to RT and stirred for 1 h. The reaction mixture was diluted with ice water and extracted with DCM. The organic layer was washed with

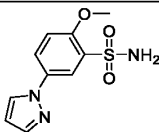
saturated NaHCO₃, dried over Na₂SO₄, and concentrated to get the title compound (1.2 g). LC-MS: 273.0 [M+H]⁺.

[0266] Step 3: 2-Methoxy-4-(1H-pyrazol-1-yl)benzenesulfonamide

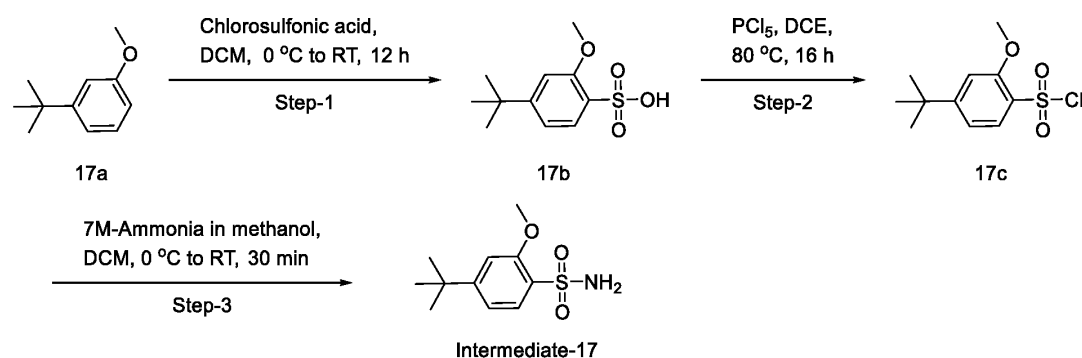
[0267] To a solution of 2-methoxy-4-(1H-pyrazol-1-yl)benzenesulfonyl chloride (1.2 g, 4.4 mmol) in DCM (10 mL) was added 7M methanolic ammonia dropwise at 0 °C. The reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was diluted with water and extracted with DCM. The organic layer was washed with saturated Aq. NaHCO₃, dried over Na₂SO₄, and concentrated to afford the title compound (0.3 g). LC-MS: 254.0 [M+H]⁺.

Intermediate 16

10 **[0268]** The following Intermediate 16 listed below was prepared by following similar procedure to that described above for Intermediate 15 using appropriate reagents with suitable modifications known to the one skilled in the art.

Intermediate	Structure	Spectral data
16		LC-MS: 254.0 [M+H] ⁺ .

Intermediate 17: 4-(Tert-butyl)-2-methoxybenzenesulfonamide



15

[0269] Step 1: 4-(Tert-butyl)-2-methoxybenzenesulfonic acid

[0270] To solution of 1-(*tert*-butyl)-3-methoxybenzene (6 g, 36.5 mmol) in anhydrous DCM (90 mL) was added chlorosulfonic acid (5.1g, 43.8 mmol) dropwise at 0 °C for 15 min. Then reaction mixture was gradually warmed to room temperature and stirred for overnight. The

reaction mixture was quenched with ice water and extracted with DCM. The organic layer was washed with saturated Aq. NaHCO_3 , dried over Na_2SO_4 , and concentrated to afford the title compound (5 g). LC-MS: 243.0 $[\text{M}-\text{H}]^-$.

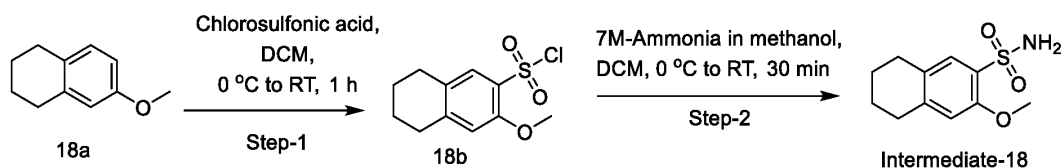
[0271] Step 2: 4-(Tert-butyl)-2-methoxybenzenesulfonyl chloride

- 5 **[0272]** To a solution of 4-(tert-butyl)-2-methoxybenzenesulfonic acid (5 g, 20.4 mmol) in 1,2-DCE (75 mL) was added PCl_5 (8.5 g, 40.9 mmol) in portions at 0 °C. After completion of addition, the reaction mixture was heated to 80 °C for 16 h. The reaction mixture was then cooled to RT and concentrated to yield the crude compound. The crude compound was purified by combi flash chromatography using 50% EtOAc in hexane to afford the title compound (6.3 g, 74.3%).
- 10

[0273] Step 3: 4-(Tert-butyl)-2-methoxybenzenesulfonamide

[0274] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications. LC-MS: 244.1 $[\text{M}+\text{H}]^+$.

15 **Intermediate 18: 3-Methoxy-5,6,7,8-tetrahydronaphthalene-2-sulfonamide**



[0275] Step 1: 3-Methoxy-5,6,7,8-tetrahydronaphthalene-2-sulfonyl chloride

- [0276]** To a stirred solution of 6-methoxy-1,2,3,4-tetrahydronaphthalene (0.5 g, 3.08 mmol) in DCM (15 mL) was added chlorosulfonic acid (1.07g, 9.2 mmol) dropwise at 0 °C. The reaction mixture was gradually warmed to RT and stirred for 1 h at RT. The reaction mixture was then poured into ice cold water and extracted with DCM. The organic layer was washed with aqueous NaHCO_3 , dried over Na_2SO_4 and concentrated to afford the title compound (0.52 g, 65%).
- 20

[0277] Step 2: 3-Methoxy-5,6,7,8-tetrahydronaphthalene-2-sulfonamide

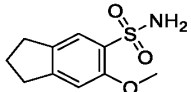
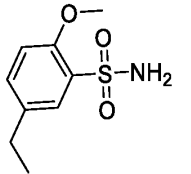
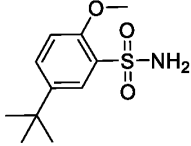
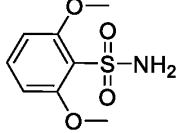
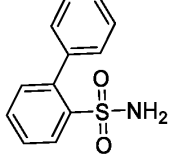
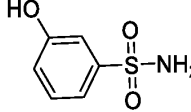
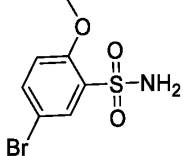
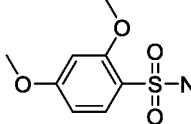
- 25 **[0278]** The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications. LC-MS: 241.9 $[\text{M}+\text{H}]^+$.

Intermediates 19 to 26f

[0279] The following intermediates in Table 5 were prepared by following similar procedure to that described above for Intermediate 18 using appropriate reagents with suitable modifications known to the one skilled in the art. In some instances, procedures began with

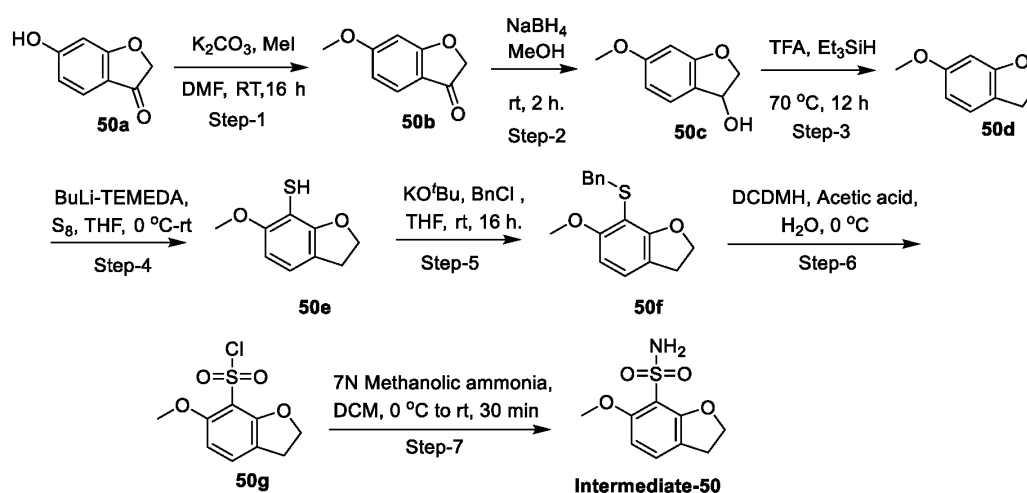
5 commercially available sulfonyl chloride building blocks.

Table 5. Intermediates

Intermediate	Structure	Spectral data
19		LC-MS: 228.0 [M+H] ⁺ .
20		¹ H NMR, DMSO-d ₆ , 400MHz): δ 7.56 (d, 1H), 7.41 (dd, 1H), 7.12 (d, 1H), 7.0 (s, 2H), 3.87 (s, 3H), 2.61 (q, 2H), 1.19 (t, 3H).
21		LC-MS: 244.1 [M+H] ⁺ .
22		LC-MS: 218.0 [M+H] ⁺ .
23		LC-MS: 232.0 [M-H] ⁻ .
24		LC-MS: 174.0 [M+H] ⁺ .
25		LC-MS: 267.8 [M+H] ⁺ .
26a		LC-MS: 218 [M+H] ⁺ .

Intermediate	Structure	Spectral data
26b		LC-MS: 236 [M+H] ⁺ .
26c		LC-MS: 252 [M+H] ⁺ .
26d		LC-MS: 297 [M+H] ⁺ .
26e		LC-MS: 252 [M+H] ⁺ .
26f		LC-MS: 224 [M+H] ⁺ .

Intermediate 50: 6-Methoxy-2,3-dihydrobenzofuran-7-sulfonamide



5 [0280] Step 1: 6-Methoxybenzofuran-3(2H)-one

[0281] To a solution of 6-hydroxybenzofuran-3(2H)-one (7.2 g 48.62 mmol) in DMF (80 mL) were added K_2CO_3 (13.44 g, 97.25 mmol) and MeI (11.45 g, 80.71 mmol) at 0 °C. The reaction mixture was slowly warmed to RT and stirred for 16 h. The reaction mixture was diluted with water, extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated to get the crude compound which was used in next step without further purification (6.10 g, 88.60%). 1H NMR (DMSO- d_6 , 400MHz): δ 7.53 (d, 1H), 6.83 (d, 1H), 6.71 (dd, 1H), 4.77 (s, 2H), 3.87 (s, 3H).

[0282] Step 2: 6-Methoxy-2,3-dihydrobenzofuran-3-ol

[0283] To a solution of 6-methoxybenzofuran-3(2H)-one (7.0 g, 42.64 mmol) in MeOH (80 mL) was added $NaBH_4$ (3.22 g, 85.27 mmol) at 0°C. The reaction mixture slowly warmed to RT and stirred for 2 h. The reaction mixture was quenched with ice-water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated to obtain the title compound (6.20 g, 84.80%). 1H NMR (DMSO- d_6 , 400MHz): δ 7.23 (d, 1H), 6.46 (dd, 1H), 6.41 (s, 1H), 5.43 (d, 1H), 5.21 – 5.16 (m, 1H), 4.52 – 4.48 (m, 1H), 4.25 – 4.21 (m, 1H), 3.72 (s, 3H).

[0284] Step 3: 6-Methoxy-2,3-dihydrobenzofuran

[0285] To a solution of 6-methoxy-2,3-dihydrobenzofuran-3-ol (6.0 g, 48.62 mmol) in TFA (8.22 g, 72.21 mmol) was added triethylsilane (4.1 g, 36.10 mmol) at 0 °C and then heated at 70 °C for 12 h. The reaction mixture was poured in aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over solid sodium sulphate, filtered, and concentrated to afford crude. The crude was purified by silica-gel flash column chromatography using 10% of ethyl acetate in hexane as eluent to obtain pure compound (1.40 g, 25.8%). 1H NMR, DMSO- d_6 , 400MHz): δ 7.11 (d, 1H), 6.39 (d, 1H), 6.37 (s, 1H), 4.55 (t, 2H), 3.72 (s, 3H), 3.08 (t, 2H).

[0286] Step 4: 6-Methoxy-2,3-dihydrobenzofuran-7-thiol

[0287] To a solution of 6-methoxy-2,3-dihydrobenzofuran (1.40 g, 9.32 mmol) in THF (14 mL) was slowly added n-BuLi (5.59 mL, 13.99 mmol) dropwise and followed by TMEDA (0.10 g, 0.93 mmol) at 0 °C. The reaction mixture was slowly warmed to RT and stirred at same temperature for 20 min. Sulphur powder (0.28 g, 8.39 mmol) in toluene (4 mL) solution was added to the reaction mixture at 0 °C. The reaction mixture was stirred at RT for 12 h. The reaction was quenched with 1N HCl solution and extracted with ethyl acetate. The combined

organic layer was dried over solid sodium sulphate, filtered, and concentrated to afford crude. The crude was purified by silica-gel flash column chromatography using 15% of ethyl acetate in hexane as eluent to obtain the title compound (1.0 g, 58.86%). LC-MS: 181.0 [M-H]⁻.

[0288] Step 5: 7-(Benzylthio)-6-methoxy-2,3-dihydrobenzofuran

5 **[0289]** To a solution of 6-methoxy-2,3-dihydrobenzofuran-7-thiol (1.0 g, 5.48 mmol) in THF (10 mL) was added potassium tertiary butoxide (0.739 g, 6.58 mmol) and followed by benzyl chloride (0.69 g, 5.48 mmol) at 0 °C. The reaction mixture was slowly warmed to RT and stirred for 16 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate, filtered, and
10 concentrated to afford the crude. The crude was purified by silica-gel flash column chromatography using 5-15% of ethyl acetate in hexane as eluent to obtain the title compound (0.45 g, 30.11%). LC-MS: 273.0 [M+H]⁺.

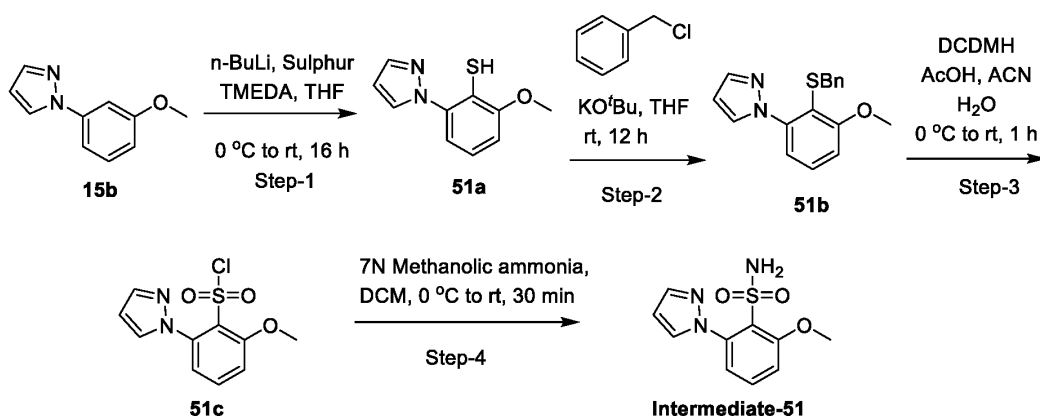
[0290] Step 6: 6-Methoxy-2,3-dihydrobenzofuran-7-sulfonyl chloride

[0291] To a solution of 7-(benzylthio)-6-methoxy-2,3-dihydrobenzofuran (0.25 g, 0.98
15 mmol) in acetonitrile (3 mL), acetic acid (2 mL) and water (1 mL), was added DCDMH (0.21 g, 1.10 mmol) at 0 °C. and stirred for 15 min. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with sodium bicarbonate solution, brine, dried over anhydrous sodium sulphate, and concentrated to afford the crude material. The crude compound was purified by silica-gel flash column
20 chromatography using 15-20% ethyl acetate in hexane as eluent to obtain the title compound (0.17 g, 74.5%). ¹H NMR (DMSO-d₆, 400MHz): δ 7.09 (d, 1H), 6.39 (d, 1H), 4.47 (t, 2H), 3.69 (s, 3H), 3.06 (t, 2H).

[0292] Step 7: 6-Methoxy-2,3-dihydrobenzofuran-7-sulfonamide

[0293] The title compound was prepared using similar procedure to that described in Step 3
25 of Intermediate 15 using appropriate reagents with suitable modifications ¹H NMR (DMSO-d₆, 400MHz): δ 7.31 (d, 1H), 6.96 (s, 2H), 6.56 (d, 1H), 4.59 (t, 2H), 3.81 (s, 3H), 3.11 (t, 2H).

Intermediate 51: 2-Methoxy-6-(1H-pyrazol-1-yl)benzenesulfonamide



[0294] Step 1: 2-Methoxy-6-(1H-pyrazol-1-yl)benzenethiol

[0295] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 50 using appropriate reagents with suitable modifications. ^1H NMR (CDCl_3 , 400MHz): δ 7.62 (d, 1H), 7.32 (t, 1H), 6.97 – 6.90 (m, 3H), 6.50 (d, 1H), 3.86 (s, 1H), 3.82 (s, 3H)

[0296] Step 2: 1-(2-(Benzylthio)-3-methoxyphenyl)-1H-pyrazole

[0297] The title compound was prepared using similar procedure to that described in Step 5 of Intermediate 50 using appropriate reagents with suitable modifications. LC-MS: 297.1.1 [M+H] $^+$.

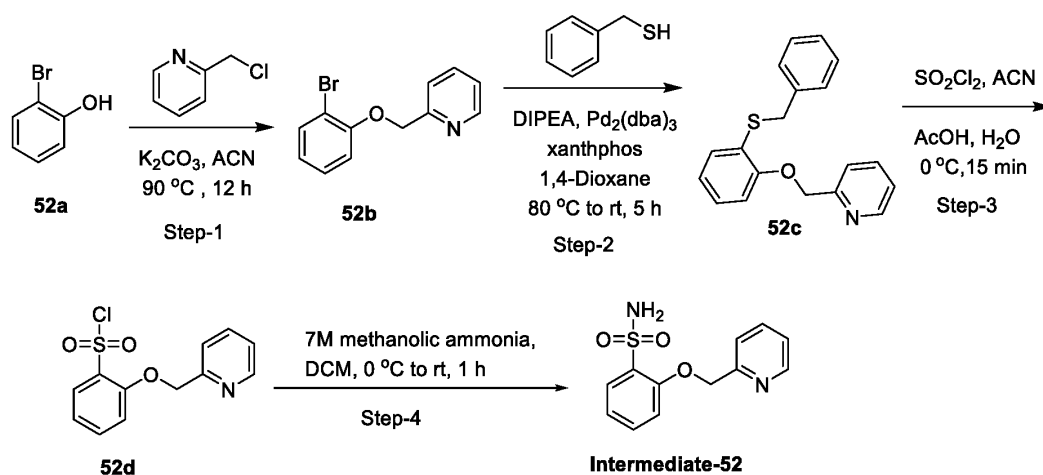
[0298] Step 3: 2-Methoxy-6-(1H-pyrazol-1-yl)benzenesulfonyl chloride

[0299] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 50 using appropriate reagents with suitable modifications: LC-MS: 273.0 [M+H] $^+$.

[0300] Step 4: 2-Methoxy-6-(1H-pyrazol-1-yl)benzenesulfonamide

[0301] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications: LC-MS: 254.0 [M+H] $^+$.

Intermediate 52: 2-(Pyridin-2-ylmethoxy)benzenesulfonamide



[0302] Step 1: 2-((2-Bromophenoxy methyl) pyridine

[0303] To a solution of 2-bromophenol (2 g, 11.56 mmol) and K_2CO_3 (3.19 g 23.12 mmol) in acetonitrile (ACN, 20 mL) was added 2-(chloromethyl) pyridine (1.17 g, 13.87 mmol) and stirred at $90\text{ }^\circ\text{C}$ for 12 h. The reaction mixture was cooled to RT, diluted with EtOAc, washed with 2 N NaOH solution (10 mL), and brine. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude. The crude was purified by silica-gel flash column chromatography using 10-15% of ethyl acetate in hexane as eluent to obtain the title compound (2.8 g, 91.7%). LC-MS: 264.8 $[M+H]^+$

10 [0304] Step 2: 2-((2-(Benzylthio)phenoxy)methyl)pyridine

[0305] To a degassed solution of 2-((2-bromophenoxy methyl pyridine) (2.8 g, 10.60 mmol) and benzyl mercaptan (1.31 g, 10.60 mmol), *N,N*-diisopropylethylamine (2.74 g, 21.20 mmol) and XantPhos (1.22 g, 2.22 mmol) in 1,4-Dioxane (30 mL) was added $Pd_2(dba)_3$ (1.94 gm 2.12 mmol) and stirred at to $80\text{ }^\circ\text{C}$ for 2 h. The reaction mixture was passed through the celite and washed with ethyl acetate. The filtrate was concentrated to get crude product which was purified by silica-gel flash column chromatography using 0-10% ethyl acetate in hexane as eluent to afford the title compound (2.5 g, 76.7%). LC-MS: 306.1 $[M-H]^-$

[0306] Step 3: 2-(Pyridin-2-ylmethoxy)benzenesulfonyl chloride

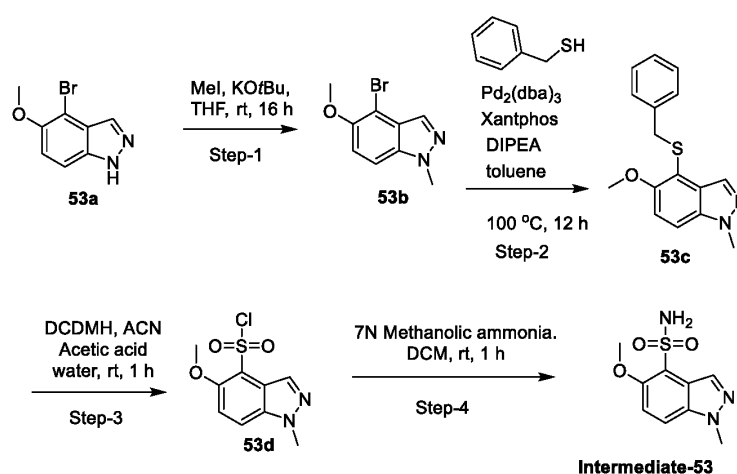
20 [0307] To a solution of 2-((2-(benzylthio)phenoxy)methyl)pyridine (1.5 g, 4.87 mmol) in acetonitrile (12 mL), acetic acid (6 mL) and water (3 mL) was added sulfonyl chloride (1.31 g, 9.75 mmol) at a $0\text{ }^\circ\text{C}$ and stirred at same temperature for 15 min. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate solution, brine, dried over sodium sulphate, filtered, and

concentrated to afford the crude compound. The crude compound was purified by silica-gel flash column chromatography using 3-5% ethyl acetate in hexane as eluent to afford the title compound (0.35 g, 25.3%). LC-MS: 281.9 [M-H]⁻

[0308] Step 4: 2-(Pyridin-2-ylmethoxy)benzenesulfonamide

- 5 **[0309]** The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications. LC-MS: 263.0 [M-H]⁻.

Intermediate 53: 5-Methoxy-1-methyl-1H-indazole-4-sulfonamide



- 10 **[0310]** Step 1: 4-Bromo-5-methoxy-1-methyl-1H-indazole

[0311] To a solution of 4-bromo-5-methoxy-1H-indazole (0.8 g 3.52 mmol) in THF (40 mL) were added KOtBu (0.59 g, 5.28 mmol) and followed by MeI (5 g, 35.2 mmol) at 0 °C. The reaction mixture was slowly warmed to RT and stirred for 16 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄,
 15 filtered, and concentrated to afford the crude compound. The crude compound was purified by silica-gel flash column chromatography using 40-50% ethyl acetate in hexane as eluent to obtain the title compound (0.8 g, 94.1%). LC-MS: 240.7 [M+H]⁺.

[0312] Step 2: 4-(Benzylthio)-5-methoxy-1-methyl-1H-indazole

[0313] To a degassed solution of 4-bromo-5-methoxy-1-methyl-1H-indazole (0.86 g, 3.57
 20 mmol) and benzyl mercaptan (0.443 g, 3.57 mmol) in toluene (15 mL) was added Pd₂(dba)₃ (0.326 g 0.35 mmol), N,N-Diisopropylethylamine (0.922 g, 7.13 mmol) and XantPhos (0.413 g, 0.71 mmol) to the reaction mixture at RT. The reaction mixture was heated at 100 °C for 12

h. After completion of the reaction the mixture was passed through the celite and washed with ethyl acetate and concentrated under reduced pressure to afford crude compound. The crude compound was purified by silica gel flash column chromatography using 30-40% EtOAc in hexane as eluent to afford the title compound (0.65 g, 64.05%); LC-MS: 285.1 [M+H]⁺.

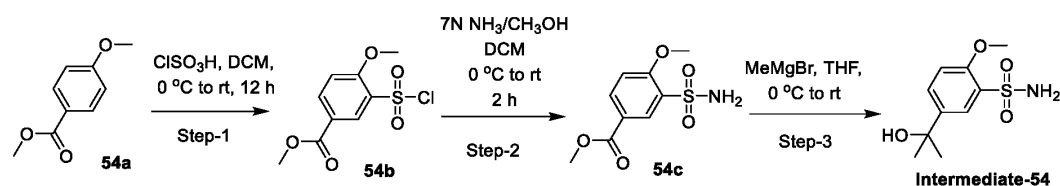
5 [0314] Step 3: 5-Methoxy-1-methyl-1H-indazole-4-sulfonyl chloride

[0315] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 50 using appropriate reagents with suitable modifications. LC-MS: 261.0 [M+H]⁺.

[0316] Step 4: 5-Methoxy-1-methyl-1H-indazole-4-sulfonamide

10 [0317] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications. LC-MS: 242.1 [M+H]⁺.

Intermediate 54: 5-(2-Hydroxypropan-2-yl)-2-methoxybenzenesulfonamide



15 [0318] Step 1: Methyl 3-(chlorosulfonyl)-4-methoxybenzoate

[0319] The title compound was prepared using similar procedure to that described in Step 1 of Intermediate 18 using appropriate reagents with suitable modifications. LC-MS: 264.1 [M+H]⁺.

[0320] Step 2: Methyl 4-methoxy-3-sulfamoylbenzoate

20 [0321] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications. LC-MS: 246.1 [M+H]⁺.

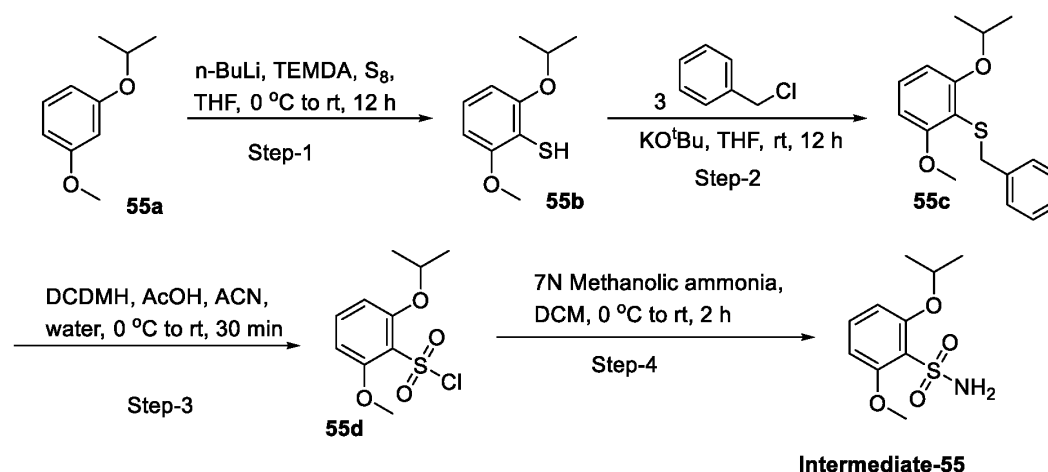
[0322] Step 3: 5-(2-Hydroxypropan-2-yl)-2-methoxybenzenesulfonamide

[0323] To a solution of methyl 4-methoxy-3-sulfamoylbenzoate (0.1 g, 0.408 mmol) in THF (2 mL) was added MeMgBr (1.2 mL, 1.22 mmol, 1 M in THF) at 0 °C and then stirred at rt for 2 h. The reaction was quenched with ice-water and extracted with ethyl acetate. The organic

25

layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. The crude compound was purified by silica-gel flash column chromatography using 80% EtOAc in hexane to afford the title compound (0.075 g, 75%). LC-MS: 246.0 [M+H]⁺.

Intermediate 55: 2-Isopropoxy-6-methoxybenzenesulfonamide



[0324] Step 1: 2-Isopropoxy-6-methoxybenzenethiol

[0325] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 50 using appropriate reagents with suitable modifications. ¹H NMR (CDCl₃, 400MHz): δ 7.20 (t, 1H), 6.50 (d, 1H), 6.48 (d, 1H), 4.40 – 4.37 (m, 1H), 3.90 (s, 3H), 1.21 (d, 6H).

10

[0326] Step 2: Benzyl(2-isopropoxy-6-methoxyphenyl)sulfane

[0327] The title compound was prepared using similar procedure to that described in Step 5 of Intermediate 50 using appropriate reagents with suitable modifications. ¹H NMR (CDCl₃, 400MHz): δ 7.28 – 7.16 (m, 6H), 6.55 (d, 1H), 6.50 (d, 1H), 4.54 – 4.51 (m, 1H), 4.03 (s, 2H), 3.84 (s, 3H), 1.36 (d, 6H).

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[0328] Step 3: 2-Isopropoxy-6-methoxybenzenesulfonyl chloride

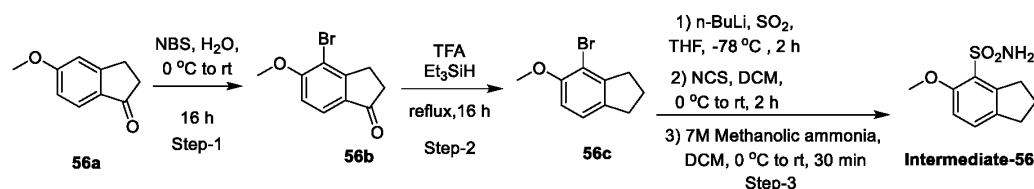
[0329] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 50 using appropriate reagents with suitable modifications. LC-MS: 264.9 [M+H]⁺.

[0330] Step 4: 2-Isopropoxy-6-methoxybenzenesulfonamide

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[0331] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications. ¹H NMR (DMSO-d₆, 400MHz): δ 7.38 (t, 1H), 7.15 (d, 1H), 6.82 (s, 2H), 6.68 (d, 1H), 4.61 – 4.58 (m, 1H), 3.82 (s, 3H), 1.28 (d, 6H).

5 Intermediate 56: 5-Methoxy-2,3-dihydro-1H-indene-4-sulfonamide



[0332] Step 1: 4-Bromo-5-methoxy-2,3-dihydro-1H-inden-1-one

[0333] To a solution of 5-methoxy-2,3-dihydro-1H-inden-1-one (10 g, 61.65 mmol) in water (120 mL) was added NBS (10.97 g, 61.65 mmol) at 0 °C. The reaction mixture was warmed to
 10 RT and stirred for 16 h. The reaction was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. Crude compound was purified by silica-gel flash column chromatography using 5% ethyl acetate in hexane as eluent to afford the title compound (12 g, 80.7%). LC-MS: 240.7 [M+H]⁺.

15 [0334] Step 2: 4-Bromo-5-methoxy-2,3-dihydro-1H-indene

[0335] To a solution of 4-bromo-5-methoxy-2,3-dihydro-1H-inden-1-one (10 g, 41.47 mmol) in TFA (60 mL) was added triethylsilane (2.39 g, 20.74 mmol) at 0 °C. The reaction mixture was slowly warmed to RT and then stirred for 16 h under reflux. The reaction was diluted with ice water, quenched with aqueous NaHCO₃, and extracted with ethyl acetate. The
 20 organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. Crude compound was purified by silica-gel flash column chromatography using hexane as eluent to afford the title compound (6 g, 63.7%). LC-MS: 227.9 [M+H]⁺.

[0336] Step 3: 5-Methoxy-2,3-dihydro-1H-indene-4-sulfonamide

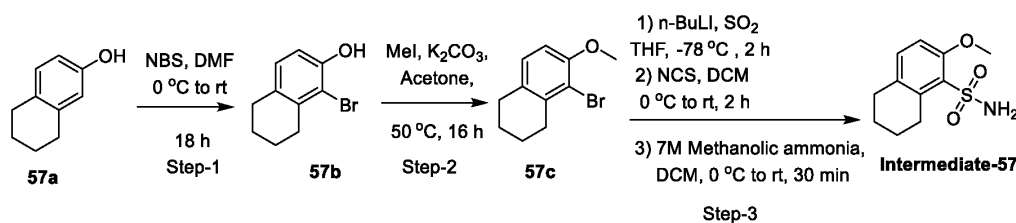
[0337] To a solution of 4-bromo-5-methoxy-2,3-dihydro-1H-indene (0.2 g, 0.88 mmol) in
 25 THF (7 mL) was added n-BuLi (1.65 mL, 2.64 mmol) at -78 °C and stirred at the same temperature for 1 h. Then SO₂ gas was bubbled into the reaction mixture for 30 min at -78 °C. The reaction mixture was slowly warmed to RT and stirred for 1 h. The reaction mixture was

concentrated to obtain the solid. The solid was dissolved in DCM and NCS (0.35 g, 2.64 mmol) was added to it at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The reaction was quenched with ice water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. The crude compound

5 was dissolved in DCM and 7N methanolic ammonia (5 mL) was added to it at RT. The reaction mixture was stirred for 30 min at RT. The reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude compound. Crude compound was purified by silica-gel flash column chromatography using 50% ethyl acetate in hexane as eluent to afford the title compound (6 g, 63.7%). LC-MS: 228.1 [M+H]⁺.

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Intermediate 57: 2-Methoxy-5,6,7,8-tetrahydronaphthalene-1-sulfonamide



[0338] Step 1: 1-Bromo-5,6,7,8-tetrahydronaphthalen-2-ol

[0339] To a solution of 5,6,7,8-tetrahydronaphthalen-2-ol (5 g, 33.73 mmol) in DMF (60 mL) was added NBS (6 g, 33.73 mmol) at 0 °C. The reaction mixture was slowly warmed to RT and stirred for 18 h. The reaction was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. Crude compound was purified by silica-gel flash column chromatography using 5% EtOAc in hexane as eluent to afford the title compound (6 g, 78.32%). ¹H NMR (CDCl₃, 400MHz): δ 6.95 (d, 1H), 6.85 (d, 1H), 5.54 (s, 1H), 2.75 – 2.68 (m, 4H), 1.88 – 1.83 (m, 2H), 1.79 – 1.73 (m, 2H).

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[0340] Step 2: 5-Bromo-6-methoxy-1,2,3,4-tetrahydronaphthalene

[0341] To a solution of 1-bromo-5,6,7,8-tetrahydronaphthalen-2-ol (6 g, 26.42 mmol) and K₂CO₃ (7.9 g, 57.24 mmol) in acetone (60 mL) was added MeI (12.2 g, 85.86 mmol) and stirred at RT for 16 h. The reaction was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. Crude compound was purified by silica-gel flash column chromatography using 5%

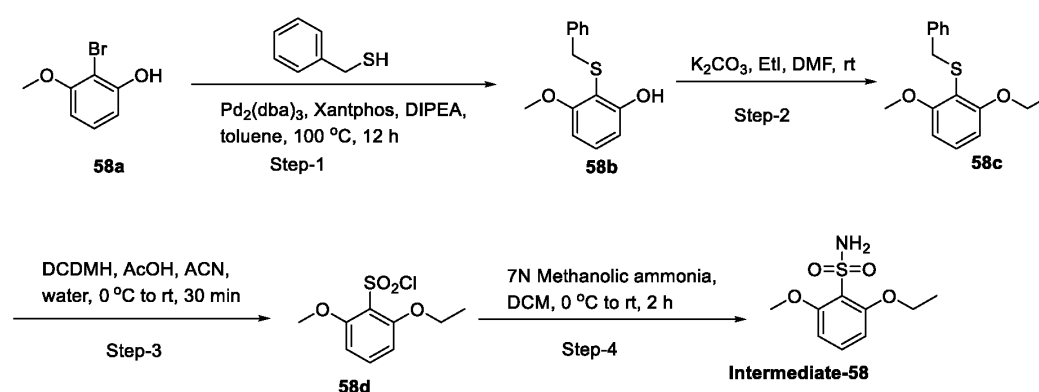
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ethyl acetate in hexane to afford the title compound (4.5 g, 70.64%). ^1H NMR (CDCl_3 , 400MHz): δ 7.00 (d, 1H), 6.73 (d, 1H), 3.88 (s, 3H), 2.80 – 2.71 (m, 4H), 1.86 – 1.79 (m, 2H), 1.78 – 1.72 (m, 2H).

[0342] Step 3: 2-Methoxy-5,6,7,8-tetrahydronaphthalene-1-sulfonamide

- 5 The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 56 using appropriate reagents with suitable modifications. LC-MS: 242.1 $[\text{M}+\text{H}]^+$.

Intermediate 58: 2-Ethoxy-6-methoxybenzenesulfonamide



- 10 **[0343]** Step 1: 2-(Benzylthio)-3-methoxyphenol

[0344] To a degassed solution of 2-bromo-3-methoxyphenol (2 g, 9.84 mmol) and phenylmethanethiol (1.22 g, 9.84 mmol), N,N-Diisopropylethylamine (3.42 mL, 19.7 mmol) and Xantphos (1.14 g, 0.197 mmol) in toluene (30 mL) was added $\text{Pd}_2(\text{dba})_3$ (0.901 gm 0.98 mmol) and stirred at 100 °C for 16 h. The reaction mixture was cooled to RT, passed through the celite pad, washed with ethyl acetate, and concentrated under reduced pressure to afford crude compound. The crude compound was purified by silica-gel flash column chromatography using 30-40% EtOAc in hexane as eluent to afford the title compound (0.4 g, 16.5%); LC-MS: 245.0 $[\text{M}+\text{H}]^+$.

[0345] Step 2: Benzyl(2-ethoxy-6-methoxyphenyl)sulfane

- 20 **[0346]** This compound was prepared using similar procedure to that described in Step 1 of Intermediate 50 using appropriate reagents with suitable modifications. LC-MS: 275.1 $[\text{M}+\text{H}]^+$.

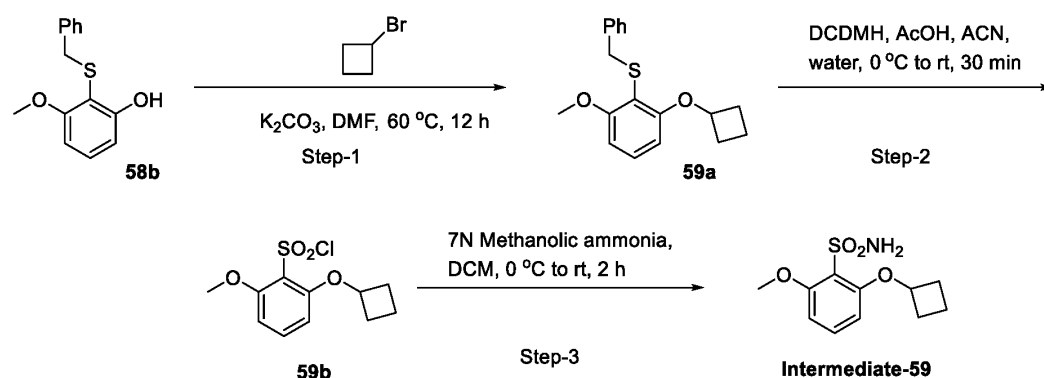
[0347] Step 3: 2-Ethoxy-6-methoxybenzenesulfonyl chloride

[0348] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 50 using appropriate reagents with suitable modifications. ^1H NMR (DMSO- d_6 , 400MHz): δ 7.25 (t, 1H), 6.64 (d, 1H), 6.63 (d, 1H), 4.00 (q, 2H), 3.72 (s, 3H), 1.28 (t, 3H).

[0349] Step 4: 2-Ethoxy-6-methoxybenzenesulfonamide

- 5 [0350] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications. LC-MS: 232.0 [M+H] $^+$.

Intermediate 59: 2-Cyclobutoxy-6-methoxybenzenesulfonamide



- 10 [0351] Step 1: Benzyl(2-cyclobutoxy-6-methoxyphenyl) sulfane

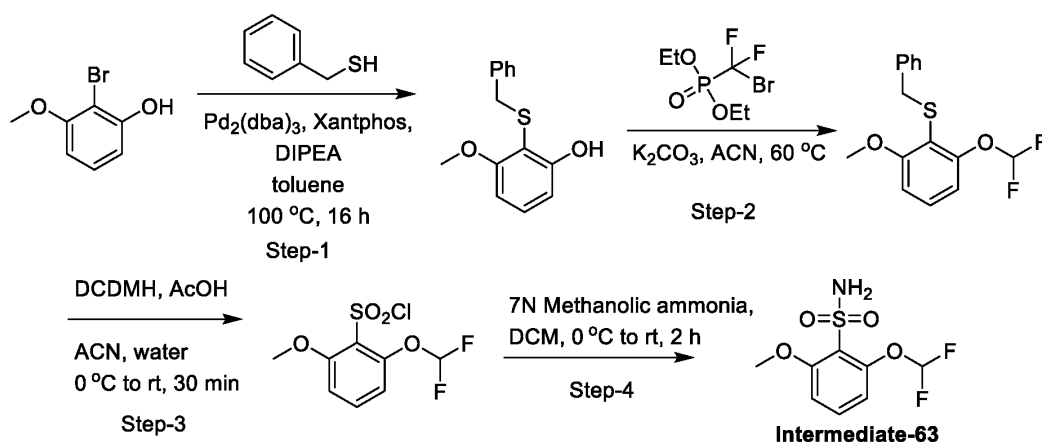
[0352] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 53 using appropriate reagents with suitable modifications. LC-MS: 301.1[M-H] $^-$

[0353] Step 2: 2-Cyclobutoxy-6-methoxybenzenesulfonyl chloride

- 15 [0354] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 50 using appropriate reagents with suitable modifications. ^1H NMR (DMSO- d_6 , 400MHz): δ 7.50 (t, 1H), 6.62 (d, 1H), 6.49 (d, 1H), 4.81 – 4.73 (m, 1H), 3.99 (s, 3H), 2.25 – 2.21 (m, 2H), 1.92 – 1.87 (m, 2H), 1.51 – 1.46 (m, 2H).

[0355] Step 3: 2-Cyclobutoxy-6-methoxybenzenesulfonamide

- 20 [0356] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications. LC-MS: 256.0 [M-H] $^-$.

Intermediate 63: 2-(Difluoromethoxy)-6-methoxybenzenesulfonamide

[0357] Step 1: 2-(Benzylthio)-3-methoxyphenol

[0358] This compound was prepared using similar procedure to that described in Step 2 of Intermediate 52 using appropriate reagents with suitable modifications. LC-MS: 245.1 [M-H]⁻.

[0359] Step 2: Benzyl(2-(difluoromethoxy)-6-methoxyphenyl)sulfane

[0360] To a solution of 2-(benzylthio)-3-methoxyphenol (0.3 g, 1.217 mmol) and diethyl (bromodifluoromethyl)phosphonate (0.650 g, 2.43 mmol) in acetonitrile (20 mL) was added potassium hydroxide (0.342 g, 6.09 mmol) at 0 °C. Then the reaction mixture was slowly warmed to RT and stirred for 16 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulphate, filtered, and concentrated to afford the crude material. The crude material was purified by silica-gel flash column chromatography using 0-20% ethyl acetate in hexane as eluent to obtain the title compound (0.2 g, 55.41%). ¹H NMR (DMSO-d₆, 400MHz): δ 7.48 – 7.15 (m, 6H), 7.00 (dd, 1H), 6.79 (t, 1H), 6.76 (dd, 1H), 4.03 (s, 2H), 3.85 (s, 3H).

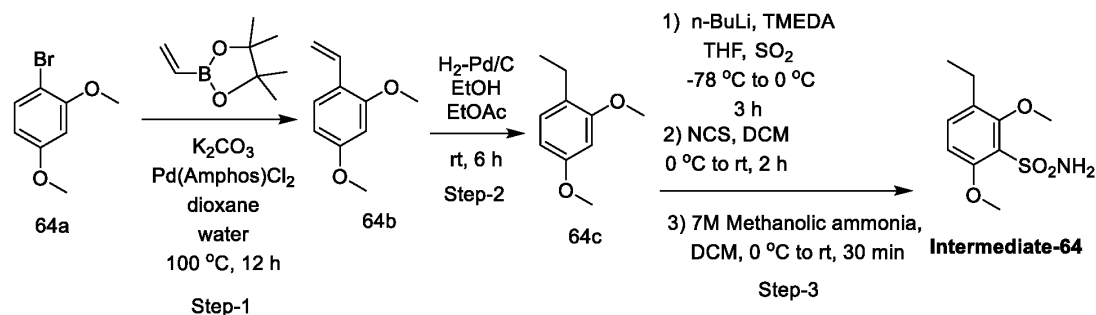
[0361] Step 3: 2-(Difluoromethoxy)-6-methoxybenzenesulfonyl chloride

[0362] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 50 using appropriate reagents with suitable modifications LC-MS: 270.8 [M-H]⁻.

[0363] Step 4: 2-(Difluoromethoxy)-6-methoxybenzenesulfonamide

[0364] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications LC-MS: 252.0 [M-H]⁻.

Intermediate 64: 3-Ethyl-2,6-dimethoxybenzenesulfonamide



[0365] Step 1: 2,4-Dimethoxy-1-vinylbenzene

[0366] To a degassed solution of 1-bromo-2,4-dimethoxybenzene (3.0 g, 13.82 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (4.25 g, 27.64 mmol), and K₂CO₃ (5.73 g, 41.46 mmol) in 1,4-dioxane (50 mL), water (10 mL) was added Pd(Amphos)Cl₂ (0.97 g, 1.38 mmol) and stirred at 100 °C for 12 h. The reaction mixture was cooled to RT, diluted with water, and extracted with 10% methanol in DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford crude compound. The crude compound was purified by silica-gel flash column chromatography using 10-15% ethyl acetate in hexane to afford the title compound (2.0 g, 88.14 %). ¹H NMR (DMSO-D₆, 400 MHz): δ 7.42 (d, 1H), 6.85 (dd, 1H), 6.55 – 6.50 (m, 2H), 5.63(dd, 1H), 5.09 (d, 1H), 3.80 (s, 3H), 3.77 (s, 3H).

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[0367] Step 2: 1-Ethyl-2,4-dimethoxybenzene

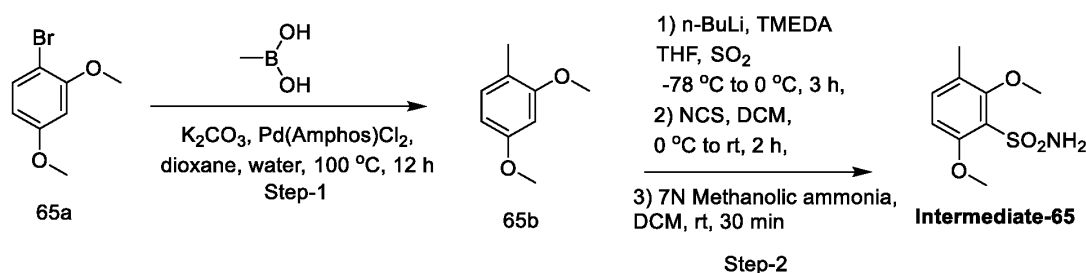
[0368] A mixture of 1-ethyl-2,4-dimethoxybenzene (1.9 g, 11.57 mmol) and Pd-C (1.84 g, 17.35 mmol) in ethanol (25 mL) and ethyl acetate (25 mL) was stirred under positive pressure of hydrogen using bladder for 6 h. The reaction mixture was filtered through celite pad and washed with 5% methanol in DCM. The filtrate was concentrated to afford the crude compound, which was taken to the next step without purification (1.85 g). ¹H NMR (DMSO-D₆, 400 MHz): δ 7.01 (d, 1H), 6.51 (s, 1H), 6.43 (dd, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 2.49 (q, 2H), 1.18 (t, 3H).

20

[0369] Step 3: 3-Ethyl-2,6-dimethoxybenzenesulfonamide

[0370] To a solution of 1-ethyl-2,4-dimethoxybenzene (1.8 g, 10.82 mmol) in THF (20 mL) was added TMEDA (2.13 g, 18.4 mmol), n-BuLi (0.73 mL, 18.4 mmol) at 0 °C and stirred at the same temperature for 1 h. Then SO₂ gas was bubbled into the reaction mixture for 30 min at -78 °C. The reaction mixture was slowly warmed to 0 °C and stirred for 1 h. The reaction mixture was concentrated to obtain the solid. The solid was dissolved in DCM and NCS (2.26 g, 16.93 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The reaction was quenched with ice water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. The crude compound was dissolved in DCM (10 mL) and 7N methanolic ammonia (10 mL) was added to the reaction mixture and stirred for 30 min at RT. The reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude compound. Crude compound was purified by silica-gel flash column chromatography using 50% ethyl acetate in hexane as eluent to afford the title compound (0.6 g). LC-MS: 244.0 [M-H]⁻.

15 **Intermediate 65: 2,6-Dimethoxy-3-methylbenzenesulfonamide**



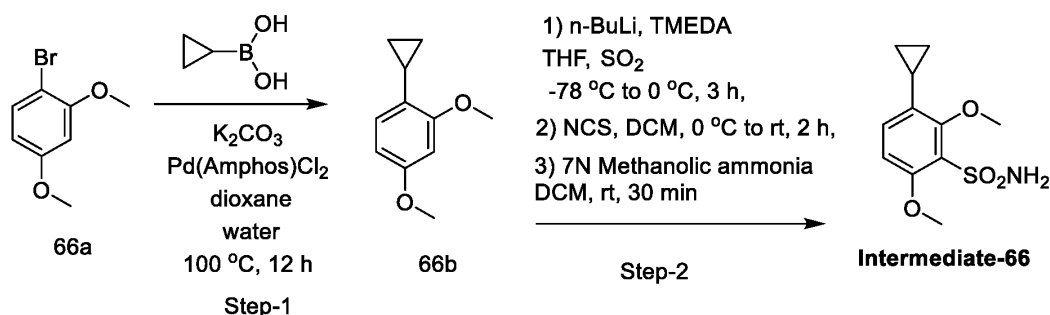
[0371] Step 1: 2,4-Dimethoxy-1-methylbenzene

[0372] The title compound was prepared using similar procedure to that described in Step 1 of Intermediate 64 using appropriate reagents with suitable modifications. ¹H NMR, CDCl₃, 400MHz): δ 7.40 (d, 1H), 6.46 (d, 1H), 6.42 (dd, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.17 (s, 3H).

[0373] Step 2: 2,6-Dimethoxy-3-methylbenzenesulfonamide

[0374] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 64 using appropriate reagents with suitable modifications. LC-MS: 230.0 [M-H]⁻.

25 **Intermediate 66: 3-Cyclopropyl-2,6-dimethoxybenzenesulfonamide**



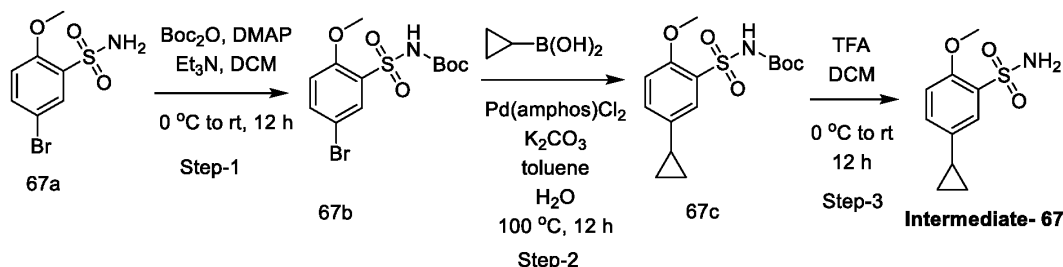
[0375] Step 1: 1-Cyclopropyl-2,4-dimethoxybenzene

[0376] The title compound was prepared using similar procedure to that described in Step 1 of Intermediate 64 using appropriate reagents with suitable modifications. LC-MS: 179.1 [M+H]⁺.

[0377] Step 2: 3-Cyclopropyl-2,6-dimethoxybenzenesulfonamide

[0378] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 64 using appropriate reagents with suitable modifications. LC-MS: 256.1 [M-H]⁻.

10 Intermediate 67: 5-Cyclopropyl-2-methoxybenzenesulfonamide



[0379] Step 1: Tert-butyl ((5-bromo-2-methoxyphenyl)sulfonyl)carbamate

[0380] To a solution of 5-bromo-2-methoxybenzenesulfonamide (10 g, 37.57 mmol) in DCM (100 mL) was added DIPEA (15.36 mL, 112.73 mmol), DMAP (0.46 g, 3.75 mmol) and followed by $(Boc)_2O$ (12.3 g, 56.36 mmol) at $0^\circ C$. The reaction mixture was slowly warmed to RT and stirred at rt for 12 h. The reaction was quenched with ice water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. Crude material was purified by silica-gel flash column chromatography

using 30-50% ethyl acetate in hexane as eluent to afford the title compound (6.5 g, 47.23%).
LC-MS: 363.9 [M-H]⁻.

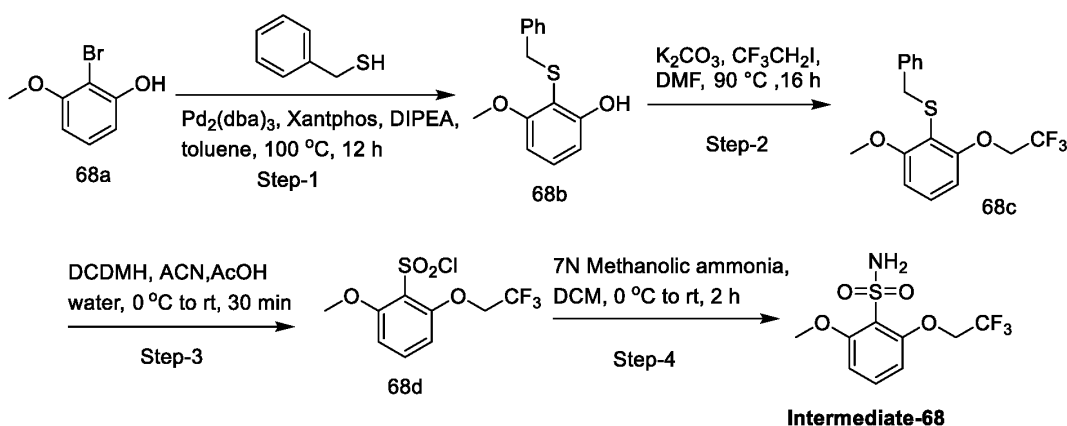
[0381] Step 2: Tert-butyl ((5-cyclopropyl-2-methoxyphenyl)sulfonyl)carbamate

[0382] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 35 using appropriate reagents with suitable modifications. LC-MS: 326.0 [M-H]⁻.

