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(54) Title: INHIBITING HISTONE DEACETYLASE 6 (HDAC6)

(57) Abstract: Provided herein are compounds that selectively inhibit HDAC6, a protein whose activity is associated with a variety of diseases (e.g., cancer, neurological disorders). Also provided are pharmaceutical compositions and kits comprising the compounds, and methods of treating HDAC6-related diseases and disorders (e.g., Alzheimer's disease, cancer) with the compounds in a subject, by administering the compounds and/or compositions described herein.

INHIBITING HISTONE DEACETYLASE 6 (HDAC6)

RELATED PATENT APPLICATIONS

[0001] This patent application claims priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application U.S.S.N. 63/329,143, filed April 8, 2022, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure provides compounds usefule for inhibiting histone deacetylase 6 (HDAC6), as well as methods of making and using these compounds.

BACKGROUND

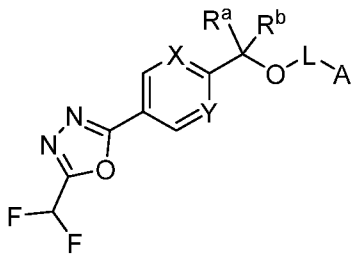
[0003] Histone deacetylases (HDACs) are divided into four classes based on sequence homology. HDAC6, a class IIb HDAC, is a cytoplasmic, microtubule-associated enzyme. HDAC6 has unique features among the HDAC paralogs. Unlike other HDACs, HDAC6 contains two deacetylase domains and a ubiquitin binding domain allowing HDAC6 to function in distinct cell signaling systems involving protein acetylation and ubiquitination, respectively. Importantly, it does not deacetylate histones. HDAC6 deacetylates tubulin, tau, Hsp90, cortactin, and other emerging targets. HDAC6 deacetylase function is involved in microtubule-based cargo transport, protein degradation/recycling and stress-induced glucocorticoid receptor signaling. HDAC6 deacetylase function is also involved in cell morphology, motility and migration, as well as cell growth and survival. In addition to deacetylase functions, HDAC6 forms complexes with partner proteins linked to ubiquitin-dependent functions, and influences protein aggregation, trafficking and degradation via the aggresome pathway. HDAC6 expression was shown to be elevated in postmortem brain samples from Alzheimer's disease patients. Small molecule compounds inhibiting HDAC6 are being developed as a potential therapy for Alzheimer's Disease patients.

SUMMARY

[0004] The cytosolic location, distinct substrates, and structure of HDAC6 are unique among the HDAC paralogs and HDAC6-selective treatment regimens show promise to avoid many of the side effects of first-generation pan-HDAC inhibitors. However, paralog selectivity is difficult to obtain. The present disclosure stems from the recognition that the unique structure and function of HDAC6, among the HDAC paralogs, provides an

opportunity for the design of selective HDAC6 inhibitors. The present disclosure also recognizes that targeting HDAC6-mediated pathways may provide improved treatments for neurological disorders. In relation to neurodegeneration, HDAC6 (1) impairs microtubule function by deacetylating tubulin, which leads to defects in axonal and mitochondrial transport; (2) promotes tau aggregation by deacetylating tau, which leads to pathological tau phosphorylation and neurofibrillary tangle formation; and (3) prevents degradation of HSP90 client proteins, including misfolded tau, by deacetylating HSP90, which stabilizes the chaperone complex associated with protein refolding/recycling. Thus, the present disclosure provides brain-penetrant, selective HDAC6 inhibitors. These compounds provide new compositions and methods for the treatment of diseases associated with HDAC6 activity (*e.g.*, neurological disorders, such as Alzheimer's disease and other tauopathies, amyotrophic lateral sclerosis, and cancer).