[0383] Step 3: 5-Cyclopropyl-2-methoxybenzenesulfonamide

[0384] To a solution of tert-butyl ((5-cyclopropyl-2-methoxyphenyl)sulfonyl)carbamate (0.8 g, 2.44 mmol) in DCM (10 mL) was added TFA (1.12 mL, 14.65 mmol) to the reaction mixture at 0 °C. The reaction mixture stirred at rt for 2 h. The reaction mass was quenched with saturated NaHCO₃ solution and extracted with DCM. The organic layer was washed with water, brine, dried over Na₂SO₄, filtered, and concentrated to get the crude compound. Crude compound was purified by silica-gel flash column chromatography using 40-50% ethyl acetate in hexane as eluent to obtain the title compound (0.25 g, 45%). LC-MS: 226.0 [M-H]⁻.

15 **Intermediate 68: 2-Methoxy-6-(2,2,2-trifluoroethoxy)benzenesulfonamide**



[0385] Step 1: 2-(Benzylthio)-3-methoxyphenol

[0386] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 53 using appropriate reagents with suitable modifications. LC-MS: 245.1 [M-H]⁻.

[0387] Step 2: Benzyl(2-methoxy-6-(2,2,2-trifluoroethoxy)phenyl)sulfane

[0388] The title compound was prepared using similar procedure to that described in Step 1 of Intermediate 52 using appropriate reagents with suitable modifications. LC-MS: 327.1 [M-H]⁻.

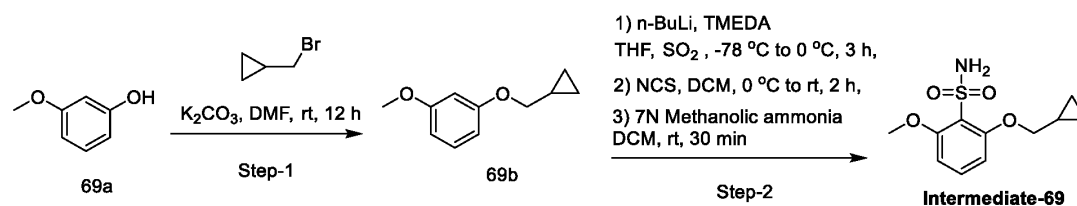
[0389] Step 3: 2-Methoxy-6-(2,2,2-trifluoroethoxy)benzenesulfonyl chloride

5 [0390] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 50 using appropriate reagents with suitable modifications. ¹H NMR (DMSO-D₆, 400MHz): δ 7.23 (t, 1H), 6.79 (d, 1H), 6.63 (d, 1H), 4.55 (q, 2H), 3.72 (s, 3H).

[0391] Step 4: 2-Methoxy-6-(2,2,2-trifluoroethoxy)benzenesulfonamide

10 [0392] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications. LC-MS: 284.0 [M-H]⁻.

Intermediate 69: 2-(Cyclopropylmethoxy)-6-methoxybenzenesulfonamide



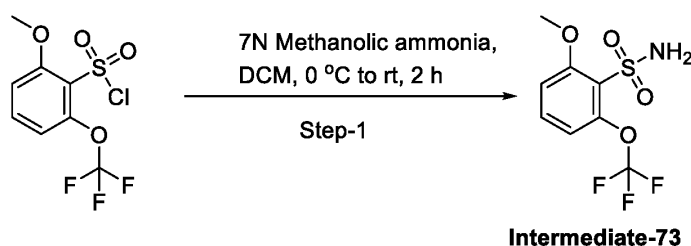
[0393] Step 1: 1-(Cyclopropylmethoxy)-3-methoxybenzene

15 [0394] The title compound was prepared using similar procedure to that described in Step 1 of Intermediate 50 using appropriate reagents with suitable modifications. LC-MS: 179.1 [M+H]⁺.

[0395] Step 2: 2-(Cyclopropylmethoxy)-6-methoxybenzenesulfonamide

20 [0396] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 64 using appropriate reagents with suitable modifications. LC-MS: 256.0 [M-H]⁻.

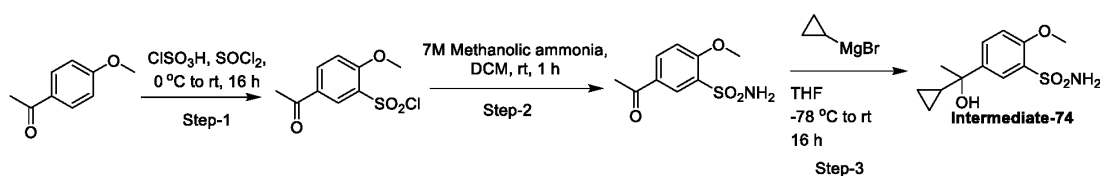
Intermediate 73: 2-Methoxy-6-(trifluoromethyl)benzenesulfonamide



[0397] Step 1: 2-Methoxy-6-(trifluoromethyl)benzenesulfonamide

[0398] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications. ¹H NMR (DMSO-D₆, 400MHz): δ 7.64 (dd, 1H), 7.38 (s, 2H), 7.28 (d, 1H), 7.03 (d, 1H), 3.95 (s, 3H).

Intermediate 74: 5-(1-Cyclopropyl-1-hydroxyethyl)-2-methoxybenzenesulfonamide



[0399] Step 1: 5-Acetyl-2-methoxybenzenesulfonyl chloride

[0400] To a stirred solution of chlorosulfonic acid (13.96 g, 119.85 mmol) and SOCl₂ (4.75 g, 39.95 mmol) was added 1-(4-methoxyphenyl)ethan-1-one (3.0 g, 19.97 mmol) dropwise at 0 °C. The reaction mixture was gradually warmed to RT and stirred for 16 h at RT. The reaction mixture was then poured into ice-cold water to get a precipitate. The precipitate was filtered and dried under vacuum to afford the title compound (4.0 g, 81.6%). LC-MS: 249.0 [M+H]⁺.

[0401] Step 2: 5-Acetyl-2-methoxybenzenesulfonamide

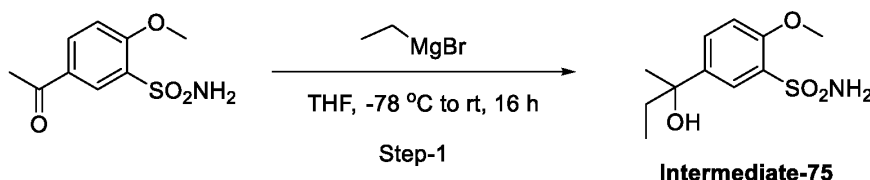
[0402] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 15 using appropriate reagents with suitable modifications. LC-MS: 230.0 [M+H]⁺.

[0403] Step 3: 5-(1-Cyclopropyl-1-hydroxyethyl)-2-methoxybenzenesulfonamide

[0404] To a solution of 5-acetyl-2-methoxybenzenesulfonamide (0.3 g, 1.30 mmol) in THF (3 mL) was added cyclopropyl magnesium bromide (2.61 mL, 7.84 mmol, 3 M in THF) at -78 °C and then stirred at rt for 16 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. The crude material was purified by

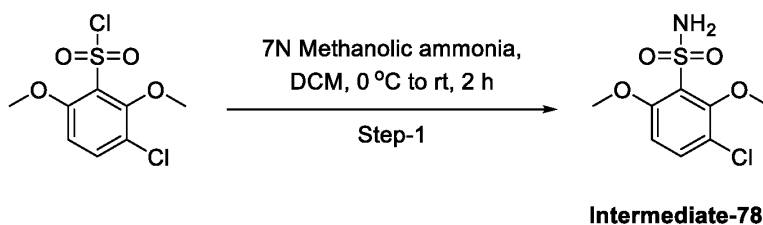
silica-gel flash column chromatography using 5% methanol in DCM as eluent to afford the title compound (0.30 g, 45%). LC-MS: 270.0 [M-H]⁻.

Intermediate 75: 5-(2-hydroxybutan-2-yl)-2-methoxybenzenesulfonamide



- 5 [0405] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate-74 using appropriate reagents with suitable modifications. LC-MS: 258.1 [M-H]⁻.

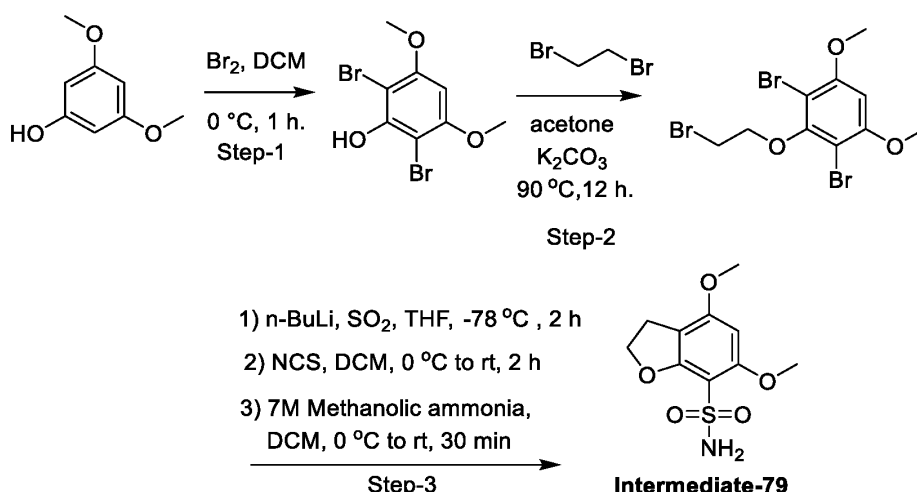
Intermediate 78: 3-Chloro-2,6-dimethoxybenzenesulfonamide



- 10 [0406] Step 1: 3-Chloro-2,6-dimethoxybenzenesulfonamide

[0407] The title compound was prepared using similar procedure to that described in Step-3 of Intermediate-15 using appropriate reagents with suitable modifications. LC-MS: 250.0 [M-H]⁻.

Intermediate 79: 4,6-Dimethoxy-2,3-dihydrobenzofuran-7-sulfonamide



[0408] Step 1: 2,6-Dibromo-3,5-dimethoxyphenol

[0409] To a solution of 3,5- dimethoxyphenol (1.0 g, 6.48 mmol) in DCM (30 mL) was added
 5 bromine (2.07 g, 12.97 mmol) at 0 °C and stirred for 1 h. The reaction mixture was then warmed
 to RT and quenched with aqueous sodium thiosulphate solution and extracted with DCM. The
 organic layer was washed with water, dried over Na₂SO₄, filtered, and concentrated to get the
 crude compound. The crude was purified by silica-gel flash column chromatography using 0-
 20% ethyl acetate in hexane as eluent to afford the title compound (2.2 g, 90.5%). LC-MS:
 10 312.9 [M+H]⁺.

[0410] Step 2: 2,4-Dibromo-3-(2-bromoethoxy)-1,5-dimethoxybenzene

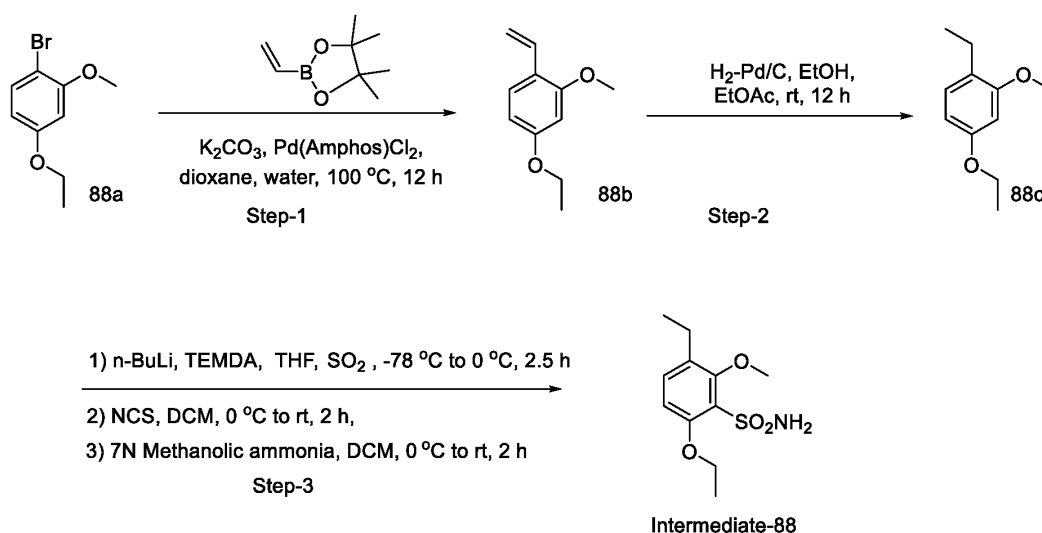
[0411] To a stirred solution of 2,6-dibromo-3,5-dimethoxyphenol (1.0 g, 3.20 mmol), and
 1,2-dibromoethane (2.40 g, 12.82 mmol) in acetone was added K₂CO₃ (1.32 g, 9.61 mmol) and
 stirred at 80 °C for 12 h. The reaction mixture was concentrated, then diluted with water and
 15 extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered,
 and concentrated to afford crude compound. The crude compound was purified by silica-gel
 flash column chromatography using 20% ethyl acetate in hexane as eluent to afford the title
 compound (1.1 g, 81.9%). ¹H NMR (DMSO-D₆, 400MHz): δ 6.72 (s, 1H), 4.24 (t, 2H), 3.91
 (s, 6H), 3.84 (t, 2H).

[0412] Step 3: 4,6-Dimethoxy-2,3-dihydrobenzofuran-7-sulfonamide

[0413] To a solution of 2,4-dibromo-3-(2-bromoethoxy)-1,5-dimethoxybenzene (0.2 g, 0.47
 mmol) in THF (7 mL) was added n-BuLi (1.48 mL, 2.38 mmol) at -78 °C and stirred at the
 same temperature for 1 h. Then SO₂ gas was bubbled into the reaction mixture for 30 min at -

78 °C. The reaction mixture was slowly warmed to RT and stirred for 1 h. Then reaction mixture was concentrated to obtain the solid. The solid was dissolved in DCM and NCS (0.19 g, 1.43 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The reaction was quenched with ice water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. The crude was dissolved in DCM and 7N methanolic ammonia (8 mL) was added to the reaction mixture at RT. The reaction mixture was stirred for 30 min at RT. The reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude compound. Crude compound was washed with 50% diethyl ether in n-pentane to obtain the title compound. (0.07 g, 32.6%). LC-MS: 258.0 [M-H]⁻

Intermediate 88: 6-Ethoxy-3-ethyl-2-methoxybenzenesulfonamide



[0414] Step 1: 4-Ethoxy-2-methoxy-1-vinylbenzene

[0415] To a degassed solution of 1-bromo-4-ethoxy-2-methoxybenzene (1.8 g, 7.79 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.4 g, 15.58 mmol), and K_2CO_3 (3.23 g, 23.36 mmol) in 1,4-dioxane (20 mL), water (4 mL) was added $Pd(Amphos)Cl_2$ (0.55 g, 0.77 mmol) and stirred at 100 °C for 12 h. The reaction mixture was cooled to RT, diluted with water, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 , filtered, and concentrated to get crude. The crude compound was purified by silica-gel flash column chromatography using 5-7% ethyl acetate in hexane to afford the title compound (1.1 g,

79.24%). ¹H NMR (DMSO-D₆, 400 MHz): δ 7.08 (d, 1H), 6.95 – 6.88 (m, 2H), 6.68 – 6.61 (m, 1H), 5.72 (dd, 1H), 5.13 (dd, 1H), 4.00 (q, 2H), 3.79 (s, 3H), 1.32 (t, 3H).

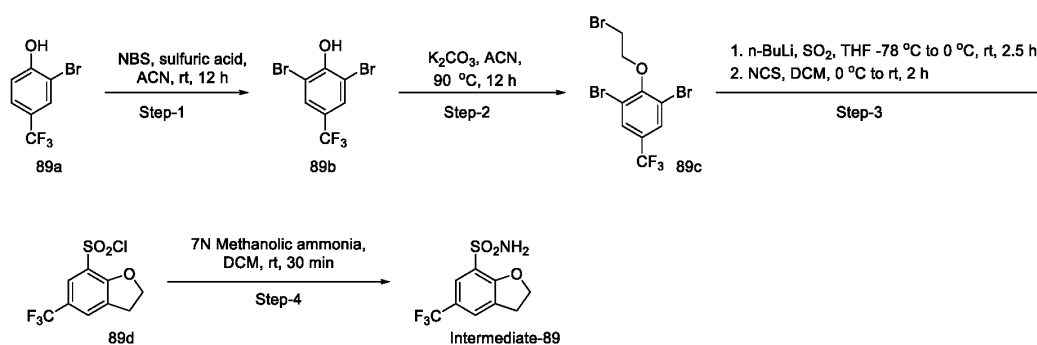
[0416] Step 2: 4-Ethoxy-1-ethyl-2-methoxybenzene

[0417] A mixture of 4-ethoxy-2-methoxy-1-vinylbenzene (2.0 g, 11.22 mmol) and Pd-C (1.79 g, 16.83 mmol) in ethanol (25 mL) and ethyl acetate (25 mL) was stirred under positive pressure of hydrogen using bladder for 12 h. The reaction mixture was filtered through celite pad and washed with 5% methanol in DCM. The filtrate was concentrated to afford the crude compound, which was taken for the next step without purification (2.0 g). LC-MS: 181.1.0 [M+H]⁺.

10 **[0418]** Step 3: 6-Ethoxy-3-ethyl-2-methoxybenzenesulfonamide

[0419] To a solution of 4-ethoxy-1-ethyl-2-methoxybenzene (0.3 g, 1.66 mmol) in THF (4 mL) was added TMEDA (0.58 g, 4.99 mmol), n-BuLi (3.1 mL, 4.99 mmol) at 0 °C and stirred at the same temperature for 1 h. Then SO₂ gas was bubbled into the reaction mixture for 30 min at -78 °C. The reaction mixture was slowly warmed to 0 °C and stirred for 1 h. The reaction mixture was concentrated to obtain the solid. The solid was dissolved in DCM (10 mL) and NCS (0.4 g, 2.99 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The reaction was quenched with ice water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. The crude compound was dissolved in DCM (2 mL) and 7N methanolic ammonia (10 mL) was added to the reaction mixture and stirred for 30 min at RT. The reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude. Crude compound was recrystallized using 50% EtOAc in pentane to afford the title compound (0.11g, 59.16%). LC-MS: 260.1 [M+H]⁺.

25 **Intermediate 89: 5-(Trifluoromethyl)-2,3-dihydrobenzofuran-7-sulfonamide**



[0420] Step 1: 2,6-Dibromo-4-(trifluoromethyl)phenol

[0421] Sulfuric acid (0.22 mL, 4.15 mmol) was added dropwise to a solution of 2-bromo-4-(trifluoromethyl)phenol (1.0 g, 4.15 mmol) in ACN (10 mL) and stirred at RT for 10 min followed by addition of N-bromosuccinimide (0.775 g, 4.35 mmol). The reaction mixture was stirred for 12 h at RT. The reaction mixture was quenched with water and extracted with DCM. The organic layer was dried over Na_2SO_4 , filtered, and concentrated to get crude compound. The crude compound was purified by silica-gel flash column chromatography using 0-10% ethyl acetate in hexane as eluent to obtain the title compound. (1.2 g, 60.3 %). LC-MS: 318.8 $[M+H]^+$.

[0422] Step 2: 1,3-Dibromo-2-(2-bromoethoxy)-5-(trifluoromethyl)benzene

[0423] To a solution of 2,6-dibromo-4-(trifluoromethyl)phenol (0.8 g, 2.50 mmol) and K_2CO_3 (1.04 g, 7.50 mmol) ACN (20 mL) was added 1,2-dibromoethane (1.88 g, 10.00 mmol) and stirred at 90 °C for 12 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude compound. The crude compound was purified by silica-gel flash column chromatography using 1-3% ethyl acetate in hexane as eluent to afford the title compound (0.7 g, 65.6%). 1H NMR (DMSO- d_6 , 400MHz): δ 8.14 (s, 2H), 4.38 (t, 2H), 3.88 (t, 2H).

[0424] Step 3: 5-(Trifluoromethyl)-2,3-dihydrobenzofuran-7-sulfonyl chloride

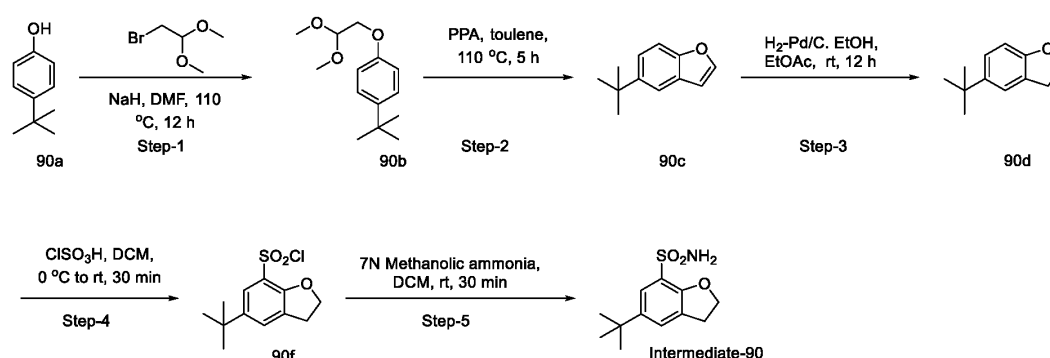
[0425] To a solution of 1,3-dibromo-2-(2-bromoethoxy)-5-(trifluoromethyl)benzene (0.5 g, 1.17 mmol) in THF (10 mL) was added n-BuLi (4.39 mL, 7.02 mmol) at -78 °C and stirred at the same temperature for 1 h. Then SO_2 gas was bubbled into the reaction mixture for 30 min at -78 °C. The reaction mixture was slowly warmed to RT and stirred for 1 h. The reaction

mixture was concentrated to obtain the solid. The solid was dissolved in DCM and NCS (0.47 g, 3.51 mmol) was added to it at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The reaction was quenched with ice water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude title compound (0.5 g). ¹H NMR (DMSO-d₆, 400MHz): δ 7.65 (s, 1H), 7.54 (s, 1H), 4.62 (m, 2H), 3.69 (t, 2H).

[0426] Step 4: 5-(Trifluoromethyl)-2,3-dihydrobenzofuran-7-sulfonamide

[0427] To a solution of 5-(trifluoromethyl)-2,3-dihydrobenzofuran-7-sulfonyl chloride (0.5 g, 1.74 mmol) in DCM (7 mL) was added 7M methanolic ammonia dropwise (7 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was diluted with water and extracted with DCM. The organic layer was washed with saturated Aq. NaHCO₃, dried over Na₂SO₄, and concentrated to afford the title compound (0.3 g). LC-MS: 265.9 [M-H]⁻.

Intermediate 90: 5-(tert-Butyl)-2,3-dihydrobenzofuran-7-sulfonamide



[0428] Step 1: 1-(tert-Butyl)-4-(2,2-dimethoxyethoxy)benzene

[0429] To a stirred solution of 4-(tert-butyl)phenol (2.0 g, 13.31 mmol) in DMF (75 mL) was added NaH (1.02 g, 26.62 mmol) at 0 °C and stirred for 30 min, followed by addition of 2-bromo-1,1-dimethoxyethane (2.7 g, 15.98 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred at 110 °C for 12 h. The reaction mixture was added into ice water and extracted with EtOAc. The organic layer was washed with brine solution, dried over Na₂SO₄, and concentrated to afford the crude title compound (3.5 g). ¹H NMR (CDCl₃, 400MHz): δ 7.30 (d, 2H), 6.88 (d, 2H), 4.72 (t, 1H), 4.01 (d, 2H), 3.45 (s, 6H), 1.30 (s, 9H).

[0430] Step 2: 5-(*tert*-Butyl)benzofuran

[0431] To a solution of 1-(*tert*-butyl)-4-(2,2-dimethoxyethoxy)benzene (2.0 g, 8.39 mmol) in toluene (25 mL) was added polyphosphoric acid (2.18 g, 10.07 mmol) and stirred at 110 °C for 5 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford crude title compound (1.5 g). ¹H NMR (CDCl₃, 400MHz): δ 7.63 – 7.61 (m, 2H), 7.46 (d, 1H), 7.39 (d, 1H), 6.77 (d, 1H), 1.41 (s, 9H).

[0432] Step 3: 5-(*tert*-Butyl)-2,3-dihydrobenzofuran

10 **[0433]** The title compound was prepared using a similar procedure to that described in Step 2 of Intermediate 88 using appropriate reagents with suitable modifications (0.36 g). LC-MS: 177.2 [M+H]⁺.

[0434] Step 4: 5-(*tert*-Butyl)-2,3-dihydrobenzofuran-7-sulfonyl chloride

15 **[0435]** To a stirred solution of 5-(*tert*-butyl)-2,3-dihydrobenzofuran (0.2 g, 1.14 mmol) in DCM (40 mL) was added chlorosulfonic acid (0.66 g, 5.67 mmol) dropwise at 0 °C. The reaction mixture was gradually warmed to RT and stirred for 30 min at RT. The reaction mixture was then poured into ice-cold water quenched with NaHCO₃ solution extracted with DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated to obtain crude title compound (0.15 g). ¹H NMR (DMSO-d₆, 400MHz): δ 7.36 (d, 1H), 7.20 (d, 1H), 4.46 (t, 2H),
20 3.11 (t, 2H), 1.23 (s, 9H).

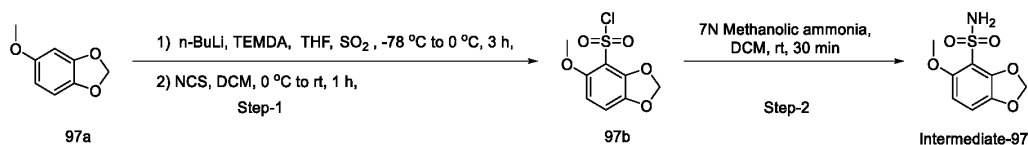
[0436] Step 5: 5-(*tert*-Butyl)-2,3-dihydrobenzofuran-7-sulfonamide

[0437] The title compound was prepared using a similar procedure to that described in Step 4 of Intermediate 89 using appropriate reagents with suitable modifications. LC-MS: 256.1 [M+H]⁺.

25 **[0438]** The following compounds listed in Table 6 were prepared by following a similar procedure as described above in Step 4 & Step 5 of Intermediate 90 using appropriate reagents with suitable modifications known to the one skilled in the art.

Table 6. Intermediates

Intermediate	Structure	Spectral data
91		^1H NMR (DMSO- d_6 , 400MHz): δ 7.00 (brs, 2H), 6.69 (d, 2H), 3.83 (s, 6H).
92		^1H NMR (DMSO- d_6 , 400MHz): δ 7.06 (brs, 2H), 6.88 (s, 2H), 3.95 (s, 6H).
93		^1H NMR (DMSO- d_6 , 400MHz): δ 7.06 (brs, 2H), 7.00 (s, 2H), 3.85 (s, 6H).
94		^1H NMR (DMSO- d_6 , 400MHz): δ 6.86 (brs, 2H), 6.57 (d, 1H), 6.45 (d, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 2.51 (s, 3H).
95		LC-MS: 325.9 [M+H] $^+$.
96		^1H NMR (DMSO- d_6 , 400MHz): δ 7.12 (s, 2H), 7.04 (brs, 2H), 3.83 (s, 6H).

Intermediate 97: 5-Methoxybenzo[d][1,3]dioxole-4-sulfonamide5 **[0439]** Step 1: 5-Methoxybenzo[d][1,3]dioxole-4-sulfonyl chloride

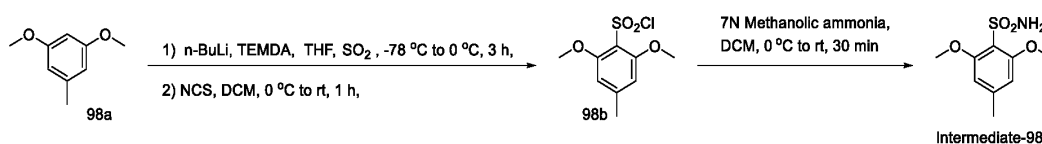
[0440] To a solution of 5-methoxybenzo[d][1,3]dioxole (0.2 g, 1.31 mmol) in THF (4 mL) was added TMEDA (0.305 g, 2.62 mmol), n-BuLi (2.46 mL, 3.94 mmol) at 0 °C and stirred at the

- same temperature for 1 h. Then SO₂ gas was bubbled into the reaction mixture for 30 min at -78 °C. The reaction mixture was slowly warmed to 0 °C and stirred for 2 h. The reaction mixture was concentrated to obtain a solid. The solid was dissolved in DCM (5 mL) and NCS (0.526 g, 3.94 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was warmed to
- 5 RT and stirred for 1 h. The reaction was quenched with ice water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material (0.3 g). ¹H NMR (DMSO-d₆, 400MHz): δ 6.75 (d, 1H), 6.33 (d, 1H), 5.90 (s, 2H), 3.65 (s, 3H).

[0441] Step 2: 5-Methoxybenzo[d][1,3]dioxole-4-sulfonamide

- 10 **[0442]** The title compound was prepared using a similar procedure to that described in Step 4 of Intermediate 89 using appropriate reagents with suitable modifications. LC-MS: 232.0 [M+H]⁺.

Intermediate 98: 2,6-Dimethoxy-4-methylbenzenesulfonamide



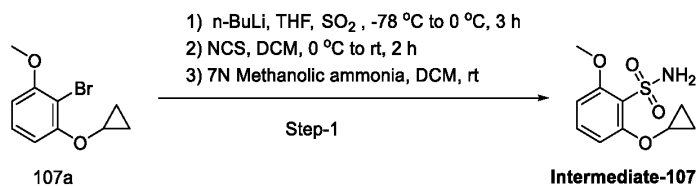
- 15 **[0443]** Step 1: 2,6-Dimethoxy-4-methylbenzenesulfonyl chloride

[0444] The title compound was prepared using a similar procedure to that described in Step 1 of Intermediate 97 using appropriate reagents with suitable modifications (1 g). ¹H NMR (DMSO-D₆, 400MHz): δ 6.49 (s, 2H), 3.72 (s, 6H), 2.57 (s, 3H).

[0445] Step 2: 2,6-Dimethoxy-4-methylbenzenesulfonamide

- 20 **[0446]** The title compound was prepared using a similar procedure to that described in Step 4 of Intermediate 89 using appropriate reagents with suitable modifications. LC-MS: 232.0 [M+H]⁺.

Intermediate 107: 2-Cyclopropoxy-6-methoxybenzenesulfonamide

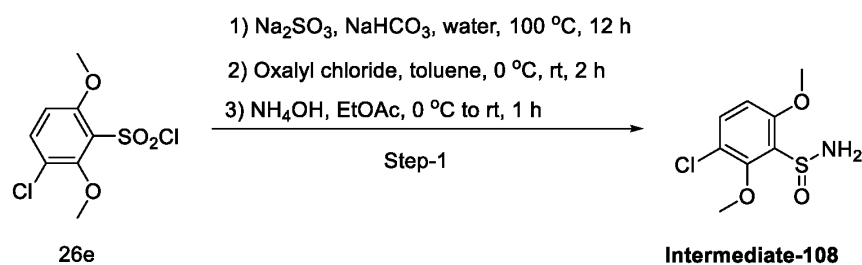


[0447] Step 1: 2-Cyclopropoxy-6-methoxybenzenesulfonamide

[0448] The title compound was prepared using a similar procedure to that described in Step 6 of Intermediate 102g in Example 16 using appropriate reagents with suitable modifications.

5 LC-MS: 244.0 [M+H]⁺.

Intermediate 108: 3-Chloro-2,6-dimethoxybenzenesulfinamide



10 [0449] Step 1: 3-Chloro-2,6-dimethoxybenzenesulfinamide

[0450] To a solution of 3-chloro-2,6-dimethoxybenzenesulfonyl chloride (3.8 g, 14.06 mmol) in water (50 mL) was added NaHCO₃ (2.35 g, 28.03 mmol) and Na₂SO₃ (7.06 g, 28.03 mmol) at rt and then stirred at 100 °C for 12 h. Reaction mixture was concentrated, then diluted with EtOH (80 mL) and stirred for 10 min. The inorganic salt was filtered and filtrate was concentrated to get the crude compound. The crude was dissolved in toluene (50 mL), and oxalyl chloride (1.42 mL, 16.82 mmol) was added to it at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h. The reaction mixture was concentrated to obtain the crude compound. The crude was dissolved in EtOAc (30 mL), and aqueous NH₄OH (30 mL) was added to it at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude compound. The crude compound was washed with 50% diethyl ether in pentane to obtain the title compound (0.5 g, 34.5%). LC-MS: 236.0 [M+H]⁺.

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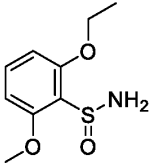
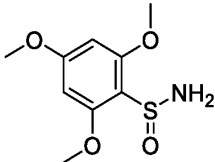
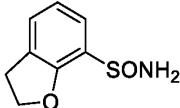
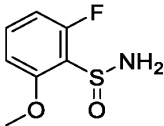
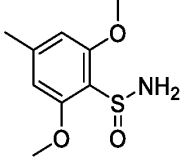
20

Intermediates 109 to 117

[0451] The following intermediates in Table 7 were prepared by following similar procedure to that described above for Intermediate 108 using appropriate reagents with suitable modifications known to the one skilled in the art. In some instances, procedures began with

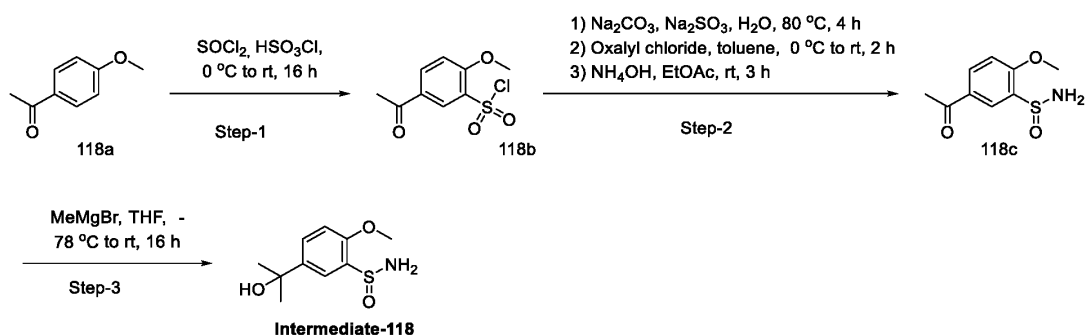
5 commercially available sulfonyl chloride building blocks.

Table 7. Intermediates

Intermediate	Structure	Spectral data
109		LC-MS: 216.1 [M+H] ⁺ .
110		LC-MS: 232.1 [M+H] ⁺ .
111		LC-MS: 184.0 [M+H] ⁺ .
112		LC-MS: 190.0 [M+H] ⁺ .
113		LC-MS: 216.1 [M+H] ⁺ .

Intermediate	Structure	Spectral data
114		LC-MS: 160.0 [M+H] ⁺ .
115		LC-MS: 178.0 [M+H] ⁺ .
116		LC-MS: 216.1 [M+H] ⁺ .
117		LC-MS: 242.1 [M+H] ⁺ .

Intermediate 118: 5-(2-Hydroxypropan-2-yl)-2-methoxybenzenesulfonamide



[0452] Step 1: 5-Acetyl-2-methoxybenzenesulfonyl chloride

- 5 [0453] A mixture of chlorosulfonic acid (3.32 ml, 49.93 mmol) and thionyl chloride (5.0 mL) was stirred in an ice bath for 30 min. Subsequently 1-(4-methoxyphenyl)ethan-1-one (5.0 g, 33.29 mmol) was added portion wise to the reaction mixture and stirred at room temperature for 16 h. the reaction mixture was slowly quenched with ice-water to get the precipitate. The

precipitate was filtered and washed with water to afford the title compound (10.0 g). LC-MS: 249.0 [M+H]⁺.

[0454] Step 2 : 5-Acetyl-2-methoxybenzenesulfinamide

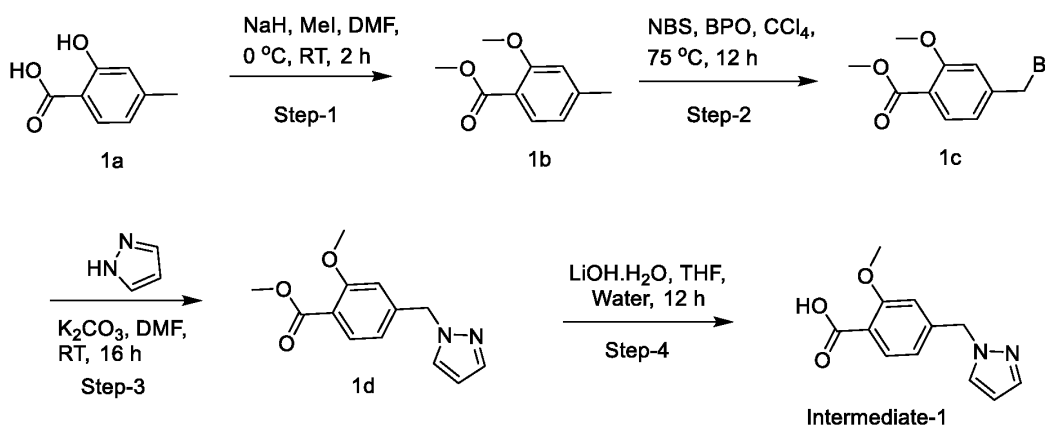
[0455] The title compound was prepared using a similar procedure to that described in Step 1 of Intermediate 108 using appropriate reagents with suitable modifications (0.50 g); LC-MS: 214.0 [M+H]⁺.

[0456] Step 3: 5-(2-Hydroxypropan-2-yl)-2-methoxybenzenesulfinamide

[0457] To a solution of 5-acetyl-2-methoxybenzenesulfinamide (0.30 g, 1.30 mmol) in THF (12 mL) was added MeMgBr (3.49 mL, 10.47 mmol, 3 M in diethyl ether) at -78 °C and stirred at same temperature for 30 min. Then reaction mixture was warmed to RT and stirred for 16 h. The reaction mixture was cooled, quenched with saturated ammonium chloride solution, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated to afford crude compound. The crude compound was purified by silica-gel flash column chromatography using 5% methanol in DCM as eluent to afford title compound (0.250 g, 83.35%). LC-MS: 230.0[M+H]⁺.

b) Benzoic Acid Intermediates

Intermediate 1: 4-((1H-pyrazol-1-yl)methyl)-2-methoxybenzoic acid



[0458] Step 1: Methyl 2-methoxy-4-methylbenzoate

[0459] A stirred solution of 2-hydroxy-4-methylbenzoic acid (5 g, 32.8 mmol) in DMF (50 mL) was cooled to 0 °C and added NaH (1.97 g, 82.1 mmol) followed by methyl iodide (5.6 g, 49.2 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred at RT for 2 h. The

reaction mixture was added into ice water and extracted with EtOAc. The organic layer was washed with brine solution, dried over Na₂SO₄, and concentrated to afford the crude compound. The crude compound was purified by combi flash chromatography using 0-10% ethyl acetate in hexane to afford the title compound (3 g, 50.6%). LC-MS: 181.1 [M+H]⁺.

5 **[0460]** Step 2: Methyl 4-(bromomethyl)-2-methoxybenzoate

[0461] To a solution of methyl 2-methoxy-4-methylbenzoate (2.6 g, 14.4 mmol) in CCl₄ (30 mL) were added N-bromosuccinimide (NBS, 2.5 g, 14.4 mmol) and benzoyl peroxide (BPO, 0.035 g, 0.14 mmol) and heated to reflux for overnight. Reaction mixture was then cooled to RT and diluted with DCM and washed with water. The organic layer was dried over Na₂SO₄ and concentrated to get the crude compound. The crude compound was purified by combi flash chromatography using 0-20% ethyl acetate in hexane to afford the title compound (2.5 g, 66.8%). LC-MS: 261.0 [M+H]⁺.

[0462] Step 3: Methyl 4-((1H-pyrazol-1-yl)methyl)-2-methoxybenzoate

[0463] To a stirred solution of methyl 4-(bromomethyl)-2-methoxybenzoate (2.5 g, 9.6 mmol), 1H-pyrazole (0.98 g, 14.4 mmol) in DMF was added K₂CO₃ (4 g, 28.4 mmol) and stirred at RT for 16 h. Reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄ and concentrated to get crude compound. The crude compound was purified by combi flash chromatography using 40% ethyl acetate in hexane to afford the title compound (2 g, 84.1%). LC-MS: 247.1 [M+H]⁺.

20 **[0464]** Step 4: 4-((1H-pyrazol-1-yl)methyl)-2-methoxybenzoic acid

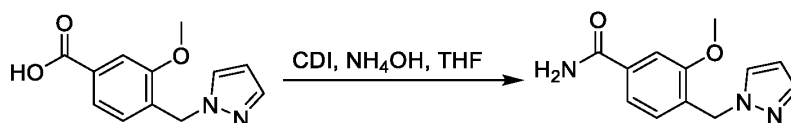
[0465] To a stirred solution of methyl 4-((1H-pyrazol-1-yl)methyl)-2-methoxybenzoate (0.8 g, 3.2 mmol) in THF (6 mL) and water (2 mL) was added LiOH.H₂O (0.38 g, 16.2 mmol) and stirred for 12 h at room temperature. Reaction mixture was diluted with ice-cold water, pH was adjusted to 5 using Aq. citric acid, and extracted with 20% methanol in DCM. The organic layer was dried over Na₂SO₄ and concentrated to afford the title compound (0.6 g). LC-MS: 233.1 [M+H]⁺.

Intermediates 2 to 7, 9 and 10

[0466] The following intermediates from Intermediate 2 to Intermediate 10 listed in Table 8 were prepared by following similar procedures described above for Intermediate 1 using appropriate reagents with suitable modifications known to the one skilled in the art.

Table 8. Intermediates.

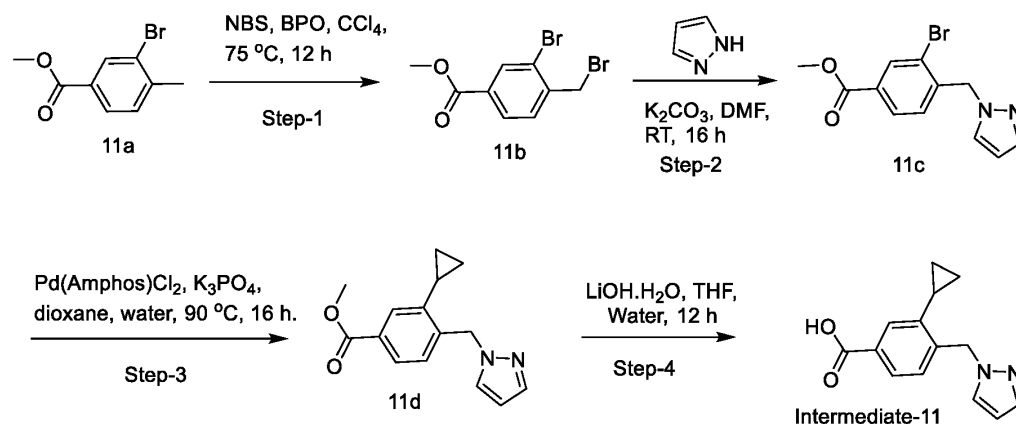
Intermediate	Structure	Spectral data
2		LC-MS: 233.0 [M+H] ⁺ .
3		LC-MS: 233.2 [M+H] ⁺ .
4		LC-MS: 221.05 [M+H] ⁺ .
5		LC-MS: 233.2 [M+H] ⁺ .
6		LC-MS: 221.0 [M+H] ⁺ .
7		LC-MS: 282.9 [M+H] ⁺ .
9		LC-MS: 236.1 [M+H] ⁺ .
10		LC-MS: 247.1 [M+H] ⁺ .

Intermediate 2a: 3-methoxy-4-(pyrazol-1-ylmethyl)benzamide

- 5 **[0467]** 3-Methoxy-4-(pyrazol-1-ylmethyl)benzoic acid (1.00 eq, 125 mg, 0.538 mmol) and CDI (1.50 eq, 131 mg, 0.807 mmol) were dissolved in THF (3 mL) and stirred for 1 h. 7 N ammonium hydroxide solution (10.00 eq, 0.770 mL) was added and stirred for 16 h. The solution was diluted with water, neutralized with 1 N HCl, and extracted with EtOAc. The organics were washed with 1 N HCl, water, and brine solution. The organics were then dried

over sodium sulfate, filtered, and dried in vacuo to give the title compound (120 mg, 96% yield). LC-MS: $m/z = 232.1$ $[M+H]^+$

Intermediate 11: 4-((1H-pyrazol-1-yl)methyl)-3-cyclopropylbenzoic acid



5 [0468] Step 1: Methyl 3-bromo-4-(bromomethyl)benzoate

[0469] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 1 using appropriate reagents with suitable modifications.

[0470] Step 2: Methyl 4-((1H-pyrazol-1-yl)methyl)-3-bromobenzoate

10 [0471] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 295.0 $[M+H]^+$.

[0472] Step 3: Methyl 4-((1H-pyrazol-1-yl)methyl)-3-cyclopropylbenzoate

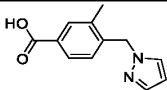
15 [0473] To a degassed solution of methyl 4-((1H-pyrazol-1-yl)methyl)-3-bromobenzoate (0.4 g, 1.35 mmol), cyclopropyl boronic acid (0.466 g, 5.41 mmol) in 1,4-dioxane (12 mL) and water (3 mL) were added Pd(Amphos)Cl₂ (0.096 g, 0.13 mmol) and K₃PO₄ (0.86 g, 4 mmol). The reaction mixture was heated to 90 °C for 16 h. The reaction mass was cooled to RT, diluted with water, and extracted with 10% methanol in DCM. The organic layer was dried over Na₂SO₄, filtered and concentrated to get crude. The crude compound was purified by combi flash chromatography using 20-25% ethyl acetate in hexane to afford the title compound. LC-MS: 257.1 $[M+H]^+$.

20 [0474] Step 4: 4-((1H-pyrazol-1-yl)methyl)-3-cyclopropylbenzoic acid

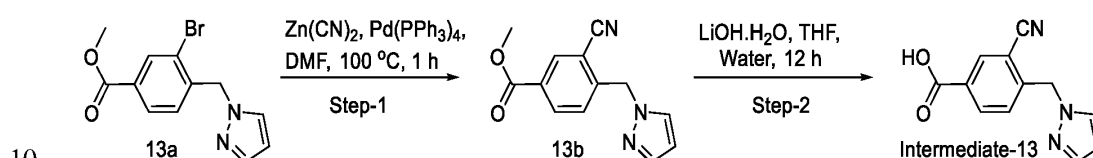
[0475] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 243.1 [M+H]⁺.

Intermediate 12

- 5 [0476] The following Intermediate 12 shown below was prepared by following similar procedure to that described above for Intermediate 11 using appropriate reagents with suitable modifications known to the one skilled in the art.

Intermediate	Structure	Spectral data
12		LC-MS: 217.1 [M+H] ⁺ .

Intermediate 13: 4-((1H-pyrazol-1-yl)methyl)-3-cyanobenzoic acid



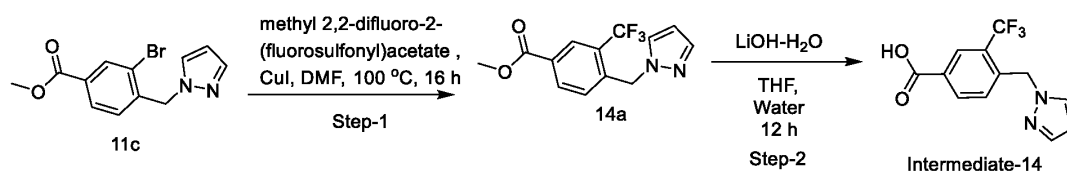
[0477] Step 1: Methyl 4-((1H-pyrazol-1-yl)methyl)-3-cyanobenzoate

- [0478] To a degassed solution of methyl 4-((1H-pyrazol-1-yl)methyl)-3-bromobenzoate (0.3 g, 1.01 mmol), Zn(CN)₂ (0.14 g, 1.21 mmol) in DMF (4 mL) was added Pd(PPh₃)₄ and stirred at 100 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with water and
 15 extracted with ethyl acetate. The organic layer was washed with water, dried over Na₂SO₄ and concentrated to get crude compound. The crude compound was purified by combi flash chromatography using 0-25% ethyl acetate in hexane to afford the title compound (0.18 g). LC-MS: 242.1 [M+H]⁺.

[0479] Step 2: 4-((1H-pyrazol-1-yl)methyl)-3-cyanobenzoic acid

- 20 [0480] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 228.0 [M+H]⁺.

Intermediate 14: 4-((1H-pyrazol-1-yl)methyl)-3-(trifluoromethyl)benzoic acid



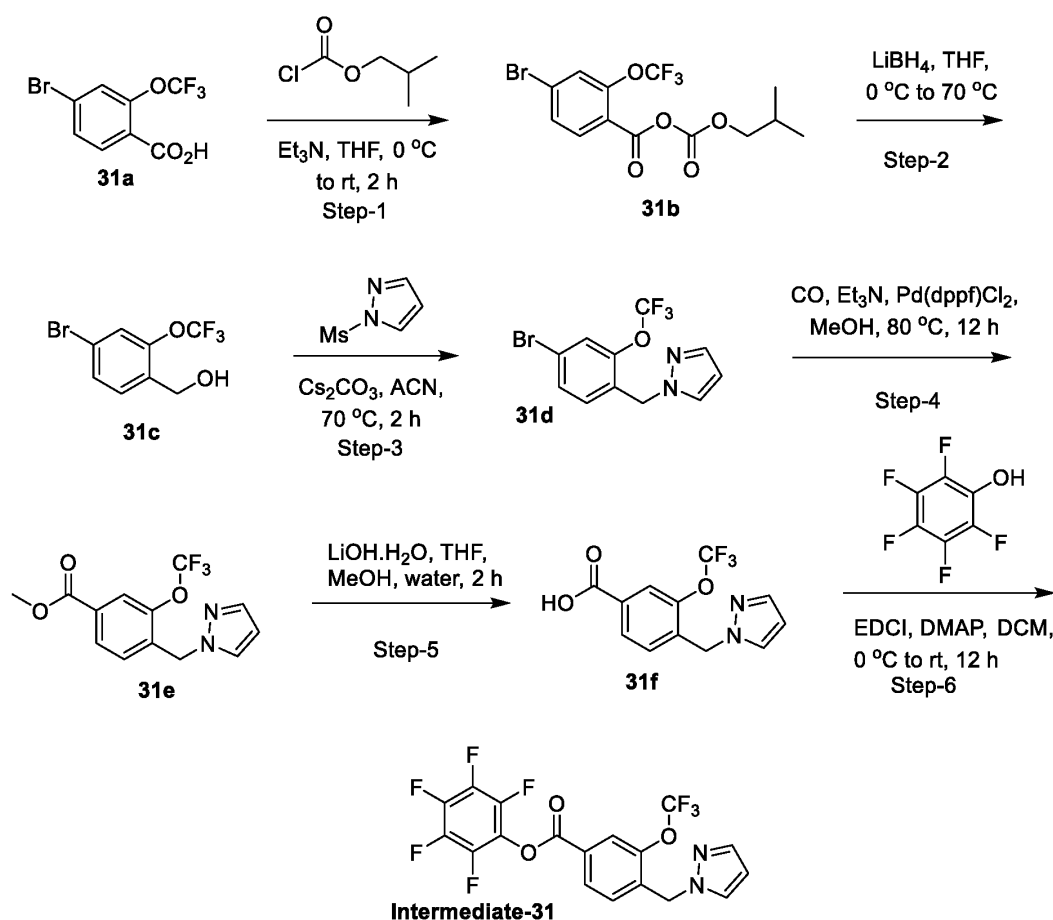
[0481] Step 1: Methyl 4-((1H-pyrazol-1-yl)methyl)-3-(trifluoromethyl)benzoate

[0482] To a stirred solution of methyl 4-((1H-pyrazol-1-yl)methyl)-3-bromobenzoate (0.15 g, 0.5 mmol) in DMF (2 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.48 g, 2.54 mmol) followed by CuI (0.19 g, 1 mmol) at RT. The mixture was heated at 100 °C for 16 h. The reaction mass was cooled to RT, quenched with ice cold water, and washed with brine solution. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford crude compound (0.15 g) which was used in next step without purification. LC-MS: 285.1 [M+H]⁺.

[0483] Step 2: 4-((1H-pyrazol-1-yl)methyl)-3-(trifluoromethyl)benzoic acid

[0484] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 271.1 [M+H]⁺.

Intermediate 31: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-3-trifluoromethoxybenzoate



[0485] Step 1: 4-Bromo-2-(trifluoromethoxy)benzoic (isobutyl carbonic) anhydride

[0486] To a solution of 4-bromo-2-(trifluoromethoxy)benzoic acid (3.0 g, 10.52 mmol), in THF (45 mL) was added Et_3N (1.6 g, 15.78 mmol) followed by isobutyl chloroformate (1.8 g, 13.16 mmol) at 0°C . The reaction was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 , filtered, and concentrated to obtain the title compound (3.8 g, 95%). ^1H NMR (DMSO-d_6 , 400MHz): δ 7.94 (d, 1H), 7.61 (d, 1H), 7.60 (s, 1H), 4.15 (d, 2H), 2.11 – 2.06 (m, 1H), 1.01 (d, 6H).

[0487] Step 2: (4-Bromo-2-(trifluoromethoxy)phenyl)methanol

[0488] To a stirred solution of methyl 4-bromo-2-(trifluoromethoxy)benzoic (isobutyl carbonic) anhydride (3.8 g, 9.90 mmol) in THF (45 mL) was added LiBH_4 (1.76 g, 11.8 mmol) at 0°C and stirred at 70°C for 2 h. The reaction mixture was quenched with ice water and

extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated to obtain the title compound (2.8 g, 90%). ¹H NMR (DMSO-d₆, 400MHz): δ 7.48 (d, 1H), 7.47 (s, 1H), 7.42 (d, 1H), 4.75 (s, 2H).

[0489] Step 3: 1-(4-Bromo-2-(trifluoromethoxy)benzyl)-1H-pyrazole

5 **[0490]** To a solution of (4-bromo-2-(trifluoromethoxy)phenyl)methanol (1.5 g, 5.53 mmol), and 1-(methylsulfonyl)-1H-pyrazole (0.97 g, 6.64 mmol) in acetonitrile (15 mL) was added Cs₂CO₃ (2.16 g, 6.64 mmol) and stirred at 70 °C for 2 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude compound, which was further purified by silica-
10 gel flash column chromatography using 30% ethyl acetate in hexane as eluent to obtain the title compound (1.5 g, 84.4%). LC-MS: 322.9 [M+H]⁺.

[0491] Step 4: Methyl 4-((1H-pyrazol-1-yl)methyl)-3-(trifluoromethoxy)benzoate

[0492] To a degassed solution of 1-(4-bromo-2-(trifluoromethoxy)benzyl)-1H-pyrazole (1.5 g, 4.67 mmol), triethylamine (1.41 g, 14.01 mmol) in methanol (60 mL) was added
15 Pd(dppf)Cl₂-DCM (0.38 g, 0.46 mmol). The reaction mixture was heated to 80 °C in autoclave with 80 PSI pressure of carbon monoxide for 16 h. The reaction mixture was cooled to RT, filtered through a pad of celite and concentrated to afford the title compound (1.0 g, 71.3%). LC-MS: 301.0 [M+H]⁺.

[0493] Step 5: 4-((1H-pyrazol-1-yl)methyl)-3-(trifluoromethoxy)benzoic acid

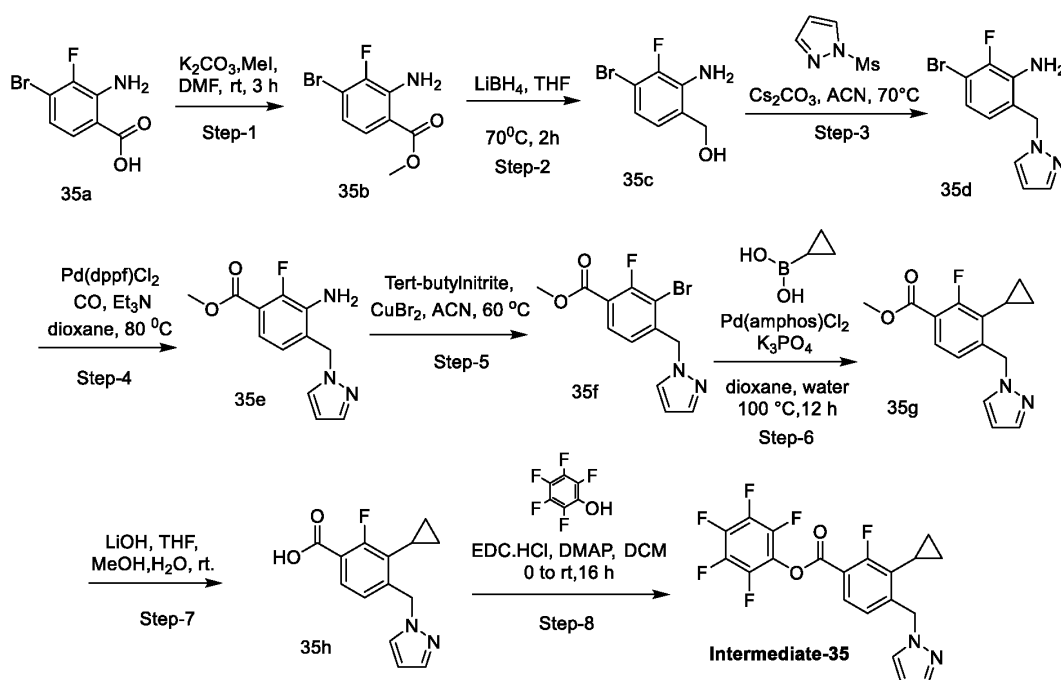
20 **[0494]** To a stirred solution of methyl 4-((1H-pyrazol-1-yl)methyl)-3-(trifluoromethoxy)benzoate (0.5 g, 1.66 mmol) in THF (5 mL), Methanol (3 mL) and water (2 mL) was added lithium hydroxide hydrate (0.15 g, 6.66 mmol) and stirred for 12 h at room temperature. Reaction mixture was diluted with ice-cold water, pH was adjusted to 5 using 1N HCl, and extracted with 20% methanol in DCM. The organic layer was dried over Na₂SO₄ and
25 concentrated to afford the title compound (0.4 g, 83.9%). LC-MS: 287.0 [M+H]⁺.

[0495] Step 6: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-3-(trifluoromethoxy)benzoate

[0496] To a solution of 4-((1H-pyrazol-1-yl)methyl)-3-(trifluoromethoxy)benzoic acid (0.2 g, 0.69 mmol), 2,3,4,5,6-pentafluorophenol (0.15 g, 0.84 mmol) and DMAP (0.017 g, 0.14 mmol) in DCM (20 mL) was added EDC.HCl (0.201 g, 1.04 mmol) at 0 °C and the solution
30 was then stirred at RT for 12 h. The reaction mixture was quenched with ice water and extracted

with DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude compound which was further purified by silica-gel flash column chromatography using 10-15% ethyl acetate in hexane as eluent to obtain the title compound (0.27 g, 85.4%). LC-MS: 453.0 [M+H]⁺. ¹H NMR (DMSO-d₆, 400MHz): δ 8.19 (d, 1H), 8.06 (s, 1H), 7.91 (d, 1H), 7.54 (d, 1H), 7.28 (d, 1H), 6.35 (t, 1H), 5.59 (s, 2H).

Intermediate 35: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-3-cyclopropyl-2-fluorobenzoate



[0497] Step 1: Methyl 2-amino-4-bromo-3-fluorobenzoate

[0498] To a solution of 2-amino-4-bromo-3-fluorobenzoic acid (5.0 g, 21.36 mmol) in DMF was added dipotassium carbonate (4.42 g, 32.04 mmol), followed by iodomethane (3.63 g, 25.63 mmol) and stirred at RT for 3 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄ and concentrated to get the crude compound. The crude compound was purified by silica gel flash column chromatography using 40% ethyl acetate in hexane as eluent to afford the title compound (4.8 g). LC-MS: 248.9 [M+H]⁺.

[0499] Step 2: (2-Amino-4-bromo-3-fluorophenyl)methanol

[0500] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 221.0 [M+H]⁺.

[0501] Step 3: 6-((1H-pyrazol-1-yl)methyl)-3-bromo-2-fluoroaniline

5 [0502] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 272.0 [M+H]⁺.

[0503] Step 4: Methyl 4-((1H-pyrazol-1-yl) methyl)-3-amino-2-fluorobenzoate

10 [0504] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 250.0 [M+H]⁺.

[0505] Step 5: Methyl 4-((1H-pyrazol-1-yl) methyl)-3-bromo-2-fluorobenzoate

15 [0506] To a solution of methyl 4-((1H-pyrazol-1-yl)methyl)-3-amino-2-fluorobenzoate (0.9 g, 3.61 mmol), and copper(I) bromide (0.80 g, 3.61 mmol) in acetonitrile (10 mL) was added tert-butyl nitrile (0.41 g, 3.97 mmol) and stirred at 60 °C for 10 min . The reaction mixture was cooled to RT, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the title compound (0.6g, 53.07%). LC-MS: 314.0 [M+H]⁺.

[0507] Step 6: Methyl 4-((1H-pyrazol-1-yl)methyl)-3-cyclopropyl-2-fluorobenzoate

20 [0508] To a degassed solution of methyl 4-((1H-pyrazol-1-yl)methyl)-3-bromo-2-fluorobenzoate (0.3g, 0.95 mmol), cyclopropyl boronic acid (0.32g, 3.83 mmol), and K₃PO₄ (0.610g, 2.87 mmol) in 1,4-dioxane (2.7 mL) and water (0.3 mL) was added Pd(Amphos)Cl₂ (0.068 g, 0.090 mmol) and stirred at 100 °C for 12 h. The reaction mixture was cooled to RT, filtered through celite, and washed with 10% methanol in DCM. The filtrate was washed with
25 water, aqueous NaHCO₃, dried over anhydrous Na₂SO₄, filtered, and concentrated and purified by silica gel flash column chromatography using 20% ethyl acetate in hexane as eluent to afford the title compound (0.150 g, 57%). LC-MS: 275.1 [M+H]⁺.

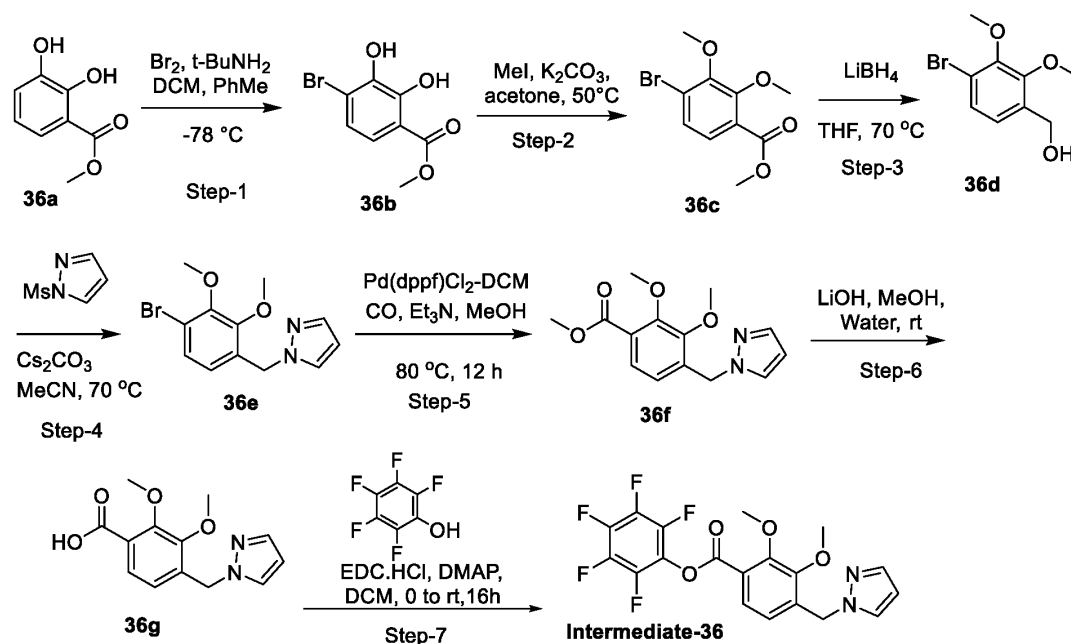
[0509] Step 7: 4-((1H-pyrazol-1-yl) methyl)-3-cyclopropyl-2-fluorobenzoic acid

[0510] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 261.0 [M+H]⁺.

[0511] Step 8: Perfluorophenyl 4-((1H-pyrazol-1-yl) methyl)-3-cyclopropyl-2-fluorobenzoate

[0512] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 427.0 [M+H]⁺.

Intermediate 36: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-2,3-dimethoxybenzoate



[0513] Step 1: Methyl 4-bromo-2,3-dihydroxybenzoate

[0514] Methyl 2,3-dihydroxybenzoate (3.0 g, 17.84 mmol) in DCM was added dropwise to a premix solution of 2-methylpropan-2-amine (2.61 g, 35.68 mmol) and bromine (2.85 g, 35.68 mmol) in toluene and DCM at -78 °C and stirred at same temperature for 30 min. The reaction mixture was slowly warmed to RT and stirred for 16 h. The reaction mixture was diluted with EtOAc, washed with 1M HCl. The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under vacuum to afford crude material. The crude material was purified by silica gel flash column chromatography 10% using ethyl acetate in hexane as eluent to afford the title compound (1.80 g, 40.8%). LC-MS: 246.9 [M-H]⁻.

[0515] Step 2: Methyl 4-bromo-2,3-dimethoxybenzoate

[0516] To a solution of methyl 4-bromo-2,3-dihydroxybenzoate (1.8 g, 7.28 mmol) and K₂CO₃ (3.0 g, 21.85 mmol) in acetone was added methyl iodide (10.34 g, 72.86 mmol) and stirred at 50 °C for 5 h. The mixture was cooled to RT, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound which was purified by silica-gel flash column chromatography using 20% ethyl acetate in hexane as eluent to afford title compound (1.75 g, 87.3%). LC-MS: 275.0 [M+H]⁺.

[0517] Step 3: (4-Bromo-2,3-dimethoxyphenyl)methanol

[0518] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 31 using appropriate reagents with suitable modifications. ¹H NMR, DMSO-d₆, 400MHz): δ 7.35 (d, 1H), 7.11 (d, 1H), 5.18 (t, 1H), 4.49 (d, 2H), 3.79 (s, 3H), 3.78 (s, 3H).

[0519] Step 4: Methyl 1-(4-bromo-2,3-dimethoxybenzyl)-1H-pyrazole

[0520] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 299.0 [M+H]⁺.

[0521] Step 5: Methyl 4-((1H-pyrazol-1-yl)methyl)-2,3-dimethoxybenzoate

[0522] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 277.0 [M+H]⁺.

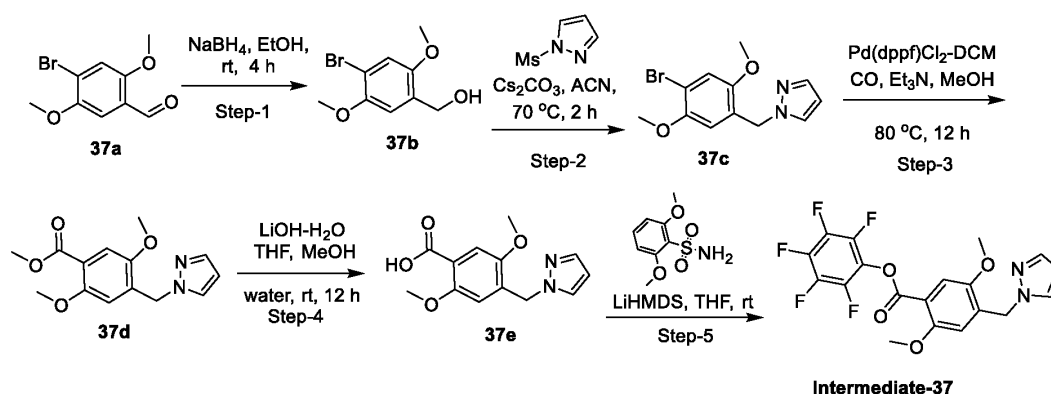
[0523] Step 6: 4-((1H-pyrazol-1-yl)methyl)-2,3-dimethoxybenzoic acid

[0524] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 263.1 [M+H]⁺.

[0525] Step 7: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-2,3-dimethoxybenzoate

[0526] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 429.0 [M+H]⁺.

Intermediate 37: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-2,5-dimethoxybenzoate



[0527] Step 1: (4-Bromo-2,5-dimethoxyphenyl)methanol

[0528] To a solution of 4-bromo-2,5-dimethoxybenzaldehyde (1.0 g, 4.08 mmol) in EtOH (10 mL) was added NaBH₄ (0.67 g, 16.32 mmol) 0 °C. The mixture was warmed to RT and stirred for 4 h. The reaction mass was quenched with water at RT, extracted with ethyl acetate, washed with water, brine solution, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the title compound (1.0 g). ¹H NMR, DMSO-d₆, 400MHz): δ 7.15 (s, 1H), 7.14 (s, 1H), 5.16 (t, 1H), 4.45 (d, 2H), 3.80 (s, 3H), 3.74 (s, 3H).

[0529] Step 2: 1-(4-Bromo-2,5-dimethoxybenzyl)-1H-pyrazole

[0530] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 299.0 [M+H]⁺.

[0531] Step 3: Methyl 4-((1H-pyrazol-1-yl)methyl)-2,5-dimethoxybenzoate

[0532] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 277.1 [M+H]⁺.

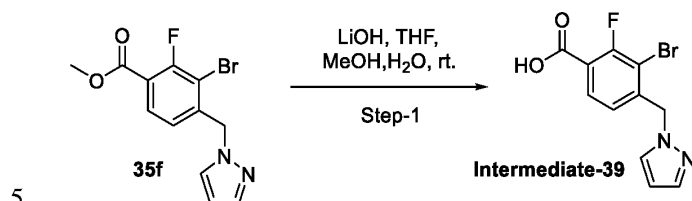
[0533] Step 4: 4-((1H-pyrazol-1-yl)methyl)-2,5-dimethoxybenzoic acid

[0534] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 263.1 [M+H]⁺.

[0535] Step 5: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-2,5-dimethoxybenzoate

[0536] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 429.1 [M+H]⁺.

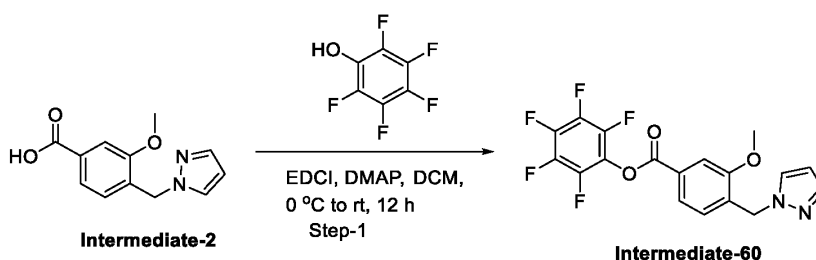
Intermediate 39: 4-((1H-pyrazol-1-yl)methyl)-3-bromo-2-fluorobenzoic acid



[0537] Step 1: 4-((1H-pyrazol-1-yl)methyl)-3-cyclopropyl-2-fluorobenzoic acid

[0538] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 301.0 [M+H]⁺.

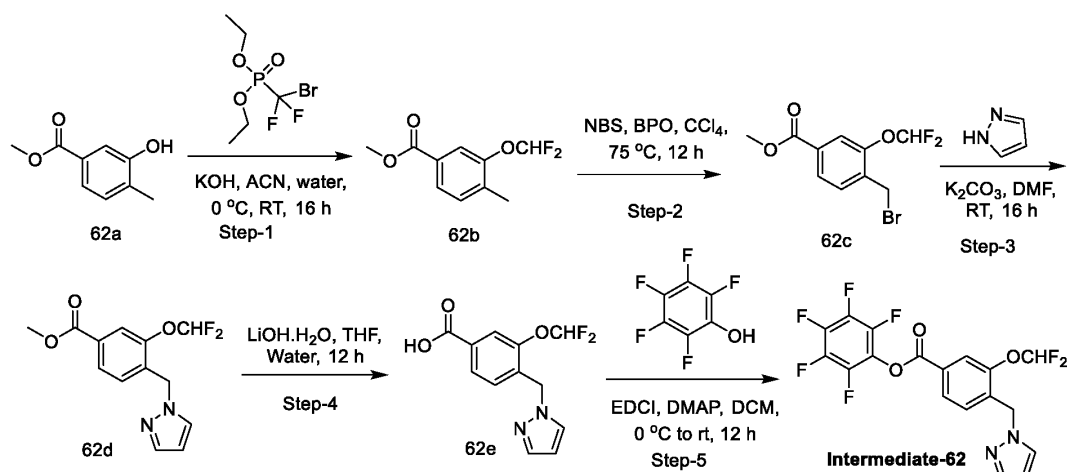
10 **Intermediate 60: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-3-methoxybenzoate**



[0539] Step 1: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-3-methoxybenzoate

15 [0540] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 399.1 [M+H]⁺.

Intermediate 62: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-3-(difluoromethoxy)benzoate



[0541] Step 1: Methyl 3-(difluoromethoxy)-4-methylbenzoate

[0542] To a solution of methyl 3-hydroxy-4-methylbenzoate (2 g, 12.03 mmol) in ACN (80 mL) was added 5N KOH solution (10 mL, 60.17 mmol) and followed by diethyl (bromodifluoromethyl)phosphonate (6.42 g, 24.07 mmol) at 0 °C. The reaction mixture was slowly warmed to RT and stirred for 16 h. The reaction was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. Crude compound was purified by silica-gel flash column chromatography using 10-20% ethyl acetate in hexane as eluent to afford the title compound (0.85 g, 32.7%). ¹H NMR (DMSO-d₆, 400MHz): δ 7.76 (dd, 1H), 7.67 (s, 1H), 7.49 (d, 1H), 7.31 (t, 1H), 3.86 (s, 3H), 2.31 (s, 3H).

[0543] Step 2: Methyl 4-(bromomethyl)-3-(difluoromethoxy)benzoate

[0544] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 1 using appropriate reagents with suitable modifications. ¹H NMR (DMSO-d₆, 400MHz): δ 7.83 (dd, 1H), 7.74 – 7.22 (m, 2H), 7.44 (t, 1H), 4.71 (s, 2H), 3.90 (s, 3H).

[0545] Step 3: Methyl 4-((1H-pyrazol-1-yl)methyl)-3-(difluoromethoxy)benzoate

[0546] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 1 using appropriate reagents with suitable modifications LC-MS: 283.0 [M+H]⁺.

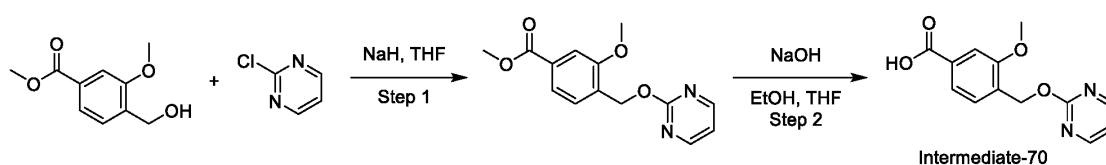
[0547] Step 4: 4-((1H-pyrazol-1-yl)methyl)-3-(difluoromethoxy)benzoic acid

[0548] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications LC-MS: 269.1 [M+H]⁺.

[0549] Step 5: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-3-(difluoromethoxy)benzoate

5 [0550] The title compound was prepared using similar procedure to that described in Step 6 of Intermediate 31 using appropriate reagents with suitable modifications LC-MS: 445.0 [M+H]⁺.

Intermediate 70: 3-methoxy-4-(pyrimidin-2-yloxymethyl)benzoic acid



10 [0551] Step 1: methyl 3-methoxy-4-(pyrimidin-2-yloxymethyl)benzoate

[0552] To a mixture of methyl 4-(hydroxymethyl)-3-methoxybenzoate (1.50 eq, 154 mg, 0.786 mmol) and tetrahydrofuran (12.0 mL) was added sodium hydride (1.50 eq, 19 mg, 0.786 mmol) portion wise. After 10 min, 2-chloropyrimidine (1.00 eq, 60 mg, 0.524 mmol) was added, and the mixture was stirred at room temperature over the weekend. The mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (153 mg, 0.556 mmol, 106.13 %). LC-MS: 275 [M+H]⁺.

[0553] Step 2: 3-methoxy-4-(pyrimidin-2-yloxymethyl)benzoic acid

20 [0554] A mixture of methyl 3-methoxy-4-(pyrimidin-2-yloxymethyl)benzoate (150 mg, 0.5469 mmol) and 3 N NaOH solution (1.4 mL, 4.3751 mmol) were stirred in 1 mL of EtOH and 1 mL of THF at ambient temperature overnight. The reaction was diluted with EtOAc, acidified with 1 N HCl (to pH 5) and extracted with EtOAc. The organics were washed with brine solution, dried over sodium sulfate, filtered, and concentrated in vacuo to afford the title compound (110 mg, 0.423 mmol, 77 %). LC-MS: 261 [M+H]⁺.

Intermediates 71 and 72

[0555] The following intermediates listed in Table 9 were prepared by following similar procedures described above for Intermediate 70 using appropriate reagents with suitable modifications known to the one skilled in the art.

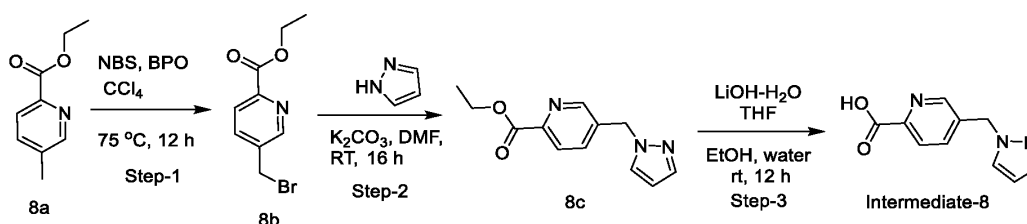
Table 9. Intermediates

Intermediate	Structure	LC-MS data
71		LC-MS: 266 [M+H] ⁺ .
72		LC-MS: 252 [M+H] ⁺ .

5

c) Pyridine- & Pyrimidine-Carboxy Intermediates

Intermediate 8: 5-((1H-pyrazol-1-yl)methyl)picolinic acid



[0556] Step 1: Ethyl 5-(bromomethyl)picolinate

10 [0557] To a solution of ethyl 5-methylpicolinate (2.0 g, 12.10 mmol) in CCl₄ (15 mL) were added NBS (2.15 g, 12.10 mmol) and benzoyl peroxide (0.293 g, 1.21 mmol) and stirred at 75 °C for 12 h. Reaction mixture was then cooled to RT and diluted with DCM and washed with water. The organic layer was dried over Na₂SO₄ and concentrated to afford the crude compound. The crude compound was purified by silica gel flash column chromatography using
15 15-20% ethyl acetate in hexane to afford the title compound (1.8 g, 60.9%). LC-MS: 244.0 [M+H]⁺.

[0558] Step 2: Ethyl 5-((1H-pyrazol-1-yl)methyl)picolinate

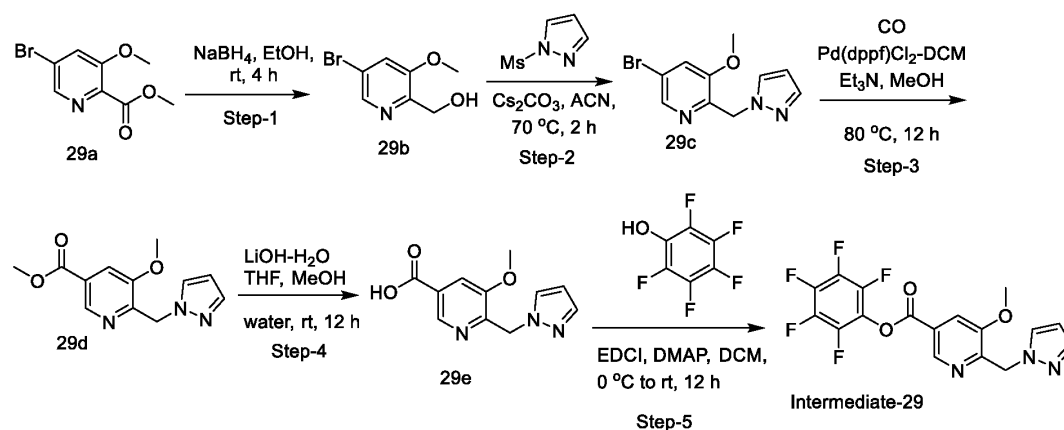
[0559] To a stirred solution of ethyl 5-(bromomethyl)picolinate (1.8 g, 7.37 mmol), 1H-pyrazole (0.653 g, 9.58 mmol) in DMF (15 mL) was added K₂CO₃ (3.05 g, 22.11 mmol) and

stirred at RT for 16 h. Reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄ and concentrated to afford crude compound. The crude compound was purified by silica gel flash column chromatography using 30% ethyl acetate in hexane to afford the title compound (0.8 g, 46.9%). LC-MS: 232.1 [M+H]⁺.

[0560] Step 3: 5-((1H-pyrazol-1-yl)methyl)picolinic acid

[0561] To a stirred solution of ethyl 5-((1H-pyrazol-1-yl)methyl)picolinate (0.2 g, 3.2 mmol) in THF (4 mL), EtOH (3 mL) and water (2 mL) was added LiOH.H₂O (0.104 g, 4.32 mmol) and stirred for 12 h at room temperature. Reaction mixture was evaporated and diluted with ice-cold water, and pH was adjusted to 5 using aqueous citric acid solution to obtain solid. The solid was filtered, washed with ice cold water and dried under vacuum to afford the title compound (0.16 g, 91%). LC-MS: 204.1 [M+H]⁺.

Intermediate 29: 6-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-5-methoxynicotinamide



[0562] Step 1: 5-Bromo-3-methoxypyridin-2-yl)methanol

[0563] To a stirred solution of methyl 5-bromo-3-methoxypicolinate (3 g, 12.19 mmol), in EtOH (30 mL) was added NaBH₄ (1.38 g, 36.57 mmol) at 0 °C and stirred at RT for 4 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude compound, which was further purified by silica-gel flash column chromatography using 20% ethyl acetate in hexane as eluent to obtain the title compound (1.4 g, 53%). LC-MS: 220.0 [M+H]⁺.

[0564] Step 2: 2-((1H-pyrazol-1-yl)methyl)-5-bromo-3-methoxypyridine

[0565] To a solution of (5-bromo-3-methoxypyridin-2-yl)methanol (1.5 g, 6.87 mmol), and 1-(methylsulfonyl)-1H-pyrazole (1.20 g, 8.25 mmol) in acetonitrile (15 mL) was added Cs₂CO₃ (2.69 g, 8.25 mmol) and stirred at 70 °C for 1 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude compound, which was further purified by silica-gel flash column chromatography using 30% ethyl acetate in hexane as eluent to obtain the title compound (1.5 g, 81%). LC-MS: 270.0 [M+H]⁺.

[0566] Step 3: Methyl 6-((1H-pyrazol-1-yl)methyl)-5-methoxynicotinate

[0567] To a degassed solution of 2-((1H-pyrazol-1-yl)methyl)-5-bromo-3-methoxypyridine (1.5 g, 5.59 mmol) in methanol (60 mL) was added Et₃N (2.32 mL, 16.78 mmol), Pd(dppf)Cl₂.DCM (0.32 g, 0.39 mmol). The reaction mixture was heated to 80 °C in autoclave with 80 PSI pressure of carbon monoxide for 16 h. The reaction mixture was cooled to RT, filtered through a pad of celite and concentrated to get crude compound. The crude compound was purified by silica-gel flash column chromatograph using 40% ethyl acetate in hexane as eluent to afford the title compound (1.1 g, 79.5%). LC-MS: 248.1 [M+H]⁺.

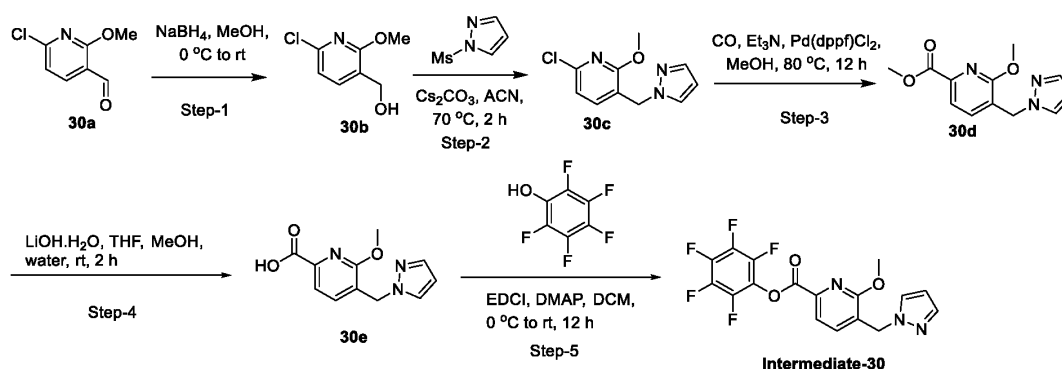
[0568] Step 4: 6-((1H-pyrazol-1-yl)methyl)-5-methoxynicotinic acid

[0569] To a stirred solution of methyl 6-((1H-pyrazol-1-yl)methyl)-5-methoxynicotinate (0.8 g, 3.23 mmol) in THF (8 mL), MeOH (4 mL) and water (4 mL) was added LiOH.H₂O (0.387 g, 16.18 mmol) and stirred for 12 h at room temperature. Reaction mixture was evaporated and diluted with ice-cold water, pH was adjusted to 5 using 1N HCl to obtain the solid. The solid was filtered, washed with ice cold water, and dried under vacuum to afford the title compound (0.45 g, 60%). LC-MS: 234.1 [M+H]⁺.

[0570] Step 5: Perfluorophenyl 6-((1H-pyrazol-1-yl)methyl)-5-methoxynicotinate

[0571] To a solution of 6-((1H-pyrazol-1-yl)methyl)-5-methoxynicotinic acid (0.2 g, 0.85 mmol), 2,3,4,5,6-pentafluorophenol (0.19 g, 1.03 mmol) and DMAP (0.021 g, 0.17 mmol) in DCM (4 mL) was added EDC.HCl (0.247 g, 1.28 mmol) at 0 °C and then stirred at RT for 12 h. The reaction mixture was quenched with ice water and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude compound which was further purified by silica-gel flash column chromatography using 10-15% ethyl acetate in hexane as eluent to obtain the title compound (0.12 g, 35%). LC-MS: 400.0 [M+H]⁺.

Intermediate 30: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinate



[0572] Step 1: (6-Chloro-2-methoxypyridin-3-yl)methanol

[0573] To a solution of 6-chloro-2-methoxynicotinaldehyde (2.0 g, 11.65 mmol), in MeOH (60 mL) was added NaBH₄ (1.76 g, 11.65 mmol) at 0 °C and stirred at RT for 2 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain the title compound (2 g, 99%). LC-MS: 174.1 [M+H]⁺.

[0574] Step 2: 3-((1H-pyrazol-1-yl)methyl)-6-chloro-2-methoxypyridine

[0575] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 29 using appropriate reagents with suitable modifications (2 g, 80%). LC-MS: 224 [M+H]⁺.

[0576] Step 3: Methyl 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinate

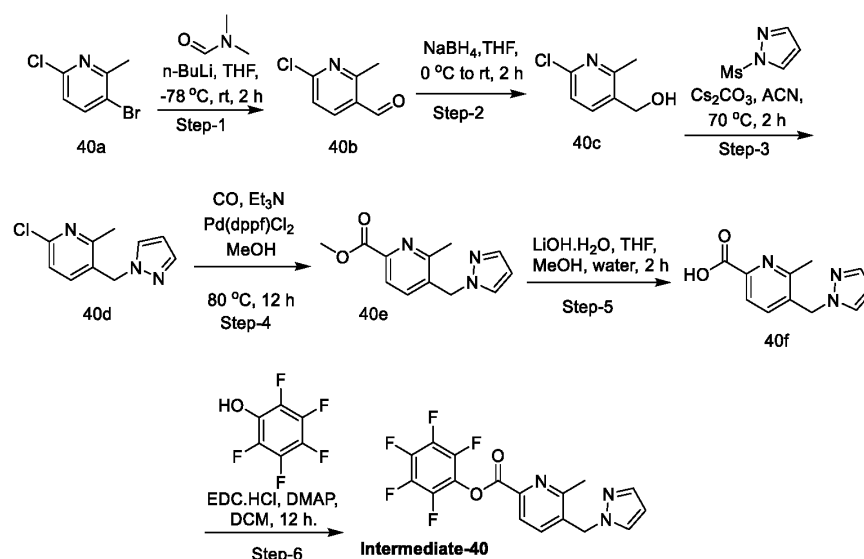
[0577] The title compound compound was prepared using similar procedure to that described in Step 3 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 248.1 [M+H]⁺.

[0578] Step 4: 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinic acid

[0579] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 234.1 [M+H]⁺.

[0580] Step 5: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinate

[0581] The title compound was prepared using similar procedure to that described in Step 5 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 400.0 [M+H]⁺.

Intermediate 40: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-methylpicolinate

[0582] Step 1: 6-Chloro-2-methylnicotinaldehyde

[0583] To a solution of 3-bromo-6-chloro-2-methylpyridine (2.0 g, 9.68 mmol) in THF was added n-BuLi (7.26 mL, 11.62 mmol, 1.6 M in THF) at $-78\text{ }^\circ\text{C}$ and stirred at same temperature for 30 min. Then to the reaction mixture was added DMF (1.41 g, 19.37 mmol) drop wise at $-78\text{ }^\circ\text{C}$ and slowly warmed to RT and stirred for 2 h. The reaction mixture was cooled to $-78\text{ }^\circ\text{C}$, quenched with brine, and extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated to afford crude compound. The crude compound which was purified by silica-gel flash column chromatography using 20% ethyl acetate in hexane as eluent to afford the title compound (0.61 g, 40%). LC-MS: 154.2 $[\text{M}-\text{H}]^-$.

[0584] Step 2: (6-Chloro-2-methylpyridin-3-yl)methanol

[0585] To a stirred solution of 6-chloro-2-methylnicotinaldehyde (0.6 g, 3.85 mmol), in THF (20 mL) was added NaBH_4 (0.438 g, 37.83 mmol) at $0\text{ }^\circ\text{C}$ and stirred at RT for 1 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 , filtered, and concentrated to afford the title compound (0.51 g, 85%). LC-MS: 158.1 $[\text{M}+\text{H}]^+$.

[0586] Step 3: 3-((1H-pyrazol-1-yl)methyl)-6-chloro-2-methylpyridine

[0587] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 208.0 [M+H]⁺.

[0588] Step 4: Methyl 5-((1H-pyrazol-1-yl)methyl)-6-methylpicolinate

5 [0589] The title compound compound was prepared using similar procedure to that described in Step 3 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 232.2 [M+H]⁺.

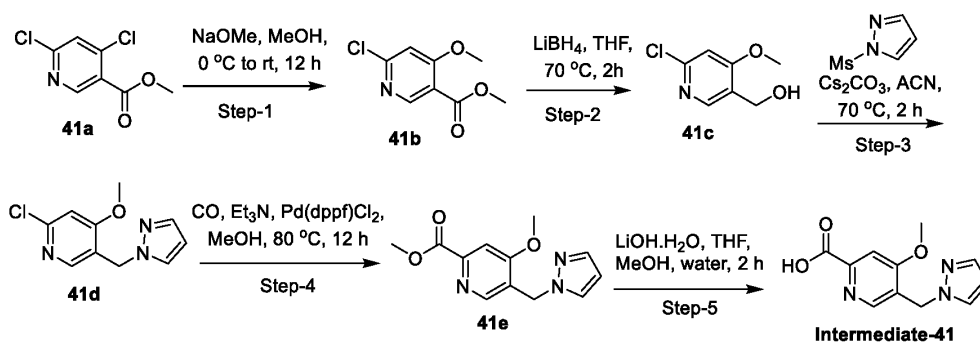
[0590] Step 5: 5-((1H-pyrazol-1-yl)methyl)-6-methylpicolinic acid

10 [0591] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 218.1 [M+H]⁺.

[0592] Step 6: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-methylpicolinate

15 [0593] The title compound was prepared using similar procedure to that described in Step 5 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 384.2 [M+H]⁺.

Intermediate 41: 5-((1H-pyrazol-1-yl)methyl)-4-methoxypicolinic acid



[0594] Step 1: Methyl 6-chloro-4-methoxynicotinate

20 [0595] To a solution of methyl 4,6-dichloronicotinate (5.0 g, 24.26 mmol) in methanol (50 mL) was added NaOMe (5.4g, 100.13 mmol) at 0 °C and slowly warmed reaction mixture to RT and stirred for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate, filtered, and

concentrated to afford the title compound which was taken to the next step without further purification (2.0 g, 41%); LC-MS: 202.0 [M+H]⁺.

[0596] Step 2: (6-Chloro-4-methoxypyridin-3-yl)methanol

[0597] To a stirred solution of methyl 6-chloro-4-methoxynicotinate (2.5 g, 12.4 mmol) in THF (40 mL) was added LiBH₄ (12.4 mL, 24.8 mmol) at 0 °C and stirred at 70 °C for 2 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated to obtain the title compound (2.12 g, 99%). LC-MS: 173.4 [M+H]⁺.

[0598] Step 3: 5-((1H-pyrazol-1-yl)methyl)-2-chloro-4-methoxypyridine

[0599] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 223.7[M+H]⁺.

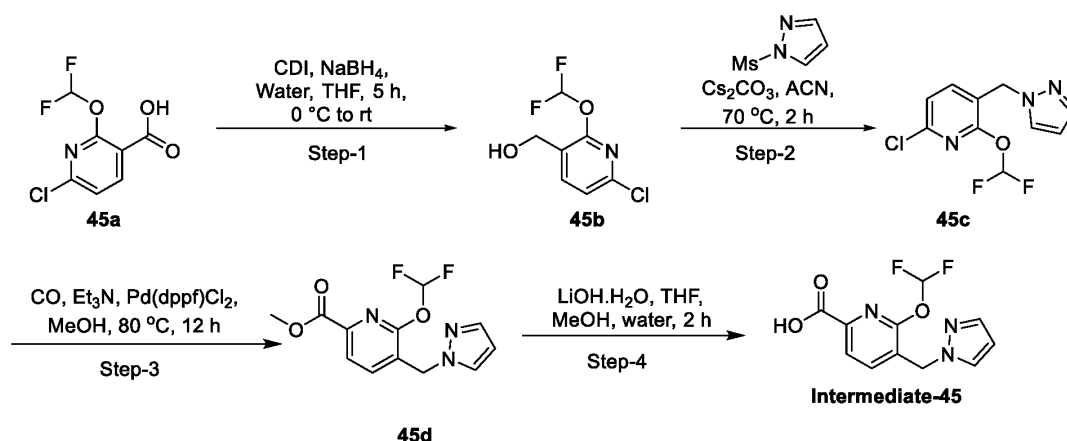
[0600] Step 4: Methyl 5-((1H-pyrazol-1-yl)methyl)-4-methoxypicolinate

[0601] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 248.9 [M+H]⁺.

[0602] Step 5: 5-((1H-pyrazol-1-yl)methyl)-4-methoxypicolinic acid

[0603] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 234.1 [M+H]⁺.

Intermediate 45: 5-((1H-pyrazol-1-yl)methyl)-6-(difluoromethoxy)picolinic acid



[0604] Step 1: (6-Chloro-2-(difluoromethoxy)pyridin-3-yl)methanol

[0605] To a solution of 6-chloro-2-(difluoromethoxy)nicotinic acid (0.5 g, 2.23 mmol) in THF was added 1,1'-carbonyldiimidazole (0.72 g, 4.47 mmol) was added at 0 °C. Then reaction mixture was slowly warmed to RT and for 5 h. Then sodium borohydride (0.42 g, 11.18 mmol) was added to the reaction mixture at 0 °C. Then reaction mixture was slowly warmed to RT and for 1 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water brine, dried over sodium sulfate, filtered, and concentrated to get the crude material. The crude material was purified by silica-gel flash column chromatography using 10% ethyl acetate in hexane as eluent to afford the title compound (0.45 g, 96%). LC-MS: 207.6 [M-H]⁻.

[0606] Step 2: 3-((1H-pyrazol-1-yl)methyl)-6-chloro-2-(difluoromethoxy)pyridine

[0607] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 259.8 [M+H]⁺.

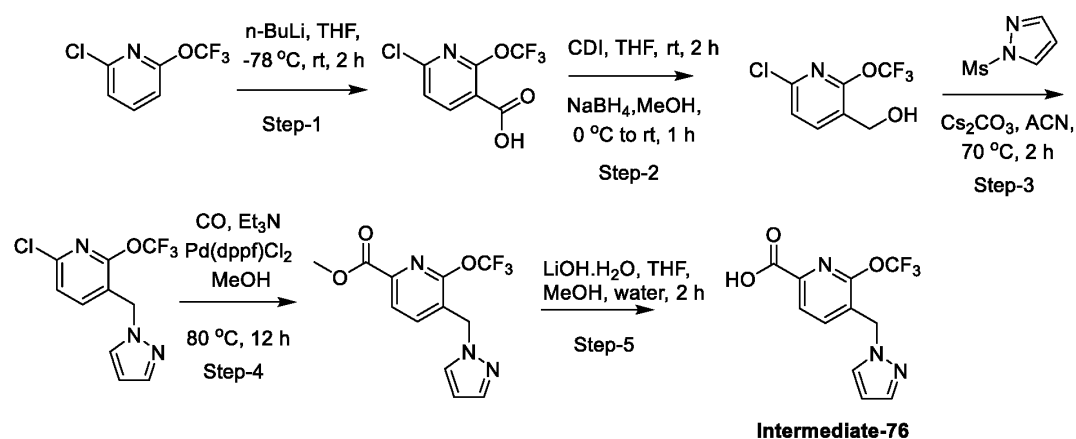
[0608] Step 3: Methyl 5-((1H-pyrazol-1-yl)methyl)-6-(difluoromethoxy)picolinate

[0609] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 283.0 [M+H]⁺.

[0610] Step 4: 5-((1H-pyrazol-1-yl)methyl)-6-(difluoromethoxy)picolinic acid

[0611] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 268.0 [M-H]⁻.

Intermediate 76: 5-((1H-pyrazol-1-yl)methyl)-6-(trifluoromethoxy)picolinic acid



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[0612] Step 1: 6-Chloro-2-(trifluoromethoxy)nicotinic acid

[0613] To a solution of 2-chloro-6-(trifluoromethoxy)pyridine (1.0 g, 5.06 mmol) in anhydrous THF (30 mL) was added LDA (freshly prepared from n-BuLi (2.0 mL, 5.0 mmol, 2.5 M in hexane) and diisopropylamine (0.65 g, 5.06 mmol) in THF (10 mL)) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. Using cannula, the reaction mixture transferred in crushed dry ice RB flask at 0 °C and stirred at rt for 30 min. The reaction mixture was quenched with ice water and adjusted pH-3 using 2N HCl to get the precipitate. The precipitate was filtered and dried under vacuum to afford the title compound (0.5 g, 40.9%) LC-MS: 240.0 [M-H]⁻.

15 [0614] Step 2: (6-Chloro-2-(trifluoromethoxy)pyridin-3-yl)methanol

[0615] To a solution of 6-chloro-2-(trifluoromethoxy)nicotinic acid (0.40 g, 1.655 mmol) in THF (10 mL) was added CDI (0.806 g, 4.96 mmol) at 0 °C and stirred the reaction mixture at rt for 2 h. NaBH₄ (0.43 g, 11.59 mmol) in water (2 mL) solution was added to the reaction mixture at 0 °C and the entire reaction mixture was stirred at rt for 1 h. The reaction mixture was acidified with HCl and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. The crude compound was purified by silica-gel flash column chromatography using 5% methanol in DCM as eluent to

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afford the title compound (0.2 g, 53.07%). ¹H NMR (DMSO-D₆, 400MHz): δ 8.12 (d, 1H), 7.58 (d, 1H), 5.58 (s, 1H), 4.52 (s, 2H).

[0616] Step 3: 3-((1H-pyrazol-1-yl)methyl)-6-chloro-2-(trifluoromethoxy)pyridine

[0617] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 278.0 [M+H]⁺

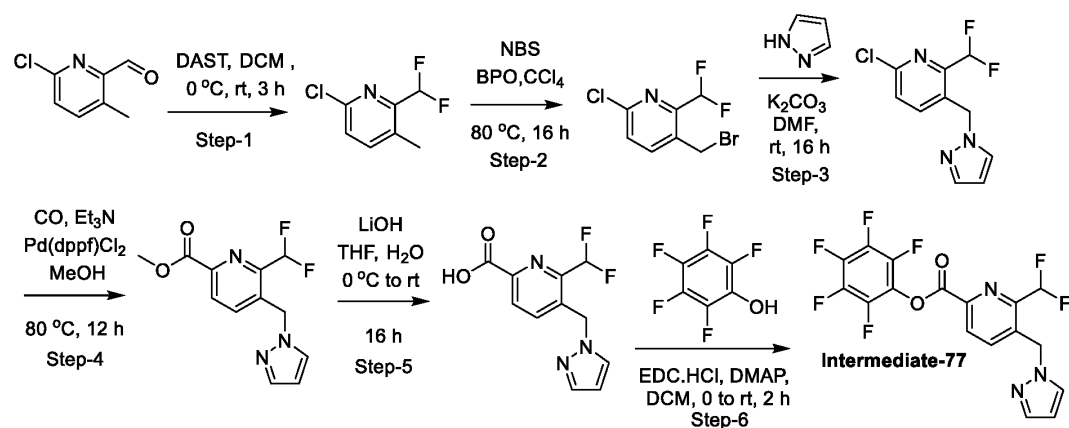
[0618] Step 4: Methyl 5-((1H-pyrazol-1-yl)methyl)-6-(trifluoromethoxy)picolinate

[0619] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 28 using appropriate reagents with suitable modifications. LC-MS: 302.1 [M+H]⁺.

[0620] Step 5: 5-((1H-pyrazol-1-yl)methyl)-6-(trifluoromethoxy)picolinic acid

[0621] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 288.0 [M+H]⁺

15 **Intermediate 77: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-(difluoromethyl)picolinate**



[0622] Step 1: 6-Chloro-2-(difluoromethyl)-3-methylpyridine

[0623] To a solution of 6-chloro-3-methylpicolinaldehyde (0.9 g, 5.78 mmol) in DCM (20 ml) was added DAST (2.79 g, 17.35 mmol) over 10 minutes at 0 °C. Then the reaction mixture was warmed to RT and stirred for 3 h. The reaction mixture was quenched with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over sodium

sulphate, filtered, and concentrated to afford the crude material. The crude material was purified by silica-gel flash column chromatography using 5% methanol in DCM as eluent to afford the title compound (0.91 g, 88.58 %). LC-MS: 178.0 [M+H]⁺

[0624] Step 2: 3-(Bromomethyl)-6-chloro-2-(difluoromethyl)pyridine

- 5 **[0625]** The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 1 using appropriate reagents with suitable modifications. ¹H NMR (DMSO-D₆, 400MHz): δ 7.92 (d, 1H), 7.48 (d, 1H), 6.70 (t, 1H), 4.69 (s, 2H).

[0626] Step 3: 3-((1H-pyrazol-1-yl)methyl)-6-chloro-2-(difluoromethyl)pyridine

- 10 **[0627]** The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 244.1 [M+H]⁺.

[0628] Step 4: Methyl 5-((1H-pyrazol-1-yl)methyl)-6-(difluoromethyl)picolinate

- 15 **[0629]** The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 28 using appropriate reagents with suitable modifications. LC-MS: 268.1 [M+H]⁺.

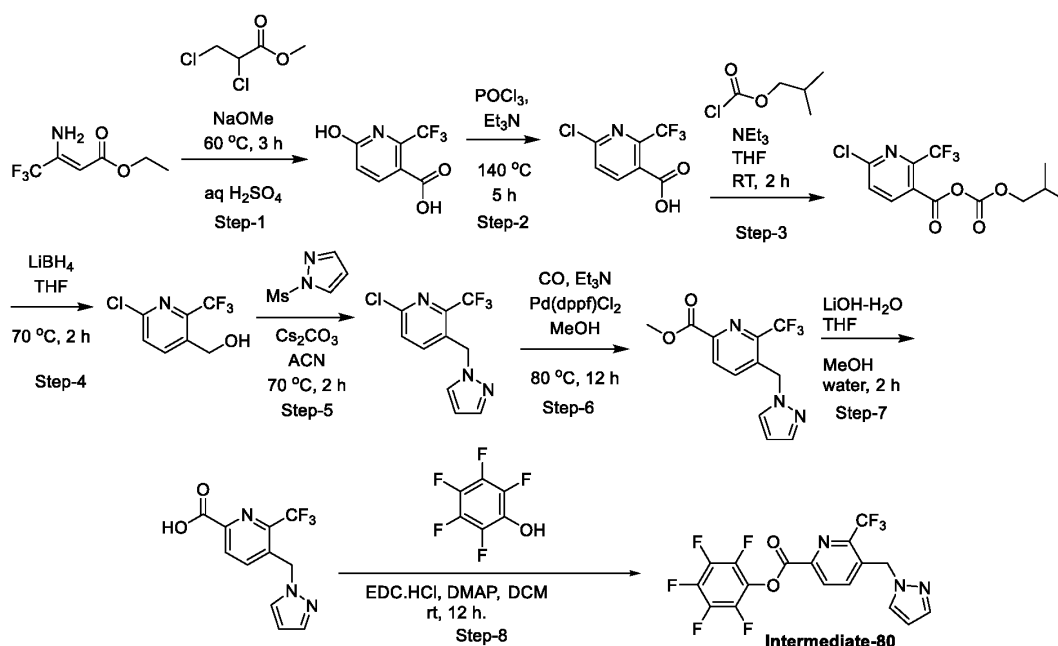
[0630] Step 5: 5-((1H-pyrazol-1-yl)methyl)-6-(difluoromethyl)picolinic acid

[0631] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 254.1 [M+H]⁺.

- 20 **[0632]** Step 6: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-(difluoromethyl)picolinate

[0633] The title compound was prepared using similar procedure to that described in Step 5 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 420.1 [M+H]⁺.

- 25 **Intermediate 80: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-(trifluoromethyl)picolinate**



[0634] Step 1: 6-Hydroxy-2-(trifluoromethyl)nicotinic acid

[0635] To a stirred solution of ethyl (Z)-3-amino-4,4,4-trifluorobut-2-enoate (5.0 g 27.30 mmol) in 25% sodium methoxide in methanol (29.5 mL) was added methyl 2,3-dichloropropanoate (4.71 g, 30.03 mmol) drop wise at 0 °C and stirred for 30 min at 0 °C. Then the reaction mixture was heated to 60 °C. Subsequently 20 % aqueous sodium hydroxide (73.5 mL) was added slowly to the reaction mixture over 2 h at 60 °C. The reaction mixture cooled to 0 °C and adjusted pH-3 using con. HCl to get the precipitate. The precipitate was filtered and washed with water to obtain the title compound (4.3 g, 90.6%).

LC-MS: 208.0 [M+H]⁺.

[0636] Step 2: 6-Chloro-2-(trifluoromethyl)nicotinic acid

[0637] To a stirred solution of 6-hydroxy-2-(trifluoromethyl)nicotinic acid (2.5 g, 12.05 mmol) and Et₃N (2.4 g 24.14 mmol) in xylene (2.5 mL) was added POCl₃ (2.5 mL 27.03 mmol) at 0 °C and then stirred at 140 °C for 5 h. The reaction mixture was cooled to RT, adjusted to pH-3 using aqueous sulfuric acid solution. The aqueous layer was extracted with xylene. The combined organic layer was dried over anhydrous sodium sulphate and concentrated to afford crude compound (2.2 g). LC-MS: 226.0 [M+H]⁺

[0638] Step 3: 6-Chloro-2-(trifluoromethyl)nicotinic (isobutyl carbonic) anhydride

[0639] To a stirred solution of 6-chloro-2-(trifluoromethyl) nicotinic acid (2.2 g, 9.75 mmol) and isobutyl carbonochloridate (1.66 g, 12.19 mmol) in THF (25 mL) was added Et₃N (1.48 g 14.63 mmol) at 0 °C and then stirred at RT for 2 h. The reaction was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. The crude was purified by silica-gel flash column chromatography using 5% ethyl acetate in hexane as eluent to afford the title compound (1.51 g, 47.5%). ¹H NMR, CDCl₃, 400MHz): δ 7.21 (d, 1H), 7.69 (d, 1H), 4.18 (d, 2H), 2.14 – 2.06 (m, 1H), 0.96 (d, 6H).