[0005] In one aspect, provided are compounds of Formula (**I**):



(**I**),

and pharmaceutically acceptable salts thereof,

wherein:

X is CR^1 or N, and Y is CR^1 or N, provided that at least one of X and Y is N;

R^1 is hydrogen or halogen;

R^a and R^b are each independently hydrogen or halogen;

L is a bond;

A is phenyl, phenyl fused to a 6-membered heteroaryl, or a 6,6 bicyclic aryl ring system, wherein A is optionally substituted with 1-3 independent substituents R^2; and

each occurrence of R^2 is independently halogen, cyano, substituted or unsubstituted amino, substituted or unsubstituted amido, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with one or more halogen or cyano.

[0006] In certain embodiments, R^1 is hydrogen or fluoro. In certain embodiments, X is N and Y is Y is CH, CF or N. In certain embodiments, R^a and R^b are each independently hydrogen or fluoro.

[0007] In certain embodiments, A is phenyl optionally substituted with 1-3 independent substituents R^2. In certain embodiments, A is phenyl optionally substituted with 1-3 independent substituents R^2 and each R^2 is fluoro or chloro. In certain embodiments, A is phenyl optionally substituted with 1-3 independent substituents R^2 and at least one of R^2 is not fluoro or chloro.

[0008] In certain embodiments, A is phenyl optionally substituted with 1-3 independent substituents R^2 and each R^2 is fluoro, chloro cyano, C_{1-4} alkyl, -(CH_2)CN, -NH_2, -$NH(CH_3)$, -$N(CH_3)_2$, -$C(O)NH_2$, -$C(O)NH(CH_3)$, or -$C(O)N(CH_3)_2$. In certain embodiments, A is phenyl optionally substituted with 1-3 independent substituents R^2 and each R^2 is cyano, C_{1-4} alkyl, -(CH_2)CN, -NH_2, -$NH(CH_3)$, -$N(CH_3)_2$, -$C(O)NH_2$, -$C(O)NH(CH_3)$, or -$C(O)N(CH_3)_2$.

[0009] In certain embodiments, A is pyridinyl optionally substituted with 1-3 independent substituents R^2. In certain embodiments, A is pyridinyl optionally substituted with 1-3 independent substituents R^2 and each R^2 is fluoro or chloro. In certain embodiments, A is pyridinyl optionally substituted with 1-3 independent substituents R^2 and each R^2 is fluoro, chloro, cyano, C_{1-4} alkyl, -(CH_2)CN, -NH_2, -$NH(CH_3)$, -$N(CH_3)_2$, -$C(O)NH_2$, -$C(O)NH(CH_3)$, or -$C(O)N(CH_3)_2$.

[0010] In certain embodiments, A is naphthalenyl. In certain embodiments, A is quinolinyl. In certain embodiments, A is quinoxalinyl. In certain embodiments, A is unsubstituted naphthalenyl, quinolinyl or quinoxalinyl.

[0011] In one aspect, provided are compounds selected from the group consisting of:

2-(difluoromethyl)-5-(2-((4-fluorophenoxy)methyl)pyrimidin-5-yl)-1,3,4-oxadiazole (1);

2-(6-((5-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (2);

2-(6-((4-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (3);

2-(6-((2-chloro-4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (4);

2-(difluoromethyl)-5-(6-((2,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (5);

2-(difluoromethyl)-5-(5-fluoro-6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (6);

2-(6-((2-chloro-5-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (7);

2-(6-((4-chlorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (8);

2-(difluoromethyl)-5-(6-((3,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (9);

2-(difluoromethyl)-5-(6-((quinolin-8-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (10);

2-(difluoromethyl)-5-(6-((naphthalen-1-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (11);

2-(difluoromethyl)-5-(6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (12);

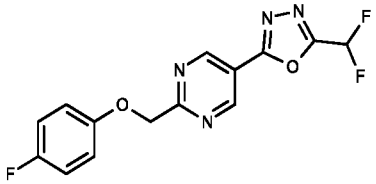
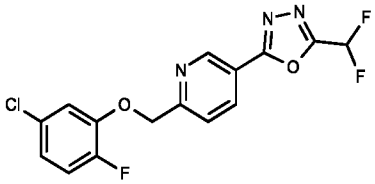
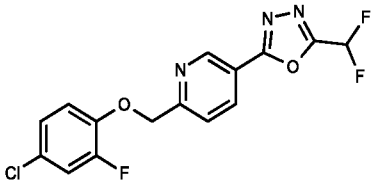
2-(6-(difluoro(quinolin-8-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (13);