[0640] Step 4: (6-Chloro-2-(trifluoromethyl)pyridine-3-yl)methanol

[0641] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 212.0 [M+H]⁺

[0642] Step 5: 3-((1H-pyrazol-1-yl)methyl)-6-chloro-2-(trifluoromethyl)pyridine

[0643] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 262.0 [M+H]⁺.

[0644] Step 6: Methyl 5-((1H-pyrazol-1-yl)methyl)-6-(trifluoromethyl)picolinate

[0645] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 28 using appropriate reagents with suitable modifications. LC-MS: 286.1 [M+H]⁺.

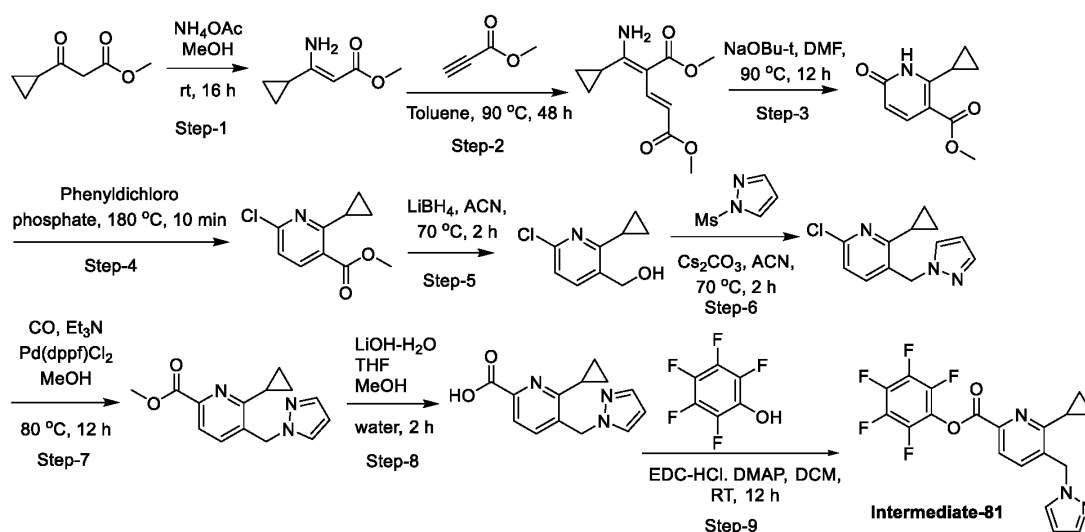
[0646] Step 7: 5-((1H-pyrazol-1-yl) methyl)-6-(trifluoromethyl)picolinic acid

[0647] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 272.0 [M+H]⁺.

[0648] Step 8: Perfluorophenyl 5-((1H-pyrazol-1-yl) methyl)-6-(trifluoromethyl)picolinate

[0649] The title compound was prepared using similar procedure to that described in Step 5 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 438.0 [M+H]⁺.

Intermediate 81: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-cyclopropylpicolinate



[0650] Step 1: Ethyl (Z)-3-amino-3-cyclopropylacrylate

[0651] To a stirred solution of ethyl 3-cyclopropyl-3-oxopropanoate (5.0 g, 35.17 mmol) in MeOH (100 mL) was added ammonium acetate (13.55 g 175.87 mmol) and stirred at RT for 16 h. The reaction mixture was concentrated, then diluted with DCM (50 mL) and stirred for 30 min to obtain solid. The solid was filtered and washed with DCM. The combined filtrate was concentrated to afford crude compound (6.55 g). LC-MS: 142.2 $[\text{M}+\text{H}]^+$.

[0652] Step 2: 5-Ethyl 1-methyl (2E,4Z)-4-(amino(cyclopropyl)methylene)pent-2-enedioate

[0653] To a stirred solution of ethyl (Z)-3-amino-3-cyclopropylacrylate (6.5 g, 46.04 mmol) in toluene (75 mL) was added methyl propiolate (5.42 g, 55.25 mmol) and stirred at 90 °C for 48 h. The reaction mixture was cooled to RT and concentrated to get the crude compound which was used in next step without any further purification (5.11 g, 46.38%). LC-MS: 238.1 $[\text{M}-\text{H}]^-$.

[0654] Step 3: Methyl 2-cyclopropyl-6-oxo-1,6-dihydropyridine-3-carboxylate

[0655] A stirred solution of 5-ethyl 1-methyl (2E,4Z)-4-(amino(cyclopropyl)methylene)pent-2-enedioate (5.1 g, 21.31 mmol) in DMF (50 mL) was added NaOtBu (0.30 g, 3.19 mmol) at 0 °C and then stirred at 90 °C for 12 h. The reaction mixture was cooled to RT and quenched with ice-water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated to get the crude compound. The crude compound was purified by silica-gel flash column chromatography using

60-70% ethyl acetate in hexane as eluent to afford the title compound (1.2 g, 29.14%). LC-MS: 194.1 [M+H]⁺.

[0656] Step 4: Methyl 6-chloro-2-cyclopropylpicotinate

[0657] A stirred solution of methyl 2-cyclopropyl-6-oxo-1,6-dihydropyridine-3-carboxylate (1.1 g, 5.69 mmol) in phenyldichloro phosphate (10 mL) and stirred at 180 °C for 10 min. The reaction mixture was added into ice water and extracted with EtOAc. The organic layer was washed with aqueous sodium bicarbonate solution, dried over Na₂SO₄, filtered, and concentrated to get the crude compound. The crude compound was purified by silica-gel flash column chromatography using 05-10% ethyl acetate in hexane as eluent to afford the title compound (1.2 g, 29.1%). LC-MS: 212.0 [M+H]⁺.

[0658] Step 5: (6-Chloro-2-cyclopropylpyridin-3-yl)methanol

[0659] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 31 using appropriate reagents with suitable modifications. LC-MS: 184.1 [M+H]⁺.

[0660] Step 6: 3-((1H-pyrazol-1-yl)methyl)-6-chloro-2-cyclopropylpyridine

[0661] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 234.1 [M+H]⁺.

[0662] Step 7: Methyl 5-((1H-pyrazol-1-yl)methyl)-6-cyclopropylpicolinate

[0663] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 28 using appropriate reagents with suitable modifications. LC-MS: 258.1 [M+H]⁺.

[0664] Step 8: 5-((1H-pyrazol-1-yl)methyl)-6-cyclopropylpicolinic acid

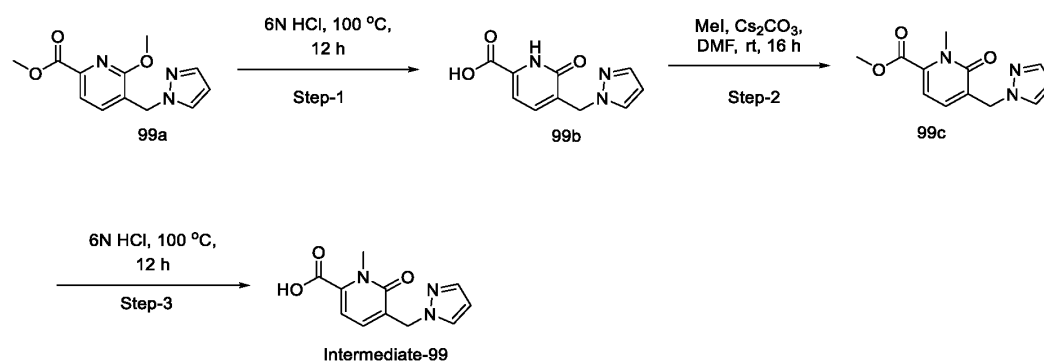
[0665] The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 1 using appropriate reagents with suitable modifications. LC-MS: 244.1 [M+H]⁺.

[0666] Step 9: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-cyclopropylpicolinate

[0667] The title compound was prepared using similar procedure to that described in Step 5 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 410.1 [M+H]⁺.

Intermediate 99: 5-((1H-pyrazol-1-yl)methyl)-1-methyl-6-oxo-1,6-dihydropyridine-2-carboxylic acid

5



[0668] Step 1: 5-((1H-Pyrazol-1-yl)methyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid

[0669] Methyl 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinate (0.5 g, 2.02 mmol) was dissolved in 6 N HCl in water (12 mL) and refluxed at 100 °C for 12 h. The reaction mixture was concentrated and washed with diethyl ether to get the crude title compound (0.5 g). LC-MS: 220.1 [M+H]⁺.

10

[0670] Step 2: Methyl 5-((1H-pyrazol-1-yl)methyl)-1-methyl-6-oxo-1,6-dihydropyridine-2-carboxylate

[0671] To a solution of 5-((1H-pyrazol-1-yl)methyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid (0.3 g, 1.37 mmol) in DMF (10 mL) was added Cs₂CO₃ (0.892 g, 2.73 mmol) and followed by MeI (0.389 g, 2.73 mmol) at 0 °C. The reaction mixture was slowly warmed to RT and stirred for 16 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated to get crude. The crude compound was purified by silica-gel flash column chromatography using 0-5% methanol in dichloromethane as eluent to obtain the title compound. (0.26 g, 76.9 %). LC-MS: 248.1 [M+H]⁺.

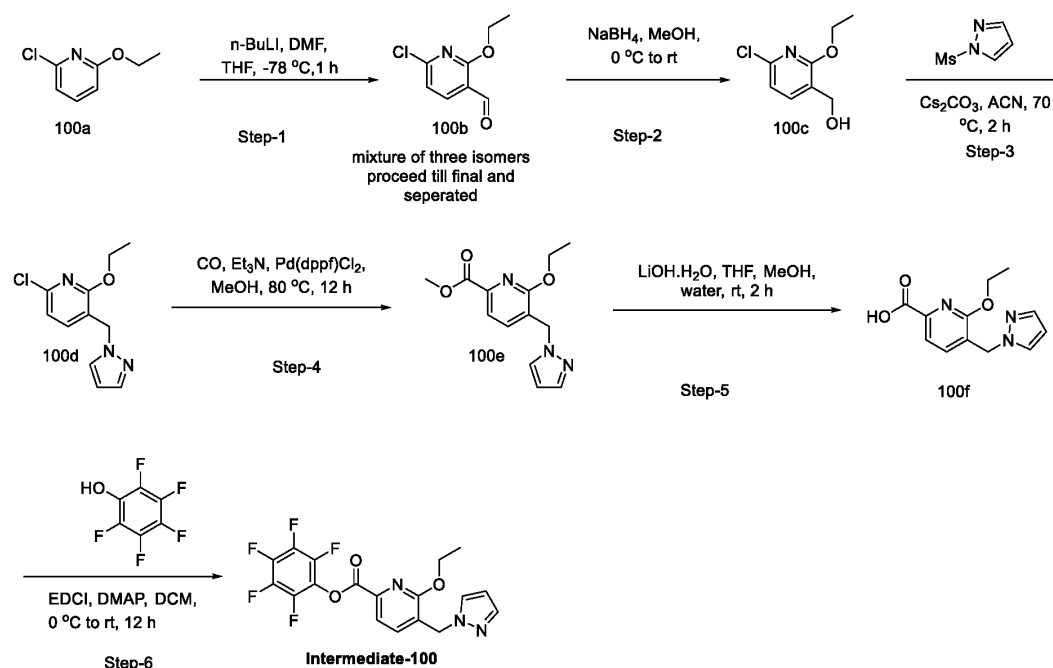
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[0672] Step 3: 5-((1H-pyrazol-1-yl)methyl)-1-methyl-6-oxo-1,6-dihydropyridine-2-carboxylic acid

[0673] Methyl 5-((1H-pyrazol-1-yl)methyl)-1-methyl-6-oxo-1,6-dihydropyridine-2-carboxylate (0.26 g, 1.05 mmol) was dissolved in 6N HCl in water (12 mL) and refluxed at 100 °C for 12 h. The reaction mixture was concentrated and washed with diethyl ether to get the crude title compound (0.24 g). LC-MS: 234.1 [M+H]⁺.

Intermediate 100: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-ethoxypicolinate



10 [0674] Step 1: 6-Chloro-2-ethoxynicotinaldehyde

[0675] To a solution of 2-chloro-6-ethoxypyridine (1.5 g, 9.51 mmol) in THF (40 mL) was added n-BuLi (8.93 mL, 14.29 mmol, 1.6 M in THF) at -78 °C and stirred at same temperature for 30 min. Then to the reaction mixture was added DMF (0.69 g, 9.54 mmol) drop wise at -78 °C and slowly warmed to RT and stirred for 16 h. The reaction mixture was cooled to -78 °C, quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated to afford crude compound. The crude compound was purified by silica-gel flash column

chromatography using 15% ethyl acetate in hexane as eluent to afford the title compound (0.50 g, 28.30%). LC-MS: 186.0 [M+H]⁺.

[0676] Step 2: (6-Chloro-2-ethoxypyridin-3-yl)methanol

[0677] The title compound was prepared using a similar procedure to that described in Step 1 of Intermediate 30 using appropriate reagents with suitable modifications (0.40 g, 98.98 %).

¹H NMR (CDCl₃, 400 MHz): δ 7.70 (d, 1H), 7.57 (d, 1H), 6.92 (d, 1H), 6.90 (s, 1H), 6.69 (d, 1H), 6.64 (d, 1H), 4.71 (d, 2H), 4.67 (d, 2H), 4.64 (d, 2H), 4.45 (q, 2H), 4.38 (q, 4H), 1.43 – 1.26 (m, 9H).

10 **[0678]** Step 3: 3-((1H-Pyrazol-1-yl)methyl)-6-chloro-2-ethoxypyridine

[0679] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 29 using appropriate reagents with suitable modifications (0.48 g, 95.71%). ¹H NMR (DMSO-D₆, 400 MHz): δ 7.88 (d, 1H), 7.79 (d, 1H), 7.78 (d, 1H), 7.53 (dd, 1H), 7.48 – 7.46 (m, 2H), 7.42 (d, 1H), 7.27 (d, 1H), 7.04 (d, 1H), 6.82 (d, 1H), 6.79 (s, 1H), 6.42 (d, 1H), 15 6.33 (d, 1H), 6.28 – 6.27 (m, 2H), 5.38 (s, 2H), 5.35 (s, 2H), 5.26 (s, 2H), 4.30 (q, 2H), 4.26 (q, 4H), 1.33 – 1.28 (m, 9H).

[0680] Step 4: Methyl 5-((1H-pyrazol-1-yl)methyl)-6-ethoxypicolinate

[0681] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 29 using appropriate reagents with suitable modifications (0.40 g, 80.87%). ¹H NMR (CDCl₃, 400 MHz): δ 7.61 (d, 1H), 7.58 – 7.57 (m, 3H), 7.5d – 7.52 (m, 3H), 7.48 (d, 20 1H), 7.24 – 7.21 (m, 2H), 6.84 – 6.82 (m, 1H), 6.57 (dd, 1H), 6.37 (dd, 1H), 6.33 (dd, 1H), 6.31 (dd, 1H), 5.66 (s, 2H), 5.36 (s, 2H), 5.35 (s, 2H), 4.55 (q, 2H), 4.46 – 4.38 (m, 4H), 3.99 (s, 3H), 3.96 (s, 6H), 1.46 – 1.26 (m, 9H).

[0682] Step 5: 5-((1H-Pyrazol-1-yl)methyl)-6-ethoxypicolinic acid

25 **[0683]** The title compound was prepared using similar procedure to that described in Step 4 of Intermediate 29 using appropriate reagents with suitable modifications (0.25 g): LC-MS: 248.1[M+H]⁺.

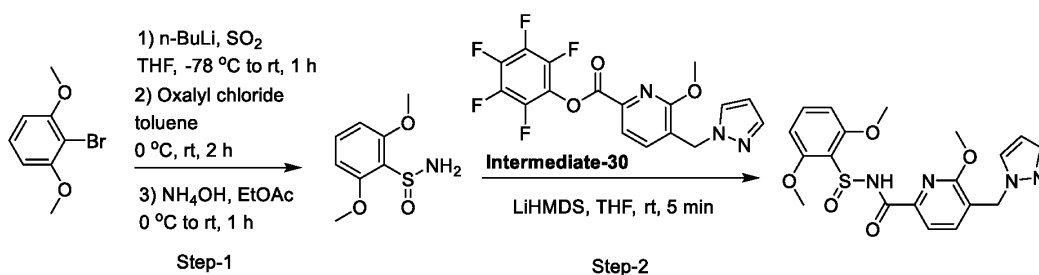
[0684] Step 6: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-ethoxypicolinate

[0685] The title compound was prepared using a similar procedure to that described in Step 5 of Intermediate 29 using appropriate reagents with suitable modifications (0.22 g, 54.82%). LC-MS: 414.1 [M+H]⁺.

5

d) Sulfinyl Intermediates

Intermediate 82: 5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfinyl)-6-methoxypicolinamide



[0686] Step 1: 2,6-Dimethoxybenzenesulfinamide

10 [0687] To a solution of 2-bromo-1,3-dimethoxybenzene (2 g, 9.21 mmol) in THF (15 mL) was added n-BuLi (17.3 mL, 27.64 mmol, 1.6M in hexane) at -78 °C and stirred at the same temperature for 1 h. Then SO₂ gas was bubbled into the reaction mixture for 30 min at -78 °C. The entire reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated to obtain the solid. The solid was dissolved in toluene and oxalyl chloride (0.93 mL, 10.8 mmol)

15 was added to the reaction mixture at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The reaction was quenched with ice-water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude compound. The crude compound was again dissolved in DCM (10 mL) and 7N methanolic ammonia (30 mL) was added to the reaction mixture and stirred for 30 min at RT. The reaction mixture was

20 diluted with water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude compound. The crude compound was purified by silica-gel flash column chromatography using 60% ethyl acetate in hexane as eluent to afford the title compound (0.5 g, 34.5%). LC-MS: 202.1 [M+H]⁺.

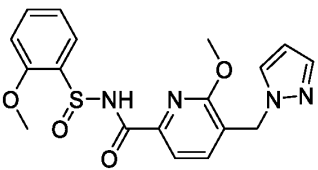
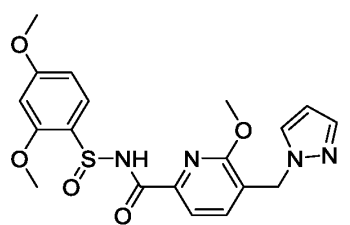
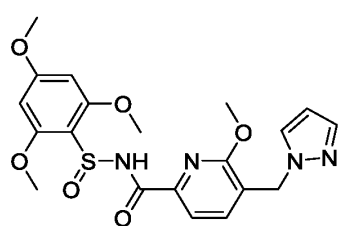
25 [0688] Step 2: 5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfinyl)-6-methoxypicolinamide

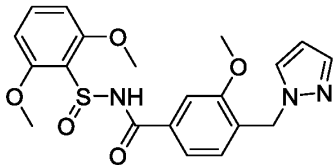
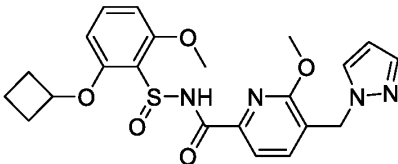
- [0689]** To a solution of perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinate (0.15 g, 0.37 mmol), and 2,6-dimethoxybenzenesulfonamide (0.091 g, 0.45 mmol) in THF (5 mL) was added LiHMDS (1.12 mL, 1.13 mmol, 1.0 M in THF) and stirred at RT for 10 min. The reaction mixture was quenched with saturated NH₄Cl solution and extracted with 10% MeOH in DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude compound. Crude compound was purified by silica-gel flash column chromatography using 2-5% MeOH in DCM as eluent to afford the title compound (0.12 g, 76.6%). LC-MS: 415.0 [M-H]⁻.

Intermediates 83 to 87

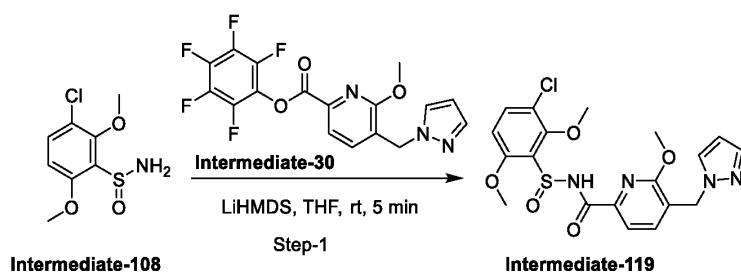
- [0690]** The following intermediates listed in Table 10 were prepared by following similar procedures described above for Intermediate 82 using appropriate reagents with suitable modifications known to the one skilled in the art.

Table 10. Intermediates

Intermediate	Structure	LC-MS
83		LC-MS: 385 [M-H] ⁻ .
84		LC-MS: 415.0 [M-H] ⁻ .
85		LC-MS: 445.0 [M-H] ⁻ .

86		LC-MS: 416.1 [M+H] ⁺ .
87		LC-MS: 455.1 [M-H] ⁻ .

Intermediate 119: 5-((1H-Pyrazol-1-yl)methyl)-N-((3-chloro-2,6-dimethoxyphenyl)sulfinyl)-6-methoxypicolinamide



- 5 **Step 1:** 5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfinyl)-6-methoxypicolinamide

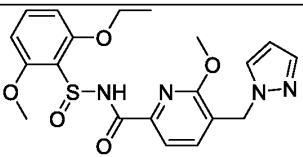
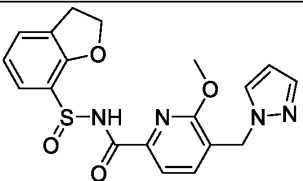
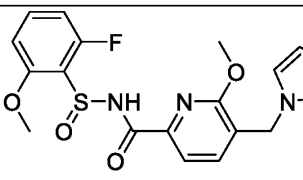
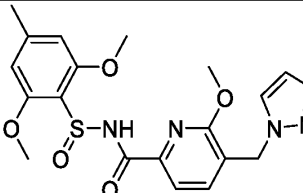
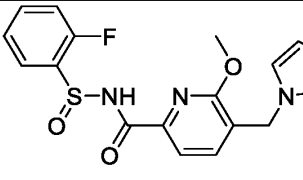
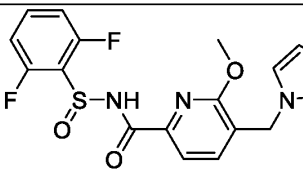
[0691] The title compound was prepared using a similar procedure to that described in Step 2 of Intermediate 82 using appropriate reagents with suitable modifications. (0.2 g, 17.71%). LC-MS: 449.0 [M-H]⁻.

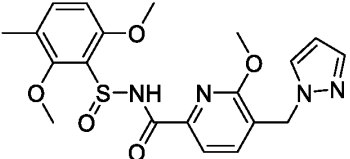
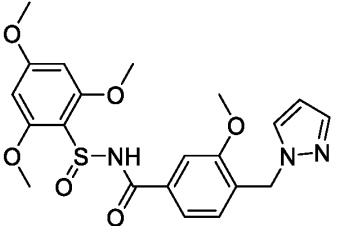
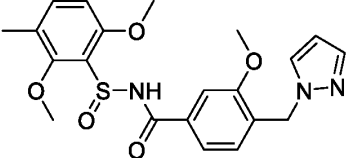
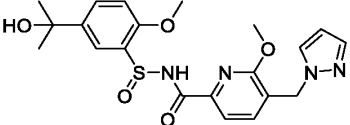
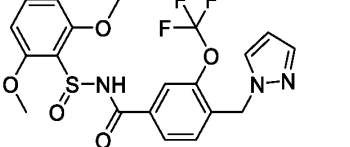
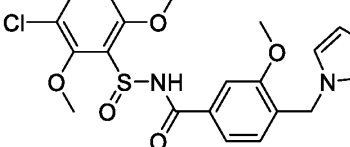
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Intermediates 120 to 131

[0692] The following intermediates listed in Table 11 were prepared by following similar procedures described above for Intermediate 119 and Step 2 of Intermediate 82 using appropriate reagents with suitable modifications known to the one skilled in the art.

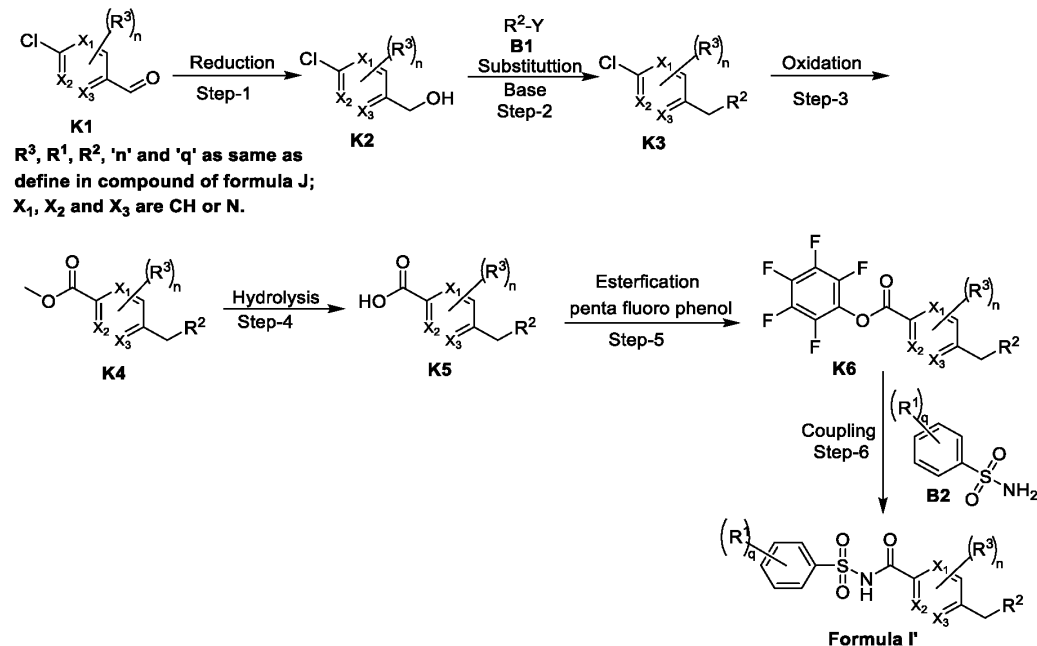
Table 11

Intermediate	Structure	Spectral data
120		LC-MS: 429.05 [M-H] ⁻ .
121		LC-MS: 397.1 [M-H] ⁻ .
122		LC-MS: 403.0 [M-H] ⁻ .
123		LC-MS: 429.3 [M-H] ⁻ .
124		LC-MS: 375.1 [M+H] ⁺ .
125		LC-MS: 393.0 [M+H] ⁺ .

Intermediate	Structure	Spectral data
126		LC-MS: 429.0 [M-H] ⁻ .
127		LC-MS: 444.1 [M-H] ⁻ .
128		LC-MS: 430.1 [M+H] ⁺ .
129		LC-MS: 443.2 [M-H] ⁻ .
130		LC-MS: 468.4 [M-H] ⁻ .
131		LC-MS: 450.1 [M+H] ⁺ .

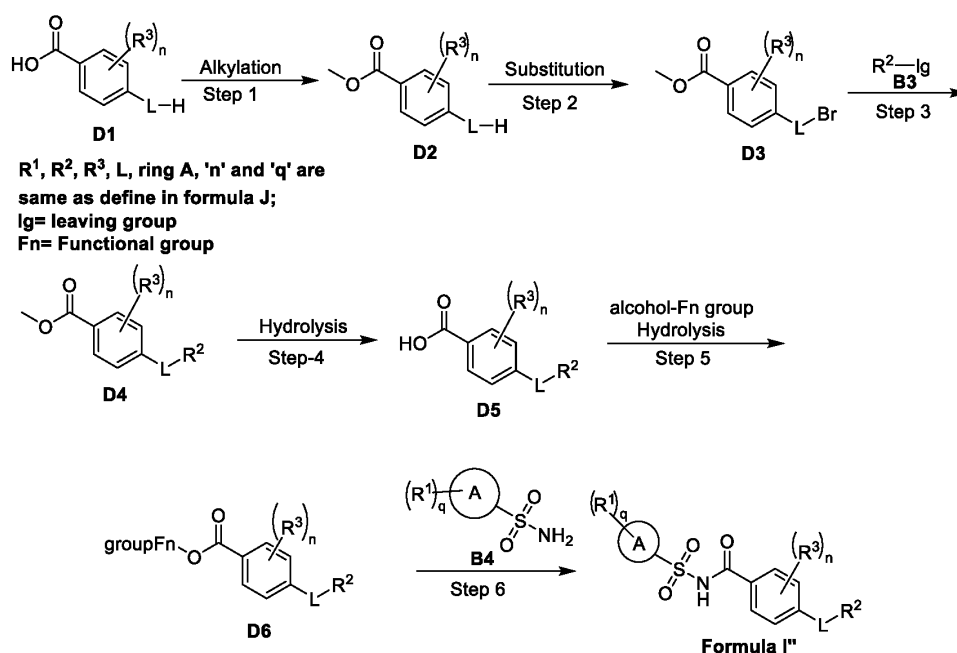
GENERAL SYNTHETIC SCHEMES:

[0693] Certain compounds of the present invention can be made by following the process as given in General scheme-I.

General scheme: I

[0694] The general scheme-I for the synthesis of compound represented by formula (I') is depicted in above scheme. The compound of formula (K_1) is undergoing reduction reaction in suitable solvent and suitable reducing reagent to yield compound of formula (K_2) which upon further react compound of formula (B_1) in presence of suitable substituent reagent and solvent can provide compound of formula (K_3). The compound of formula (K_3) undergoes oxidation reaction followed by substitution reaction to result in compound of formula (K_4) which further hydrolysis with suitable base and solvent to yield compound of formula (K_5). The compound of formula (K_5) reacts with pentafluoro phenol with suitable solvent to result ester compound of (K_6). The compound of formula (K_6) can react with formula (B_2) in suitable reagent and solvent to result in the compound of formula (I').

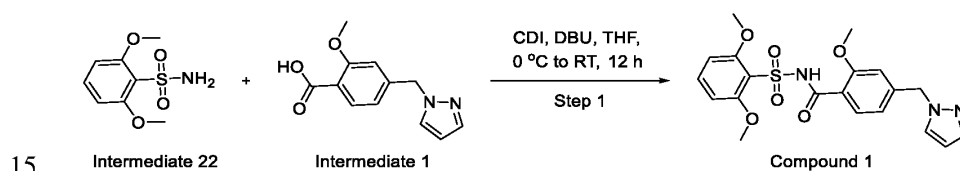
General scheme: II



[0695] The general scheme-II for the synthesis of compound represented by formula (I') is depicted in above scheme. The compound of formula (D₁) is reacted with alkylation reagent in suitable solvent and to yield compound of formula (D₂) which upon further undergoes substitution reaction in presence of suitable substituent reagent and solvent can provide compound of formula (D₃). The compound of formula (D₃) reacts with formula (B₃) to result in compound of formula (D₄) which further hydrolysis with suitable base and solvent to yield compound of formula (D₅). The compound of formula (D₅) reacts with alcohol in suitable solvent to result ester compound of (D₆). The compound of formula (D₆) can react with formula (B₄) in suitable reagent and solvent to result in the compound of formula (I').

e) Compound Examples

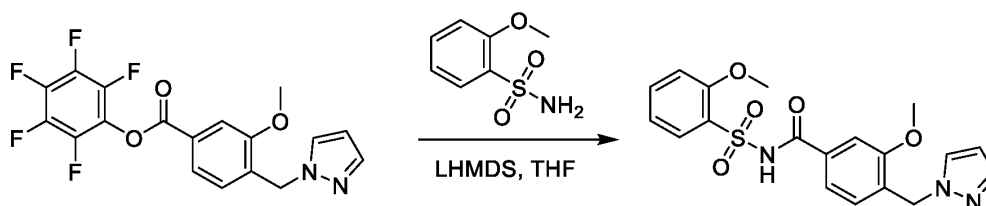
Example 1. Compound 1: 4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-2-methoxybenzamide



[0696] To a solution of 4-((1H-pyrazol-1-yl)methyl)-2-methoxybenzoic acid (0.2 g, 0.86 mmol) in THF (10 mL) was added CDI (0.16 g, 1.03 mmol) and stirred at RT for 1 h. The reaction mixture was cooled to 0 °C, were added 2,6-dimethoxybenzenesulfonamide (0.2 g, 0.94 mmol), DBU (0.18 g, 1.2 mmol) and stirred for 15 minutes at same temperature, then gradually warmed to RT and stirred for overnight. The reaction mixture was concentrated to get crude compound. The crude compound was purified by preparative HPLC to afford the title compound (0.015 g, 4%).

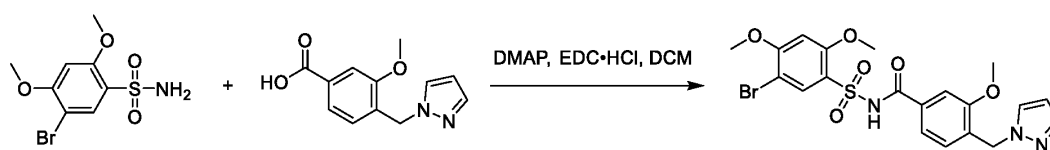
[0697] Preparative HPLC method: Mobile phase A-0.05 % TFA in water; B-Acetonitrile; column used- Luna Omega PS, C-18 (250 ×21.2mm), 5μ. Gradient programme: 0 %B at 10 minutes, 20% B at 2 minutes, 40% B at 10 minutes. LC-MS: 432.2 [M+H]⁺; ¹H NMR (DMSO-d₆, 400 MHz): δ 11.27 (s, 1H), 7.87 (d, 1H), 7.55-7.45 (m, 3H), 7.07, (s, 1H), 6.80 (s, 1H), 6.78 (s, 1H), 6.75 (d, 1H), 6.30 (t, 1H), 5.39 (s, 2H), 3.88 (s, 3H), 3.79 (s, 6H).

Example 2. Compound 26: N-(2-methoxyphenyl)sulfonyl-3-methoxy-4-(pyrazol-1-ylmethyl)benzamide



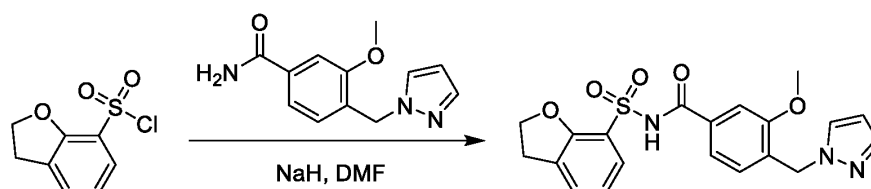
[0698] To a solution of perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-3-methoxybenzoate (0.100 g, 0.251 mmol), 2-methoxybenzenesulfonamide (0.056 g, 0.301 mmol) in THF (3 mL) was added LiHMDS (1.0 M in THF solution) (1.0 mL, 1.0 mmol) and the entire reaction mixture stirred at RT for 10 min. The reaction mixture was quenched ice then diluted with saturated NH₄Cl solution and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and concentrated to afford the crude compound, which was further purified by prep TLC eluted at 80 % ethyl acetate in hexane (0.03 g, 30%): LC-MS: 402.3 [M+H]⁺; ¹H NMR (DMSO-d₆, 400 MHz): δ 12.50 (s, 1H), 7.91 (dd, 1H), 7.78 (d, 1H), 7.63 (dd, 1H), 7.55 (d, 1H), 7.47 (dd, 1H), 7.41 (dd, 1H), 7.21 (d, 1H), 7.16 (t, 1H), 6.78 (d, 1H), 6.31 (t, 1H), 5.33 (s, 2H), 3.91 (d, 3H), 3.85 (d, 3H).

Example 3. Compound 45: N-(5-bromo-2,4-dimethoxy-phenyl)sulfonyl-3-methoxy-4-(pyrazol-1-ylmethyl)benzamide



[0699] A vial equipped with a stir bar was charged with 5-bromo-2,4-dimethoxybenzenesulfonamide (1.00 eq, 40 mg, 0.135 mmol) and 3-methoxy-4-(pyrazol-1-ylmethyl)benzoic acid (1.24 eq, 39 mg, 0.167 mmol) in DCM (1.4 mL) and 4-dimethylaminopyridine (4.00 eq, 66 mg, 0.540 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.50 eq, 39 mg, 0.203 mmol) was added to the reaction vial and left to stir at room temperature under nitrogen for 1.5 h. Reaction mixture diluted with DCM (5 mL), quenched with water (15 mL), and extracted with DCM (10 mL x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Crude product was purified via HPLC (Column: Luna 5uM, C18, LC column 100 x 30 mm. Flow rate: 42 mL/min. Gradient: 13-70%; isocratic at 70%; Acetonitrile-water. Run time: 14 min. Modifier: 0.1% formic acid) to yield the title compound (48 mg, 0.092 mmol, 68%): LC-MS: 512 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 12.54 (s, 1H), 7.94 (s, 1H), 7.78 (dd, J = 2.3, 0.6 Hz, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.47 (dd, J = 1.9, 0.7 Hz, 1H), 7.41 (dd, J = 7.9, 1.6 Hz, 1H), 6.86 (s, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.28 (t, J = 2.1 Hz, 1H), 5.33 (s, 2H), 3.97 (s, 3H), 3.91 (d, J = 6.1 Hz, 6H).

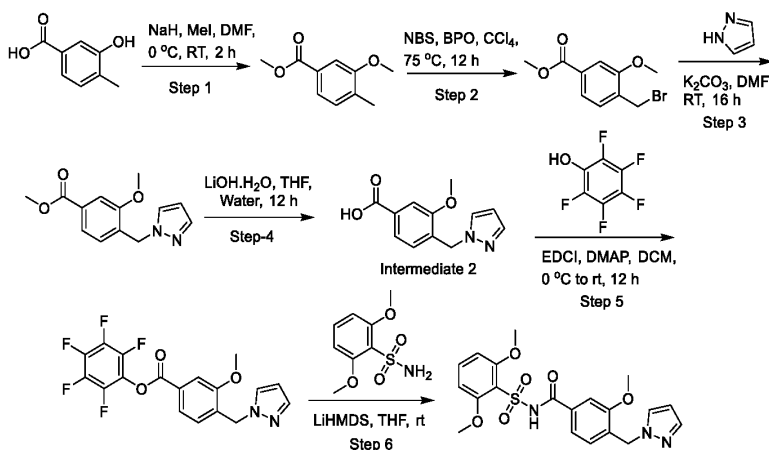
Example 4. Compound 70: N-(2,3-dihydrobenzofuran-7-yl)sulfonyl-3-methoxy-4-(pyrazol-1-ylmethyl)benzamide



[0700] 3-Methoxy-4-(pyrazol-1-ylmethyl)benzamide (1.00 eq, 40 mg, 0.173 mmol) was dissolved in DMF (1.5 mL) and cooled to 0 °C. Sodium hydride 60% in mineral oil (1.30 eq, 5.4 mg, 0.225 mmol) was added and stirred for 30 min. 2,3-Dihydro-1-benzofuran-7-sulfonyl chloride (1.10 eq, 42 mg, 0.190 mmol) was added and stirred for 2 h allowing to warm to room temperature. The reaction mixture was directly purified by HPLC on a Kinetex 5 um C18 100 Å column (size: 100 x 30.0 mm; gradient: 5-55% 0.1% formic acid in ACN in 0.1% formic acid in water) then lyophilized to give the title compound (3.4 mg, 5% yield): LC-MS: m/z = 414.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 7.75 (s, 1H), 7.54 (d, J = 1.5 Hz, 2H), 7.46 (d, J = 1.8

Hz, 1H), 7.42 (dd, J = 7.8, 1.5 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.53 (d, J = 3.2 Hz, 1H), 6.27 (t, J = 2.1 Hz, 1H), 5.31 (s, 2H), 4.56 (s, 2H), 3.87 (s, 3H), 3.18 (s, 2H).

Example 5. Compound 14: 4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide



5

[0701] Step 1: Methyl 3-methoxy-4-methylbenzoate

[0702] To a stirred solution of 3-hydroxy-4-methylbenzoic acid (20 g, 32.8 mmol) in DMF (250 mL) was cooled to 0 °C and added NaH (7.9 g, 328.62 mmol) followed by methyl iodide (24.6 mL, 394.3 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 1 h.

10 The reaction mixture was poured into ice water to obtain a precipitate, which was filtered and washed with water and dried under vacuum to obtain the title compound (20 g, 97.4%). LC-MS: 181.3 [M+H]⁺.

[0703] Step 2: Methyl 4-(bromomethyl)-3-methoxybenzoate

[0704] To a solution of methyl 3-methoxy-4-methylbenzoate (23 g, 127.63 mmol) in CCl₄ (300 mL) were added NBS (31.8 g, 178.69 mmol) and benzoyl peroxide (BPO, 4.63 g, 19.14 mmol) and stirred at 75 °C for overnight. Reaction mixture was then cooled to RT and diluted with DCM and washed with water. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude compound (33 g) which was used in the next step without further purification. LC-MS: 260.9 [M+H]⁺.

15

20 **[0705]** Step 3: Methyl 4-((1H-pyrazol-1-yl)methyl)-3-methoxybenzoate

[0706] To a stirred solution of methyl 4-(bromomethyl)-3-methoxybenzoate (33 g, 127.36 mmol), and 1H-pyrazole (13 g, 191.04 mmol) in DMF (300 mL) was added K₂CO₃ (44 g,

318.41 mmol) and stirred at RT for 16 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄, filtered, and concentrated to afford crude compound. The crude compound was purified by silica-gel flash column chromatography using 10-40% ethyl acetate in hexane as eluent to afford the title compound (11 g, 35%). LC-MS: 247.2 [M+H]⁺.

[0707] Step 4: 4-((1H-pyrazol-1-yl)methyl)-3-methoxybenzoic acid

[0708] To a stirred solution of methyl 4-((1H-pyrazol-1-yl)methyl)-3-methoxybenzoate (10 g, 40.6 mmol) in THF (150 mL), MeOH (40 mL) and water (60 mL) was added LiOH.H₂O (4.87 g, 203.03 mmol) and stirred for 12 h at RT. The reaction mixture was diluted with ice-cold water, adjusted pH to 3 using 1N HCl solution to obtain a precipitate. The precipitate was filtered, washed with water, and dried under vacuum to afford the title compound (9 g, 95%). LC-MS: 233.2 [M+H]⁺.

[0709] Step 5: Perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-3-methoxybenzoate

[0710] To a solution of 4-((1H-pyrazol-1-yl)methyl)-2-methoxybenzoic acid (1.2 g, 5.17 mmol), and 2,3,4,5,6-pentafluorophenol (1.14 g, 6.20 mmol) in DCM (25 mL) was added DMAP (0.127 g, 1.03 mmol) followed by EDC.HCl (1.49 g, 7.75 mmol) and stirred at RT for 12 h. The reaction mixture was quenched with ice water and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude compound which was purified by silica-gel flash column chromatography using 10-15% ethyl acetate in hexanes as eluent to obtain the title compound (1.8 g, 87%). LC-MS: 399.1 [M+H]⁺.

[0711] Step 6: 4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide

[0712] To a solution of perfluorophenyl 4-((1H-pyrazol-1-yl)methyl)-3-methoxybenzoate (1 g, 2.551 mmol), and 2,6-dimethoxybenzenesulfonamide (Intermediate 22, 0.545 g, 2.511 mmol) in THF (30 mL) was added LiHMDS (7.51 mL, 7.53 mmol, 1.0 M in THF) and stirred at RT for 10 min. The reaction mixture was quenched with saturated NH₄Cl solution and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude compound. The crude compound was purified by silica-gel flash column chromatography using 60-80% EtOAc in hexane as eluent to get the title compound which was again triturated in ethyl acetate to obtain the title compound (0.3 g, 28%). LC-MS: 432.2 [M+H]⁺; ¹H NMR (DMSO-D₆, 400MHz): δ 12.20 (s, 1H), 7.80 (s, 1H), 7.58

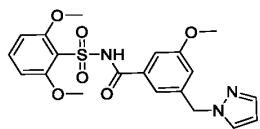
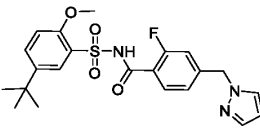
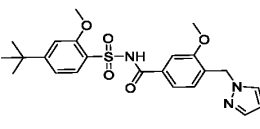
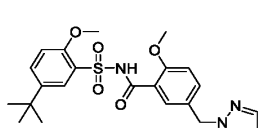
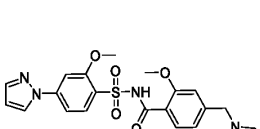
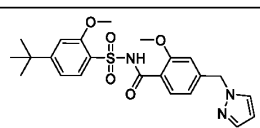
(s, 1H), 7.48 (d, 1H), 7.45 (dd, 2H), 6.85 – 6.75 (m, 3H), 6.28 (t, 1H), 5.34 (s, 2H), 3.92 (s, 3H), 3.78 (s, 6H).

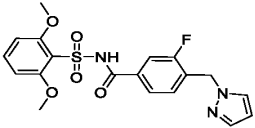
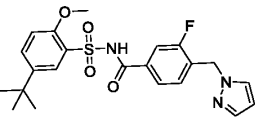
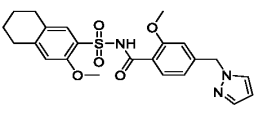
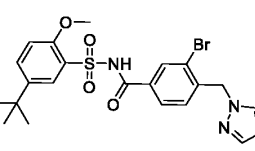
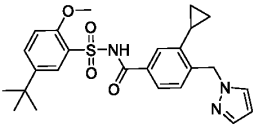
Example 6. Compounds 2 to 65

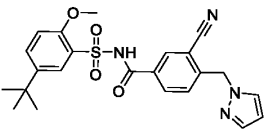
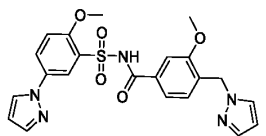
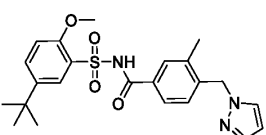
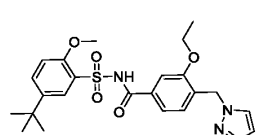
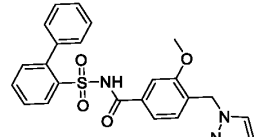
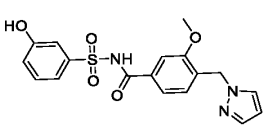
[0713] The following compounds listed in Table 12 were prepared by following similar procedures as described above using appropriate reagents with suitable modifications known to the one skilled in the art. Intermediates and Example procedure for coupling are shown in the table below. Intermediates are commercially available if syntheses are not indicated.

Table 12. Compound Synthesis and Characterization

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
2		Intermediate 1 & Example 1	LC-MS: 402.1 [M+H] ⁺ ; ¹ H NMR: δ 11.60 (s, 1H), 7.85-7.82 (m, 2H), 7.66-7.61 (m, 1H), 7.45 (d, 1H), 7.34 (d, 1H), 7.21 (d, 1H), 7.10 (t, 1H), 7.01 (s, 1H), 6.70 (d, 1H), 6.26 (t, 1H), 5.34 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H).
3		Intermediate 1 & Intermediate 20/ Example 1	LC-MS: 430.2 [M+H] ⁺ ; ¹ H NMR: δ 11.55 (1H), 7.83 (d, 1H), 7.65 (d, 1H), 7.48 (dd, 1H), 7.45 (d, 1H), 7.35 (d, 1H), 7.13 (d, 1H), 7.01 (s, 1H), 6.70 (d, 1H), 6.26 (t, 1H), 5.34 (s, 2H), 3.81 (s, 6H), 2.60 (q, 2H), 1.14 (t, 3H).
4		Intermediate 1 & Intermediate 21/ Example 1	LC-MS: 458.3 [M+H] ⁺ ; ¹ H NMR (CD ₃ OD): δ 11.56 (s, 1H), 7.83 (d, 1H), 7.78 (d, 1H), 7.67 (dd, 1H), 7.45 (d, 1H), 7.36 (d, 1H), 7.14 (d, 1H), 7.01 (s, 1H), 6.70 (d, 1H), 6.26 (t, 1H), 5.34 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 1.26 (s, 9H).
5		Intermediate -1 & Intermediate -19/ Example 1	LC-MS: 442.1 [M+H] ⁺ ; ¹ H NMR: δ 11.67 (s, 1H), 7.85 (dd, 1H), 7.68 (s, 1H), 7.48 (dd, 1H), 7.38 (d, 1H), 7.09 (s, 1H), 7.01 (s, 1H), 6.73 (dd, 1H), 6.29 (t, 1H), 5.36 (s, 2H), 3.82 (s,

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
			6H), 2.91 (t, 2H), 2.86 (t, 2H), 2.09-2.01 (m, 2H).
6		Intermediate -3 & Intermediate 22/ Example 1	LC-MS: 432.2 [M+H] ⁺ ; ¹ H NMR: δ 12.21 (s, 1H), 7.84 (dd, 1H), 7.52 (t, 1H), 7.47 (dd, 1H), 7.44 (dd, 1H), 7.31 (s, 1H), 6.99 (s, 1H), 6.79 (d, 2H), 6.28 (t, 1H), 5.34 (s, 2H), 3.81 (s, 3H), δ 3.77 (s, 6H).
7		Intermediate -4 & Intermediate 21/ Example 1	LC-MS: 446.1 [M+H] ⁺ ; ¹ H NMR: δ 9.08 (dd, 1H), 8.42 (dd, 1H), 7.98 (d, 1H), 7.61 (d, 1H), 7.51 (dd, 1H), 7.36 (d, 1H), 7.31 – 7.28 (m, 3H), 6.30 (t, 1H), 5.82 (s, 2H), 4.15 (s, 3H), 1.29 (s, 9H).
8		Intermediate 2 & Intermediate -17/ Example 1	LC-MS: 458.2 [M+H] ⁺ ; ¹ H NMR: δ 12.46 (s, 1H), 7.86 (d, 1H), 7.79 (d, 1H), 7.69 (dd, 1H), 7.54 (d, 1H), 7.47 (d, 1H), 7.41 (dd, 1H), 7.14 (d, 1H), 6.77 (d, 1H), 6.28 (t, 1H), 5.33 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 1.30 (s, 9H).
9		Intermediate -5 & Intermediate 21/ Example 1	LC-MS: 458.0 [M+H] ⁺ ; ¹ H NMR: δ 11.66 (s, 1H), 7.83 (d, 1H), 7.79 (d, 1H), 7.71 (dd, 1H), 7.44-7.41 (m, 2H), 7.35 (d, 1H), 7.19 (d, 1H), 7.14 (d, 1H), 6.24 (t, 1H), 5.27 (s, 2H), 3.86 (d, 6H), 1.30 (s, 9H).
10		Intermediate -1 & Intermediate -15/ Example 1	LC-MS: 468.1 [M+H] ⁺ ; ¹ H NMR: δ 11.75 (s, 1H), 8.71 (d, 1H), 7.97 (d, 1H), 7.87 – 7.84 (m, 2H), 7.68 – 7.60 (m, 2H), 7.49 (s, 1H), 7.38 (d, 1H), 7.05 (s, 1H), 6.75 (d, 1H), 6.64 (s, 1H), 6.29 (s, 1H), 5.38 (s, 2H), 3.99 (s, 3H), 3.85 (s, 3H).
11		Intermediate -1 & Intermediate -17/ Example 1	LC-MS: 458.1 [M+H] ⁺ ; ¹ H NMR: δ 11.52 (s, 1H), 7.86 (dd, 1H), 7.79 (d, 1H), 7.49 (d, 1H),

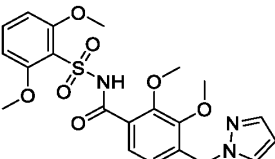
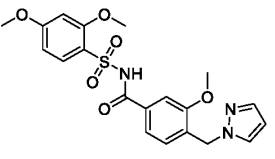
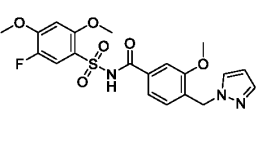
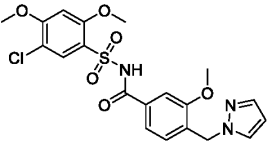
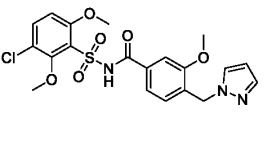
Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
		Example 1	7.41 (d, 1H), 7.18-7.14 (m, 2H), 7.06 (s, 1H), 6.75 (dd, 1H), 6.30 (t, 1H), 5.38 (s, 2H), 3.92 (s, 3H), 3.86 (s, 3H), 1.32 (s, 9H).
12		Intermediate -6 & Intermediate 22/ Example 1	LC-MS: 420.0 [M+H] ⁺ ; ¹ H NMR: δ 12.30 (s, 1H), 7.87 (d, 1H), 7.76 (d, 1H), 7.71 (d, 1H), 7.54-7.49 (m, 2H), 7.14 (t, 1H), 6.78 (d, 2H), 6.30 (t, 1H), 5.46 (s, 2H), 3.77 (s, 6H).
13		Intermediate -6 & Intermediate 21/ Example 1	LC-MS: 446.0 [M+H] ⁺ ; ¹ H NMR: δ 12.58 (s, 1H), 7.86-7.84 (m, 2H), 7.75-7.66 (m, 3H), 7.48 (d, 1H), 7.16 – 7.12 (m, 2H), 6.29 (t, 1H), 5.45 (s, 2H), 3.82 (s, 3H), 1.30 (s, 9H).
15		Intermediate -1 & Intermediate -18/ Example 1	LC-MS: 456.2 [M+H] ⁺ ; ¹ H NMR: δ 7.82 (d, 1H), 7.48-7.45 (m, 2H), 7.30 (d, 1H), 6.87 (s, 1H), 6.74 (s, 1H), 6.68 (d, 1H), 6.27 (t, 1H), 5.31 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 2.78 – 2.71 (m, 2H), 2.70 – 2.63 (m, 2H), 1.74-1.71(m, 4H).
16		Intermediate -7 & Intermediate 21/ Example 1	LC-MS: 506.0 [M+H] ⁺ ; ¹ H NMR: δ 12.65 (s, 1H), 8.15 (d, 1H), 7.87 (d, 1H), 7.84 (d, 1H), 7.78 (dd, 1H), 7.54 – 7.52 (m, 2H), 7.08 (s, 1H), 6.79 (d, 1H), 6.33 (t, 1H), 5.45 (s, 2H), 3.76 (s, 3H), 1.29 (s, 9H).
17		Intermediate -11 & Intermediate 21/ Example 1	LC-MS: 466.1 [M-H] ⁻ ; ¹ H NMR: δ 12.45 (s, 1H), 7.85 (d, 1H), 7.83 (d, 1H), 7.68 (brs, 1H), 7.60 (dd, 1H), 7.56 (d, 1H), 7.51 (d, 1H), 7.15 (brd, 1H), 6.80 (d, 1H), 6.31 (t, 1H), 5.58 (s, 2H), 3.81 (s, 3H), 2.10-2.04 (m, 1H), 1.30 (s, 9H), 0.99-0.94 (m, 2H), 0.79 – 0.70 (brm, 2H).

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ^1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
18		Intermediate -13 & Intermediate 21/ Example 1	LC-MS: 453.1 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.7 (s, 1H), 8.33 (d, 1H), 8.05 (dd, 1H), 7.88 (d, 1H), 7.82 (d, 1H), 7.67 (dd, 1H), 7.48 (d, 1H), 7.17 (d, 1H), 7.12 (d, 1H), 6.30 (t, 1H), 5.58 (t, 2H), 3.79 (s, 3H), 1.27 (s, 9H).
19		Intermediate 2 & Intermediate -16/ Example 1	LC-MS: 468.1 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.69 (s, 1H), 8.50 (brs, 1H), 8.32 (s, 1H), 8.03 (brs, 1H), 7.77 – 7.75 (m, 2H), 7.55 (s, 1H), 7.47 (dd, 1H), 7.42 (dd, 1H), 7.30 (brs, 1H), 6.78 (d, 1H), 6.56 (t, 1H), 6.28 (t, 1H), 5.32 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H).
20		Intermediate -12 & Intermediate 21/ Example 1	LC-MS: 442.1 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.37 (s, 1H), 7.86 (d, 1H), 7.79 (d, 1H), 7.73 (s, 1H), 7.67 – 7.64 (m, 2H), 7.50 (dd, 1H), 7.11 (d, 1H), 6.83 (d, 1H), 6.31 (t, 1H), 5.40 (s, 2H), 3.81 (s, 3H), 2.33 (s, 3H), 1.30 (s, 9H).
21		Intermediate -10 & Intermediate 21/ Example 1	LC-MS: 472.05 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.44 (s, 1H), 7.86 (d, 1H), 7.78 (d, 1H), 7.68 (d, 1H), 7.54 (d, 1H), 7.47 (dd, 1H), 7.41 (dd, 1H), 7.14 (d, 1H), 6.84 (d, 1H), 6.29 (t, 1H), 5.33 (s, 2H), 4.16 (q, 2H), 3.82 (s, 3H), 1.38 (t, 3H), 1.31 (s, 9H).
22		Intermediate 2 & Intermediate 23/ Example 1	LC-MS: 448.2 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.07 (s, 1H), 8.17 (dd, 1H), 7.78 (d, 1H), 7.77-7.61 (m, 2H), 7.48 (dd, 1H), 7.41-7.18 (m, 8H), 6.72 (d, 1H), 6.30 (t, 1H), 5.35 (s, 2H), 3.85 (s, 3H).
23		Intermediate 2 & Intermediate 24/ Example 1	LC-MS: 388.0 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.50 (s, 1H), 10.21 (s, 1H), 7.77 (d, 1H), 7.45 (dd, 2H), 7.42 – 7.37 (m, 4H), 7.07 – 7.05 (m, 1H), 6.78 (d, 1H), 6.28 (t, 1H), 5.32 (s, 2H), 3.89 (s, 3H).

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
24		Intermediate 2 & Intermediate 25/ Example 1	LC-MS: 480.0 [M+H] ⁺ ; ¹ H NMR: δ 12.75 (s, 1H), 8.14 (s, 1H), 7.93 (d, 1H), 7.77 – 7.76 (m, 1H), 7.53 (s, 1H), 7.47 (d, 1H), 7.43 – 7.42 (dd, 1H), 7.22 – 7.12 (m, 1H), 6.76 (d, 1H), 6.28 (t, 1H), 5.32 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H).
25		Intermediate -14 & Intermediate 21/ Example 1	LC-MS: 496.1[M+H] ⁺ ; ¹ H NMR: δ 12.79 (bs, 1H), 8.28 (s, 1H), 8.075 (d, 1H), 8.04 (s, 1H), 7.91 (d, 1H), 7.87 (d, 1H), 7.56 (dd, 1H), 7.17 (d, 1H), 6.87 (d, 1H), 6.37 (s, 1H), 5.61 (s, 2H), 3.83 (s, 3H), 1.30 (s, 9H).
27		Intermediate 2 & Intermediate -19/ Example 1	LC-MS: 442.1 [M+H] ⁺ ; ¹ H NMR: δ 8.14 (s, 1H), 7.76 (d, 1H), 7.71 (s, 1H), 7.54 (d, 1H), 7.47 (dd, 1H), 7.38 (dd, 1H), 7.08(s, 1H), 6.76 (d, 1H), 6.28 (t, 1H), 5.32 (s, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 2.92 – 2.84 (m, 4H), 2.09 – 2.01 (m, 2H)
28		Intermediate -11 & Intermediate 22/ Example 1	LC-MS: 442.1 [M+H] ⁺ ; ¹ H NMR: δ 12.18 (brs, 1H), 7.86 (d, 1H), 7.64 (dd, 1H), 7.56 (d, 1H), 7.55 – 7.50 (m, 2H), 6.80 – 6.77 (m, 3H), 6.32 (d, 1H), 5.60 (s, 2H), 3.78 (s, 6H), 2.14 – 2.08 (m, 1H), 1.0 – 0.94 (m, 2H), 0.83 – 0.78 (m, 2H).
29		Intermediate 2 & Intermediate 67/ Example 2	LC-MS: 442.1 [M+H] ⁺ ; ¹ H NMR: δ 12.47 (s, 1H), 7.77 (d, 1H), 7.60 (s, 1H), 7.54 (d, 1H), 7.47 (d, 1H), 7.41 (dd, 1H), 7.25 (brs, 1H), 7.05 (brs, 1H), 6.77 (d, 1H), 6.28 (t, 1H), 5.32 (s, 2H), 3.89 (s, 3H), 3.77 (s, 3H), 2.10 – 1.92 (m, 1H), 0.98 – 0.93 (m, 2H), 0.64 – 0.60 (m, 2H).

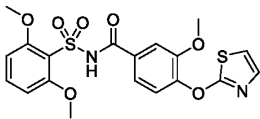
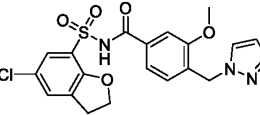
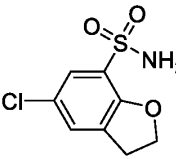
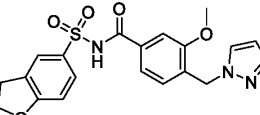
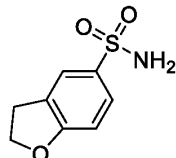
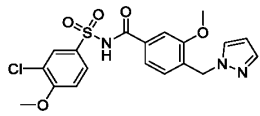
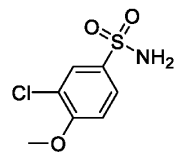
Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ^1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
30		Intermediate 2 & Intermediate 20/ Example 2	LC-MS: 430.2 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.45 (s, 1H), 7.78 (d, 1H), 7.71 (s, 1H), 7.55 – 7.40 (m, 4H), 7.11 (brs, 1H), 6.77 (d, 1H), 6.29 (t, 1H), 5.33 (s, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 2.64 (q, 2H), 1.19 (t, 3H).
31		Intermediate 2 & Example 2	LC-MS: 470.1 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.78 (brs, 1H), 8.12 (d, 1H), 7.78 (d, 1H), 7.56 – 7.51 (m, 3H), 7.48 (d, 1H), 7.42 (dd, 1H), 6.79 (d, 1H), 6.29 (t, 1H), 5.33 (s, 2H), 3.96 (s, 3H), 3.91 (s, 3H).
32		Intermediate 2 & Example 2	LC-MS: 470.1 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.78 (s, 1H), 8.13 (d, 1H), 7.97 (brs, 1H), 7.76 (d, 1H), 7.53 (d, 1H), 7.47 (dd, 1H), 7.43 (d, 1H), 7.42 (d, 1H), 6.77 (d, 1H), 6.28 (t, 1H), 5.32 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H).
33		Intermediate 22 & Intermediate -31 / Example 2	LC-MS: 486.1 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.62 (s, 1H), 7.85 – 7.81 (m, 3H), 7.50 (dd, 1H), 7.35 – 7.22 (m, 1H), 7.03 (d, 1H), 6.65 (d, 2H), 6.31 (dd, 1H), 5.44 (s, 2H), 3.66 (s, 6H).
34		Intermediate 22 & Intermediate 12 / Example 1	LCMS: 416.1 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3) : δ 7.68 (s, 1H), 7.61 – 7.59 (m, 2H), 7.46 (dd, 1H), 7.38 (d, 1H), 6.93 (d, 1H), 6.66 (d, 2H), 6.34 (dd, 1H), 5.37 (s, 2H), 3.93 (s, 6H), 2.33 (s, 3H).
35		Intermediate 22 & Intermediate 14 / Example 1	LCMS: 470.0 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3) : δ 8.18 (s, 1H), 7.91 (d, 1H), 7.62 (d, 1H), 7.47 (d, 1H), 7.42 (dd, 1H), 6.87 (d, 1H), 6.63 (d, 2H), 6.38 (dd, 1H), 5.57 (s, 2H), 3.90 (s, 6H).

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
36		Intermediate 51 & Intermediate 2 / Example 1	LC-MS: 468.2 [M+H] ⁺ ; ¹ H NMR: δ 7.87 (d, 1H), 7.79 (d, 1H), 7.49 (d, 1H), 7.38 (t, 1H), 7.28 (d, 1H), 7.25 – 7.22 (m, 2H), 7.08 (dd, 1H), 7.06 (dd, 1H), 7.02 (dd, 1H), 6.76 (d, 1H), 6.30 (dd, 1H), 5.33 (s, 2H), 3.86 (s, 3H), 3.62 (s, 3H).
37		Intermediate 22 & Intermediate 62 / Example 2	LC-MS: 468.0 [M+H] ⁺ ; ¹ H NMR: δ 12.33 (br s, 1H), 7.83 (d, 1H), 7.73 – 7.12 (m, 2H), 7.52 – 7.48 (m, 1H), 7.33 (t, 1H), 6.97 (d, 1H), 6.82 – 6.73 (m, 2H), 6.32 (dd, 1H), 5.42 (s, 2H), 3.75 (s, 6H).
38		Intermediate 50 & Intermediate 60 / Example 2	LCMS: 444.1 [M+H] ⁺ ; ¹ H NMR: δ 12.28 (s, 1H), 7.79 (br s, 1H), 7.55 (s, 1H), 7.48 (d, 1H), 7.42 (dd, 1H), 7.40 – 7.34 (m, 1H), 6.78 (d, 1H), 6.56 – 6.54 (m, 1H), 6.29 (dd, 1H), 5.33 (s, 2H), 4.62 (t, 2H), 3.92 (s, 3H), 3.75 (s, 3H), 3.12 (t, 2H).
39		 & Intermediate 60 / Example 2	LC-MS: 418.2 [M+H] ⁺ ; ¹ H NMR: δ 12.46 (br s, 1H), 9.60 (br s, 1H), 7.78 (d, 1H), 7.55 (d, 1H), 7.47 (d, 1H), 7.41 (dd, 1H), 7.33 (d, 1H), 7.04 (br s, 2H), 6.78 (d, 1H), 6.29 (dd, 1H), 5.33 (s, 2H), 3.91 (s, 3H), 3.75 (s, 3H).
40		Intermediate 22 & Intermediate 35 / Example 2	LC-MS: 460.1 [M+H] ⁺ ; ¹ H NMR: δ 12.28 (s, 1H), 7.87 (d, 1H), 7.56 – 7.52 (m, 2H), 7.28 (dd, 1H), 6.81 (d, 2H), 6.52 (d, 1H), 6.33 (dd, 1H), 5.60 (s, 2H), 3.80 (s, 6H), 1.76 – 1.78 (m, 1H), 1.07 – 1.02 (m, 2H), 0.78 – 0.75 (m, 2H).

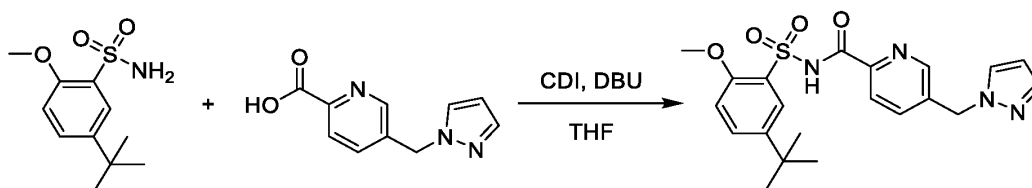
Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ^1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
41		Intermediate 22 & Intermediate 36 / Example 2	LC-MS: 462.1 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 11.91 (s, 1H), 7.83 (dd, 1H), 7.54 (dd, 1H), 7.48 (dd, 1H), 7.10 (d, 1H), 6.81 (d, 2H), 6.70 (d, 1H), 6.30 (dd, 1H), 5.37 (s, 2H), 3.82 (s, 6H), 3.79 (s, 3H), 3.77 (s, 3H).
42		Intermediate 2 & Intermediate 26a/ Example 3	LC-MS: 432.2 $[\text{M}+\text{H}]^+$; ^1H NMR δ 12.35 (s, 1H), 7.85 – 7.81 (m, 1H), 7.78 (dd, $J = 2.3, 0.7$ Hz, 1H), 7.54 (d, $J = 1.6$ Hz, 1H), 7.47 (dd, $J = 1.8, 0.7$ Hz, 1H), 7.39 (dd, $J = 7.8, 1.7$ Hz, 1H), 6.78 (d, $J = 7.9$ Hz, 1H), 6.74 – 6.67 (m, 2H), 6.28 (t, $J = 2.1$ Hz, 1H), 5.33 (s, 2H), 3.91 (s, 3H), 3.85 (d, $J = 2.2$ Hz, 6H).
43		Intermediate 2 & Intermediate 26b/ Example 1	LC-MS: 450.2 $[\text{M}+\text{H}]^+$; ^1H NMR δ 12.52 (s, 1H), 7.81 – 7.76 (m, 1H), 7.64 (d, $J = 10.9$ Hz, 1H), 7.55 – 7.51 (m, 1H), 7.47 (dd, $J = 1.9, 0.7$ Hz, 1H), 7.41 (dd, $J = 7.9, 1.6$ Hz, 1H), 6.93 (d, $J = 6.8$ Hz, 1H), 6.78 (d, $J = 7.9$ Hz, 1H), 6.29 (q, $J = 2.0$ Hz, 1H), 5.33 (s, 2H), 3.96 (s, 3H), 3.90 (d, $J = 7.6$ Hz, 6H).
44		Intermediate 2 & Intermediate 26c/ Example 1	LC-MS: 466.2 $[\text{M}+\text{H}]^+$; ^1H NMR δ 12.55 (s, 1H), 7.82 – 7.74 (m, 1H), 7.53 (d, $J = 1.6$ Hz, 1H), 7.41 (dd, $J = 7.8, 1.6$ Hz, 1H), 6.85 (s, 1H), 6.77 (d, $J = 7.9$ Hz, 1H), 6.52 (s, 1H), 6.27 (t, $J = 2.0$ Hz, 1H), 5.31 (s, 1H), 3.96 (s, 2H), 3.88 (d, $J = 3.4$ Hz, 3H), 3.32 (s, 6H).
46		Intermediate 2 & Intermediate 26e/ Example 3	LC-MS: 466.3 $[\text{M}+\text{H}]^+$; ^1H NMR δ 12.52 (s, 1H), 7.80 (d, $J = 2.3$ Hz, 1H), 7.74 (d, $J = 9.0$ Hz, 1H), 7.57 (d, $J = 1.6$ Hz, 1H), 7.50 – 7.42 (m, 1H), 7.03 (d, $J = 9.2$ Hz, 1H), 6.77 (d, $J = 7.9$ Hz, 1H), 6.29 (t, $J = 2.1$ Hz, 1H), 5.34 (s, 2H), 3.92 (d, $J = 2.8$ Hz, 6H), 3.79 (s, 3H).

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ^1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
47		Intermediate 2 & Intermediate 26f / Example 3	LC-MS: 462.1 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.07 (s, 1H), 7.79 (dd, J = 2.3, 0.7 Hz, 1H), 7.56 (d, J = 1.6 Hz, 1H), 7.47 (dd, J = 1.9, 0.7 Hz, 1H), 7.42 (dd, J = 7.9, 1.6 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.28 (q, J = 1.5 Hz, 3H), 5.33 (s, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 3.77 (s, 6H).
48		Intermediate 22 & Intermediate 37 / Example 2	LC-MS: 462.1 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 11.24 (s, 1H), 7.79 (d, 1H), 7.53 (dd, 1H), 7.49 (dd, 1H), 7.18 (s, 1H), 6.81 (d, 2H), 6.72 (s, 1H), 6.29 (dd, 1H), 5.33 (s, 2H), 3.81 (s, 6H), 3.80 (s, 3H), 3.78 (s, 3H).
49		Intermediate 22 & Intermediate 39 / Example 1	LC-MS: 498.1 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.45 (s, 1H), 7.90 (dd, 1H), 7.57 – 7.52 (m, 2H), 7.48 (dd, 1H), 6.81 (d, 2H), 6.62 (d, 1H), 6.35 (dd, 1H), 5.51 (s, 2H), 3.80 (s, 6H).
50		Intermediate 70 & Intermediate 22 / Example 3	LC-MS: 460.0 $[\text{M}+\text{H}]^+$. ^1H NMR: δ 12.23 (s, 1H), 8.63 (d, J = 4.8 Hz, 2H), 7.62 – 7.37 (m, 4H), 7.17 (t, J = 4.8 Hz, 1H), 6.79 (d, J = 8.5 Hz, 2H), 5.41 (s, 2H), 3.91 (s, 3H), 3.79 (s, 6H).
52		 & Intermediate 60 / Example 2	LC-MS: 458.2 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 12.14 (br s, 1H), 7.80 (s, 1H), 7.61 – 7.49 (m, 3H), 7.44 (d, 1H), 7.06 (d, 1H), 6.81 (d, 1H), 6.76 (d, 1H), 6.30 (s, 1H), 5.35 (s, 2H), 3.92 (s, 4H), 3.79 (s, 3H), 0.72 – 0.65 (m, 2H), 0.58 – 0.52 (m, 2H).
53		Intermediate 52 & Intermediate 60 /	LC-MS: 479.1 $[\text{M}+\text{H}]^+$; ^1H NMR: δ 8.45 (d, 1H), 7.93 (d, 1H), 7.75 (br s, 1H), 7.58 – 7.38

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
		Example 2	(m, 5H), 7.28 – 7.05 (m, 4H), 6.77 (d, 1H), 6.27 (dd, 1H), 5.34 (brs, 4H), 3.79 (s, 3H).
54		Intermediate 54 & Intermediate 60 / Example 2	LC-MS: 458.1 [M-H] ⁻ ; ¹ H NMR: δ 12.46 (br s, 1H), 8.02 (br s, 1H), 7.79 (s, 1H), 7.73 – 7.64 (m, 1H), 7.55 (s, 1H), 7.47 (d, 1H), 7.42 (dd, 1H), 7.18 – 7.10 (m, 1H), 6.76 (d, 1H), 6.29 (dd, 1H), 5.33 (s, 2H), 5.23 (brs, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 1.44 (s, 6H).
55		Intermediate 55 & Intermediate 60 / Example 2	LC-MS: 460.2 [M+H] ⁺ ; ¹ H NMR: δ 12.07 (br s, 1H), 7.80 (s, 1H), 7.63 (s, 1H), 7.49 – 7.46 (m, 3H), 6.80 – 6.73 (m, 3H), 6.30 (s, 1H), 5.35 (s, 2H), 4.76 – 4.64 (m, 1H), 3.92 (s, 3H), 3.78 (s, 3H), 1.18 (d, 6H).
56		Intermediate 56 & Intermediate 60 / Example 2	LC-MS: 442.2 [M+H] ⁺ ; ¹ H NMR: δ 12.38 (s, 1H), 7.79 (d, 1H), 7.56 (d, 1H), 7.48 – 7.42 (m, 3H), 6.98 (d, 1H), 6.77 (d, 1H), 6.29 (dd, 1H), 5.33 (s, 2H), 3.91 (s, 3H), 3.79 (s, 3H), 3.31 (t, 2H), 2.85 (t, 2H), 2.08 – 1.98 (m, 2H).
57		Intermediate 57 & Intermediate 60 / Example 2	LC-MS: 456.2 [M+H] ⁺ ; ¹ H NMR: δ 12.33 (s, 1H), 7.80 (d, 1H), 7.57 (d, 1H), 7.49 (d, 1H), 7.46 (dd, 1H), 7.31 (d, 1H), 7.0 (d, 1H), 6.77 (d, 1H), 6.29 (dd, 1H), 5.34 (s, 2H), 3.92 (s, 3H), 3.77 (s, 3H), 3.23 (t, 2H), 2.74 (t, 2H), 1.72 – 1.65 (m, 4H).
58		Intermediate 71 & Intermediate 22/ Example 3	LC-MS: 465.0 [M+H] ⁺ . ¹ H NMR: δ 12.25 (s, 1H), 7.60 (d, J = 1.4 Hz, 1H), 7.56 – 7.46 (m, 3H), 7.18 (d, J = 3.8 Hz, 1H), 7.07 (d, J = 3.8 Hz, 1H), 6.79 (d, J = 8.5 Hz, 2H), 5.45 (s, 2H), 3.91 (s, 3H), 3.78 (s, 6H).

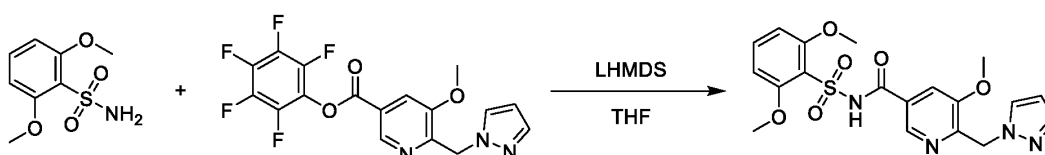
Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ^1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
59		Intermediate 72 & Intermediate 22/ Example 3	MS: 451.0[M+H] $^+$. ^1H NMR δ 12.28 (s, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.60 – 7.46 (m, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.21 (q, J = 3.7 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 6H).
63		Intermediate 2 &  Example 1	LC-MS: 448.0 [M+H] $^+$; ^1H NMR δ 7.75 (d, J = 2.3 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.47 – 7.41 (m, 2H), 6.77 (d, J = 7.8 Hz, 1H), 6.53 (d, J = 3.0 Hz, 1H), 6.27 (t, J = 2.1 Hz, 1H), 5.31 (s, 2H), 4.60 (s, 2H), 3.87 (s, 3H), 3.19 (t, J = 8.9 Hz, 2H).
64		Intermediate 2 &  Example 1	LC-MS: 414.1 [M+H] $^+$; ^1H NMR δ 7.83 (d, J = 1.9 Hz, 1H), 7.77 (dt, J = 5.6, 2.4 Hz, 2H), 7.49 (dd, J = 12.7, 1.7 Hz, 2H), 7.41 (dd, J = 7.9, 1.7 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.28 (t, J = 2.1 Hz, 1H), 5.33 (s, 2H), 4.66 (t, J = 8.8 Hz, 2H), 3.90 (s, 3H), 3.27 (t, J = 8.8 Hz, 2H).
65		Intermediate 2 &  Example 1	LC-MS: 436.0 [M+H] $^+$; ^1H NMR δ 7.94 (d, J = 2.2 Hz, 1H), 7.90 (dd, J = 8.7, 2.3 Hz, 1H), 7.76 (dd, J = 2.2, 0.7 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.47 (dd, J = 1.9, 0.6 Hz, 1H), 7.41 (dd, J = 7.9, 1.6 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.28 (t, J = 2.1 Hz, 1H), 5.32 (s, 2H), 3.95 (s, 3H), 3.88 (s, 3H).

Example 7. Compound 201: 5-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)picolinamide



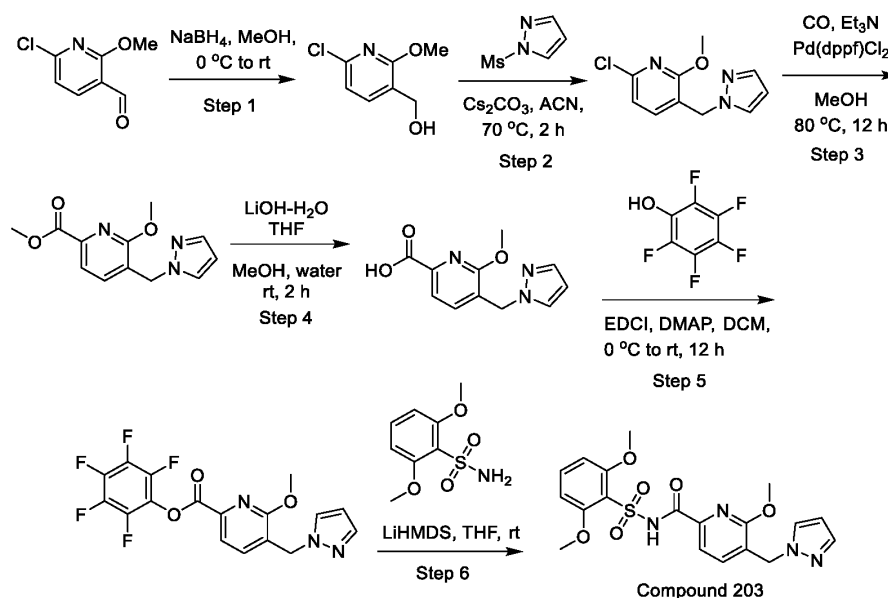
[0714] To a solution of 5-((1H-pyrazol-1-yl)methyl)picolinic acid (0.25 g, 1.229 mmol) in THF (5 mL) was added CDI (0.4 g, 2.46 mmol) and stirred at RT for 1 h. The reaction mixture was cooled to 0 °C, were added 5-((tert-butyl)-2-methoxybenzenesulfonyl)pyridine-2-carboxylic acid (Intermediate 17, 0.45 g, 1.84 mmol), DBU (0.75 g, 4.92 mmol) and stirred for 15 minutes at same temperature, then gradually warmed to RT and stirred for 12 h. The reaction mixture was concentrated to afford crude compound. The crude compound was purified by preparative HPLC to afford the title compound (0.03 g, 4%). LC-MS: 429.1 [M+H]⁺; ¹H NMR (DMSO-d₆, 400MHz): δ 11.71 (s, 1H), 8.57 (s, 1H), 7.95-7.91 (m, 2H), 7.87 (d, 1H), 7.74 (dd, 1H), 7.68 (d, 1H), 7.51 (dd, 1H), 7.12 (d, 1H), 6.31 (t, 1H), 5.51 (s, 2H), 3.78 (s, 3H), 1.29 (s, 9H).

Example 8. Compound 202: 6-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-5-methoxynicotinamide



[0715] To a solution of perfluorophenyl 6-((1H-pyrazol-1-yl)methyl)-5-methoxynicotinate (0.12 g, 0.301 mmol), 2,6-dimethoxybenzenesulfonamide (Intermediate 22, 0.078 g, 0.361 mmol) in THF (4 mL) was added LiHMDS (1.0 M in THF solution) (1 mL, 1.2 mmol) and the entire reaction mixture was stirred at RT for 30 min. The reaction mixture was quenched with ice water followed by saturated NH₄Cl solution and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and concentrated to afford the crude compound, which was further purified by preparative TLC and eluted at 80 % ethyl acetate in hexane (0.01 g, 8%): LC-MS: 433.1 [M+H]⁺; ¹H NMR (DMSO-d₆, 400 MHz): δ 12.60 (s, 1H), 8.52 (s, 1H), 7.82 (br s, 1H), 7.72 (s, 1H), 7.38 (d, 1H), 7.33 (br s, 1H), 6.70 (br m, 2H), 6.23 (t, 1H), 5.42 (s, 2H), 3.89 (s, 3H), 3.70 (s, 6H).

Example 9. Compound 203: 5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide



[0716] Step 1: (6-Chloro-2-methoxypyridin-3-yl)methanol

[0717] To a solution of 6-chloro-2-methoxynicotinaldehyde (10 g, 87.42 mmol), in MeOH (200 mL) was added NaBH₄ (13.3 g, 349.7 mmol) at 0 °C and stirred at RT for 2 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain the title compound (9.5 g, 94%). LC-MS: 174.0 [M+H]⁺.

[0718] Step 2: 3-((1H-pyrazol-1-yl)methyl)-6-chloro-2-methoxypyridine

[0719] To a solution of 6-chloro-2-methoxypyridin-3-yl)methanol (16 g, 92.16 mmol), and
1-(methylsulfonyl)-1H-pyrazole (16.16, 110.6 mmol) in acetonitrile (150 mL) was added
Cs₂CO₃ (60 g, 325.82 mmol) and stirred at 70 °C for 2 h. The reaction mixture was quenched
with ice water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄,
filtered, and concentrated to afford the crude compound, which was further purified by silica-
gel flash column chromatography using 20-30% ethyl acetate in hexane as eluent to obtain the
title compound (20 g, 95.8%). LC-MS: 224.1 [M+H]⁺.

[0720] Step 3: Methyl 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinate

[0721] To a degassed solution of 3-((1H-pyrazol-1-yl)methyl)-6-chloro-2-methoxypyridine (20 g, 89.42 mmol), and Et₃N (37.8 mL, 268.26 mmol) in methanol (400 mL) was added Pd(dppf)Cl₂-DCM (7.32 g, 8.94 mmol). The reaction mixture was heated to 80 °C in autoclave with 80 PSI pressure of carbon monoxide for 16 h. The reaction mixture was cooled to RT,

filtered through a pad of celite and concentrated to get the crude compound. The crude compound was further purified by silica-gel flash column chromatography using 30-50% ethyl acetate in hexane as eluent to obtain the title compound (16 g, 72.37%). LC-MS: 248.0 [M+H]⁺.

[0722] Step 4: 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinic acid

- 5 **[0723]** To a stirred solution of methyl 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinate (5 g, 20.22 mmol) in THF (40 mL), Methanol (20 mL) and water (20 mL) was added LiOH.H₂O (3.4 g, 41.96 mmol) and stirred for 12 h at room temperature. Reaction mixture was diluted with ice-cold water, adjusted pH to 4 using aqueous citric acid solution to obtain a precipitate. The precipitate was filtered, washed with water, and dried under vacuum to obtain the title
10 compound (4.5 g, 95.5%); LC-MS: 234.1[M+H]⁺.

[0724] Step 5: Perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinate

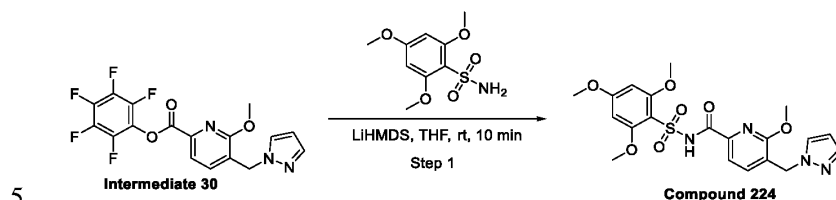
- [0725]** To a solution of 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinic acid (1.0 g, 4.28 mmol), 2,3,4,5,6-pentafluorophenol (0.947 g, 5.144 mmol) in DCM (20 mL) was added DMAP (0.106 g, 0.85 mmol) and followed by EDC-HCl (1.65 g, 8.57 mmol) at 0 °C and stirred at RT
15 for 12 h. The reaction mixture was quenched with ice water and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude compound. The crude compound was purified by silica-gel flash column chromatography using 15-30% ethyl acetate in hexane as eluent to obtain the title compound (1.5 g, 87.6%). LC-MS: 400.0 [M+H]⁺.

- 20 **[0726]** Step 6: 5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide

- [0727]** To a solution of perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinate (0.6 g, 1.50 mmol), and 2,6-dimethoxybenzenesulfonamide (Intermediate 22, 0.327 g, 1.50 mmol) in THF (20 mL) was added LiHMDS (1.5 mL, 1.50 mmol, 1.0 M in THF) and stirred
25 at RT for 10 min. The reaction mixture was quenched with ice water followed by saturated NH₄Cl solution and extracted with 10% MeOH in DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford the crude compound. The crude compound was further purified by silica gel flash column chromatography using 2-5% MeOH in DCM as eluent to obtain the crude compound. The crude compound was again triturated in ethyl acetate
30 to obtain the pure title compound (0.2 g, 30.8%); LC-MS: 433.2 [M+H]⁺; ¹H NMR (DMSO-

d_6 , 400 MHz): δ 11.56 (s, 1H), 7.85 (dd, 1H), 7.55 – 7.48 (m, 3H), 7.20 (d, 1H), 6.78 (d, 2H), 6.32 (dd, 1H), 5.36 (s, 2H), 4.11 (s, 3H), 3.77 (s, 6H).

Example 10. Compound 224: 5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)picolinamide



[0728] Step 1: 5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)picolinamide

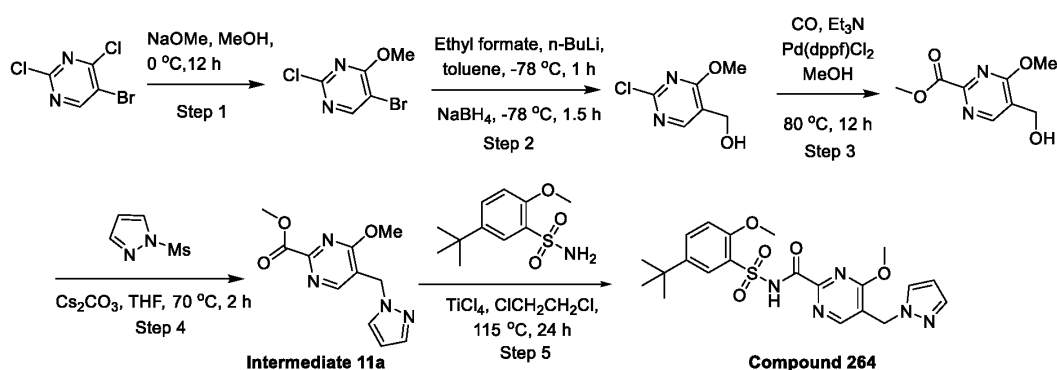
[0729] To a solution of perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinate (1.25 g, 3.15 mmol) and 2,4,6-trimethoxybenzenesulfonamide (commercial, 0.6 g, 2.43 mmol) in THF (40 mL) was added LiHMDS (2.5 mL, 2.43 mmol, 1.0 M in THF) and stirred at RT for 10 min. The reaction mixture was quenched with ice water followed by saturated NH_4Cl solution and extracted with 10% MeOH in DCM. The organic layer was dried over Na_2SO_4 , filtered, and concentrated to afford the crude compound. The crude compound was further purified by silica gel flash column chromatography using 2-5% MeOH in DCM as eluent and triturated in ethyl acetate to obtain the title compound (0.38 g, 34%): LC-MS: 461.1 $[\text{M}-\text{H}]^-$; ^1H NMR ($\text{DMSO}-d_6$, 400MHz): δ 11.51 (s, 1H), 7.83 (dd, 1H), 7.54 – 7.50 (m, 2H), 7.19 (d, 1H), 6.31 (dd, 1H), 6.27 (s, 2H), 5.35 (s, 2H), 4.07 (s, 3H), 3.82 (s, 3H), 3.76 (s, 6H).

10

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Example 11. Compound 264: 5-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-4-methoxypyrimidine-2-carboxamide

20



[0730] Step 1: 5-Bromo-2-chloro-4-methoxypyrimidine

[0731] To a solution of 5-bromo-2,4-dichloropyrimidine (10 g, 43.88 mmol) in MeOH (100 mL) was added NaOMe (7.7 mL, 43.88 mmol, 25% in MeOH) at 0 °C and stirred at same temperature for 2 h. The reaction was quenched with ice-water and evaporated the MeOH completely to obtain a precipitate. The precipitate was filtered and washed with water to obtain
5 title compound (10 g). LC-MS: 224.9 [M+H]⁺.

[0732] Step 2: (2-Chloro-4-methoxypyrimidin-5-yl)methanol

[0733] To a solution of 5-bromo-2-chloro-4-methoxypyrimidine (10 g, 44.75 mmol) in toluene (150 mL) was added n-BuLi (29.3 mL, 46.99 mmol, 1.6 M in hexane) at -78 °C and stirred at the same temperature for 30 min. Ethyl formate (3.98 g, 53.7 mmol) was added to the
10 reaction mixture at -78 °C and stirred for 30 min. The reaction mixture was diluted with MeOH (20 mL) and NaBH₄ (2.03 g, 37.84 mmol) was added to it at -78 °C and stirred at same temperature for 15 min. The reaction was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude material. Crude compound was purified by silica-gel flash column chromatography
15 using 40% ethyl acetate in hexane as eluent to afford the title compound (4 g, 51.2%). LC-MS: 175.1 [M+H]⁺.

[0734] Step 3: Methyl 5-(hydroxymethyl)-4-methoxypyrimidine-2-carboxylate

[0735] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 28 using appropriate reagents with suitable modifications. LC-MS: 199.1
20 [M+H]⁺.

[0736] Step 4: Methyl 5-((1H-pyrazol-1-yl)methyl)-4-methoxypyrimidine-2-carboxylate

[0737] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 29 using appropriate reagents with suitable modifications. LC-MS: 249.1 [M+H]⁺.

25 [0738] Step 5: 5-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-4-methoxypyrimidine-2-carboxamide

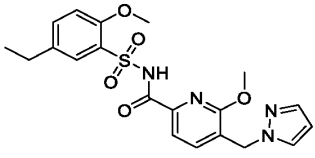
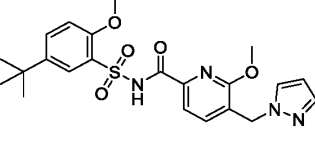
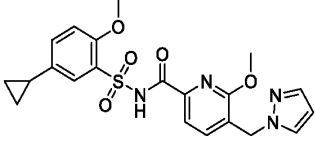
[0739] To a solution of methyl 5-((1H-pyrazol-1-yl)methyl)-4-methoxypyrimidine-2-carboxylate (0.2 g, 0.806 mmol), and 5-(tert-butyl)-2-methoxybenzenesulfonamide (Intermediate 17, 0.098 g, 0.403 mmol) in DCE (5 mL) was added titanium(IV) chloride (0.07
30 mL, 0.6 mmol) at 50 °C and then stirred at 115 °C for 16 h. The reaction was cooled to RT and

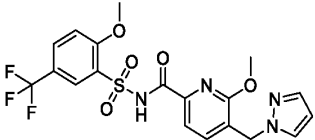
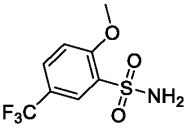
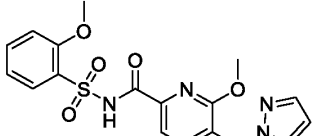
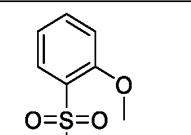
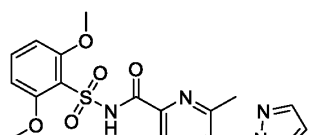
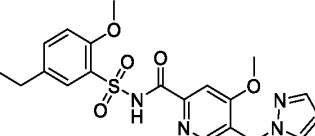
extracted with 10% MeOH in DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude compound. Crude compound was purified by preparative HPLC to obtain the title compound: LC-MS: 460.1 [M+H]⁺; ¹H NMR (CD₃OD, 400MHz): δ 8.19 (s, 1H), 8.08 (d, 1H), 7.80 (d, 1H), 7.73 (dd, 1H), 7.57 (d, 1H), 7.13 (d, 1H), 6.38 (dd, 1H), 5.41 (s, 2H), 4.14 (s, 3H), 3.89 (s, 3H), 1.38 (s, 9H).

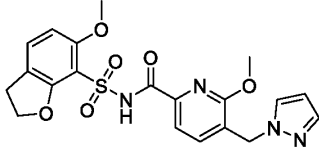
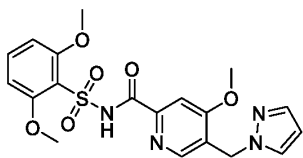
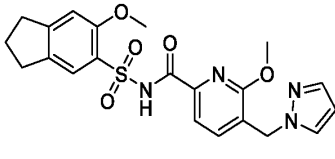
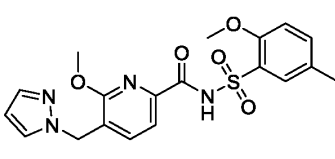
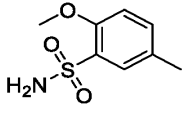
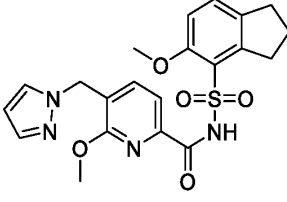
Example 12. Compounds 204 to 231, 235, 236, 239 to 241, 245 and 253

[0740] The following compounds listed in Table 13 were prepared by following a similar procedure as described above using appropriate reagents with suitable modifications known to the one skilled in the art. Intermediates and Example procedure for coupling are shown in the table below. Intermediates are commercially available if syntheses are not indicated.

Table 13. Compound Synthesis and Characterization

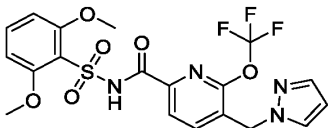
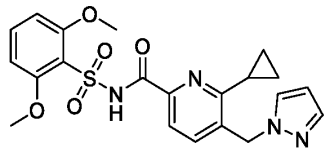
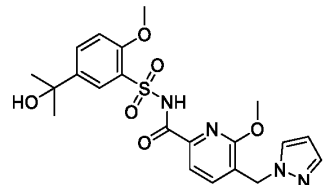
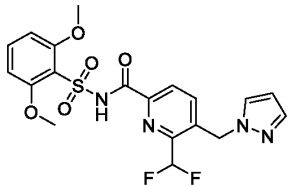
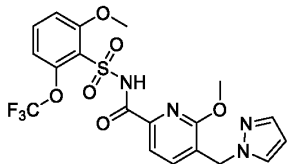
Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
204		Intermediate 20 & Intermediate 30 / Example 8	LCMS: 431.1[M+H] ⁺ ; ¹ H NMR δ 11.69 (s, 1H), 7.84 (d, 1H), 7.73 (d, 1H), 7.52 – 7.60 (m, 3H), 7.20 (dd, 1H), 7.16 (d, 1H), 6.31 (dd, 1H), 5.36 (s, 2H), 4.13 (s, 3H), 3.82 (s, 3H), 2.68 – 2.61 (m, 2H), 1.19 (t, 3H).
205		Intermediate 21 & Intermediate 30 / Example 8	LC-MS: 459.2 [M+H] ⁺ ; ¹ H NMR δ 11.74 (brs, 1H), 7.87 (d, 1H), 7.85 (d, 1H), 7.71 (dd, 1H), 7.51 (d, 1H), 7.21 – 7.15 (m, 2H), 7.17 (d, 1H), 6.31 (dd, 1H), 5.36 (s, 2H), 4.13 (s, 3H), 3.83 (s, 3H), 1.30 (s, 9H).
206		Intermediate 67 & Intermediate 30 / Example 8	LC-MS: 443.4 [M+H] ⁺ ; ¹ H NMR δ 11.76 (s, 1H), 7.84 (dd, 1H), 7.63 (d, 1H), 7.51 – 7.49 (m, 2H), 7.34 (dd, 1H), 7.20 (d, 1H), 7.12 (d, 1H), 6.31 (dd, 1H), 5.36 (s, 2H), 4.13 (s,

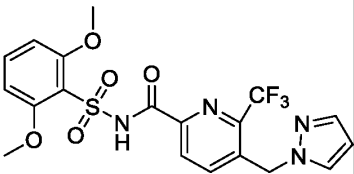
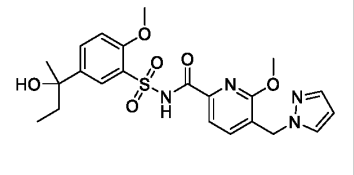
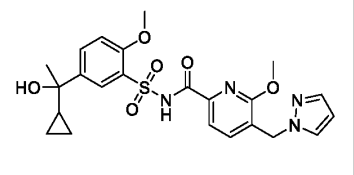
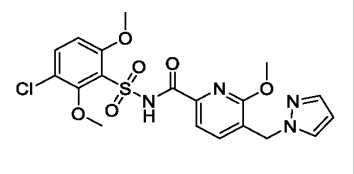
Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ^1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
			3H), 3.80 (s, 3H), 2.06 – 1.97 (m, 1H), 0.99 – 0.95 (m, 2H), 0.68 – 0.62 (m, 2H).
207		 & Intermediate 30 / Example 8	LC-MS: 471.1 $[\text{M}+\text{H}]^+$; ^1H NMR δ 12.30 (s, 1H), 8.14 (d, 1H), 8.09 (dd, 1H), 7.84 (dd, 1H), 7.51 – 7.45 (m, 3H), 7.19 (d, 1H), 6.31 (dd, 1H), 5.36 (s, 2H), 4.14 (s, 3H), 3.96 (s, 3H).
208		 & Intermediate 30 / Example 8	LC-MS: 403.1 $[\text{M}+\text{H}]^+$; ^1H NMR δ 11.75 (s, 1H), 7.92 (dd, 1H), 7.84 (d, 1H), 7.71 – 7.66 (m, 1H), 7.51 – 7.49 (m, 2H), 7.25 – 7.14 (m, 3H), 6.31 (dd, 1H), 5.36 (s, 2H), 4.14 (s, 3H), 3.86 (s, 3H).
209		Intermediate 22 & Intermediate 40 / Example 8	LC-MS: 417.1 $[\text{M}+\text{H}]^+$; ^1H NMR (DMSO- d_6 , 400 MHz): δ 11.23 (brs, 1H), 7.87 (dd, 1H), 7.80 (d, 1H), 7.56 – 7.51 (m, 2H), 7.29 (d, 1H), 6.80 (d, 2H), 6.34 (dd, 1H), 5.53 (s, 2H), 3.78 (s, 6H), 2.64 (s, 3H).
210		Intermediate 20 & Intermediate 41 / Example 7	LC-MS: 431.3 $[\text{M}+\text{H}]^+$; ^1H NMR δ 8.07 – (brs, 1H), 7.81 (d, 1H), 7.71 (s, 1H), 7.59 (s, 1H), 7.47 (d, 1H), 7.45 – 7.38 (brm, 1H), 7.11 – 7.03 (brm, 1H), 6.28 (dd, 1H), 5.36 (s, 2H), 3.94 (s, 3H), 3.75 (s, 3H), 2.62 (q, 2H), 1.18 (t, 3H).

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ^1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
211		Intermediate 50 & Intermediate 30 / Example 8	LCMS: 445.2 $[\text{M}+\text{H}]^+$; ^1H NMR δ 11.58 (brs, 1H), 7.83 (d, 1H), 7.54 – 7.50 (m, 2H), 7.31 (d, 1H), 7.19 (d, 1H), 6.52 (d, 1H), 6.31 (dd, 1H), 5.34 (s, 2H), 4.59 (t, 2H), 4.05 (s, 3H), 3.71 (s, 3H), 3.11 (t, 2H).
212		Intermediate 22 & Intermediate 41 / Example 7	LCMS: 433.1 $[\text{M}+\text{H}]^+$; ^1H NMR δ 8.42 (s, 1H), 7.79 (d, 1H), 7.65 (s, 1H), 7.46 (d, 1H), 7.26 (dd, 1H), 6.70 (d, 1H), 6.63 (d, 1H), 6.27 (dd, 1H), 5.33 (s, 2H), 3.94 (s, 3H), 3.67 (s, 6H).
213		Intermediate 19 & Intermediate 30 / Example 8	LC-MS: 443.1 $[\text{M}+\text{H}]^+$; ^1H NMR δ 11.56 (s, 1H), 7.84 (d, 1H), 7.74 (s, 1H), 7.51 – 7.49 (m, 2H), 7.21 (d, 1H), 7.12 (s, 1H), 6.31 (dd, 1H), 5.36 (s, 2H), 4.13 (s, 3H), 3.81 (s, 3H), 2.93 – 2.86 (m, 4H), 2.11 – 2.00 (m, 2H).
214		 & Intermediate 30 / Example 8	LC-MS: 417.1 $[\text{M}+\text{H}]^+$; ^1H NMR δ 7.84 (d, 1H), 7.72 (d, 1H), 7.51 – 7.47 (m, 3H), 7.21 (d, 1H), 7.13 (d, 1H), 6.31 (dd, 1H), 5.36 (s, 2H), 4.13 (s, 3H), 3.82 (s, 3H), 2.34 (s, 3H).
216		Intermediate 56 & Intermediate 30 / Example 8	LC-MS: 443.1 $[\text{M}+\text{H}]^+$; ^1H NMR δ 11.58 (s, 1H), 7.84 (d, 1H), 7.53 – 7.46 (m, 3H), 7.20 (d, 1H), 7.00 (d, 1H), 6.31 (dd, 1H), 5.36 (s, 2H), 4.13 (s, 3H), 3.79 (s, 3H) 3.32 (t,

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ^1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
			2H), 2.85 (t, 2H), 2.08 – 2.02 (m, 2H).
217		Intermediate 57 & Intermediate 30 / Example 8	LC-MS: 457.2 $[\text{M}+\text{H}]^+$; ^1H NMR δ 11.49 (s, 1H), 7.84 (d, 1H), 7.55 – 7.50 (m, 2H), 7.33 (d, 1H), 7.20 (d, 1H), 7.02 (d, 1H), 6.32 (dd, 1H), 5.36 (s, 2H), 4.13 (s, 3H) 3.78 (s, 3H), 3.23 (t, 2H), 2.74 (t, 2H), 1.73 – 1.67 (m, 4H).
218		Intermediate 58 & Intermediate 30 / Example 8	LCMS: 447.2 $[\text{M}+\text{H}]^+$; ^1H NMR δ 11.25 (s, 1H), 7.85 (dd, 1H), 7.57 (d, 1H), 7.53 – 7.48 (m, 2H), 7.22 (d, 1H), 6.80 – 6.77 (m, 2H), 6.32 (dd, 1H), 5.38 (s, 2H), 4.12 (s, 3H), 4.10 (q, 2H), 3.79 (s, 3H), 1.21(t, 3H).
219		Intermediate 59 & Intermediate 30 / Example 8	LC-MS: 473.2 $[\text{M}+\text{H}]^+$; ^1H NMR δ 11.51 (brs, 1H), 7.83 (d, 1H), 7.58 (d, 1H), 7.51 (dd, 1H), 7.42 (dd, 1H), 7.22 (d, 1H), 6.75 (d, 1H), 6.54 (d, 1H), 6.31 (dd, 1H), 5.36 (s, 2H), 4.74 – 4.65 (m, 1H), 4.10 (s, 3H), 3.78 (s, 3H), 2.27 – 2.18 (m, 2H), 1.96 – 1.84 (m, 2H), 1.54 – 1.44 (m, 2H).
220		Intermediate 63 & Intermediate 30 / Example 8	LC-MS: 469.1 $[\text{M}+\text{H}]^+$; ^1H NMR δ 11.96 (s, 1H), 7.85 (dd, 1H), 7.68 (t, 1H), 7.55 (d, 1H), 7.51 (dd, 1H), 7.26 (t, 1H) 7.21 – 7.16 (m, 2H),

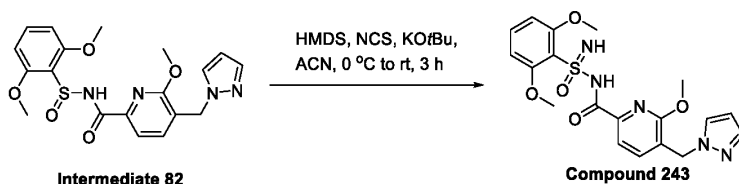
Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ^1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
			6.96 (d, 1H), 6.32 (dd, 1H), 5.37 (s, 2H), 4.14 (s, 3H), 3.85 (s, 3H).
222		Intermediate 65 & Intermediate 30 / Example 8	LCMS: 447.1 [M+H] $^+$; ^1H NMR δ 11.48 (s, 1H), 7.85 (dd, 1H), 7.55 (d, 1H), 7.51 (dd, 1H), 7.46 (d, 1H), 7.21 (d, 1H), 6.91 (d, 1H), 6.32 (dd, 1H), 5.37 (s, 2H), 4.14 (s, 3H), 3.85 (s, 3H), 3.75 (s, 3H), 2.21 (s, 3H).
223		Intermediate 66 & Intermediate 30 / Example 8	LCMS: 473.1 [M+H] $^+$; ^1H NMR δ 11.62 (brs, 1H), 7.85 (dd, 1H), 7.56 (d, 1H), 7.51 (dd, 1H), 7.20 (d, 1H), 7.09 (d, 1H), 6.86 (d, 1H), 6.32 (dd, 1H), 5.36 (s, 2H), 4.11 (s, 3H), 3.93 (s, 3H), 3.72 (s, 3H), 2.09 – 2.02 (m, 1H), 0.97 – 0.92 (m, 2H), 0.68 – 0.65 (m, 2H).
225		Intermediate 64 & Intermediate 30 / Example 8	LC-MS: 461.1 [M-H] $^-$; ^1H NMR δ 11.47 (s, 1H), 7.85 (dd, 1H), 7.56 (d, 1H), 7.52 – 7.48 (m, 2H), 7.21 (d, 1H), 6.95 (d, 1H), 6.32 (dd, 1H), 5.38 (s, 2H), 4.14 (s, 3H), 3.86 (s, 3H), 3.76 (s, 3H), 2.59 (q, 2H), 1.16 (t, 3H).
227		Intermediate 68 & Intermediate 30 / Example 8	LC-MS: 501.1 [M+H] $^+$; ^1H NMR δ 11.34 (s, H), 7.85 (dd, 1H), 7.60 (t, 1H), 7.56 (d, 1H), 7.51 (dd, 1H), 7.21 (d, 1H), 6.94 – 6.90 (m, 2H), 6.32 (dd, 1H), 5.37 (s, 2H), 4.84 (q, 2H), 4.12 (s, 3H), 3.79 (s, 3H).