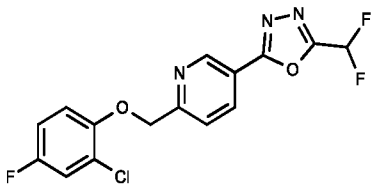
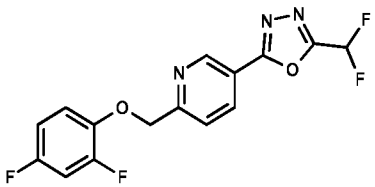
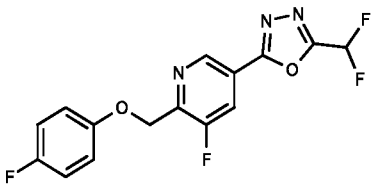
2-(6-(difluoro(naphthalen-1-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (14); and

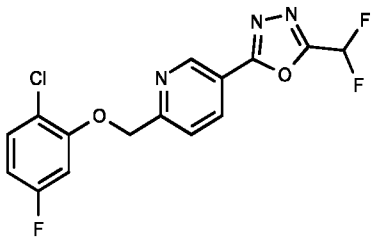
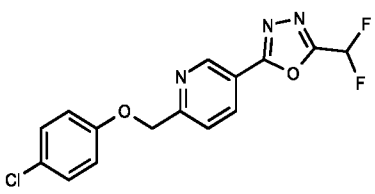
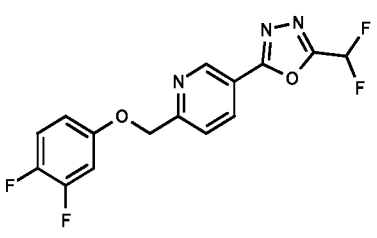
2-(6-(difluoro(4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (15);

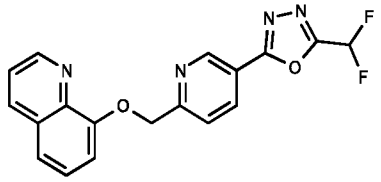
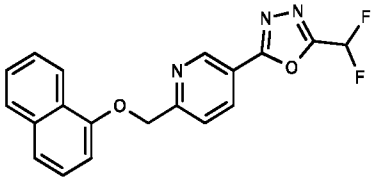
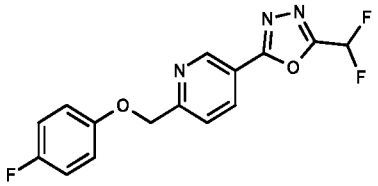
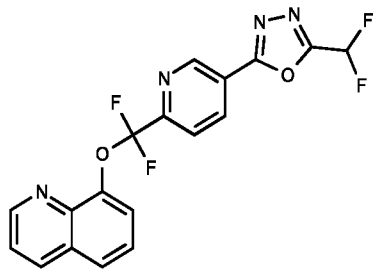
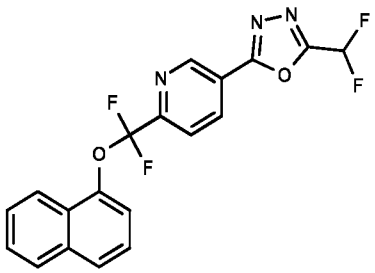
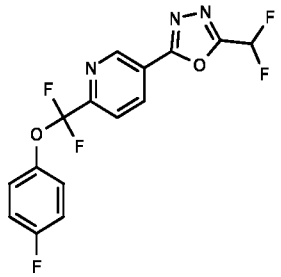
or a pharmaceutically acceptable salt thereof.

[0012] In one aspect, provided are pharmaceutical compositions comprising a compound of formula:


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or a pharmaceutically acceptable salt thereof.