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ^1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
228		Intermediate 22 & Intermediate 76 / Example 7	LC-MS: 487.1 $[\text{M}+\text{H}]^+$; ^1H NMR δ 10.01 (s, 1H), 8.00 (d, 1H), 7.62 (dd, 1H), 7.54 (dd, 1H), 7.48 – 7.43 (m, 2H), 6.64 (d, 2H), 6.39 (dd, 1H), 5.45 (s, 2H), 3.93 (s, 6H).
229		Intermediate 22 & Intermediate 28 / Example 8	LC-MS: 443.1 $[\text{M}+\text{H}]^+$; ^1H NMR δ 8.27 (s, 1H), 7.82 (d, 1H), 7.63 (d, 1H), 7.50 (d, 1H), 7.31 (t, 1H), 7.21 (d, 1H), 6.67 (d, 2H), 6.31 (dd, 1H), 5.57 (s, 2H), 3.69 (s, 6H), 2.34 – 2.27 (m, 1H), 1.08 – 1.01 (m, 2H), 0.92 – 0.85 (m, 2H).
230		Intermediate 54 & Intermediate 30 / Example 8	LC-MS: 459.0 $[\text{M}-\text{H}]^-$; ^1H NMR δ 11.92 (s, 1H), 8.01 (d, 1H), 7.83 (d, 1H), 7.62 (brd, 1H), 7.52 – 7.49 (m, 2H), 7.18 (d, 1H), 7.08 (brd, 1H), 6.30 (dd, 1H), 5.34 (s, 2H), 5.16 (s, 1H), 4.06 (s, 3H), 3.78 (s, 3H), 1.43 (s, 6H).
231		Intermediate 22 & Intermediate 77 / Example 8	LC-MS: 453.2 $[\text{M}+\text{H}]^+$; ^1H NMR δ 11.56 (s, 1H), 8.09 (d, 1H), 7.93 (dd, 1H), 7.57 – 7.56 (m, 2H), 7.46 (d, 1H), 7.36 (t, 1H), 6.80 (d, 2H), 6.36 (dd, 1H), 5.72 (s, 2H), 3.78 (s, 6H).
235		Intermediate 73 & Intermediate 30 / Example 8	LC-MS: 487.0 $[\text{M}+\text{H}]^+$; ^1H NMR δ 12.50 (s, 1H), 7.81 (d, 1H), 7.52 – 7.49 (m, 3H), 7.15 – 7.13 (m, 2H), 6.98 (brd, 1H), 6.30 (dd, 1H), 5.31 (s, 2H), 3.99 (s, 3H), 3.77 (s, 3H).

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ^1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
236		Intermediate 22 & Intermediate 80 / Example 8	LC-MS: 471.1 $[\text{M}+\text{H}]^+$; ^1H NMR δ 11.71 (s, 1H), 8.17 (d, 1H), 7.94 (d, 1H), 7.58 – 7.52 (m, 2H), 7.42 (d, 1H), 6.80 (d, 2H), 6.38 (dd, 1H), 5.71 (s, 2H), 3.79 (s, 6H).
239		Intermediate 75 & Intermediate 30 / Example 8	LC-MS: 473.1 $[\text{M}-\text{H}]^-$; ^1H NMR δ 11.63 (s, 1H), 7.99 (d, 1H), 7.84 (d, 1H), 7.65 (dd, 1H), 7.52 – 7.50 (m, 2H), 7.21 (d, 1H), 7.16 (d, 1H), 6.31 (dd, 1H), 5.36 (s, 2H), 5.04 (s, 1H), 4.13 (s, 3H), 3.84 (s, 3H), 1.69 (q, 2H), 1.42 (s, 3H), 0.70 (t, 3H).
240		Intermediate 74 & Intermediate 30 / Example 8	LC-MS: 485.1 $[\text{M}-\text{H}]^-$; ^1H NMR δ 12.06 (s, 1H), 7.99 (d, 1H), 7.81 (d, 1H), 7.58 (d, 1H), 7.51 – 7.48 (m, 2H), 7.15 (d, 1H), 7.02 (d, 1H), 6.30 (dd, 1H), 5.32 (s, 2H), 4.77 (s, 1H), 4.00 (s, 3H), 3.75 (s, 3H), 1.41 (s, 3H), 1.24 – 1.11 (m, 1H), 0.45 – 0.40 (m, 1H), 0.40 – 0.31 (m, 2H), 0.26 – 0.18 (m, 1H).
241		Intermediate 78 & Intermediate 30 / Example 8	LC-MS: 467.1 $[\text{M}+\text{H}]^+$; ^1H NMR δ 11.86 (s, 1H), 7.85 (d, 1H), 7.76 (d, 1H), 7.55 (d, 1H), 7.51 (d, 1H), 7.20 (d, 1H), 7.05 (d, 1H), 6.32 (dd, 1H), 5.37 (s, 2H), 4.14 (s, 3H), 3.94 (s, 3H), 3.80 (s, 3H).

Comp. No.	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
245		Intermediate 69 & Intermediate 30 / Example 8	LC-MS: 473.2[M+H] ⁺ ; ¹ H NMR δ 11.19 (s, 1H), 7.84 (d, 1H), 7.57 (d, 1H), 7.51 – 7.47 (m, 2H), 7.23 (d, 1H), 6.78(d, 2H), 6.31 (dd, 1H), 5.37 (s, 2H), 4.11 (s, 3H), 3.91 (d, 2H), 3.78 (s, 3H), 1.99 – 1.11 (m, 1H), 0.39 – 0.36 (m, 2H), 0.27 – 0.24 (m, 2H).
253		Intermediate 79 & Intermediate 30 / Example 8	LC-MS: 475.1 [M+H] ⁺ ; ¹ H NMR δ 7.85 (d, 1H), 7.54 (d, 1H), 7.51 (d, 1H), 7.22 (d, 1H), 6.32 (dd, 1H), 6.25 (s, 1H), 5.37 (s, 2H), 4.62 (t, 2H), 4.12 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.01 (t, 2H).

Example 13. Compound 243: 5-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxyphenylsulfonimidoyl)-6-methoxypicolinamide



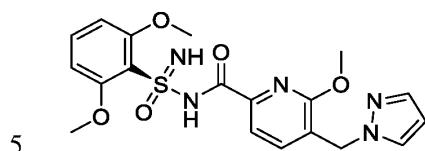
5

[0741] To a solution of 5-((1H-pyrazol-1-yl)methyl)-N-(2,6-dimethoxyphenyl)sulfinyl-6-methoxypicolinamide (0.1 g, 0.24 mmol) in ACN (5 mL) was added KOtBu (0.05 g, 0.48) followed by HMDS (0.116 g, 0.72 mmol), and NCS (0.096 g, 0.72 mmol) at 0 °C and stirred for 15 min. Then additional HMDS (0.116 g, 0.72 mmol), and NCS (0.096 g, 0.72 mmol) was added to the reaction mixture 0 °C and then stirred at rt for 2 h. The reaction mixture was diluted with water and extracted with 10% MeOH in DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude compound. Crude compound was purified by preparative HPLC to obtain the title compound (0.03 g). LC-MS: 432.2 [M+H]⁺;

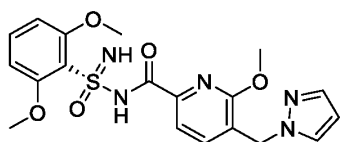
10

¹H NMR (DMSO-d₆, 400MHz): δ 7.82 (d, 1H), 7.63 (d, 1H), 7.50 – 7.48 (m, 2H), 7.46 – 7.43 (m, 2H), 7.18 (d, 1H), 6.78 (d, 2H), 6.31 (dd, 1H), 3.93 (s, 3H), 3.77 (s, 6H).

[0742] Compound 243 was separated by chiral HPLC into its respective isomers, with arbitrary assignment of stereochemistry.



[0743] Compound 243a: peak 1: LC-MS: 432.1 [M+H]⁺; ¹H NMR (CD₃OD, 400MHz): δ 7.78 (d, 1H), 7.75 (d, 1H), 7.56 (d, 1H), 7.51 (t, 1H), 7.24 (d, 1H), 6.81 (d, 2H), 6.37 (dd, 1H), 5.38 (s, 2H), 4.06 (s, 3H), 3.86 (s, 6H).



10 [0744] Compound 243b: peak 2: LC-MS: 432.1 [M+H]⁺; ¹H NMR (CD₃OD, 400MHz): δ 7.78 (d, 1H), 7.75 (d, 1H), 7.56 (d, 1H), 7.51 (t, 1H), 7.24 (d, 1H), 6.81 (d, 2H), 6.37 (dd, 1H), 5.38 (s, 2H), 4.06 (s, 3H), 3.86 (s, 6H).

Example 14. Compounds 71, 232, and 261 to 263

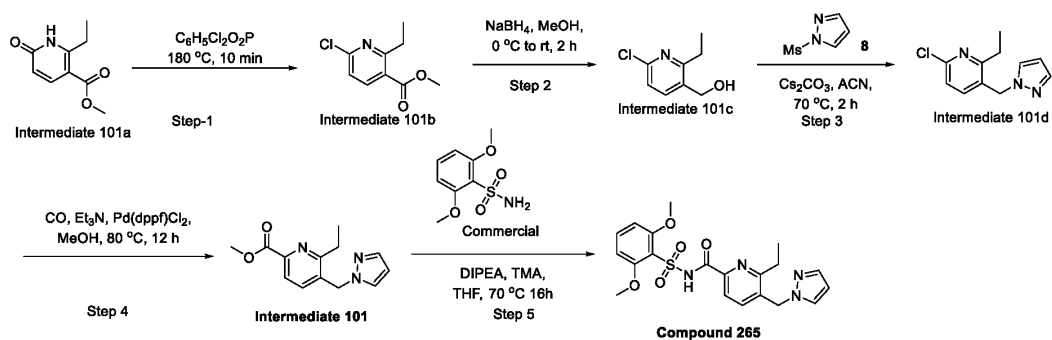
15 [0745] The following compounds listed in Table 14 were prepared by following a similar procedure as described above for Compound 243 using appropriate reagents with suitable modifications known to the one skilled in the art.

Table 14. Compound Synthesis and Characterization

Comp. No	Structure	Intermediates	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
71		Intermediate 82	LC-MS: 431.1 [M+H] ⁺ ; ¹ H NMR δ 7.77 (d, 1H), 7.55 – 7.45 (m, 4H), 7.40 (brs, 1H), 6.81 – 6.75 (m, 3H), 6.28 (dd, 1H), 5.33 (s, 2H), 3.87 (s, 3H), 3.75 (s, 6H).

Comp. No	Structure	Intermediates	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
232		Intermediate 83	LC-MS: 402.1 [M+H] ⁺ ; ¹ H NMR δ 7.90 (dd, 1H), 7.81 (d, 1H), 7.64 – 7.55 (m, 4H), 7.49 (d, 1H), 7.21 (d, 1H), 7.19 (d, 1H), 7.15 – 7.10 (m, 1H), 6.30 (dd, 1H), 5.32 (s, 2H), 3.92 (s, 3H), 3.83 (s, 3H).
261		Intermediate 86	LC-MS: 472.2 [M+H] ⁺ ; ¹ H NMR δ 8.48 (brs, 1H), 7.80 (d, 1H), 7.66 (d, 1H), 7.49 (d, 1H), 7.41 (t, 1H), 7.19 (d, 1H), 6.76 (d, 1H), 6.54 (d, 1H), 6.29 (dd, 1H), 5.32 (s, 2H), 4.72 – 4.64 (m, 1H), 3.93 (s, 3H), 3.79 (s, 3H), 2.29 – 2.16 (m, 2H), 1.98 – 1.84 (m, 2H), 1.55 – 1.45 (m, 2H).
262		Intermediate 84	LC-MS: 432.1 [M+H] ⁺ ; ¹ H NMR δ 8.34 (s, 1H), 7.81 – 7.78 (m, 2H), 7.60 (d, 1H), 7.49 (d, 1H), 7.19 (d, 1H), 6.69 – 6.66 (m, 2H), 6.30 (dd, 1H), 5.31 (s, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H).
263		Intermediate 85	LC-MS: 462.1 [M+H] ⁺ ; ¹ H NMR δ 8.27 (s, 1H), 7.82 (d, 1H), 7.61 (d, 1H), 7.50 (d, 1H), 7.18 (d, 1H), 6.31 – 6.29 (m, 3H), 5.32 (s, 2H), 3.93 (s, 3H), 3.83 (s, 3H), 3.76 (s, 6H).

Example 15: (Compound 265) 5-((1H-Pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-ethylpicolinamide



[0746] Step 1: Methyl 6-chloro-2-ethynicotinate

[0747] To a solution of methyl 2-ethyl-6-oxo-1,6-dihydropyridine-3-carboxylate (1.0 g, 5.51 mmol) in dichloro-hydroxy-(phenoxy)phosphonium (11.64 g, 55.18 mmol) and stirred at 180°C for 10 min. Reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 , filtered, and concentrated to afford the crude compound, which was further purified by silica-gel flash column chromatography using 20-30% ethyl acetate in hexane as eluent to obtain the title compound as white solid (0.8 g, 72.61%). LC-MS: 200.1 $[\text{M}+\text{H}]^+$.

[0748] Step 2: (6-Chloro-2-ethylpyridin-3-yl)methanol

[0749] The title compound was prepared using a similar procedure to that described in Step 1 of Intermediate 30 using appropriate reagents with suitable modifications (0.7 g). LC-MS: 172.1 $[\text{M}+\text{H}]^+$.

[0750] Step 3: 3-((1H-pyrazol-1-yl)methyl)-6-chloro-2-ethylpyridine

[0751] The title compound was prepared using similar procedure to that described in Step 2 of Intermediate 29 using appropriate reagents with suitable modifications (0.9 g, 99.55%). LC-MS: 222.1 $[\text{M}+\text{H}]^+$.

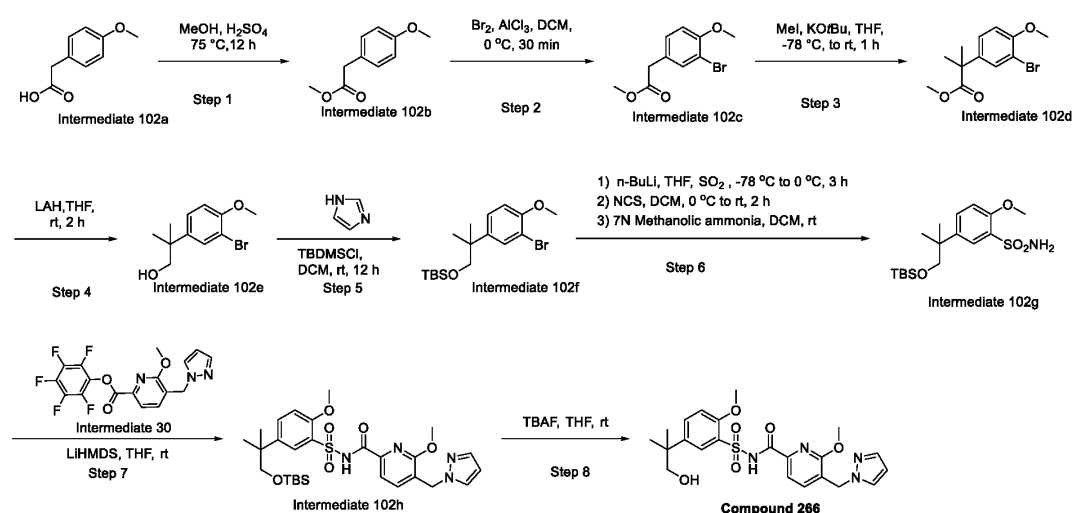
[0752] Step 4: Methyl 5-((1H-pyrazol-1-yl)methyl)-6-ethylpicolinate

[0753] The title compound was prepared using similar procedure to that described in Step 3 of Intermediate 29 using appropriate reagents with suitable modifications. (0.65 g, 83.91%). LC-MS: 246.2 $[\text{M}+\text{H}]^+$.

[0754] Step 5: 5-((1H-Pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-ethylpicolinamide

[0755] To a stirred solution of methyl 5-((1H-pyrazol-1-yl)methyl)-6-ethylpicolinate (0.20 g, 0.815 mmol), 2,6-dimethoxybenzenesulfonamide (0.17 g, 0.815 mmol) in THF (40 mL) was added DIPEA (0.35 mL, 2.03 mmol) and TMA (0.14 g, 2.03 mmol) at 0 °C and stirred at 70 °C for 12 h. The reaction mixture was quenched with ice water and extracted with 10% methanol and DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated to obtain the title crude compound. Crude compound was purified by preparative HPLC to obtain the title compound (0.13 g, 37.05%). LC-MS: 431.1 [M+H]⁺; ¹H NMR (DMSO-D₆, 400 MHz): δ 11.15 (brs, 1H), 7.87 (d, 1H), 7.80 (d, 1H), 7.55 – 7.51 (m, 2H), 7.34 (d, 1H), 6.80 (d, 2H), 6.34 (dd, 1H), 5.55 (s, 2H), 3.77 (s, 6H), 2.96 (q, 2H), 1.27 (t, 3H).

Example 16: (Compound-266) 5-((1H-Pyrazol-1-yl)methyl)-N-((5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide



15 [0756] Step 1: Methyl 2-(4-methoxyphenyl)acetate

[0757] To a solution of 2-(4-methoxyphenyl)acetic acid (5.0 g, 30.08 mmol) in methanol (70 mL) was added sulfuric acid (2.95 g, 30.08 mmol) and stirred at 70 °C for 12 h. Reaction mixture was evaporated, quenched with ice water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, dried over Na₂SO₄, filtered, and concentrated to afford the crude compound, which was taken for the next step

without purification (5.0 g). ^1H NMR (CDCl_3 , 400MHz): δ 7.23 (d, 2H), 6.90 (d, 2H), 3.82 (s, 3H), 3.71 (s, 3H), 3.62 (s, 2H).

[0758] Step 2: Methyl 2-(3-bromo-4-methoxyphenyl)acetate

[0759] To a stirred solution of AlCl_3 (1.11 g, 8.23 mmol), methyl 2-(4-methoxyphenyl) acetate (3.0 mL, 16.64 mmol) in DCM was add bromine (1.46 g, 18.31 mmol) dropwise at 0 °C. The reaction mixture was warmed to rt and stirred for 1h. Reaction mixture was quenched with ice water and extracted with DCM. The organic layer was washed with sodium thiosulphate, dried over Na_2SO_4 , filtered, and concentrated to afford the crude compound, which was used in next step without purification. (3.0 g). ^1H NMR ($\text{DMSO}-\text{D}_6$, 400MHz): δ 7.49 (d, 2H), 7.24 (dd, 1H), 7.06 (d, 1H), 3.83 (s, 3H), 3.64 (s, 3H).

[0760] Step 3: Methyl 2-(3-bromo-4-methoxyphenyl)-2-methylpropanoate

[0761] To a solution of methyl 2-(3-bromo-4-methoxyphenyl)acetate (3.0 g, 11.57 mmol) and methyl iodide (4.93 g, 34.73 mmol) in THF (30 mL) was added KOt-Bu (3.89 g, 34.73 mmol) at -78 °C. stirred at same temperature for 60 min. Then the reaction mixture was warmed to rt and stirred for 12 h. The reaction mixture was quenched with ice water and extracted with EtOAc. The organic layer was washed with brine solution, dried over Na_2SO_4 , and concentrated to get the crude compound. The crude compound purified by silica-gel flash chromatography using 0-30% ethyl acetate in hexane as eluent to afford the pure title compound (3.2 g, 96.24%). LC-MS: 289.0 $[\text{M}+2+\text{H}]^+$.

[0762] Step 4: 2-(3-Bromo-4-methoxyphenyl)-2-methylpropan-1-ol

[0763] To a solution of methyl 2-(3-bromo-4-methoxyphenyl)-2-methylpropanoate (2.5 g, 8.70 mmol) in THF (15 mL) was added LAH (0.26 g, 0.80 mmol) at 0 °C and stirred at same temperature for 1 h. The reaction mixture was quenched with saturated sodium sulphate and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated to afford the crude compound, which was used in next step without purification (2.3 g). ^1H NMR ($\text{DMSO}-\text{d}_6$, 400MHz): δ 7.50 (s, 1H), 7.31 (d, 1H), 7.02 (d, 1H), 4.68 (t, 1H), 3.81 (s, 3H), 3.38 (d, 2H), 1.18 (s, 6H).

[0764] Step 5: (2-(3-Bromo-4-methoxyphenyl)-2-methylpropoxy)(tert-butyl)dimethylsilane

[0765] To a solution of 2-(3-bromo-4-methoxyphenyl)-2-methylpropan-1-ol (1.0 g, 3.85 mmol) in DCM (25 mL) was added imidazole (0.52 g, 7.71 mmol) followed by TBDMSCl (0.68 g, 4.63 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 12 h. The reaction mixture was added into ice water and extracted with DCM. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated to get the crude compound. The crude compound was purified by silica-gel flash chromatography using 0-10% ethyl acetate in hexane as eluent to afford the pure title compound (1 g, 69.40%). ¹H NMR (DMSO-d₆, 400MHz): δ 7.52 (s, 1H), 7.33 (d, 1H), 7.02(d, 1H), 3.81 (s, 3H), 3.48 (s, 2H), 1.21 (s, 6H), 0.82 (s, 9H), 0.014 (s, 6H).

10 [0766] Step 6: 5-(1-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-methoxybenzenesulfonamide

[0767] To a solution of (2-(3-bromo-4-methoxyphenyl)-2-methylpropoxy)(*tert*-butyl)dimethylsilane (1.0 g, 2.67 mmol) in THF (20 mL) was added *n*-BuLi (5.0 mL, 8.03 mmol, 1.6M in hexane) at -78 °C and stirred at the same temperature for 1 h. Then SO₂ gas was bubbled into the reaction mixture for 30 min at -78 °C. The entire reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated to obtain the solid. The solid was dissolved in DCM and NCS (1.07 g, 8.03 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The reaction was quenched with ice-water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude compound. The crude compound was again dissolved in DCM (5 mL) and 7N methanolic ammonia (10 mL) was added to the reaction mixture and stirred for 30 min at RT. The reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude which was taken for the next step without purification. (0.3 g). LC-MS: 374.2 [M+H]⁺.

25 [0768] Step 7: 5-((1H-Pyrazol-1-yl)methyl)-N-((5-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide

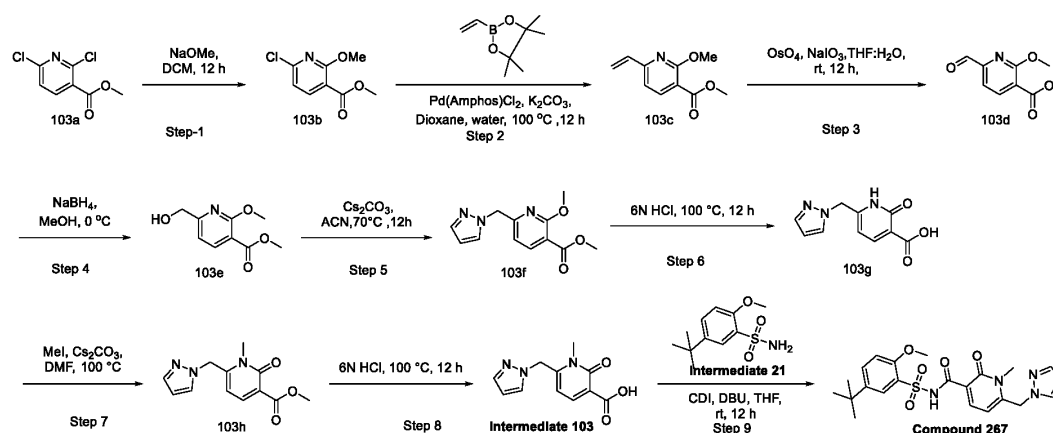
[0769] To a solution of perfluorophenyl 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinate (0.40 g, 1.002 mmol), and 5-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-methoxybenzenesulfonamide (0.29 g, 0.80 mmol) in THF (10 mL) was added LiHMDS (2.0 mL, 2.0 mmol, 1.0 M in THF) and stirred at RT for 10 min. The reaction mixture was quenched with saturated NH₄Cl solution and extracted with 10% MeOH in DCM. The organic layer was

dried over Na₂SO₄, filtered, and concentrated to afford the crude compound. Crude compound was purified by silica-gel flash column chromatography using 2-5% MeOH in DCM as eluent to afford the title compound (0.3 g, 50.85%). LC-MS: 589.2 [M+H]⁺.

[0770] Step 8: 5-((1H-pyrazol-1-yl)methyl)-N-((5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide

[0771] To a solution of 5-((1H-pyrazol-1-yl)methyl)-N-((5-(1-((tert-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide (0.30 g, 0.51 mmol) in THF 15 mL) was added TBAF (0.28 g, 1.73 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred at RT for 12 h. The reaction mixture concentrated to get the crude compound. Crude compound was purified by preparative HPLC to obtain the title compound (0.140 g, 57.85 %). LC-MS: 475.1 [M+H]⁺; ¹H NMR (DMSO-D₆, 400 MHz): δ 11.65 (s, 1H), 7.87 (d, 1H), 7.84 (d, 1H), 7.67 (dd, 1H), 7.53 – 7.50 (m, 2H), 7.21 (d, 1H), 7.16 (d, 1H), 6.31 (dd, 1H), 5.36 (s, 2H), 4.13 (s, 3H), 3.83 (s, 3H), 3.41 (s, 2H), 1.24 (s, 6H).

Example 17: (Compound 267) 6-((1H-Pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



[0772] Step 1: Methyl 6-chloro-2-methoxynicotinate

[0773] To a solution of methyl 2,6-dichloronicotinate (2.0 g, 9.70 mmol) in DCM (10 mL) was added NaOMe (2.28 mL, 43.88 mmol, 25% in MeOH) at 0 °C and stirred at room temperature for 12 h. The reaction was quenched with saturated sodium bicarbonate solution and extracted

with DCM. The organic layer was dried over sodium sulphate, filtered, and concentrated to afford the crude which was used in next step without purification. (2.0 g) LC-MS: 202.0 [M+H]⁺.

[0774] Step 2: Methyl 2-methoxy-6-vinylnicotinate

- 5 **[0775]** The title compound was prepared using a similar procedure to that described in Step 1 of Intermediate 88 using appropriate reagents with suitable modifications. (0.8 g, 41.74 %) LC-MS: 194.1 [M+H]⁺.

[0776] Step 3: Methyl 6-formyl-2-methoxynicotinate

- 10 **[0777]** To a solution of methyl 2-methoxy-6-vinylnicotinate (0.5 g, 2.58 mmol) in water-THF (5 mL and 5 mL) was Added 4% aqueous solution of osmium tetroxide (0.007 g, 0.020 mmol), followed by sodium periodate (1.10 g, 5.17 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred at RT for 12 h. The reaction was quenched ice water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated to obtain the crude compound. The crude compound was purified by silica-gel flash column chromatography using 20-60% ethyl acetate in hexane as eluent to afford the title compound
15 (0.3 g, 59.39%). LC-MS: 196.1 [M+H]⁺.

[0778] Step 4: Methyl 6-(hydroxymethyl)-2-methoxynicotinate

- 20 **[0779]** The title compound was prepared using a similar procedure to that described in Step 1 of Intermediate 30 using appropriate reagents with suitable modifications (0.25 g). LC-MS: 198.1 [M+H]⁺.

[0780] Step 5: Methyl 6-((1H-pyrazol-1-yl)methyl)-2-methoxynicotinate

[0781] The title compound was prepared using a similar procedure to that described in Step 2 of Intermediate 29 using appropriate reagents with suitable modifications (0.23 g, 73.36%). LC-MS: 248.1 [M+H]⁺.

- 25 **[0782]** Step 6: 6-((1H-Pyrazol-1-yl)methyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

[0783] The title compound was prepared using a similar procedure to that described in Step 1 of Intermediate 99 using appropriate reagents with suitable modifications (0.2 g). LC-MS: 220.1 [M+H]⁺.

[0784] Step 7: 6-((1H-Pyrazol-1-yl)methyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

- 5 [0785] The title compound was prepared using a similar procedure to that described in Step 2 of Intermediate 99 using appropriate reagents with suitable modifications (0.2 g). LC-MS: 248.1 [M+H]⁺.

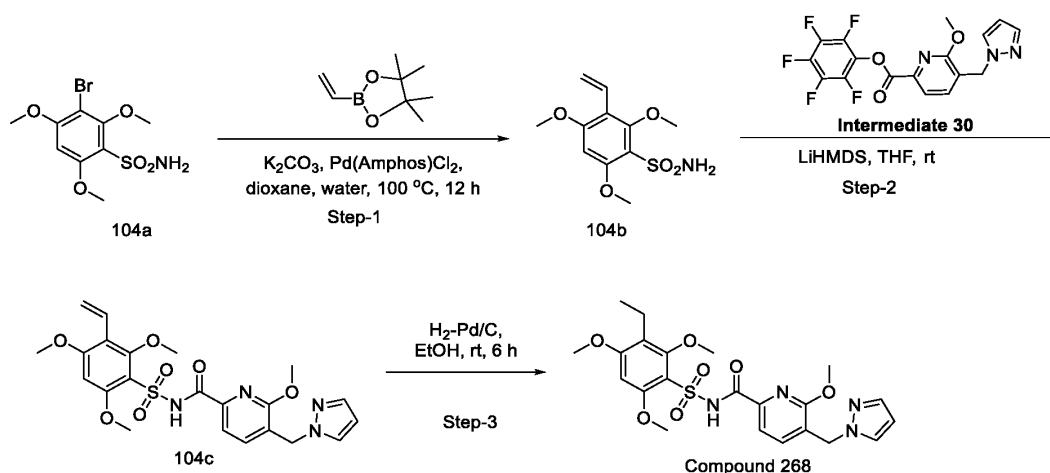
[0786] Step 8: 6-((1H-pyrazol-1-yl)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

- 10 [0787] The title compound was prepared using a similar procedure to that described in Step 3 of Intermediate 99 using appropriate reagents with suitable modifications (0.07 g). LC-MS: 234.1 [M+H]⁺.

[0788] Step 9: 6-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

- 15 [0789] To a solution of 6-((1H-pyrazol-1-yl)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (0.07 g, 0.3 mmol), in THF (5 mL) was added CDI (0.15 g, 0.900 mmol) and stirred at RT for 1 h. The reaction mixture was cooled to 0 °C, and to it was added 5-(tert-butyl)-2-methoxybenzenesulfonamide (0.08 g, 0.36 mmol), DBU (0.14 g, 0.900 mmol) and stirred for 15 min at the same temperature. Then reaction mixture was warmed to RT and stirred
20 for overnight. The reaction mixture was quenched with ice water and extracted with 10% methanol and DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated to obtain the crude compound. The crude compound was purified by preparative HPLC to obtain the title compound (30 mg, 21.81%). LC-MS: 459.2 [M+H]⁺; ¹H NMR (DMSO-D₆, 400 MHz): δ 13.06 (s, 1H), 8.18 (d, 1H), 7.86 – 7.84 (m, 2H), 7.71 (dd, 1H), 7.61 (dd, 1H), 7.16 (d, 1H),
25 6.41 (dd, 1H), 5.71 (d, 1H), 5.68 (s, 2H), 3.81 (s, 3H), 3.65 (s, 3H), 1.28 (s, 9H).

Example 18: (Compound 268) 5-((1H-Pyrazol-1-yl)methyl)-N-((3-ethyl-2,4,6-trimethoxyphenyl)sulfonyl)-6-methoxypicolinamide



[0790] Step 1: 2,4,6-Trimethoxy-3-vinylbenzenesulfonamide

[0791] The title compound was prepared using a similar procedure to that described in Step 1 of Intermediate 88 using appropriate reagents with suitable modifications. ¹H NMR (DMSO-D₆, 400 MHz): δ 6.68 – 6.61 (m, 1H), 6.54 (s, 1H), 5.91 (d, 1H), 5.27 (d, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.71 (s, 1H).

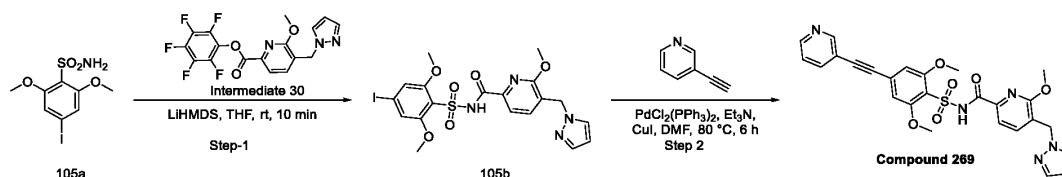
[0792] Step 2: 5-((1H-Pyrazol-1-yl)methyl)-6-methoxy-N-((2,4,6-trimethoxy-3-vinylphenyl)sulfonyl)picolinamide

[0793] The title compound was prepared using similar procedure to that described in Example 10 using appropriate reagents with suitable modifications (0.16 g). LC-MS: 489.1 [M+H]⁺.

[0794] Step 3: 5-((1H-Pyrazol-1-yl)methyl)-N-((3-ethyl-2,4,6-trimethoxyphenyl)sulfonyl)-6-methoxypicolinamide

[0795] The title compound was prepared using a similar procedure to that described in Step 2 of Intermediate 88 using appropriate reagents with suitable modifications (4 mg, 2.66%). LC-MS: 491.1 [M+H]⁺; ¹H NMR (DMSO-D₆, 400 MHz): δ 10.24 (brs, 1H), 7.69 (d, 1H), 7.60 (d, 1H), 7.52 (d, 1H), 7.22 (d, 1H), 6.35 (dd, 1H), 6.28 (s, 1H), 5.37 (s, 2H), 4.13 (s, 3H), 4.03 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 2.62 (q, 2H), 1.13 (t, 3H).

Example 19: (Compound 269) 5-((1H-Pyrazol-1-yl)methyl)-N-((2,6-dimethoxy-4-(pyridin-3-ylethynyl)phenyl)sulfonyl)-6-methoxypicolinamide



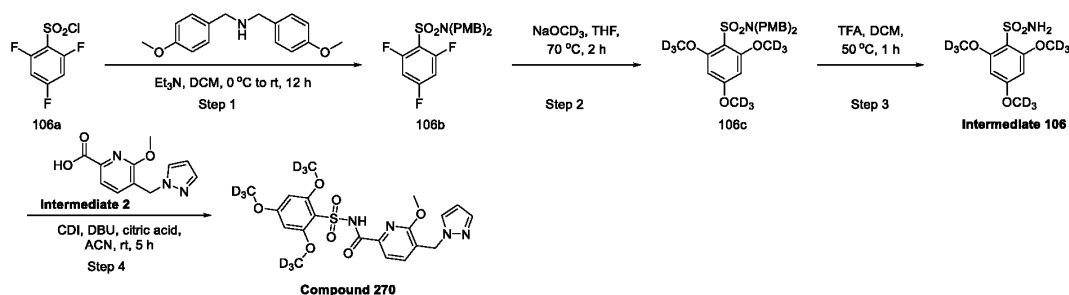
[0796] Step 1: 5-((1H-Pyrazol-1-yl)methyl)-N-((4-iodo-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide

- 5 **[0797]** The title compound was prepared using a similar procedure to that described in Example 10 using appropriate reagents with suitable modifications LC-MS: 559.0 [M+H]⁺.

[0798] Step 2: 5-((1H-Pyrazol-1-yl)methyl)-N-((2,6-dimethoxy-4-(pyridin-3-ylethynyl)phenyl)sulfonyl)-6-methoxypicolinamide

- 10 **[0799]** To a degassed solution of 5-((1H-pyrazol-1-yl)methyl)-N-((4-iodo-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide (0.09 g, 0.16 mmol), 3-ethynylpyridine (0.019 g, 0.19 mmol) and DIPEA (0.3 mL, 1.6 mmol) in DMF (5 mL) was added copper iodide (0.003 g, 0.1 mmol) and Pd(PPh₃)₂Cl₂ (0.019 g, 0.1 mmol). The reaction mixture was heated at 70 °C for 12 h. The reaction mixture was cooled to RT, diluted with water, and extracted
- 15 with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated to obtain crude compound. Crude compound was purified by preparative HPLC to obtain the title compound (7 mg, 8.15%). LC-MS: 534.1 [M+H]⁺; ¹H NMR (DMSO-D₆, 400MHz): δ 8.82 (dd, 1H), 8.62 (d, 1H), 8.03 – 8.00 (m, 1H), 7.83 (d, 1H), 7.65 – 7.62 (m, 2H), 7.60 – 7.48 (m, 3H), 7.19 (d, 1H), 6.96 (brs, 1H), 6.31 (dd, 1H), 5.34 (s, 2H), 4.06 (s, 3H), 3.79 (s, 6H).

- 20 **Example 20: (Compound 270) 5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2,4,6-tris(methoxy-d3)phenyl)sulfonyl)picolinamide**



[0800] Step 1: 2,4,6-Trifluoro-N,N-bis(4-methoxybenzyl)benzenesulfonamide

[0801] To a solution of 2,4,6-trifluorobenzenesulfonyl chloride (3.0 g, 13.00 mmol), in DCM (30 mL) was added Et₃N (5.44 mL, 39.03 mmol) and followed by bis(4-methoxybenzyl)amine (4 g, 15.61 mmol) at 0 °C. The reaction mixture was warmed to rt stirred at for 12 h. The reaction mixture was quenched with water and extracted with DCM. The organic layer was washed with brine and dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain the crude compound. The crude compound was purified by silica-gel flash column chromatography using 20-30% ethyl acetate in hexane as eluent to obtain the title compound as an off-white solid. (4.9 g, 83.5%). ¹H NMR (CDCl₃, 400MHz): δ 7.05 (d, 4H), 6.79 (d, 4H), 6.80 -6.70 (m, 2H), 4.42 (s, 4H), 3.80 (s, 6H).

[0802] Step 2: 2,4,6-Tris(methoxy-d₃)-N,N-bis(4-methoxybenzyl)benzenesulfonamide

[0803] To a solution of 2,4,6-trifluoro-N,N-bis(4-methoxybenzyl)benzenesulfonamide (0.1 g, 0.22 mmol), in THF (1 mL) was added freshly prepared 20% NaOCD₃ solution (0.25 mL, 0.88 mmol) at rt to the reaction mixture. The reaction mixture was stirred at 70 °C for 2 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain the crude compound. The crude compound was purified by silica-gel flash column chromatography using 30-40% ethyl acetate in hexane as eluent to obtain the title compound (0.105 g, 95.25%). LC-MS: 497.2 [M+H]⁺.

[0804] Step 3: 2,4,6-tris(Methoxy-d₃)benzene sulfonamide

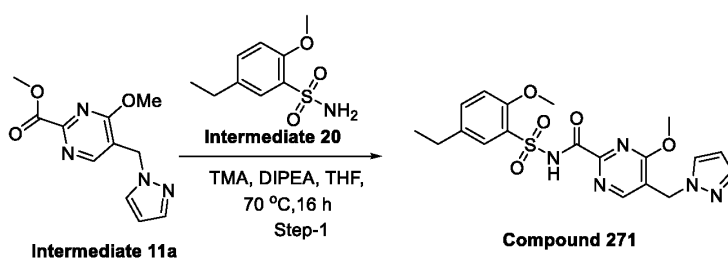
[0805] To a solution of 2,4,6-tris(methoxy-d₃)-N,N-bis(4-methoxybenzyl)benzenesulfonamide (2.5 g, 5.03 mmol), in DCM (10 mL) was added TFA (20 mL) at rt. The reaction mixture was heated at 60 °C for 2 h. The reaction mixture was

concentrated, then neutralized with saturated NaHCO_3 and extracted with 10% MeOH in DCM. The organic layer was washed with brine solution and dried over anhydrous Na_2SO_4 , filtered, and concentrated to get the crude. The crude compound was purified by silica-gel flash column chromatography using 80-100% ethyl acetate in hexane as eluent and was recrystallized using DCM to obtain the title compound (0.55 g, 42.6%). LC-MS: 257.1 $[\text{M}+\text{H}]^+$. ^1H NMR (DMSO- D_6 , 400MHz): δ 6.81 (brs, 2H), 6.28 (s, 2H).

[0806] Step 4: 5-((1H-Pyrazol-1-yl)methyl)-6-methoxy-N-((2,4,6-tris(methoxy- d_3)phenyl)sulfonyl)picolinamide

[0807] To a suspension of 5-((1H-pyrazol-1-yl)methyl)-6-methoxypicolinic acid (1.6 g, 6.86 mmol), in ACN (30 mL) was added citric acid (0.395 g, 2.05 mmol) followed by CDI (1.98 g, 10.29 mmol) at rt and stirred for 2 h. 2,4,6-tris(Methoxy- d_3)benzenesulfonamide (1.58 g, 6.17 mmol) and followed by DBU (2.11 g, 10.97 mmol) at rt was added to the reaction mixture and stirred at rt for 3 h. The reaction mixture was quenched with saturated citric acid solution and extracted with 10% MeOH in DCM. The organic layer was washed with brine and dried over anhydrous Na_2SO_4 , filtered, and concentrated to get the crude. The crude compound was purified by silica-gel flash column chromatography using 0-1% MeOH in DCM as and recrystallized using ethyl acetate to obtain the title compound (1.6 g, 49.46%). LC-MS: 472.2 $[\text{M}+\text{H}]^+$. ^1H NMR (DMSO- D_6 , 400MHz): δ 11.16 (brs, 1H), 7.85 (dd, 1H), 7.55 – 7.51 (m, 2H), 7.21 (d, 1H), 6.32 (dd, 1H), 6.30 (s, 2H), 5.37 (s, 2H), 4.12 (s, 3H).

Example 21: (Compound 271) 5-((1H-Pyrazol-1-yl)methyl)-N-((5-ethyl-2-methoxyphenyl)sulfonyl)-4-methoxypyrimidine-2-carboxamide

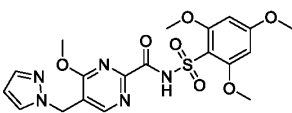
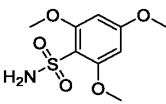
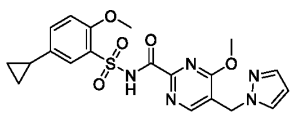


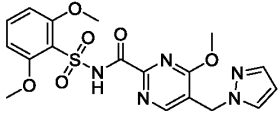
[0808] Step 1: 5-((1H-Pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-4-methoxypyrimidine-2-carboxamide

[0809] To a solution of methyl 5-((1H-pyrazol-1-yl)methyl)-4-methoxypyrimidine-2-carboxylate (Intermediate 11a) (0.2 g, 0.806 mmol), and 5-ethyl-2-methoxybenzenesulfonamide (Intermediate 20) (0.174 g, 0.806 mmol) in THF (10 mL) was added DIPEA (0.35 mL, 2.5 mmol), trimethylaluminum (0.119 mg, 2.5 mmol) at 0 °C and then the reaction mixture stirred at 70 °C for 16 h. The reaction was cooled to RT and diluted with 10% MeOH in DCM. The reaction mixture was filtered through celite, dried over sodium sulphate, filtered, and concentrated to afford the crude compound. Crude compound was purified by preparative HPLC to obtain the title compound as an off-white solid. LC-MS: 432.1 [M+H]⁺; ¹H NMR (DMSO-D₆, 400MHz): δ 12.28 (brs, 1H), 8.24 (s, 1H), 7.85 (d, 1H), 7.73 (d, 1H), 7.53 (dd, 1H), 7.49 (d, 1H), 7.17 (d, 1H), 6.30 (dd, 1H), 5.36 (s, 2H), 4.05 (s, 3H), 3.83 (s, 3H), 2.65 (q, 2H), 1.19 (t, 3H).

[0810] The following compounds listed in Table 15 were prepared by following a similar procedure (Example 21) as described above using appropriate reagents with suitable modifications known to the one skilled in the art.

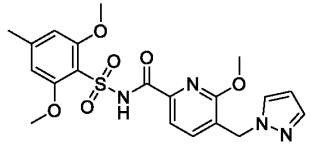
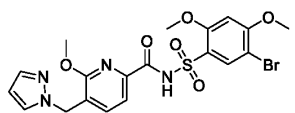
Table 15

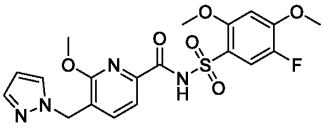
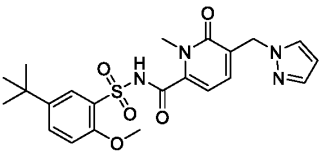
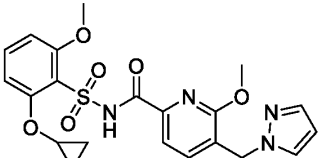
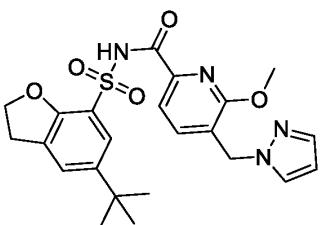
Com. No	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
272	 Exact Mass: 463.12	 Commercial & Intermediate 11a / Example 21	LC-MS: 464.3 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 11.76 (s, 1H), 8.22 (s, 1H), 7.84 (d, 1H), 7.49 (d, 1H), 6.31 – 6.30 (m, 3H), 5.36 (s, 2H), 4.05 (s, 3H), 3.84 (s, 3H), 3.79 (s, 6H).
273	 Exact Mass: 443.13	Intermediate 67 & Intermediate 11a / Example 21	LC-MS: 444.1[M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 12.29 (brs, 1H), 8.23 (s, 1H), 7.84 (d, 1H), 7.62 (d, 1H), 7.48 (dd, 1H), 7.35 (dd, 1H), 7.13 (d, 1H) 6.30 (dd, 1H), 5.35 (s, 2H), 4.05 (s, 3H), 3.81 (s, 3H), 2.03 – 1.99 (m,

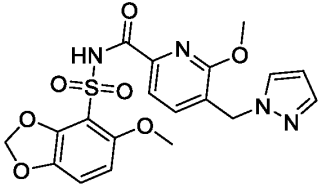
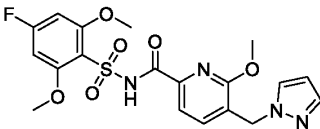
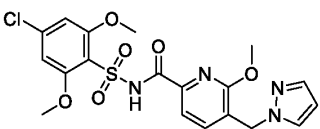
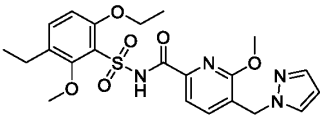
Com. No	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
			2H)–0.99 - 0.95 (m, 2H), 0.66 – 0.65 (m, 2H).
274	 Exact Mass: 433.11	Intermediate 22 & Intermediate 11a / Example 21	LC-MS: 434.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 11.95 (s, 1H), 8.24 (s, 1H), 7.85 (dd, 1H), 7.54 (dd, 1H), 7.50 (dd, 1H), 6.81 (d, 2H), 6.30 (dd, 1H), 5.37 (s, 2H), 4.06 (s, 3H), 3.80 (s, 6H).

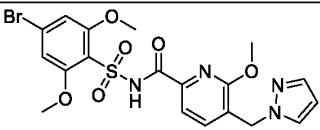
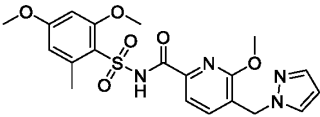
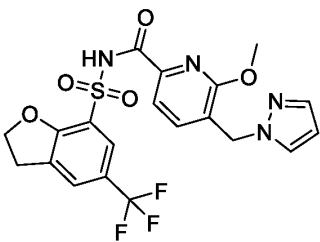
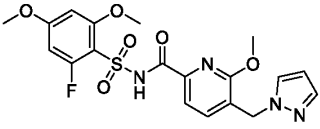
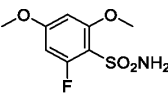
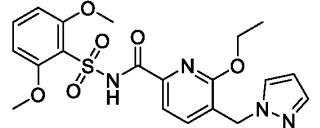
[0811] The following compounds listed in Table 16 were prepared by following a similar procedure (**Example 10**) as described above using appropriate reagents with suitable modifications known to the one skilled in the art.

5 **Table 16:**

Com. No	Structure	Intermediates / Coupling example	Spectral data
275		Intermediate 98 & Intermediate 30 / Example 10	LC-MS: 447.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 11.26 (brs, 1H), 7.85 (dd, 1H), 7.54 (d, 1H), 7.51 (dd, 1H), 7.21 (d, 1H), 6.64 (s, 2H), 6.32 (dd, 1H), 5.37 (s, 2H), 4.12 (s, 3H), 3.76 (s, 6H), 2.32 (s, 3H).
276	 Exact Mass: 510.02	Intermediate 26d & Intermediate 30 / Example 10	LC-MS: 513.1 [M+2+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 12.37 (brs, 1H), 7.94 (s, 1H), 7.81 (d, 1H), 7.50 (d, 1H), 7.49 (d, 1H), 7.15 (d, 1H), 6.76 (s, 1H), 6.29 (dd,

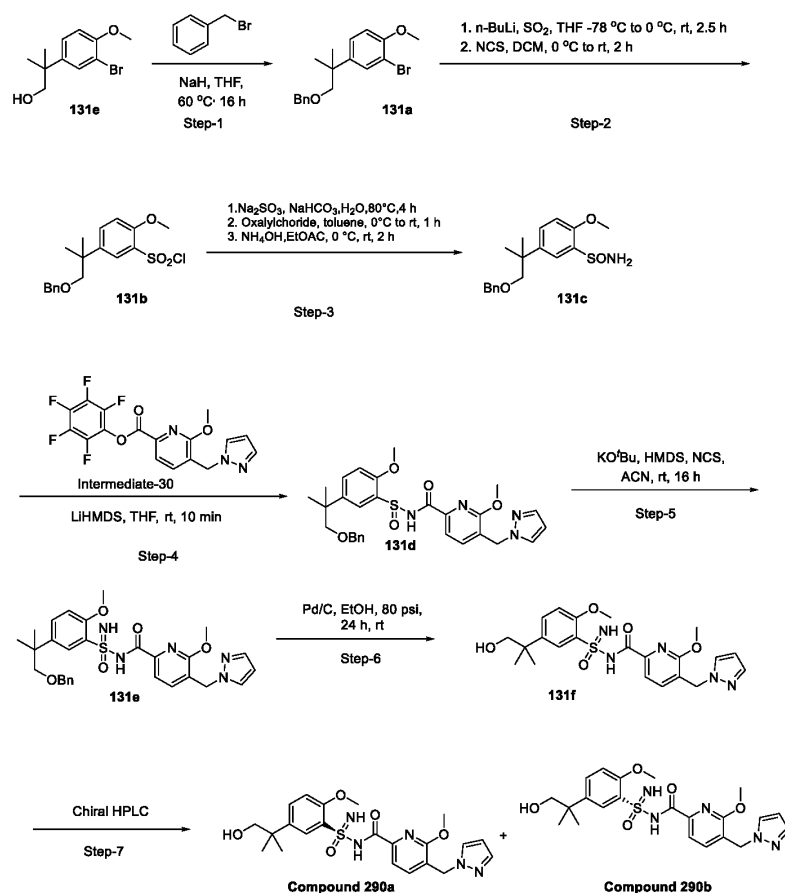
			1H), 5.31 (s, 2H), 3.99 (s, 3H), 3.93 (s, 3H), 3.82 (s, 3H).
277	 Exact Mass: 450.10	Intermediate 26b & Intermediate 30 / Example 10	LC-MS: 451.3 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 11.83 (s, 1H), 7.84 (d, 1H), 7.66 (d, 1H), 7.51 – 7.49 (m, 2H), 7.21 (d, 1H), 6.95 (d, 1H), 6.31 (dd, 1H), 5.36 (s, 2H), 4.13 (s, 3H), 3.96 (s, 3H), 3.89 (s, 3H).
278	 Exact Mass: 458.16	Intermediate 21 & Intermediate 99 / Example 7	LC-MS: 457.1 [M-H] ⁻ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 13.15 (brs, 1H), 7.83 (d, 1H), 7.80 (d, 1H), 7.74 (dd, 1H), 7.48 (d, 1H), 7.21 (d, 1H), 6.92 (d, 1H), 6.35 (d, 1H), 6.28 (dd, 1H), 5.15 (s, 2H), 3.91 (s, 3H), 3.28 (s, 3H), 1.30 (s, 9H).
279	 Exact Mass: 458.13	Intermediate 107 & Intermediate 30 / Example 10	LC-MS: 459.1 [M+H] ⁺ ; ¹ H NMR (CDCl ₃ , 400 MHz): δ 10.13 (brs, 1H), 7.70 (d, 1H), 7.60 (d, 1H), 7.52 (d, 1H), 7.46 (dd, 1H), 7.21 (d, 1H), 7.01 (d, 1H), 6.66 (d, 1H), 6.36 (dd, 1H), 5.38 (s, 2H), 4.13 (s, 3H), 3.93 (s, 3H), 3.84 – 3.83 (m, 1H), 0.83 – 0.81 (m, 2H), 0.80 – 0.77 (m, 2H).
280		Intermediate 90 & Intermediate 30 / Example 10	LC-MS: 471.2 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 11.92 (s, 1H), 7.84 (d, 1H), 7.63 (s, 1H), 7.56 (d, 1H), 7.53 – 7.50 (m, 2H), 7.20 (d, 1H), 6.31 (dd, 1H), 5.36 (s, 2H),

	Exact Mass: 470.16		4.62 (t, 2H), 4.12 (s, 3H), 3.24 (t, 2H), 1.29 (s, 9H).
281	 Exact Mass: 446.09	Intermediate 97 & Intermediate 30 / Example 10	LC-MS: 447.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 11.86 (brs, 1H), 7.83 (d, 1H), 7.54 (d, 1H), 7.51 (d, 1H), 7.21 (d, 1H), 7.12 (d, 1H), 6.53 (d, 1H), 6.32 (dd, 1H), 6.13 (s, 2H), 5.36 (s, 2H), 4.12 (s, 3H), 3.72 (s, 3H).
282	 Exact Mass: 450.10	Intermediate 91 & Intermediate 30 / Example 10	LC-MS: 451.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 11.50 (s, 1H), 7.85 (d, 1H), 7.54 (d, 1H), 7.51 (d, 1H), 7.21 (d, 1H), 6.74 (d, 2H), 6.32 (dd, 1H), 5.37 (s, 2H), 4.12 (s, 3H), 3.80 (s, 6H).
283	 Exact Mass: 466.07	Intermediate 92 & Intermediate 30 / Example 10	LC-MS: 467.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 11.59 (s, 1H), 7.85 (dd, 1H), 7.54 (d, 1H), 7.51 (dd, 2H), 7.21 (d, 1H), 6.93 (s, 2H), 6.32 (dd, 1H), 5.37 (s, 2H), 4.13 (s, 3H), 3.82 (s, 6H).
284	 Exact Mass: 474.16	Intermediate 1 & Intermediate 30 / Example 10	LC-MS: 475.2 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 11.25 (s, 1H), 7.85 (dd, 1H), 7.59 (d, 1H), 7.52 (dd, 1H), 7.48 (d, 1H), 7.21 (d, 1H), 6.94 (d, 1H), 6.32 (dd, 1H), 5.38 (s, 2H), 4.12 (s, 3H), 4.06 (q, 2H), 3.86 (s, 3H), 2.59 (q, 2H), 1.17 (t, 6H).
285		Intermediate 93 &	LC-MS: 511.0 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 11.62

	 Exact Mass: 510.02	Intermediate 30 / Example 10	(brs, 1H), 7.84 (d, 1H), 7.53 (d, 1H), 7.51 (dd, 1H), 7.20 (d, 1H), 7.02 (s, 2H), 6.32 (dd, 1H), 5.36 (s, 2H), 4.11 (s, 3H), 3.80 (s, 6H).
286	 Exact Mass: 446.13	Intermediate 94 & Intermediate 30 / Example 10	LC-MS: 447.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D6, 400 MHz): δ 7.83 (d, 1H), 7.51 – 7.49 (m, 2H), 7.19 (d, 1H), 6.52 (s, 1H), 6.49 (s, 1H), 6.30 (dd, 1H), 5.34 (s, 2H), 4.07 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 2.62 (s, 3H).
287	 Exact Mass: 482.09	Intermediate 2 & Intermediate 30 / Example 10	LC-MS: 483.0 [M+H] ⁺ ; ¹ H NMR (DMSO-D6, 400 MHz): δ 12.39 (brs, 1H), 7.92 – 7.89 (m, 2H), 7.83 (d, 1H), 7.52 (d, 1H), 7.50 (dd, 1H), 7.20 (d, 1H), 6.31 (dd, 1H), 5.35 (s, 2H), 4.78 (t, 2H), 4.11 (s, 3H), 3.31 (t, 2H).
288		 & Intermediate 30 / Example 10	LC-MS: 451.0 [M+H] ⁺ ; ¹ H NMR (DMSO-D6, 400 MHz): δ 11.85 (s, 1H), 7.84 (d, 1H), –7.54 - 7.50 (m, 2H), 7.22 (d, 1H), 6.63 (dd, 1H), 6.54 (s, 1H), 6.32 (d, 1H), 5.36 (s, 2H), 4.13 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H).
289		Intermediate 22 / Intermediate 100 / Example 10	LC-MS: 447.2 [M+H] ⁺ ; ¹ H NMR (CD ₃ OD, 400 MHz): δ 7.88 (d, 1H), 7.63 (d, 1H), 7.56 – 7.54 (m, 2H), 7.34 (d, 1H), 6.81 (d, 1H), 6.38 (dd,

			1H), 5.42 (s, 2H), 4.61 (q, 2H), 3.88 (s, 6H), 1.50 (t, 3H).
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Example 22: 5-((1H-Pyrazol-1-yl)methyl)-N-(5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide (Compound 290a & 290b)



5 [0812] Step 1: 4-(1-(Benzyloxy)-2-methylpropan-2-yl)-2-bromo-1-methoxybenzene

[0813] To a stirred solution of 2-(3-bromo-4-methoxyphenyl)-2-methylpropan-1-ol (1.7g, 6.56 mmol) in THF (30 mL) was added NaH (0.226g, 9.84 mmol) at 0 °C. After 20 min, (bromomethyl)benzene (2.2g, 13.12 mmol) was added to the reaction mixture at 0 °C. The reaction was heated 60 °C for 16 h. The reaction mixture was cooled to rt, quenched with ice water, and extracted with EtOAc. The organic layer was washed with water, brine, dried over

10

Na₂SO₄ and concentrated to get crude compound. The crude compound was purified by silica-gel flash column chromatography using 20% ethyl acetate in hexane as eluent to afford the title compound (1.4 g, 61.1%). ¹H NMR (DMSO-D₆, 400MHz): δ 7.52 (d, 1H), 7.36 – 7.31 (m, 3H), 7.29 – 7.23 (m, 3H), 7.04 (d, 1H), 4.45 (s, 2H), 3.82 (s, 3H), 3.42 (s, 2H), 1.25 (s, 6H).

5 **[0814]** Step 2: 5-(1-(benzyloxy)-2-methylpropan-2-yl)-2-methoxybenzenesulfonyl chloride

[0815] The title compound was prepared using a similar procedure to that described in Step 3 of Intermediate 89 using appropriate reagents with suitable modifications. (1.4 g, 61.1%). ¹H NMR (DMSO-D₆, 400MHz): δ 7.73 (d, 1H), 7.34 – 7.31 (m, 3H), 7.30 – 7.26 (m, 3H), 6.90 (d, 1H), 4.45 (s, 2H), 3.73 (s, 3H), 3.41 (s, 2H), 1.26 (s, 6H).

10 **[0816]** Step 3: 5-(1-(Benzyloxy)-2-methylpropan-2-yl)-2-methoxybenzenesulfonamide

[0817] The title compound was prepared using a similar procedure to that described in Step 1 of Intermediate 108 using appropriate reagents with suitable modifications. (0.29 g, 16.87%). ¹H NMR (DMSO-D₆, 400MHz): δ 7.78 (d, 1H), 7.45 (dd, 1H), 7.35 – 7.26 (m, 5H), 7.02 (d, 1H), 5.92 (s, 2H), 4.47 (s, 2H), 3.81 (s, 3H), 3.47 – 3.42 (m, 2H), 1.30 (s, 6H).

15 **[0818]** Step 4: 5-((1H-Pyrazol-1-yl)methyl)-N-((5-(1-(benzyloxy)-2-methylpropan-2-yl)-2-methoxyphenyl)sulfinyl)-6-methoxypicolinamide

[0819] The title compound was prepared using a similar procedure to that described in Step 2 of Intermediate 82 using appropriate reagents with suitable modifications (0.21 g, 30.57%). LC-MS: 547.1 [M-H]⁻.

20 **[0820]** Step 5: 5-((1H-Pyrazol-1-yl)methyl)-N-(5-(1-(benzyloxy)-2-methylpropan-2-yl)-2-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide

[0821] The title compound was prepared using a similar procedure to that described in Example 13 using appropriate reagents with suitable modifications (0.370 g); LC-MS: 564.2 [M+H]⁺.

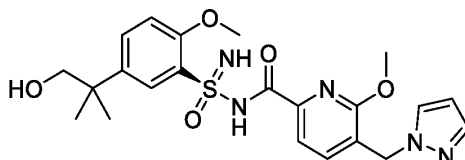
25 **[0822]** Step 6: 5-((1H-pyrazol-1-yl)methyl)-N-(5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide

[0823] To a solution of 5-((1H-pyrazol-1-yl)methyl)-N-(5-(1-(benzyloxy)-2-methylpropan-2-yl)-2-methoxyphenylsulfonimidoyl)-6-methoxypicolinamide (0.31g, 0.055 mmol) in ethanol (15 mL) was carefully added 10% Pd-C (0.11g, ~10% W/W) and stirred under positive pressure of hydrogen using a bladder for 12 h. The reaction mixture was filtered through celite

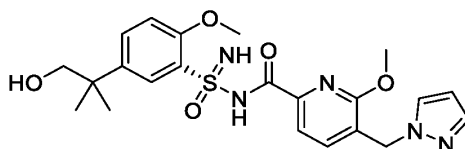
30

and filtrate was concentrated to obtain the crude compound as a white solid. Crude compound was purified by preparative HPLC to obtain the racemic title compound (60 mg).

[0824] Step 7: Intermediate 131f was separated by chiral HPLC into its respective enantiomers. (6.2 mg (peak 1) + 8.2 mg (peak 2) = (15 mg, 7.68 %), with arbitrary assignment of stereochemistry.

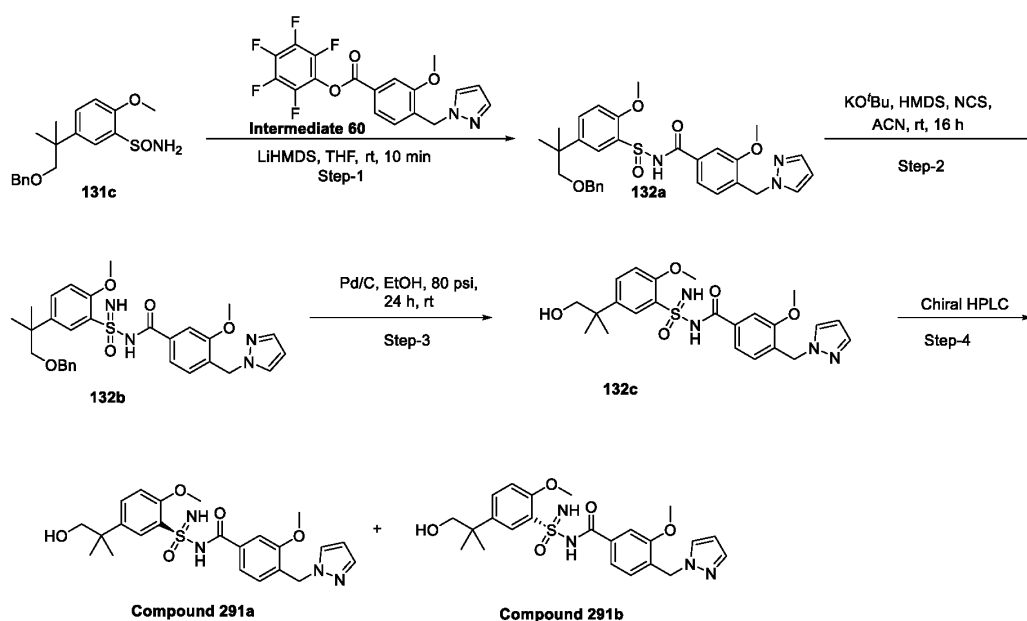


[0825] Compound 290a: peak 1; LCMS: 474.2 [M+H]⁺; ¹H NMR (DMSO-D₆, 400 MHz) :
 δ 7.81 (d, 1H), 7.80 (dd, 1H), 7.61 – 7.58 (m, 2H), 7.49 (d, 1H), 7.48 (brs, 2H), 7.18 (d, 1H),
 7.12 (d, 1H), 6.30 (dd, 1H), 5.32 (s, 2H), 4.77 (t, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 3.40 (d, 2H),
 1.23 (s, 6H).



[0826] Compound 290b: peak 2; LCMS: 474.1 [M+H]⁺; ¹H NMR (DMSO-D₆, 400 MHz) :
 δ 7.87 (d, 1H), 7.81 (dd, 1H), 7.61 – 7.59 (d, 2H), 7.49 (dd, 1H), 7.44 (brs, 2H), 7.18 (d, 1H),
 7.11 (d, 1H), 6.30 (dd, 1H), 5.31 (s, 2H), 4.76 (t, 1H), 3.93 (s, 3H), 3.79 (s, 3H), 3.40 (d, 2H),
 1.23 (s, 6H).

Example 23: 4-((1H-Pyrazol-1-yl)methyl)-N-(5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenylsulfonimidoyl)-3-methoxybenzamide (Compound 291a & 291b)



[0827] Step 1: 5-((1H-pyrazol-1-yl)methyl)-N-((5-(1-(benzyloxy)-2-methylpropan-2-yl)-2-methoxyphenyl)sulfinyl)-6-methoxypicolinamide

[0828] The title compound was prepared using a similar procedure to that described in Step 2 of Intermediate 82 using appropriate reagents with suitable modifications. LCMS: 548.2 [M+H]⁺

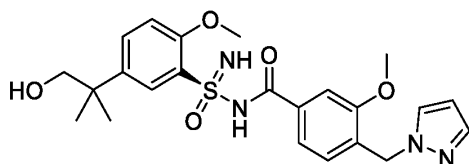
Step 2: 4-((1H-pyrazol-1-yl)methyl)-N-(5-(1-(benzyloxy)-2-methylpropan-2-yl)-2-methoxyphenyl)sulfonimidoyl)-3-methoxybenzamide

[0829] The title compound was prepared using a similar procedure to that described in Example 13 using appropriate reagents with suitable modifications. LCMS: 563.1 [M+H]⁺

Step 3: 4-((1H-Pyrazol-1-yl)methyl)-N-(5-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenyl)sulfonimidoyl)-3-methoxybenzamide

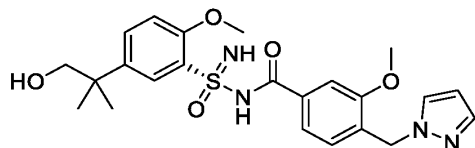
[0830] The title compound was prepared using a similar procedure to that described in Step 2 of Example 88 using appropriate reagents with suitable modifications. Crude compound was purified by preparative HPLC to obtain the racemic title compound (100 mg).

Step 4: Intermediate 132c was separated by chiral HPLC into its respective enantiomers (15 mg (peak 1) + 20 mg (peak 2) = (35 mg, 10.7%), with arbitrary assignment of stereochemistry



[0831] Compound-291a; LCMS: 473.2 [M+H]⁺; ¹H NMR (DMSO-D₆, 400 MHz): δ 7.87 (d, 1H), 7.75 (d, 1H), 7.59 (dd, 1H), -7.53 - 7.46 (m, 5H), 7.11 (d, 1H), 6.80 (d, 1H), 6.28 (dd, 1H), 5.32 (s, 2H), 4.77 (t, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.40 (dd, 2H), 1.23 (d, 6H).

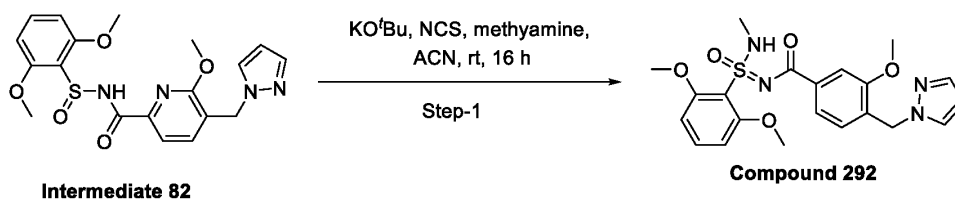
5



[0832] Compound-291b; LCMS: 473.2 [M+H]⁺; ¹H NMR (DMSO-D₆, 400 MHz): δ 7.85 (d, 1H), 7.76 (dd, 1H), 7.58 (dd, 1H), -7.53 - 7.46 (m, 5H), 7.11 (d, 1H), 6.80 (d, 1H), 6.28 (dd, 1H), 5.32 (s, 2H), 4.76 (t, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.40 (d, 2H), 1.23 (d, 6H).

Example 24: 4-((1H-Pyrazol-1-yl)methyl)-N-((2,6-

10 **dimethoxyphenyl)(methylamino)(oxo)-16-sulfaneylidene)-3-methoxybenzamide**
(Compound 292)

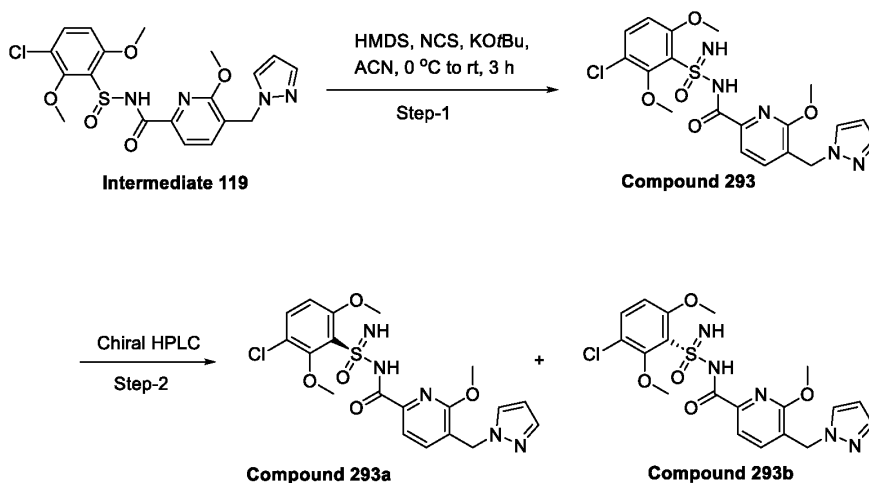


[0833] Step 1: 4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)(methylamino)(oxo)-16-sulfaneylidene)-3-methoxybenzamide

15 [0834] To a solution of 5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfinyl)-6-methoxypicolinamide (0.02 g, 0.048 mmol) in ACN (2.0 ml) was added potassium tert-butoxide (0.011 g, 0.09 mmol) followed by NCS (0.038 g, 0.28 mmol) and methylamine in THF (2.0M) (0.15 mL, 0.28 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 16 h. The reaction mixture was quenched with water and extracted with 10% methanol in DCM. The combined organic layers were washed with brine, dried over sodium sulphate, filtered, and concentrated to get the crude compound. Crude compound was purified by preparative TLC using 100% EtOAc as eluent (0.01 g, 46.87%). LC-MS: 445.1 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz): δ 7.71 (d, 1H), 7.69 (d, 1H), 7.54 (d, 1H), 7.47 - 7.42 (m, 2H), 7.14 - 7.11 (m, 1H), 6.96 (d, 1H), 6.66 (d, 2H), 6.26 (dd, 1H), 5.37 (s, 2H), 3.93 (s, 6H), 3.90 (s, 3H), 2.83 (d, 3H).

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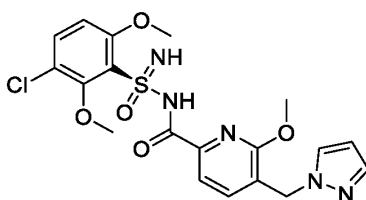
Example 25: 5-((1H-Pyrazol-1-yl)methyl)-N-(3-chloro-2,6-dimethoxyphenylsulfonimidoyl)-6-methoxypicolinamide (Compound 293a & 293b)



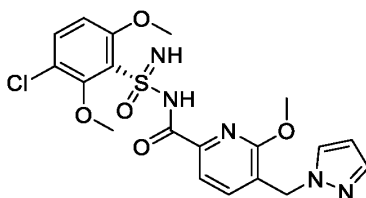
5 **[0835]** Step 1: Compound 293 was prepared using a similar procedure to that described in Example 13 using appropriate reagents with suitable modifications. Crude compound was purified by preparative HPLC to obtain the racemic title compound (70 mg).

[0836] Step 2: Compound 293 was separated by chiral HPLC into its respective enantiomers, with arbitrary assignment of stereochemistry

10



[0837] Compound 293a; LC-MS: 466.1 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz): δ 7.93 (d, 1H), 7.60 (d, 1H), 7.53 – 7.50 (m, 2H), 7.21 (d, 1H), 6.77 (d, 1H), 6.51 (d, 2H), 6.35 (dd, 1H), 5.38 (s, 2H), 4.12 (s, 3H), 4.05 (s, 3H), 3.80 (s, 3H).



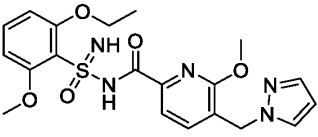
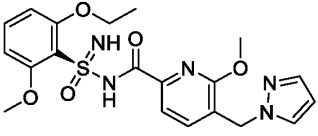
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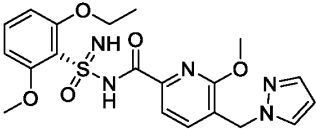
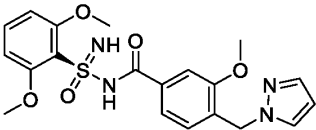
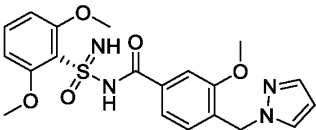
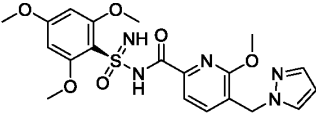
[0838] Compound 293b; LC-MS: 466.1 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz): δ 7.93 (d, 1H), 7.60 (dd, 1H), 7.53 – 7.50 (m, 2H), 7.21 (d, 1H), 6.77 (d, 1H), 6.73 (brs, 2H), 6.35 (dd, 1H), 5.38 (s, 2H), 4.12 (s, 3H), 4.05 (s, 3H), 3.80 (s, 3H).

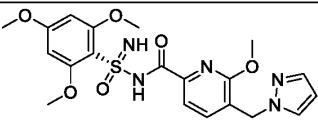
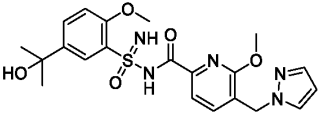
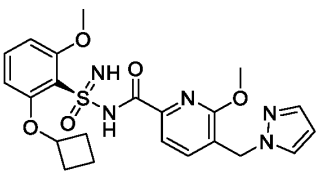
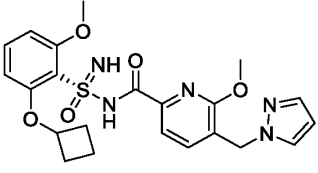
5 **Example 26. Compounds 294, 294a, 294b, 295a, 295b, 296a, 296b, 297, 298a, 298b, 299, 299a, 299b, 300a, 300b, 301a, 301b, 302a, 302b, 303a, 303b, 304a, 304b, 305a, 305a, 306a, 306b, 307a, 307b, 308a, and 308b.**

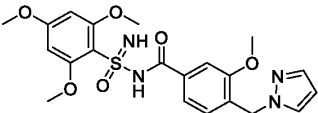
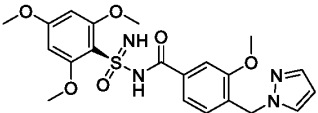
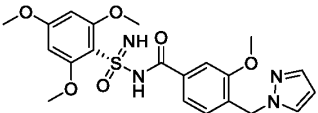
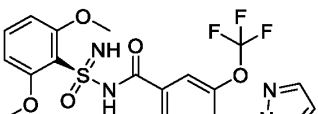
[0839] The following compounds listed in Table 17 were prepared by following a similar procedure as described above in Example 13 using appropriate reagents with suitable modifications known to the one skilled in the art.

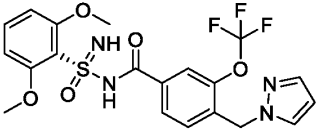
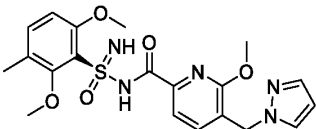
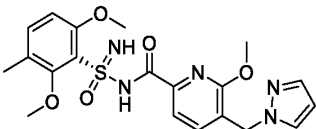
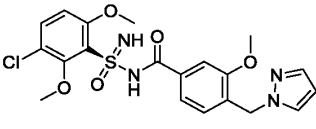
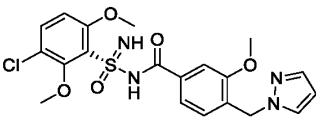
10 **Table 17:**

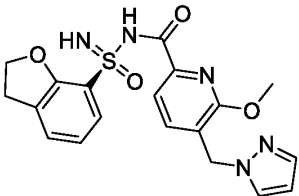
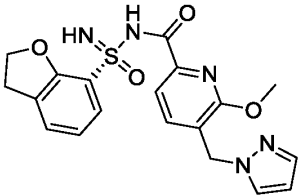
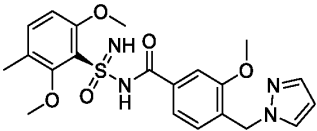
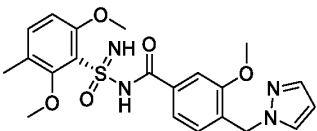
Com. No	Structure	Intermediate / Coupling example	Spectral data
294	 (racemic) Exact Mass: 445.14	Intermediate 120 / Example 13	LC-MS: 446.2 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 7.80 (d, 1H), 7.59 (d, 1H), 7.49 (d, 1H), 7.32 – 7.28 (m, 1H), 7.14 (d, 1H), 6.68 (d, 2H), 6.29 (dd, 1H), 5.30 (s, 2H), 4.07 – 3.99 (m, 2H), 3.92 (s, 3H), 3.74 (s, 3H), 1.24 (t, 3H).
294a	 (peak 1) Exact Mass: 430.13	Intermediate 120 / Example 13	LC-MS: 446.05 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 7.82 (dd, 1H), 7.64 (d, 1H), 7.50 (dd, 1H), 7.45 (dd, 1H), 7.34 (brs, 2H), 7.17 (d, 1H), 6.77 (d, 1H), 6.76 (d, 1H), 6.31 (dd, 1H), 5.32 (s, 2H), 4.06 (q, 2H), 3.93 (s, 3H), 3.79 (s, 3H), 1.21 (t, 3H).
294b		Intermediate 120 /	LC-MS: 446.1 [M+H] ⁺ ; ¹ H NMR (CDCl ₃ , 400 MHz): δ 7.97 (d, 1H),

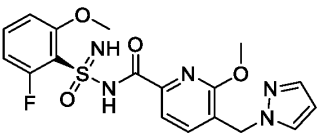
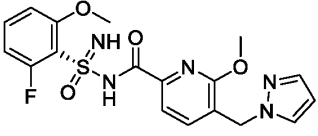
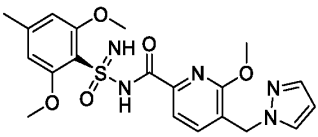
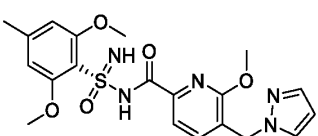
	 (peak 2) Exact Mass: 445.14	Example 13	7.60 (dd, 1H), 7.51 (dd, 1H), 7.40 (dd, 1H), 7.21 (d, 1H), 6.72 (brs, 2H), 6.63 (t, 2H, two H partially overlapped), 6.34 (dd, 1H), 5.38 (s, 2H), 4.15 (q, 2H), 4.12 (s, 3H), 3.79 (s, 3H), 1.38 (t, 3H).
295a	 (peak 1) Exact Mass: 430.13	Intermediate 86 / Example 13	LC-MS: 431.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 7.76 (d, 1H), 7.54 (d, 1H), 7.52 – 7.45 (m, 3H), 7.41 (brs, 2H), 6.80 – 6.76 (m, 3H), 6.28 (dd, 1H), 5.33 (s, 2H), 3.87 (s, 3H), 3.75 (s, 6H).
295b	 (peak 2) Exact Mass: 430.13	Intermediate 86 / Example 13	LC-MS: 431.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 7.76 (d, 1H), 7.54 (d, 1H), 7.52 – 7.45 (m, 3H), 7.40 (brs, 2H), 6.80 – 6.75 (m, 3H), 6.28 (dd, 1H), 5.33 (s, 2H), 3.87 (s, 3H), 3.75 (s, 6H).
296a	 (peak 1) Exact Mass: 461.14	Intermediate 85 / Example 13	LC-MS: 462.2 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 7.82 (dd, 1H), 7.62 (d, 1H), 7.50 (dd, 1H), 7.31 (brs, 2H), 7.17 (d, 1H), 6.30 (dd, 1H), 6.29 (s, 2H), 5.32 (s, 2H), 3.93 (s, 3H), 3.83 (s, 3H), 3.76 (s, 6H).
296b		Intermediate 85 / Example 13	LC-MS: 462.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 7.81 (dd, 1H), 7.60 (d, 1H), 7.50 (dd, 1H),

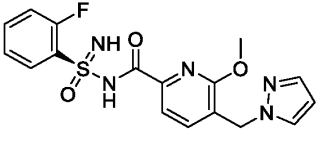
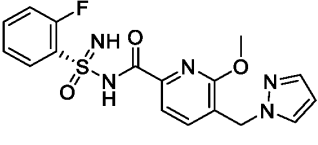
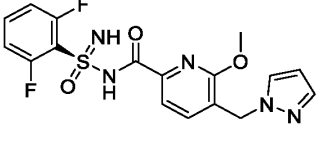
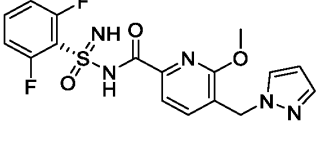
	 (peak 2) Exact Mass: 461.14		7.31 (brs, 2H), 7.17 (d, 1H), 6.30 (dd, 1H), 6.28 (s, 2H), 5.32 (s, 2H), 3.93 (s, 3H), 3.83 (s, 3H), 3.75 (s, 6H).
297	 (racemic) Exact Mass: 459.16	Intermediate 129 / Example 13	LC-MS: 460.2 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 8.03 (d, 1H), 7.81 (d, 1H), 7.65 (dd, 1H), 7.61 (d, 1H), 7.50 (brs, 2H), 7.49 (d, 1H), 7.19 (d, 1H), 7.12 (d, 1H), 6.30 (dd, 1H), 5.31 (s, 2H), 5.17 (s, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 1.44 (s, 6H).
298a	 (peak 1) Exact Mass: 471.16	Intermediate 87 / Example 13	LC-MS: 472.2 [M+H] ⁺ ; ¹ H NMR (CDCl ₃ , 400MHz): δ 7.97 (d, 1H), 7.60 (d, 1H), 7.50 (d, 1H), 7.36 (dd, 1H), 7.24 (d, 1H), 6.60 (d, 1H), 6.48 (d, 1H), 6.34 (dd, 1H), 5.38 (s, 2H), 4.73 – 4.68 (m, 1H), 4.11 (s, 3H), 3.80 (s, 3H), 2.44 – 2.37 (m, 1H), 2.35 – 2.21 (m, 1H), 2.20 – 2.07 (m, 2H), 1.81 – 1.76 (m, 1H), 1.74 – 1.67 (m, 1H).
298b	 (peak 2) Exact Mass: 471.16	Intermediate 87 / Example 13	LC-MS: 472.2 [M+H] ⁺ ; ¹ H NMR (CDCl ₃ , 400MHz): δ 7.97 (d, 1H), 7.60 (d, 1H), 7.50 (d, 1H), 7.36 (dd, 1H), 7.24 (d, 1H), 6.60 (d, 1H), 6.48 (d, 1H), 6.34 (dd, 1H), 5.38 (s, 2H), 4.73 – 4.69 (m, 1H), 4.12 (s, 3H), 3.81 (s, 3H), 2.44 – 2.39 (m, 1H), 2.31 – 2.25 (m, 1H), 2.19 – 2.06 (m,

			2H), 1.79 – 1.75 (m, 1H), 1.67 – 1.59 (m, 1H).
299	 (racemic) Exact Mass: 460.14	Intermediate 127 / Example 13	LC-MS: 461.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 7.76 (d, 1H), 7.54 (d, 1H), 7.50 (d, 1H), 7.47 (d, 1H), 7.27 (brs, 2H), 6.79 (d, 1H), 6.28 (s, 3H), 5.32 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.74 (s, 6H).
299a	 (peak 1) Exact Mass: 460.14	Intermediate 127 / Example 13	LC-MS: 461.2 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 7.76 (dd, 1H), 7.54 (d, 1H), 7.51 (dd, 1H), 7.47 (dd, 1H), 7.29 (brs, 2H), 6.79 (d, 1H), 6.28 (s, 3H), 5.33 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.74 (s, 6H).
299b	 (peak 2) Exact Mass: 460.14	Intermediate 127 / Example 13	LC-MS: 461.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 7.76 (dd, 1H), 7.53 (d, 1H), 7.51 (dd, 1H), 7.47 (dd, 1H), 7.29 (brs, 2H), 6.79 (d, 1H), 6.28 (s, 3H), 5.32 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.74 (s, 6H).
300a	 (peak 1) Exact Mass: 484.10	Intermediate 130 / Example 13	LC-MS: 485.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 7.90 – 7.85 (m, 3H), 7.51 – 7.46 (m, 4H), 7.10 (d, 1H), 6.78 (d, 2H), 6.32 (dd, 1H), 5.47 (s, 2H), 3.74 (s, 6H).
300b		Intermediate 130 / Example 13	LC-MS: 485.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 7.90 – 7.85 (m, 3H), 7.51 – 7.46 (m, 4H),

	 (peak 2) Exact Mass: 484.10		7.10 (d, 1H), 6.77 (s, 2H), 6.32 (dd, 1H), 5.47 (s, 2H), 3.74 (s, 6H).
301a	 (peak 1) Exact Mass: 445.14	Intermediate 126 / Example 13	LC-MS: 446.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 7.82 (d, 1H), 7.64 (d, 1H), 7.50 (d, 1H), 7.45 (brs, 2H), 7.40 (d, 1H), 7.17 (d, 1H), 6.89 (d, 1H), 6.30 (dd, 1H), 5.32 (s, 2H), 3.92 (s, 3H), 3.76 (s, 6H), 2.18 (s, 3H).
301b	 (peak 2) Exact Mass: 445.14	Intermediate 126 / Example 13	LC-MS: 446.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400MHz): δ 7.82 (dd, 1H), 7.62 (d, 1H), 7.50 (dd, 1H), 7.36 (d, 1H), 7.26 (brs, 2H), 7.17 (d, 1H), 6.87 (d, 1H), 6.30 (dd, 1H), 5.32 (s, 2H), 3.92 (s, 3H), 3.76 (s, 6H), 2.17 (s, 3H).
302a	 (peak 1) Exact Mass: 464.09	Intermediate 131 / Example 13	LC-MS: 465.1 [M+H] ⁺ ; ¹ H NMR (CDCl ₃ , 400 MHz): δ 7.81 (dd, 1H), 7.76 (d, 1H), 7.58 (dd, 1H), 7.52 (d, 1H), 7.48 (dd, 1H), 6.97 (d, 1H), 6.77 (d, 1H), 6.31 (dd, 1H), 5.42 (s, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 3.73 (s, 3H).
302b	 (peak 2)	Intermediate 131 / Example 13	LC-MS: 465.1 [M+H] ⁺ ; ¹ H NMR (CDCl ₃ , 400 MHz): δ 7.81 (dd, 1H), 7.76 (d, 1H), 7.58 (dd, 1H), 7.52 (d, 1H), 7.48 (dd, 1H), 6.97 (d, 1H), 6.77 (d, 1H), 6.31 (dd, 1H),

	Exact Mass: 464.09		5.42 (s, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 3.73 (s, 3H).
303a	 (peak 1) Exact Mass: 413.12	Intermediate 121 / Example 13	LC-MS: 414.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 7.80 (dd, 1H), 7.62 – 7.57 (m, 2H), 7.49 (dd, 1H), 7.43 (d, 1H), 7.19 (d, 1H), 6.95 (dd, 1H), 6.30 (dd, 1H), 5.31 (s, 2H), 4.62 – 4.56 (m, 2H), 3.92 (s, 3H), 3.20 (t, 2H).
303b	 (peak 2) Exact Mass: 413.12	Intermediate 121 / Example 13	LC-MS: 414.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 7.81 (dd, 1H), 7.62 – 7.58 (m, 2H), 7.49 (dd, 1H), 7.44 (dd, 1H), 7.19 (d, 1H), 6.96 (dd, 1H), 6.30 (dd, 1H), 5.31 (s, 2H), 4.62 – 4.57 (m, 2H), 3.92 (s, 3H), 3.21 (t, 2H).
304a	 (peak 1) Exact Mass: 444.15	Intermediate 128 / Example 13	LC-MS: 445.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 7.77 (dd, 1H), 7.53 (dd, 1H), 7.51 (d, 1H), 7.47 (dd, 1H), 7.42 (brs, 2H), 7.39 (d, 2H), 6.88 (d, 1H), 6.79 (d, 1H), 6.28 (dd, 1H), 5.32 (s, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 2.18 (s, 3H).
304b	 (peak 2) Exact Mass: 444.15	Intermediate 128 / Example 13	LC-MS: 445.2 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 7.77 (dd, 1H), 7.55 (dd, 1H), 7.51 (dd, 1H), 7.47 (dd, 1H), 7.37 (d, 1H), 6.87 (d, 1H), 6.78 (d, 1H), 6.28 (dd, 1H), 5.32 (s, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 2.17 (s, 3H).

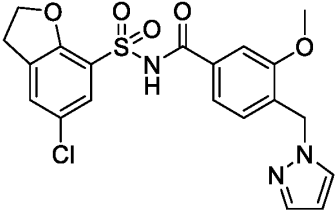
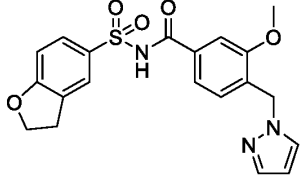
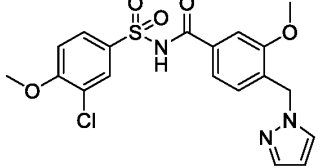
305a	 (peak 1) Exact Mass: 419.11	Intermediate 122 / Example 13	LC-MS: 420.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 7.81 (dd, 1H), 7.74 (brs, 2H), 7.61 (d, 1H), 7.59 – 7.55 (m, 1H), 7.49 (dd, 1H), 7.19 (d, 1H), 7.02 (d, 1H), 6.95 – 6.90 (m, 1H), 6.30 (dd, 1H), 5.32 (s, 2H), 3.92 (s, 3H), 3.84 (s, 3H).
305b	 (peak 2) Exact Mass: 419.11	Intermediate 122 / Example 13	LC-MS: 420.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 7.81 (dd, 1H), 7.74 (brs, 2H), 7.61 (d, 1H), 7.59 – 7.54 (m, 1H), 7.49 (dd, 1H), 7.19 (d, 1H), 7.01 (d, 1H), 6.95 – 6.90 (m, 1H), 6.30 (dd, 1H), 5.32 (s, 2H), 3.92 (s, 3H), 3.84 (s, 3H).
306a	 (peak 1) Exact Mass: 445.14	Intermediate 123 / Example 13	LC-MS: 446.2 [M+H] ⁺ ; ¹ H NMR (CDCl ₃ , 400 MHz): δ 7.96 (d, 1H), 7.60 (d, 1H), 7.51 (d, 1H), 7.21 (d, 1H), 6.65 (brs, 2H), 6.44 (s, 2H), 6.34 (dd, 1H), 5.41 – 5.33 (m, 2H), 4.12 (s, 3H), 3.81 (s, 6H), 2.36 (s, 3H).
306b	 (peak 2) Exact Mass: 445.14	Intermediate 123 / Example 13	LC-MS: 446.1 [M+H] ⁺ ; ¹ H NMR (CDCl ₃ , 400 MHz): δ 7.96 (d, 1H), 7.60 (dd, 1H), 7.51 (d, 1H), 7.20 (d, 1H), 6.63 (brs, 2H), 6.44 (s, 2H), 6.34 (dd, 1H), 5.41 – 5.33 (m, 2H), 4.12 (s, 3H), 3.81 (s, 6H), 2.36 (s, 3H).
		Intermediate 124 / Example 13	LC-MS: 390.1 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 8.05 (brs, 2H), 7.98 – 7.94 (m, 1H), 7.81 (dd,

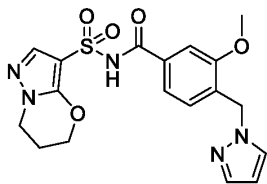
307a	 (peak 1) Exact Mass: 389.10		1H), -7.72 - 7.62 (m, 2H), 7.49 (dd, 1H), 7.44 - 7.37 (m, 2H), 7.20 (d, 1H), 6.30 (dd, 1H), 5.32 (s, 2H), 3.93 (s, 3H).
307b	 (peak 2) Exact Mass: 389.10	Intermediate 124 / Example 13	LC-MS: 390.0 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 8.06 (brs, 2H), 7.98 - 7.94 (m, 1H), 7.81 (dd, 1H), -7.71 - 7.69 (m, 1H), 7.64 (d, 1H), 7.49 (dd, 1H), 7.43 - 7.38 (m, 2H), 7.21 (d, 1H), 6.30 (dd, 1H), 5.32 (s, 2H), 3.93 (s, 3H).
308a	 (peak 1) Exact Mass: 407.09	Intermediate 125 / Example 13	LC-MS: 408.0 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 8.36 (brs, 2H), 7.81 (dd, 1H), -7.72 - 7.63 (m, 2H), 7.50 (dd, 1H), 7.29 - 7.20 (m, 3H), 6.30 (dd, 1H), 5.32 (s, 2H), 3.93 (s, 3H).
308b	 (peak 2) Exact Mass: 407.09	Intermediate 125 / Example 13	LC-MS: 408.0 [M+H] ⁺ ; ¹ H NMR (DMSO-D ₆ , 400 MHz): δ 7.80 (dd, 1H), -7.61 - 7.60 (m, 2H), 7.50 (dd, 1H), 7.20 - 7.16 (m, 3H), 6.29 (dd, 1H), 5.31 (s, 2H), 3.92 (s, 3H)

Example 27. Compounds 309, 310, 311, and 312.

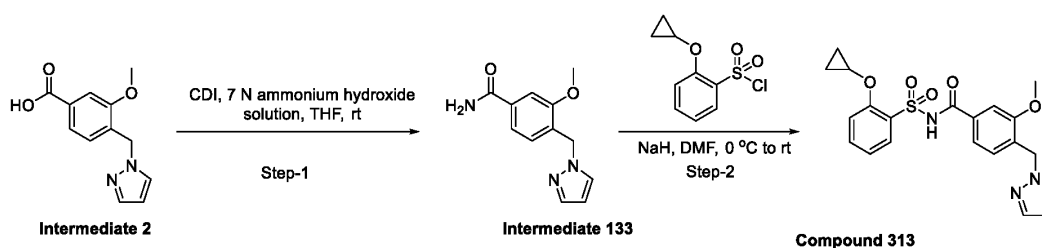
[0840] The following compounds listed in Table 18 were prepared by following a similar procedure as described above in Step 1 of Example 1 using appropriate reagents with suitable modifications known to the one skilled in the art.

Table 18

Com. No	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
309		Intermediate 2 / Example 1	LCMS: 448.0 [M+H] ⁺ ¹ H NMR (400 MHz, DMSO) δ 7.75 (d, J = 2.3 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.47 – 7.41 (m, 2H), 6.77 (d, J = 7.8 Hz, 1H), 6.53 (d, J = 3.0 Hz, 1H), 6.27 (t, J = 2.1 Hz, 1H), 5.31 (s, 2H), 4.60 (s, 2H), 3.87 (s, 3H), 3.19 (t, J = 8.9 Hz, 2H).
310		Intermediate 2 / Example 1	LCMS: 414.1 [M+H] ⁺ ¹ H NMR (400 MHz, DMSO) δ 7.83 (d, J = 1.9 Hz, 1H), 7.77 (dt, J = 5.6, 2.4 Hz, 2H), 7.49 (dd, J = 12.7, 1.7 Hz, 2H), 7.41 (dd, J = 7.9, 1.7 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.28 (t, J = 2.1 Hz, 1H), 5.33 (s, 2H), 4.66 (t, J = 8.8 Hz, 2H), 3.90 (s, 3H), 3.27 (t, J = 8.8 Hz, 2H).
311		Intermediate 2 / Example 1	LCMS: 436.0 [M+H] ¹ H NMR (400 MHz, DMSO) δ 7.94 (d, J = 2.2 Hz, 1H), 7.90 (dd, J = 8.7, 2.3 Hz, 1H), 7.76 (dd, J = 2.2, 0.7 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.47 (dd, J = 1.9, 0.6 Hz, 1H), 7.41 (dd, J = 7.9, 1.6 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.28 (t, J = 2.1 Hz, 1H), 5.32 (s, 2H), 3.95 (s, 3H), 3.88 (s, 3H).

Com. No	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
312		Intermediate 2 / Example 1	LCMS: m/z = 418.1 [M+H] ⁺

Example 28: (Compound 313) 4-((1H-pyrazol-1-yl)methyl)-N-((2-cyclopropoxyphenyl)sulfonyl)-3-methoxybenzamide



[0841] Step 1: 4-((1H-pyrazol-1-yl)methyl)-3-methoxybenzamide

3-Methoxy-4-(pyrazol-1-ylmethyl)benzoic acid (216 mg, 0.93 mmol) and CDI (226 mg, 1.40 mmol) were dissolved in THF (3 mL) and stirred for 1 h. 7 N ammonium hydroxide solution (0.770 mL) was added and stirred for 16 h. The solution was diluted with water, neutralized with 1 N HCl, and extracted with EtOAc. The organics were washed with 1 N HCl, water, and brine solution. They were then dried over sodium sulfate, filtered, and dried in-vacuo to give the title product (140 mg, 65% yield). LCMS: m/z = 232.2 [M+H]⁺.

[0842] Step 2: 4-((1H-pyrazol-1-yl)methyl)-N-((2-cyclopropoxyphenyl)sulfonyl)-3-methoxybenzamide

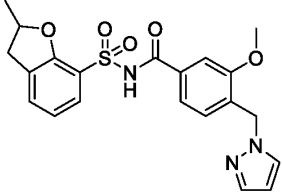
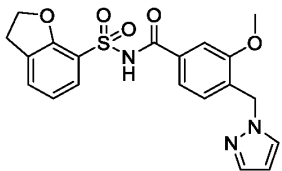
[0843] 3-Methoxy-4-(pyrazol-1-ylmethyl)benzamide (0.04 g, 0.17 mmol) was dissolved in DMF (0.15 – 0.3 M) and cooled to 0 °C and 90% sodium hydride (0.09 g, 0.34 mmol) was added and stirred for 30 min. Arylsulfonyl chloride (0.044 g, 0.19 mmol) was added and stirred for 2 h, allowing to warm to room temperature. The reaction was directly purified by HPLC on

a Kinetex 5 μ m C18 100 Å column (size: 100 x 30.0 mm; gradient: 5-55% 0.1% formic acid in ACN in 0.1% formic acid in water) then lyophilized to give the title compound as a white solid. (9 mg). LCMS: m/z = 428.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO) δ 12.58 (s, 1H), 7.96 – 7.80 (m, 1H), 7.78 (d, J = 5.9 Hz, 1H), 7.55 (s, 1H), 7.49 (dd, J = 6.4, 1.5 Hz, 1H), 7.41 (dd, J = 7.9, 1.6 Hz, 1H), 7.24 – 7.34 (m, 1H), 6.88 – 6.92 (m, 1H), 6.74 (d, J = 7.9 Hz, 1H), 6.58 – 6.52 (m, 1H), 6.33 – 6.27 (m, 1H), 5.33 (s, 2H), 3.89 (s, 3H), 2.36 – 2.41 (m, 1H), 0.77 – 0.60 (m, 2H), 0.54 – 0.37 (m, 2H).

Example 29. Compounds 314 and 315

[0844] The following compounds listed in Table 19 were prepared by following a similar procedure as described above in Step 2 of Example 28 using appropriate reagents with suitable modifications known to the one skilled in the art.

Table 19

Com. No	Structure	Intermediates / Coupling example	LC-MS and 1H NMR (400 MHz, DMSO- d_6) unless otherwise shown
314		Intermediate 133 / Example 28	LCMS: $[M+H]^+$; 1H NMR (400 MHz, DMSO) δ 12.56 (s, 1H), 7.77 (d, J = 2.3 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.51 (dd, J = 29.4, 1.7 Hz, 2H), 7.42 (dd, J = 7.8, 1.6 Hz, 1H), 6.95 (s, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.53 (s, 1H), 6.28 (t, J = 2.1 Hz, 1H), 5.32 (s, 2H), 3.89 (s, 3H), 2.79 (dd, J = 15.9, 7.0 Hz, 1H), 2.38 (d, J = 6.0 Hz, 2H) 1.28 (d, J = 6.2 Hz, 3H).
315		Intermediate 133 / Example 28	LCMS: 414.4 $[M+H]^+$; 1H NMR (400 MHz, DMSO) δ 7.75 (s, 1H), 7.54 (d, J = 1.5 Hz, 2H), 7.46 (d, J = 1.8 Hz, 1H), 7.42 (dd, J = 7.8, 1.5 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.53 (d, J = 3.2 Hz, 1H), 6.33 – 6.28 (m, 1H), 6.27

Com. No	Structure	Intermediates / Coupling example	LC-MS and ¹ H NMR (400 MHz, DMSO-d ₆) unless otherwise shown
			(t, J = 2.1 Hz, 1H), 5.31 (s, 2H), 4.56 (s, 2H), 3.87 (s, 3H), 3.18 (s, 2H).

f) **Biological Examples****Example 30. KAT6A Biochemical assay**

[0845] TR-FRET based methods were used for assaying compounds of the present invention for KAT6A enzyme inhibitory activity. TR-FRET is a homogeneous proximity assay where

5 Europium-labelled anti-acetyl lysine antibody binds to the acetylated substrate labelled with biotin, which in turn binds to streptavidin-labelled APC fluorescence acceptor. Europium can transfer energy to APC in the complex and the interaction of two dye-labelled binding partners is detected by the energy transfer between a donor and an acceptor dye and the subsequent light emission by the acceptor dye. KAT6A transfer an acetyl group from acetyl CoA to lysine amino

10 acids of histones/target proteins. Typically, 5 μ L of human-KAT6A (MYST domain 507-778 aa) in assay buffer (100 mM Tris HCl (pH 7.8), 15 mM NaCl, 1 mM EDTA, 0.01% Tween-20, 0.02% BSA, 1mM DTT) is added to 384-well plate containing 5 μ L of selected test compound in final 1% DMSO, serially diluted in 1:3 in an 8–10-point titration. The selected compound of the present invention and enzyme are incubated for 30 min on plate shaker at 300 rpm at 25°C.

15 Next, 5 μ L of substrate mix containing histone H4 peptide and acetyl-CoA in assay buffer is added to the plate. The final concentrations of H4 peptide and acetyl-CoA are 200 nM and 600 nM, respectively. Following 60 min reaction at 25°C on plate shaker at 300 rpm, 5 μ L of detection mix containing Europium-labelled anti-acetyl antibody and streptavidin-APC is added to the reaction wells. The plate is further incubated at 25°C on shaker at 300 rpm and is

20 read in TR-FRET mode (Ex:340 nm; Em: 615 nm and 665 nm) on a plate reader to achieve ~ 5-7-fold activity. The percent inhibition was calculated from the ratio of the fluorescence (FL) intensities $[(F_{665}/F_{615}) \times 10000]$ using the formula $(\text{Control FL ratio} - (\text{Sample FL ratio}/\text{Control FL ratio})) \times 100$. IC₅₀ values of the compounds were determined by fitting the dose-response data to sigmoidal curve fitting equation using Graph pad prism software V9.

25 The results are summarized in Table 20 below.

Table 20. KAT6A Activity

Compound	KAT6A IC ₅₀ (nM)*
1	247
2	741
3	137
4	82
5	178
6	*26% @ 10 μM
7	99
8	17
9	*13% @ 10 μM
10	1484
11	500
12	48
13	47
14	32, 7
15	576
16	26
17	20
18	70
19	42
20	39
21	28
22	49
23	32
24	12
25	10
26	25
27	12

Compound	KAT6A IC ₅₀ (nM)*
28	19
29	10
30	11
31	44
32	16
33	10
34	36
35	30
36	198
37	10
38	-
39	24
40	15
41	*35% @ 1 μM
42	8
43	18
44	9
45	10
46	12
47	9
48	51
49	8
50	96
51	51
52	9
53	31
54	3
55	11
56	7

Compound	KAT6A IC ₅₀ (nM)*
57	11
58	177
59	33
60	8
61	6
62	32
63	17
64	112
65	135
66	13
67	11
68	23
69	114
70	-
71	34
201	731
202	104
203	9
204	6
205	8
206	8
207	10
208	22
209	71
210	64
211	8
212	140
213	12
214	12
215	*16% @ 1 μ M
216	12

Compound	KAT6A IC ₅₀ (nM)*
217	11
218	8
219	9
220	7
221	5
222	18
223	17
224	11
225	10
226	27
227	11
228	21
229	13
230	11
231	14
232	95
233	94
234	42
235	7
236	4
237	44
238	37
239	12
240	11
241	10
242	10
243	23
243a	17
243b	82
244	14
245	12

Compound	KAT6A IC ₅₀ (nM)*
253	9
261	38
262	115
263	36
264	12
265	14
266	10
267	45% @ 1 μ M
268	16
269	12
270	6
271	37
272	33
273	34
274	30
275	10
276	10
277	14
278	25% @ 1 μ M
279	14
280	5
281	10
282	14
283	10
284	10
285	6
286	11
287	11
288	8
289	19
290a	14

Compound	KAT6A IC ₅₀ (nM)*
290b	33
291a	93
291b	9
292	47% @ 1 μ M
293a	374
293b	16
294	35
294a	271
294b	22
295a	16
295b	271
296a	16
296b	677
297	39
298a	23
298b	511
299	25
299a	15
299b	226
300a	125
300b	18
301a	313
301b	17
302a	21
302b	304
303a	26
303b	108
304a	18
304b	130
305a	15
305b	318

Compound	KAT6A IC ₅₀ (nM)*
306a	12
306b	280
307a	108
307b	46% @ 1 μM
308a	1584
308b	49

Compound	KAT6A IC ₅₀ (nM)*
309	17
310	112
311	135
312	-
313	32
314	13
315	-

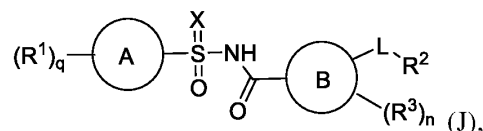
*Percent inhibition at specific concentration reported where IC₅₀ could not be determined.

Example 31. Cell Proliferation for Drug Combination Analysis

- 5 **[0844]** Cells were plated in 96-wp at optimized densities in appropriate complete medium and incubated for ~36 hours before being treated with serial dilutions of compounds for 7, 10 or 14-days. Cell number was assessed using CTG and normalized to T=0. Synergism was evaluated using the Zero Interaction Potency (ZIP) model, assuming that the combined effect of two molecules is the sum of their individual responses, without any interaction. Deviations
- 10 from this predicted combined effect indicate either synergy (greater effect) or antagonism (lesser effect). FIG. 1 provides synergy scores of Compound 282 in combination with everolimus at various concentrations. FIG. 2 provides synergy scores of Compound 282 in combination with inavolisib at various concentrations. FIG. 3 provides synergy scores of Compound 282 in combination with alpelisib at various concentrations.
- 15 **[0845]** Although the foregoing invention has been described in some detail by way of illustration and Example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference.
- 20 Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

WHAT IS CLAIMED IS:

1. A compound of Formula (J):



or a pharmaceutically acceptable salt thereof,

wherein

5 X is O or NR⁴;

ring A is a phenyl or heteroaryl;

ring B is a phenyl or heteroaryl;

each R¹ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -C(O)R^{1a}, -C(O)OR^{1a}, -OC(O)R^{1a}, -C(O)N(R^{1a})(R^{1b}), -N(R^{1a})C(O)(R^{1b}), -OC(O)N(R^{1a})(R^{1b}), -N(R^{1a})C(O)(OR^{1b}), -S(O)R^{1a}, -S(O)₂R^{1a}, -S(O)₂N(R^{1a})(R^{1b}), -S(O)(NH)R^{1a}, -S(O)(NH)N(R^{1a})(R^{1b}), -N(R^{1a})(R^{1b}), OH, -CN, -NO₂, C₃-C₈ cycloalkyl, (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), heterocycloalkyl, (C₁-C₃ alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, (C₁-C₃ alkyl)(C₆-C₁₀ aryl), -O-(C₆-C₁₀ aryl), heteroaryl, (C₁-C₃ alkyl)(heteroaryl), or -O-(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{1c}, each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d}, and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{1e};

20 each R^{1a} and R^{1b} is independently hydrogen or C₁-C₆ alkyl;

each R^{1c} is independently C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkoxy, -NR^{1c1}R^{1c2}, OH, or -CN;

each R^{1c1} and R^{1c2} is independently hydrogen or C₁-C₆ alkyl;

25 each R^{1d} is independently deuterium, C₃-C₈ cycloalkyl, heterocycloalkyl, C₆-C₁₀ aryl, or heteroaryl;

each R^{1e} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, OH, or -CN;

alternatively, two R¹ groups on adjacent carbons together with the atoms to which they are attached combine to form a C₅-C₈ cycloalkyl or a heterocycloalkyl substituted with 0, 1, 2, 3, 4, 5, or 6 halogen, C₁-C₄ alkyl, OH or -CN;

L is $-C_1-C_4$ alkylene-, $-(C_1-C_4 \text{ alkylene})-O-$, or $-O-$;

R^2 is a heteroaryl, which is substituted with 0, 1, 2, 3, or 4 R^{2a} ;

each R^{2a} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-C(O)R^{2b}$, $-C(O)OR^{2b}$, $-OC(O)R^{2b}$, $-C(O)N(R^{2b})(R^{2c})$, $-N(R^{2b})C(O)(R^{2c})$, $-S(O)_2R^{2b}$, $-S(O)_2N(R^{2b})(R^{2c})$, $-N(R^{2b})(R^{2c})$, OH, $-CN$, or $-NO_2$;

each R^{2b} and R^{2c} is independently hydrogen or C_1-C_6 alkyl;

each R^3 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{3a}$, $-OC(O)R^{3a}$, $-C(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(R^{3b})$, $-OC(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(OR^{3b})$, $-S(O)R^{3a}$, $-S(O)_2R^{3a}$, $-S(O)_2N(R^{3a})(R^{3b})$, $-S(O)(NH)R^{3a}$, $-S(O)(NH)N(R^{3a})(R^{3b})$, $-N(R^{3a})(R^{3b})$, OH, $-CN$, $-NO_2$, C_3-C_8 cycloalkyl, $(C_1-C_3 \text{ alkyl})(C_3-C_8 \text{ cycloalkyl})$, $-O-(C_3-C_8 \text{ cycloalkyl})$, heterocycloalkyl, $(C_1-C_3 \text{ alkyl})(\text{heterocycloalkyl})$, $-O-(\text{heterocycloalkyl})$, C_6-C_{10} aryl, $(C_1-C_3 \text{ alkyl})(C_6-C_{10} \text{ aryl})$, $-O-(C_6-C_{10} \text{ aryl})$, heteroaryl, $(C_1-C_3 \text{ alkyl})(\text{heteroaryl})$, or $-O-(\text{heteroaryl})$, wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{3c} , each alkoxy is substituted with 0, 1, 2, or 3 R^{3d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{3e} ; or,

two R^3 on the same carbon atom together represent an oxo group;

each R^{3a} and R^{3b} is independently hydrogen or C_1-C_6 alkyl;

each R^{3c} is independently C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkoxy, $-NR^{3c1}R^{3c2}$, OH, or $-CN$;

each R^{3c1} and R^{3c2} is independently hydrogen or C_1-C_6 alkyl;

each R^{3d} is independently C_3-C_8 cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl;

each R^{3e} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, or C_1-C_6 haloalkoxy;

R^4 is hydrogen or C_1-C_6 alkyl;

subscript n is 0, 1, 2, 3, or 4; and

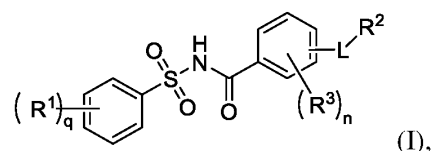
subscript q is 0, 1, 2, 3, or 4;

wherein

each heterocycloalkyl is a 3- to 8-membered ring that includes 1 to 4 heteroatoms each independently N, O or S; and

each heteroaryl is a 5- to 6-membered ring that includes 1 to 4 heteroatoms each independently N, O or S.

2. The compound of claim 1, having Formula (I):



5 or a pharmaceutically acceptable salt thereof,

wherein

each R^1 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-OC(O)R^{1a}$, $-C(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(R^{1b})$, $-OC(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(OR^{1b})$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)_2N(R^{1a})(R^{1b})$, $-S(O)(NH)R^{1a}$, $-S(O)(NH)N(R^{1a})(R^{1b})$, $-N(R^{1a})(R^{1b})$, OH, $-CN$, $-NO_2$, C_3 - C_8 cycloalkyl, $(C_1$ - C_3 alkyl)(C_3 - C_8 cycloalkyl), $-O$ -(C_3 - C_8 cycloalkyl), heterocycloalkyl, $(C_1$ - C_3 alkyl)(heterocycloalkyl), $-O$ -(heterocycloalkyl), C_6 - C_{10} aryl, $(C_1$ - C_3 alkyl)(C_6 - C_{10} aryl), $-O$ -(C_6 - C_{10} aryl), heteroaryl, $(C_1$ - C_3 alkyl)(heteroaryl), or $-O$ -(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{1c} , each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{1e} ;

each R^{1a} and R^{1b} is independently hydrogen or C_1 - C_6 alkyl;

20 each R^{1c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, $-NR^{1c1}R^{1c2}$, OH, or $-CN$;

each R^{1c1} and R^{1c2} is independently hydrogen or C_1 - C_6 alkyl;

each R^{1d} is independently deuterium, C_3 - C_8 cycloalkyl, heterocycloalkyl, C_6 - C_{10} aryl, or heteroaryl;

25 each R^{1e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, or $-CN$;

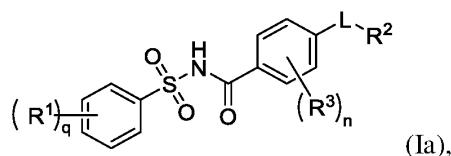
alternatively, two R^1 groups on adjacent carbons together with the atoms to which they are attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl substituted with 0, 1, 2, 3, 4, 5, or 6 halogen, C_1 - C_4 alkyl, OH or $-CN$;

30 L is $-C_1$ - C_4 alkylene-, $-(C_1$ - C_4 alkylene)-O-, or $-O$ -;

R^2 is a heteroaryl, which is substituted with 0, 1, 2, 3, or 4 R^{2a} ;

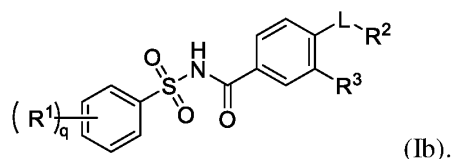
- each R^{2a} is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-C(O)R^{2b}$, $-C(O)OR^{2b}$, $-OC(O)R^{2b}$, $-C(O)N(R^{2b})(R^{2c})$, $-N(R^{2b})C(O)(R^{2c})$, $-S(O)_2R^{2b}$, $-S(O)_2N(R^{2b})(R^{2c})$, $-N(R^{2b})(R^{2c})$, OH, -CN, or $-NO_2$;
- each R^{2b} and R^{2c} is independently hydrogen or C_1 - C_6 alkyl;
- each R^3 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{3a}$, $-OC(O)R^{3a}$, $-C(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(R^{3b})$, $-OC(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(OR^{3b})$, $-S(O)R^{3a}$, $-S(O)_2R^{3a}$, $-S(O)_2N(R^{3a})(R^{3b})$, $-S(O)(NH)R^{3a}$, $-S(O)(NH)N(R^{3a})(R^{3b})$, $-N(R^{3a})(R^{3b})$, OH, -CN, $-NO_2$, C_3 - C_8 cycloalkyl, $(C_1$ - C_3 alkyl)(C_3 - C_8 cycloalkyl), $-O$ -(C_3 - C_8 cycloalkyl), heterocycloalkyl, $(C_1$ - C_3 alkyl)(heterocycloalkyl), $-O$ -(heterocycloalkyl), C_6 - C_{10} aryl, $(C_1$ - C_3 alkyl)(C_6 - C_{10} aryl), $-O$ -(C_6 - C_{10} aryl), heteroaryl, $(C_1$ - C_3 alkyl)(heteroaryl), or $-O$ -(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{3c} , each alkoxy is substituted with 0, 1, 2, or 3 R^{3d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{3e} ; or,
- two R^3 on the same carbon atom together represent an oxo group;
- each R^{3a} and R^{3b} is independently hydrogen or C_1 - C_6 alkyl;
- each R^{3c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, $-NR^{3c1}R^{3c2}$, OH, or -CN;
- each R^{3c1} and R^{3c2} is independently hydrogen or C_1 - C_6 alkyl;
- each R^{3d} is independently C_3 - C_8 cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl;
- each R^{3e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, or C_1 - C_6 haloalkoxy;
- subscript n is 0, 1, 2, 3, or 4; and
- subscript q is 0, 1, 2, 3, or 4;
- wherein
- each heterocycloalkyl is a 3- to 8-membered ring that includes 1 to 4 heteroatoms each independently N, O or S; and
- each heteroaryl is a 5- to 6-membered ring that includes 1 to 4 heteroatoms each independently N, O or S.

3. The compound of claim 2, having Formula (Ia):



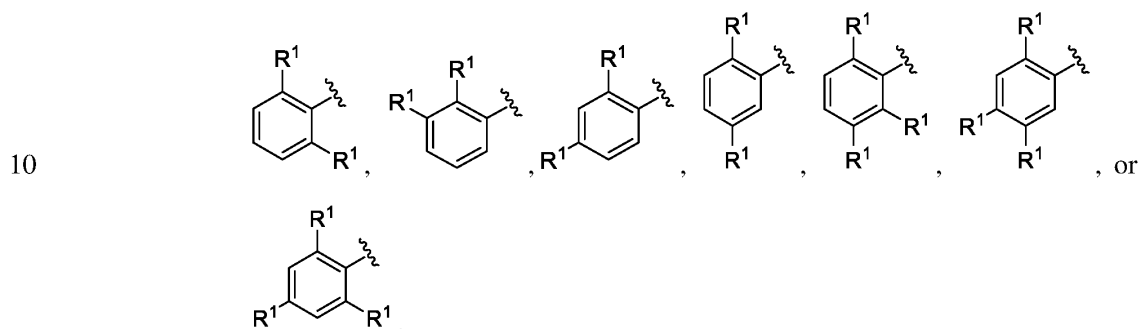
or a pharmaceutically acceptable salt thereof.

4. The compound of claim 2 or 3, or pharmaceutically acceptable salt thereof, having Formula (Ib):



5. The compound of any one of claims 2 to 4, or pharmaceutically acceptable salt thereof, wherein

the group has the structure:



6. The compound of any one of claims 2 to 5, or pharmaceutically acceptable salt thereof, wherein

each R¹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, OH, -CN, C₃-C₈ cycloalkyl, (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), heterocycloalkyl, (C₁-C₃ alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, or heteroaryl, wherein each alkyl is substituted with 0, 1, 2, or 3 R^{1c}, and each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d}; or

alternatively, two R¹ on adjacent carbons together with the atoms to which they are attached combine to form a C₅-C₈ cycloalkyl or a heterocycloalkyl.

7. The compound of any one of claims 2 to 6, or pharmaceutically acceptable salt thereof, wherein

5 each R¹ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, OH, C₃-C₈ cycloalkyl, (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), C₆-C₁₀ aryl, or heteroaryl, wherein each alkyl is substituted with 0 or 1 R^{1c}, and each alkoxy and alkynyl is substituted with 0 or 1 R^{1d}; or

10 alternatively, two R¹ on adjacent carbons together with the atoms to which they are attached combine to form a C₅-C₈ cycloalkyl or a heterocycloalkyl.

8. The compound of any one of claims 2 to 7, or pharmaceutically acceptable salt thereof, wherein

each R^{1a} and R^{1b} is independently hydrogen or C₁-C₄ alkyl.

15 9. The compound of any one of claims 2 to 8, or pharmaceutically acceptable salt thereof, wherein

each R^{1c} is independently halogen, -NR^{1c1}R^{1c2}, OH, or -CN.

10. The compound of any one of claims 2 to 9, or pharmaceutically acceptable salt thereof, wherein

20 each R^{1d} is independently heteroaryl.

11. The compound of any one of claims 2 to 10, or pharmaceutically acceptable salt thereof, wherein

each R^{1e} is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, or -CN.

25 12. The compound of any one of claims 2 to 11, or pharmaceutically acceptable salt thereof, wherein

each R¹ is independently CH₃, CH₂CH₃, -C(CH₃)₃, OCH₃, CH₂CH₃, -OCH(CH₃)₂, OCH₂-pyridyl, C(CH₃)₂OH, F, Cl, Br, CF₃, OCHF₂, OCF₃, OCH₂CF₃, OH, cyclopropyl, cyclopropyloxy, cyclobutyloxy, phenyl, or pyrazolyl; or

alternatively, two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a cyclopentyl, cyclohexyl, dihydrofuran, tetrahydrofuran, methyltetrahydrofuran, 1,3-dioxole, dihydro-1,3-oxazine, or methyldihydrofuran.

5 13. The compound of any one of claims 2 to 12, or pharmaceutically acceptable salt thereof, wherein

L is $-\text{CH}_2-$, $-\text{CH}_2\text{O}-$, or $-\text{O}-$.

14. The compound of any one of claims 2 to 13, or pharmaceutically acceptable salt thereof, wherein

10 L is $-\text{CH}_2-$.

15. The compound of any one of claims 2 to 14, or pharmaceutically acceptable salt thereof, wherein

R^2 is pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidyl, or
15 pyrazinyl, which are each substituted by 0, 1, or 2 R^{2a} .

16. The compound of any one of claims 2 to 15, or pharmaceutically acceptable salt thereof, wherein

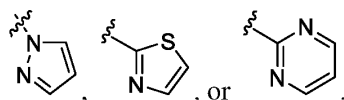
each R^{2a} is independently $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ hydroxyalkyl, $\text{C}_2\text{-C}_6$ alkoxyalkyl, halogen, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, OH, or $-\text{CN}$.

20 17. The compound of any one of claims 2 to 16, or pharmaceutically acceptable salt thereof, wherein

each R^{2b} and R^{2c} is independently hydrogen or $\text{C}_1\text{-C}_4$ alkyl.

18. The compound of any one of claims 2 to 17, or pharmaceutically acceptable salt thereof, wherein

25 R^2 is



19. The compound of any one of claims 2 to 18, or pharmaceutically acceptable salt thereof, wherein

R² is



20. The compound of any one of claims 2 to 19, or pharmaceutically acceptable salt thereof, wherein

- 5 each R³ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -C(O)R^{3a}, -C(O)OR^{3a}, -OC(O)R^{3a}, -C(O)N(R^{3a})(R^{3b}), -N(R^{3a})C(O)(R^{3b}), -S(O)₂R^{3a}, -S(O)₂N(R^{3a})(R^{3b}), OH, -CN, C₃-C₈ cycloalkyl, or heterocycloalkyl.

21. The compound of any one of claims 2 to 20, or pharmaceutically acceptable salt thereof, wherein

each R^{3a} and R^{3b} is independently hydrogen or C₁-C₄ alkyl.

22. The compound of any one of claims 2 to 21, or pharmaceutically acceptable salt thereof, wherein

each R^{3c} is halogen, -NR^{3c1}R^{3c2}, OH, or -CN.

23. The compound of any one of claims 2 to 22, or pharmaceutically acceptable salt thereof, wherein

each R^{3d} is independently heteroaryl.

24. The compound of any one of claims 2 to 23, or pharmaceutically acceptable salt thereof, wherein

- 20 each R^{3e} is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₁-C₄ haloalkyl.

25. The compound of any one of claims 2 to 24, or pharmaceutically acceptable salt thereof, wherein

each R³ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -CN, or C₃-C₈ cycloalkyl.

26. The compound of any one of claims 2 to 25, or pharmaceutically acceptable salt thereof, wherein

each R³ is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, -CN, or C₃-C₆ cycloalkyl.

27. The compound of any one of claims 2 to 26, or pharmaceutically acceptable salt thereof, wherein

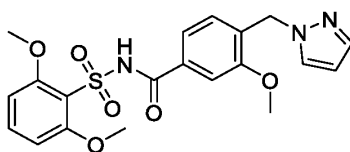
each R³ is independently Me, oMe, OEt, CHF₂, CF₃, OCHF₂, OCF₃, F, Br, CN, or cyclopropyl.

5 28. The compound of any one of claims 2 to 27, or pharmaceutically acceptable salt thereof, wherein subscript q is 1, 2, or 3.

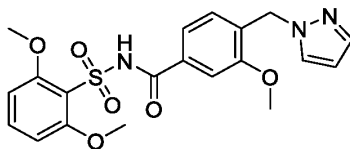
29. The compound of any one of claims 2 to 28, or pharmaceutically acceptable salt thereof, wherein subscript n is 1 or 2.

10 30. The compound of any one of claims 2 to 29, or pharmaceutically acceptable salt thereof, wherein the compound has a structure as shown in Table 1.

31. The compound of any one of claims 2 to 29, or pharmaceutically acceptable salt thereof, wherein the compound has the structure:

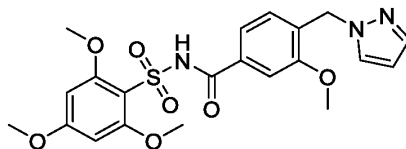


32. The compound of any one of claims 2 to 29, having the structure:

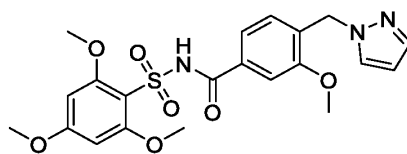


15

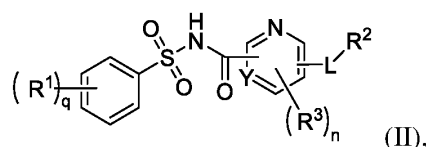
33. The compound of any one of claims 2 to 29, or pharmaceutically acceptable salt thereof, wherein the compound has the structure:



34. The compound of any one of claims 2 to 29, having the structure:



35. The compound of claim 1, having Formula (II):



or a pharmaceutically acceptable salt thereof,

wherein

each R^1 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-OC(O)R^{1a}$, $-C(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(R^{1b})$, $-OC(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(OR^{1b})$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)_2N(R^{1a})(R^{1b})$, $-S(O)(NH)R^{1a}$, $-S(O)(NH)N(R^{1a})(R^{1b})$, $-N(R^{1a})(R^{1b})$, OH, $-CN$, $-NO_2$, C_3 - C_8 cycloalkyl, $(C_1$ - C_3 alkyl)(C_3 - C_8 cycloalkyl), $-O$ -(C_3 - C_8 cycloalkyl), heterocycloalkyl, $(C_1$ - C_3 alkyl)(heterocycloalkyl), $-O$ -(heterocycloalkyl), C_6 - C_{10} aryl, $(C_1$ - C_3 alkyl)(C_6 - C_{10} aryl), $-O$ -(C_6 - C_{10} aryl), heteroaryl, $(C_1$ - C_3 alkyl)(heteroaryl), or $-O$ -(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{1c} , each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{1e} ;

each R^{1a} and R^{1b} is independently hydrogen or C_1 - C_6 alkyl;

each R^{1c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, $-NR^{1c1}R^{1c2}$, OH, or $-CN$;

each R^{1c1} and R^{1c2} is independently hydrogen or C_1 - C_6 alkyl;

each R^{1d} is independently deuterium, C_3 - C_8 cycloalkyl, heterocycloalkyl, C_6 - C_{10} aryl, or heteroaryl;

each R^{1e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, or $-CN$;

alternatively, two R^1 groups on adjacent carbons together with the atoms to which they are attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl substituted with 0, 1, 2, 3, 4, 5, or 6 halogen, C_1 - C_4 alkyl, OH or $-CN$;

L is $-C_1-C_4$ alkylene-, $-(C_1-C_4 \text{ alkylene})-O-$, or $-O-$;

R^2 is a heteroaryl, which is substituted with 0, 1, 2, 3, or 4 R^{2a} ;

each R^{2a} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-C(O)R^{2b}$, $-C(O)OR^{2b}$, $-OC(O)R^{2b}$, $-C(O)N(R^{2b})(R^{2c})$, $-N(R^{2b})C(O)(R^{2c})$, $-S(O)_2R^{2b}$, $-S(O)_2N(R^{2b})(R^{2c})$, $-N(R^{2b})(R^{2c})$, OH, $-CN$, or $-NO_2$;

each R^{2b} and R^{2c} is independently hydrogen or C_1-C_6 alkyl;

Y is CH, CR^3 , or N;

each R^3 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, halogen, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{3a}$, $-OC(O)R^{3a}$, $-C(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(R^{3b})$, $-OC(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(OR^{3b})$, $-S(O)R^{3a}$, $-S(O)_2R^{3a}$, $-S(O)_2N(R^{3a})(R^{3b})$, $-S(O)(NH)R^{3a}$, $-S(O)(NH)N(R^{3a})(R^{3b})$, $-N(R^{3a})(R^{3b})$, OH, $-CN$, $-NO_2$, C_3-C_8 cycloalkyl, $(C_1-C_3 \text{ alkyl})(C_3-C_8 \text{ cycloalkyl})$, $-O-(C_3-C_8 \text{ cycloalkyl})$, heterocycloalkyl, $(C_1-C_3 \text{ alkyl})(\text{heterocycloalkyl})$, $-O-(\text{heterocycloalkyl})$, C_6-C_{10} aryl, $(C_1-C_3 \text{ alkyl})(C_6-C_{10} \text{ aryl})$, $-O-(C_6-C_{10} \text{ aryl})$, heteroaryl, $(C_1-C_3 \text{ alkyl})(\text{heteroaryl})$, or $-O-(\text{heteroaryl})$, wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{3c} , each alkoxy is substituted with 0, 1, 2, or 3 R^{3d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{3e} ; or,

two R^3 on the same carbon atom together represent an oxo group;

each R^{3a} and R^{3b} is independently hydrogen or C_1-C_6 alkyl;

each R^{3c} is independently C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkoxy, $-NR^{3c1}R^{3c2}$, OH, or $-CN$;

each R^{3c1} and R^{3c2} is independently hydrogen or C_1-C_6 alkyl;

each R^{3d} is independently C_3-C_8 cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl;

each R^{3e} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, or C_1-C_6 haloalkoxy;

subscript n is 0, 1, 2, 3, or 4; and

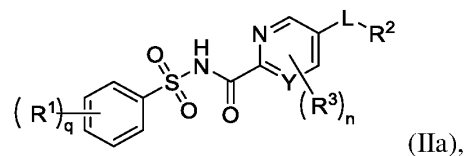
subscript q is 0, 1, 2, 3, or 4;

wherein

each heterocycloalkyl is a 3- to 8-membered ring that includes 1 to 4 heteroatoms each independently N, O or S; and

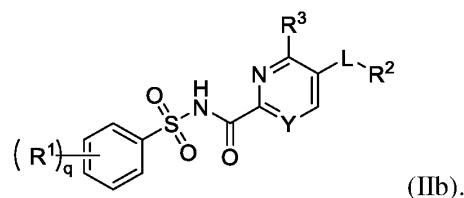
each heteroaryl is a 5- to 6-membered ring that includes 1 to 4 heteroatoms each independently N, O or S.

36. The compound of claim 35, having Formula (IIa):

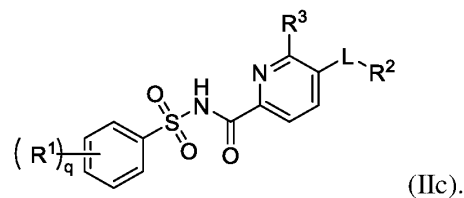


5 or a pharmaceutically acceptable salt thereof.

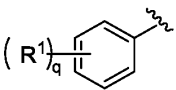
37. The compound of claim 35 or 36, or pharmaceutically acceptable salt thereof, having Formula (IIb):

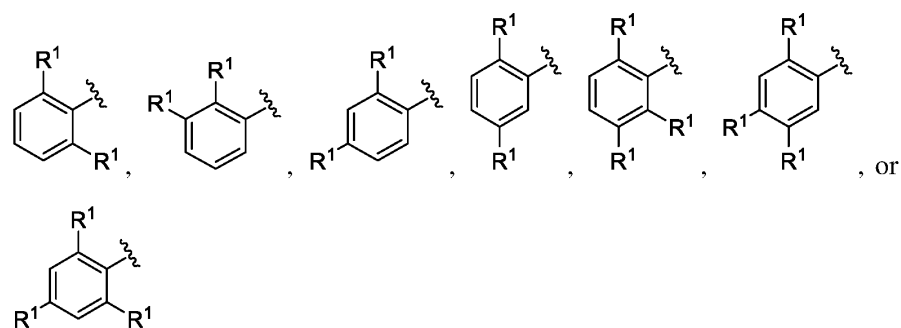


38. The compound of claim 35 or 36, or pharmaceutically acceptable salt thereof, having Formula (IIc):



39. The compound of any one of claims 35 to 38, or pharmaceutically acceptable salt thereof, wherein

the group $(R^1)_q$  has the structure:



40. The compound of any one of claims 35 to 39, or pharmaceutically acceptable salt thereof, wherein

Each R^1 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, -CN, C_3 - C_8 cycloalkyl, $(C_1$ - C_3 alkyl)(C_3 - C_8 cycloalkyl), -O-(C_3 - C_8 cycloalkyl), heterocycloalkyl, $(C_1$ - C_3 alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C_6 - C_{10} aryl, or heteroaryl, wherein each alkyl is substituted with 0, 1, 2, or 3 R^{1c} , and each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d} ; or alternatively, two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl.

41. The compound of any one of claims 35 to 40, or pharmaceutically acceptable salt thereof, wherein

each R^1 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, C_3 - C_8 cycloalkyl, $(C_1$ - C_3 alkyl)(C_3 - C_8 cycloalkyl), -O-(C_3 - C_8 cycloalkyl), C_6 - C_{10} aryl, or heteroaryl, wherein each alkyl is substituted with 0 or 1 R^{1c} , and each alkoxy and alkynyl is substituted with 0 or 1 R^{1d} ; or alternatively, two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a C_5 - C_8 cycloalkyl or a heterocycloalkyl.

42. The compound of any one of claims 35 to 41, or pharmaceutically acceptable salt thereof, wherein

each R^{1a} and R^{1b} is independently hydrogen or C_1 - C_3 alkyl.

43. The compound of any one of claims 35 to 42, or pharmaceutically acceptable salt thereof, wherein

each R^{1c} is halogen, $-NR^{1c1}R^{1c2}$, OH, or -CN.

44. The compound of any one of claims 35 to 43, or pharmaceutically acceptable salt thereof, wherein

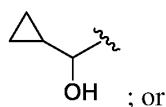
each R^{1d} is independently heteroaryl.

45. The compound of any one of claims 35 to 44, or pharmaceutically acceptable salt thereof, wherein

each R^{1e} is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, or -CN.

46. The compound of any one of claims 35 to 45, or pharmaceutically acceptable salt thereof, wherein

each R^1 is independently CH₃, CH₂CH₃, -C(CH₃)₃, OCH₃, CH₂CH₃, -OCH(CH₃)₂, -C(CH₃)₂OH, -C(CH₃)(CH₂CH₃)OH, F, Cl, Br, CF₃, OCHF₂, OCF₃, OCH₂CF₃, cyclopropyl, cyclopropyloxy, cyclobutyloxy, or



two R^1 on adjacent carbons together with the atoms to which they are attached combine to form a cyclopentyl, cyclohexyl, dihydrofuran, tetrahydrofuran, methyltetrahydrofuran, 1,3-dioxole, dihydro-1,3-oxazine, or methyldihydrofuran.

47. The compound of any one of claims 35 to 46, or pharmaceutically acceptable salt thereof, wherein

L is -CH₂-, -CH₂O-, or -O-.

48. The compound of any one of claims 35 to 47, or pharmaceutically acceptable salt thereof, wherein

25 L is -CH₂-.

49. The compound of any one of claims 35 to 48, or pharmaceutically acceptable salt thereof, wherein

R^2 is pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidyl, or pyrazinyl, which are each substituted by 0, 1, or 2 R^{2a} .

50. The compound of any one of claims 35 to 49, or pharmaceutically acceptable salt thereof, wherein

each R^{2a} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, or $-CN$.

51. The compound of any one of claims 35 to 50, or pharmaceutically acceptable salt thereof, wherein

10 each R^{2b} and R^{2c} is independently hydrogen or C_1 - C_4 alkyl.

52. The compound of any one of claims 35 to 51, or pharmaceutically acceptable salt thereof, wherein

R^2 is



15 53. The compound of any one of claims 35 to 52, or pharmaceutically acceptable salt thereof, wherein

each R^3 is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{3a}$, $-OC(O)R^{3a}$, $-C(O)N(R^{3a})(R^{3b})$, $-N(R^{3a})C(O)(R^{3b})$, $-S(O)_2R^{3a}$, $-S(O)_2N(R^{3a})(R^{3b})$, OH, $-CN$, C_3 - C_8 cycloalkyl, or heterocycloalkyl.

54. The compound of any one of claims 35 to 53, or pharmaceutically acceptable salt thereof, wherein

each R^{3a} and R^{3b} is independently hydrogen or C_1 - C_4 alkyl.

55. The compound of any one of claims 35 to 57, or pharmaceutically acceptable salt thereof, wherein

each R^{3c} is halogen, $-NR^{3c1}R^{3c2}$, OH, or $-CN$.

56. The compound of any one of claims 35 to 54, or pharmaceutically acceptable salt thereof, wherein

each R^{3d} is independently heteroaryl.

57. The compound of any one of claims 35 to 56, or pharmaceutically acceptable salt thereof, wherein

each R^{3e} is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₁-C₄ haloalkyl.

5 58. The compound of any one of claims 35 to 55, or pharmaceutically acceptable salt thereof, wherein

each R³ is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -CN, or C₃-C₈ cycloalkyl.

59. The compound of any one of claims 35 to 58, or pharmaceutically acceptable salt thereof, wherein

each R³ is independently C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, -CN, or C₃-C₆ cycloalkyl.

60. The compound of any one of claims 35 to 59, or pharmaceutically acceptable salt thereof, wherein

15 each R³ is independently Me, OMe, CHF₂, CF₃, OCHF₂, OCF₃, or cyclopropyl.

61. The compound of any one of claims 35 to 60, or pharmaceutically acceptable salt thereof, wherein

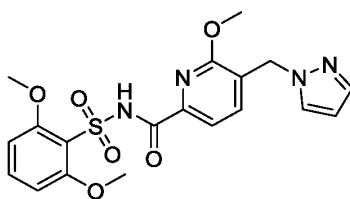
subscript q is 1, 2, or 3.

62. The compound of any one of claims 35 to 61, or pharmaceutically acceptable salt thereof, wherein

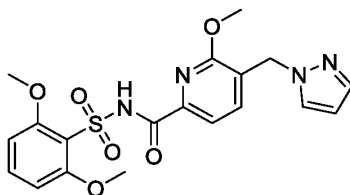
subscript n is 0 or 1.

63. The compound of any one of claims 35 to 62, or pharmaceutically acceptable salt thereof, wherein the compound has a structure as shown in Table 2.

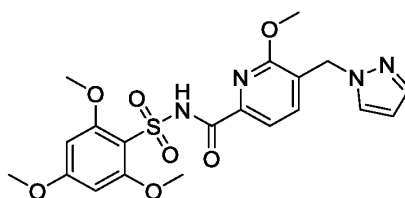
64. The compound of any one of claims 35 to 62, or pharmaceutically acceptable salt thereof, wherein the compound has the structure:



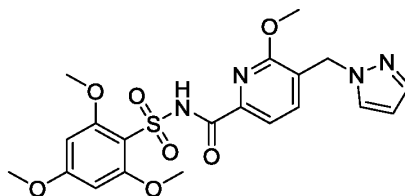
65. The compound of any one of claims 35 to 62, having the structure:



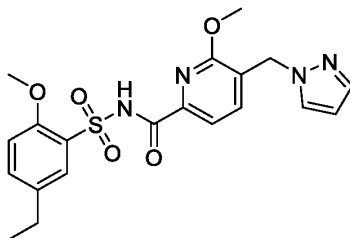
66. The compound of any one of claims 35 to 62, or pharmaceutically
5 acceptable salt thereof, wherein the compound has the structure:



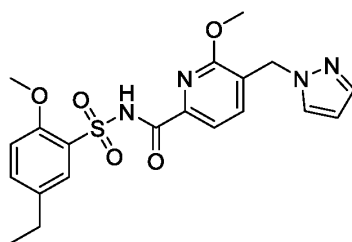
67. The compound of any one of claims 35 to 62, having the structure:



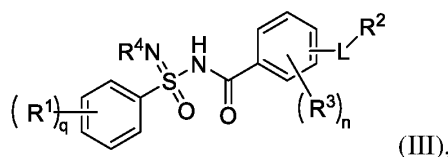
68. The compound of any one of claims 35 to 62, or pharmaceutically
10 acceptable salt thereof, wherein the compound has the structure:



69. The compound of any one of claims 35 to 62, having the structure:



70. The compound of claim 1, having Formula (III):



or a pharmaceutically acceptable salt thereof,

5 wherein

each R^1 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkoxyalkyl, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-OC(O)R^{1a}$, $-C(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(R^{1b})$, $-OC(O)N(R^{1a})(R^{1b})$, $-N(R^{1a})C(O)(OR^{1b})$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)_2N(R^{1a})(R^{1b})$, $-S(O)(NH)R^{1a}$, $-S(O)(NH)N(R^{1a})(R^{1b})$, $-N(R^{1a})(R^{1b})$, OH, $-CN$, $-NO_2$, C_3 - C_8 cycloalkyl, $(C_1$ - C_3 alkyl)(C_3 - C_8 cycloalkyl), $-O$ -(C_3 - C_8 cycloalkyl), heterocycloalkyl, $(C_1$ - C_3 alkyl)(heterocycloalkyl), $-O$ -(heterocycloalkyl), C_6 - C_{10} aryl, $(C_1$ - C_3 alkyl)(C_6 - C_{10} aryl), $-O$ -(C_6 - C_{10} aryl), heteroaryl, $(C_1$ - C_3 alkyl)(heteroaryl), or $-O$ -(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{1c} , each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{1e} ;

each R^{1a} and R^{1b} is independently hydrogen or C_1 - C_6 alkyl;

each R^{1c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, $-NR^{1c1}R^{1c2}$, OH, or $-CN$;

each R^{1c1} and R^{1c2} is independently hydrogen or C_1 - C_6 alkyl;

each R^{1d} is independently deuterium, C_3 - C_8 cycloalkyl, heterocycloalkyl, C_6 - C_{10} aryl, or heteroaryl;

each R^{1e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, OH, or $-CN$;

alternatively, two R^1 groups on adjacent carbons together with the atoms to which they are attached combine to form a C₅-C₈ cycloalkyl or a heterocycloalkyl substituted with 0, 1, 2, 3, 4, 5, or 6 halogen, C₁-C₄ alkyl, OH or -CN;

L is -C₁-C₄ alkylene-, -(C₁-C₄ alkylene)-O-, or -O-;

5 R^2 is a heteroaryl, which is substituted with 0, 1, 2, 3, or 4 R^{2a} ;

each R^{2a} is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -C(O) R^{2b} , -C(O)OR^{2b}, -OC(O) R^{2b} , -C(O)N(R^{2b})(R^{2c}), -N(R^{2b})C(O)(R^{2c}), -S(O)₂ R^{2b} , -S(O)₂N(R^{2b})(R^{2c}), -N(R^{2b})(R^{2c}), OH, -CN, or -NO₂;

each R^{2b} and R^{2c} is independently hydrogen or C₁-C₆ alkyl;

each R^3 is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -C(O) R^{3a} , -C(O)OR^{3a}, -OC(O) R^{3a} , -C(O)N(R^{3a})(R^{3b}), -N(R^{3a})C(O)(R^{3b}), -OC(O)N(R^{3a})(R^{3b}), -N(R^{3a})C(O)(OR^{3b}), -S(O) R^{3a} , -S(O)₂ R^{3a} , -S(O)₂N(R^{3a})(R^{3b}), -S(O)(NH) R^{3a} , -S(O)(NH)N(R^{3a})(R^{3b}), -N(R^{3a})(R^{3b}), OH, -CN, -NO₂, C₃-C₈ cycloalkyl, (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), heterocycloalkyl, (C₁-C₃ alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, (C₁-C₃ alkyl)(C₆-C₁₀ aryl), -O-(C₆-C₁₀ aryl), heteroaryl, (C₁-C₃ alkyl)(heteroaryl), or -O-(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{3c} , each alkoxy is substituted with 0, 1, 2, or 3 R^{3d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{3e} ; or,

two R^3 on the same carbon atom together represent an oxo group;

25 each R^{3a} and R^{3b} is independently hydrogen or C₁-C₆ alkyl;

each R^{3c} is independently C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkoxy, -NR^{3c1} R^{3c2} , OH, or -CN;

each R^{3c1} and R^{3c2} is independently hydrogen or C₁-C₆ alkyl;

each R^{3d} is independently C₃-C₈ cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl;

30 each R^{3e} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy;

R^4 is hydrogen or C₁-C₆ alkyl;

subscript n is 0, 1, 2, 3, or 4; and

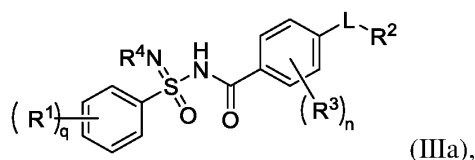
subscript q is 0, 1, 2, 3, or 4;

wherein

each heterocycloalkyl is a 3- to 8-membered ring that includes 1 to 4 heteroatoms each independently N, O or S; and

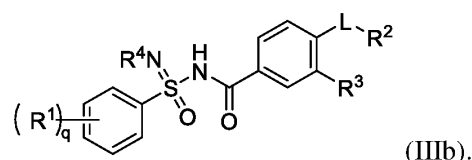
each heteroaryl is a 5- to 6-membered ring that includes 1 to 4 heteroatoms each independently N, O or S.

71. The compound of claim 70, having Formula (IIIa):



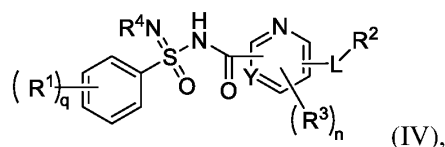
or a pharmaceutically acceptable salt thereof.

72. The compound of claim 70 or 71, or pharmaceutically acceptable salt thereof, having Formula (IIIb):



73. The compound of any one of claims 70 to 72, or pharmaceutically acceptable salt thereof, wherein the compound has a structure as shown in Table 3.

74. The compound of claim 1, having Formula (IV):



or a pharmaceutically acceptable salt thereof,

wherein

each R¹ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -C(O)R^{1a}, -C(O)OR^{1a}, -OC(O)R^{1a}, -C(O)N(R^{1a})(R^{1b}), -N(R^{1a})C(O)(R^{1b}), -OC(O)N(R^{1a})(R^{1b}), -N(R^{1a})C(O)(OR^{1b}), -S(O)R^{1a}, -S(O)₂R^{1a}, -S(O)₂N(R^{1a})(R^{1b}), -S(O)(NH)R^{1a}, -S(O)(NH)N(R^{1a})(R^{1b}), -N(R^{1a})(R^{1b}), OH, -CN, -NO₂, C₃-C₈ cycloalkyl, (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), heterocycloalkyl, (C₁-C₃

- alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, (C₁-C₃ alkyl)(C₆-C₁₀ aryl), -O-(C₆-C₁₀ aryl), heteroaryl, (C₁-C₃ alkyl)(heteroaryl), or -O-(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{1c}, each alkoxy and alkynyl is substituted with 0, 1, 2, or 3 R^{1d}, and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{1e};
- each R^{1a} and R^{1b} is independently hydrogen or C₁-C₆ alkyl;
- each R^{1c} is independently C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkoxy, -NR^{1c1}R^{1c2}, OH, or -CN;
- each R^{1c1} and R^{1c2} is independently hydrogen or C₁-C₆ alkyl;
- each R^{1d} is independently deuterium, C₃-C₈ cycloalkyl, heterocycloalkyl, C₆-C₁₀ aryl, or heteroaryl;
- each R^{1e} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, OH, or -CN;
- alternatively, two R¹ groups on adjacent carbons together with the atoms to which they are attached combine to form a C₅-C₈ cycloalkyl or a heterocycloalkyl substituted with 0, 1, 2, 3, 4, 5, or 6 halogen, C₁-C₄ alkyl, OH or -CN;
- L is -C₁-C₄ alkylene-, -(C₁-C₄ alkylene)-O-, or -O-;
- R² is a heteroaryl, which is substituted with 0, 1, 2, 3, or 4 R^{2a};
- each R^{2a} is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -C(O)R^{2b}, -C(O)OR^{2b}, -OC(O)R^{2b}, -C(O)N(R^{2b})(R^{2c}), -N(R^{2b})C(O)(R^{2c}), -S(O)₂R^{2b}, -S(O)₂N(R^{2b})(R^{2c}), -N(R^{2b})(R^{2c}), OH, -CN, or -NO₂;
- each R^{2b} and R^{2c} is independently hydrogen or C₁-C₆ alkyl;
- Y is CH, CR³, or N;
- each R³ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkoxyalkyl, halogen, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -C(O)R^{3a}, -C(O)OR^{3a}, -OC(O)R^{3a}, -C(O)N(R^{3a})(R^{3b}), -N(R^{3a})C(O)(R^{3b}), -OC(O)N(R^{3a})(R^{3b}), -N(R^{3a})C(O)(OR^{3b}), -S(O)R^{3a}, -S(O)₂R^{3a}, -S(O)₂N(R^{3a})(R^{3b}), -S(O)(NH)R^{3a}, -S(O)(NH)N(R^{3a})(R^{3b}), -N(R^{3a})(R^{3b}), OH, -CN, -NO₂, C₃-C₈ cycloalkyl, (C₁-C₃ alkyl)(C₃-C₈ cycloalkyl), -O-(C₃-C₈ cycloalkyl), heterocycloalkyl, (C₁-C₃ alkyl)(heterocycloalkyl), -O-(heterocycloalkyl), C₆-C₁₀ aryl, (C₁-C₃ alkyl)(C₆-C₁₀ aryl), -O-(C₆-C₁₀ aryl), heteroaryl, (C₁-C₃ alkyl)(heteroaryl), or -O-

(heteroaryl), wherein each alkyl is substituted with 0, 1, 2, 3, 4, 5, or 6 R^{3c} , each alkoxy is substituted with 0, 1, 2, or 3 R^{3d} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0, 1, 2, or 3 R^{3e} ; or, two R^3 on the same carbon atom together represent an oxo group;

5 each R^{3a} and R^{3b} is independently hydrogen or C_1 - C_6 alkyl;

each R^{3c} is independently C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkoxy, $-NR^{3c1}R^{3c2}$, OH, or -CN;

each R^{3c1} and R^{3c2} is independently hydrogen or C_1 - C_6 alkyl;

each R^{3d} is independently C_3 - C_8 cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl;

10 each R^{3e} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, C_1 - C_6 haloalkyl, or C_1 - C_6 haloalkoxy;

R^4 is hydrogen or C_1 - C_6 alkyl;

subscript n is 0, 1, 2, 3, or 4; and

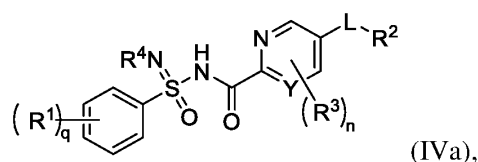
subscript q is 0, 1, 2, 3, or 4;

15 wherein

each heterocycloalkyl is a 3- to 8-membered ring that includes 1 to 4 heteroatoms each independently N, O or S; and

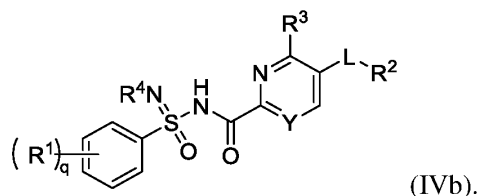
each heteroaryl is a 5- to 6-membered ring that includes 1 to 4 heteroatoms each independently N, O or S.

20 75. The compound of claim 74, having Formula (IVa):



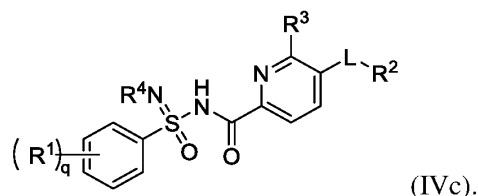
or a pharmaceutically acceptable salt thereof.

76. The compound of claim 74 or 75, or pharmaceutically acceptable salt thereof, having Formula (IVb):



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77. The compound of claim 74 or 75, or pharmaceutically acceptable salt thereof, having Formula (IVc):



78. The compound of any one of claims 74 to 77, or pharmaceutically acceptable salt thereof, wherein the compound has a structure as shown in Table 4.

79. The compound of claim 1, wherein the compound is selected from the group consisting of:

- 4-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-3-methoxybenzamide (14)e
- 4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)benzamide
- 4-((1H-pyrazol-1-yl)methyl)-N-((2-ethoxy-6-methoxyphenyl)sulfonyl)-3-methoxybenzamide (67),
- 5-((1H-pyrazol-1-yl)methyl)-N-((2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide (203),
- 5-((1H-pyrazol-1-yl)methyl)-N-((5-ethyl-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide (204),
- 5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)picolinamide (224),
- 5-((1H-pyrazol-1-yl)methyl)-6-cyclopropyl-N-((2,6-dimethoxyphenyl)sulfonyl)picolinamide (229),
- 5-((1H-pyrazol-1-yl)methyl)-N-((3-chloro-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide (241),
- 5-((1H-pyrazol-1-yl)methyl)-N-((4-bromo-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide (285),
- 4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methyl-2,3-dihydrobenzofuran-7-yl)sulfonyl)benzamide (314),

and pharmaceutically acceptable salts thereof.

80. The compound of claim 79, wherein the compound is 4-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-3-(trifluoromethyl)benzamide or a pharmaceutically acceptable salt thereof.

81. The compound of claim 79, wherein the compound is 4-((1H-pyrazol-1-yl)methyl)-N-((5-hydroxy-2-methoxyphenyl)sulfonyl)-3-methoxybenzamide or a pharmaceutically acceptable salt thereof.

82. The compound of claim 79, wherein the compound is 4-((1H-pyrazol-1-yl)methyl)-N-((2-ethoxy-6-methoxyphenyl)sulfonyl)-3-methoxybenzamide or a pharmaceutically acceptable salt thereof.

83. The compound of claim 79, wherein the compound is 4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-(2-methoxy-6-(2,2,2-trifluoroethoxy)phenylsulfonimidoyl)benzamide or a pharmaceutically acceptable salt thereof.

84. The compound of claim 79, wherein the compound is 5-((1H-pyrazol-1-yl)methyl)-N-((5-(tert-butyl)-2-methoxyphenyl)sulfonyl)-6-methoxypicolinamide or a pharmaceutically acceptable salt thereof.

85. The compound of claim 79, wherein the compound is 5-((1H-pyrazol-1-yl)methyl)-6-methoxy-N-((2,4,6-trimethoxyphenyl)sulfonyl)picolinamide or a pharmaceutically acceptable salt thereof.

86. The compound of claim 79, wherein the compound is 5-((1H-pyrazol-1-yl)methyl)-6-cyclopropyl-N-((2,6-dimethoxyphenyl)sulfonyl)picolinamide or a pharmaceutically acceptable salt thereof.

87. The compound of claim 79, wherein the compound is 5-((1H-pyrazol-1-yl)methyl)-N-((3-chloro-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide or a pharmaceutically acceptable salt thereof.

88. The compound of claim 79, wherein the compound is 5-((1H-pyrazol-1-yl)methyl)-N-((4-bromo-2,6-dimethoxyphenyl)sulfonyl)-6-methoxypicolinamide or a pharmaceutically acceptable salt thereof.

89. The compound of claim 79, wherein the compound is 4-((1H-pyrazol-1-yl)methyl)-3-methoxy-N-((2-methyl-2,3-dihydrobenzofuran-7-yl)sulfonyl)benzamide or a pharmaceutically acceptable salt thereof.

5 90. A pharmaceutical composition comprising a compound of any one of claims 1 to 89 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

91. A compound according to any one of claims 1 to 89 or a pharmaceutically acceptable salt thereof, for use as a medicament.

10 92. A method of modulating KAT6A in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of compound according to any one of claims 1 to 89 or a pharmaceutically acceptable salt thereof.

15 93. A method of treating a disease or disorder mediated by KAT6A in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 89 or a pharmaceutically acceptable salt thereof.

94. The method of claim 93, wherein the disease or disorder is cancer.

95. The method of claim 94, wherein the cancer is selected from brain gliomas, glioblastomas, astrocytomas, multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, colon cancer, head and neck cancer, kidney, liver, lung cancer, bone cancer, colorectal cancer, germ cell cancer, melanoma, ovarian cancer, pancreatic cancer, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma and thyroid cancer, lymphoblastic T cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, mantle cell leukemia, megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, erythroleukemia, malignant lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval

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cancer, uterine cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, gastrointestinal stromal tumor, neuroendocrine cancers, testicular cancer, and virus-related cancer.

5 96. Use of a compound according to any one of claims 1 to 89 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment of a disease or disorder mediated by KAT6A.

 97. Compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 89 for use in the treatment of a disease or disorder mediated by KAT6A.

10 98. The method of any one of claims 93-95, further comprising administering an additional anti-cancer agent.

 99. The method of claim 98, wherein the additional anti-cancer agent is selected from a HER2 inhibitor, an mTOR inhibitor, a CDK4/6 inhibitor, a CDK2-selective inhibitor, a CDK4-selective inhibitor, a PI3 kinase inhibitor, a PIK3CA inhibitor, an aromatase
15 inhibitor, an antibody to or inhibitor of PD-1, PD-L1 or CTLA-4, an antibody to or inhibitor of EGFR, PGFR, or IGFR, a USP inhibitor, or an AKT inhibitor.

 100. The method of claim 99, wherein the additional anti-cancer agent is a HER2 inhibitor.

 101. The method of claim 100, wherein the HER2 inhibitor is selected from
20 tucatinib, trastuzumab, pertuzumab, ado-trastuzumab, trastuzumab emtansine, ado-trastuzumab emtansine, trastuzumab deruxtecan, pertuzumab, lapatinib, and neratinib.

 102. The method of claim 99, wherein the anti-cancer agent is an mTOR inhibitor.

 103. The method of claim 102, wherein the mTOR inhibitor is selected from
25 everolimus, temsirolimus, and LY30234

 104. The method of claim 99, wherein the anti-cancer agent is a CDK4/6 inhibitor,

105. The method of claim 104, wherein the CDK4/6 inhibitor is selected from palbociclib, abemaciclib, ribociclib, lerociclib, trilaciclib, and SHR6390.

112. The method of claim 99, wherein the additional anti-cancer agent is a CDK2-selective inhibitor.

5 113. The method of claim 112, wherein the CDK2-selective inhibitor is PF-07104091 (tagtociclib).

114. The method of claim 99, wherein the additional anti-cancer agent is a CDK4-selective inhibitor.

10 115. The method of claim 114, wherein the CDK-4 selective inhibitor is PF-07220060 (atirmociclib).

116. The method of claim 99, wherein the anti-cancer agent is a PI3 kinase inhibitor.

117. The method of claim 102, wherein the PI3 kinase inhibitor is selected from perifosine, CAL101, BEZ235, XL147, XL765, GDC-0941, and IPI-145.

15 118. The method of claim 99, wherein the additional anti-cancer agent is a PIK3CA inhibitor.

119. The method of claim 104, wherein the PIK3CA inhibitor is selected from alpelisib, taselisib, LY3023414, Inavolisib, STX-478, RLY-2608, LOXO-783, OKI-219, and TOS-358.

20 120. The method of claim 99, wherein the additional anti-cancer agent is an aromatase inhibitor.

25 121. The method of claim 106, wherein the aromatase inhibitor is selected from aminoglutethimide, testolactone, anastrozole, letrozole, exemestane, vorozole, formestane, fadrozole, 4-hydroxyandrostenedione, 1,4,6-androstatrien-3,17-dione, and 4-androstene-3,6,17-trione.

122. The method of claim 106, wherein the aromatase inhibitor is selected from anastrozole, letrozole, and exemestane.

123. The method of claim 199, wherein the additional anti-cancer agent is a USP1 inhibitor.
123. The method of claim 99, wherein the additional anti-cancer agent is an AKT inhibitor.
- 5 124. The method of claim 123, wherein the AKT inhibitor is selected from capivasertib, ipatasertib, afuresertib, and uprosertib.
125. The method of claim 124, wherein the AKT inhibitor is capivasertib.
126. The method of any one of claims 93-95, further comprising administering an estrogen receptor antagonist or an estrogen receptor partial antagonist.
- 10 127. The method of claim 126, wherein the estrogen receptor antagonist or estrogen receptor partial antagonist is a selective estrogen receptor modulator.
128. The method of claim 127, wherein the selective estrogen receptor modulator is selected from tamoxifen, endoxifene, raloxifene, toremifene, lasofoxifene, ospemifene, elacestrant, and bazedoxifene.
- 15 129. The method of claim 126, wherein the estrogen receptor antagonist or estrogen receptor partial antagonist is a selective estrogen receptor degrader.
130. The method of claim 129, wherein the selective estrogen receptor degrader is selected from fulvestrant, camizestrant, palazestrant, imlunestrant, elacestrant, and giredestrant.
- 20 131. The method of claim 130, wherein the selective estrogen receptor degrader is palazestrant.
132. The method of claim 126, wherein the estrogen receptor antagonist or estrogen receptor partial antagonist is a complete estrogen receptor antagonist.
133. The method of claim 132, wherein the complete estrogen receptor
25 antagonist is selected from fulvestrant and palazestrant.

134. The method of claim 133, wherein the complete estrogen receptor antagonist is palazestrant.