[0013] In another aspect, provided are pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

[0014] In another aspect, provided are methods of treating a neurological or peripheral disease or disorder in a subject in need thereof, the method comprising administering a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound disclosed herein, to the subject. In some embodiments, provided are methods of treating a neurological disorder in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound disclosed herein. In some embodiments, provided are methods of treating amyotrophic lateral sclerosis in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound disclosed herein. In some embodiments, provided are methods of treating a tauopathy in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound disclosed herein.

[0015] In certain embodiments, the neurological disease or disorder being treated using a compound or composition described herein is a neurodegenerative, neurodevelopmental, neuropsychiatric, or neuropathy disease.

[0016] In some embodiments, provided are methods of treating autosomal dominant polycystic kidney disease in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound disclosed herein.

[0017] In some embodiments, provided are methods of treating chemotherapy-induced peripheral neuropathy in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound disclosed herein. In some embodiments, provided are methods of treating chemotherapy-induced cognitive dysfunction in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound disclosed herein.

[0018] In some embodiments, provided are methods of treating cardiac dysfunction in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound disclosed herein. In some embodiments, provided are methods of treating cardiomyopathy in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound disclosed herein. In some embodiments, provided are methods of treating cardiovascular disease in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound disclosed herein.

[0019] In another aspect, provided are methods of inhibiting the activity of HDAC6, the method comprising contacting HDAC6 with a compound disclosed herein, or a pharmaceutically acceptable salt thereof. In certain embodiments, inhibiting the activity of HDAC6 comprises selectively inhibiting the activity of HDAC6 over the activity of HDAC8. In certain embodiments, the HDAC6 is in a cell (*e.g.*, a human cell). In certain embodiments,

the inhibiting of the activity of HDAC6 takes place *in vitro*. In certain embodiments, the inhibiting of the activity of HDAC6 takes place *in vivo*.

[0020] The details of certain embodiments of the invention are set forth in the Detailed Description of Certain Embodiments, as described below. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, Examples, and Claims.

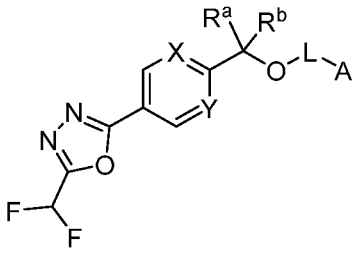
DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0021] Provided herein are compounds that are HDAC inhibitors (*e.g.*, HDAC6 inhibitors). The compounds described herein possess advantageous properties, such as selective inhibition of HDAC6 and/or the ability to cross the blood-brain-barrier, that allow the compounds to be useful as therapeutic agents. In one aspect, the provided HDAC6 inhibitors are compounds disclosed herein, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and pharmaceutical compositions thereof. Accordingly, the compounds are useful for the treatment and/or prevention of diseases and disorders associated with HDAC6 activity (*e.g.*, neurological disorder or disease, or peripheral disease or disorder) in a subject in need thereof.

[0022] The compounds described herein interact with HDAC6. As described herein, the therapeutic effect may be a result of inhibition, modulation, binding, and/or modification of HDAC6 by the compounds described herein. The compounds may be provided for use in any composition, kit, or method described herein as a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

Compounds

[0023] In one aspect, disclosed is a compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof, wherein:

X is CR^1 or N, and Y is CR^1 or N, provided that at least one of X and Y is N;

R^1 is hydrogen or halogen;

R^a and R^b are each independently hydrogen or halogen;

L is a bond;

A is phenyl, phenyl fused to a 6-member heteroaryl, or a 6,6 bicyclic aryl ring system, wherein A is optionally substituted with 1-3 independent substituents R^2;

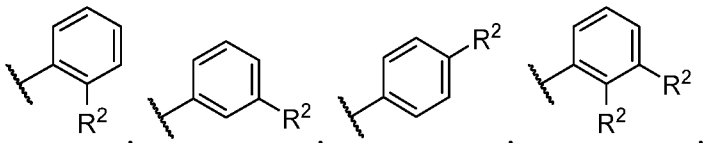
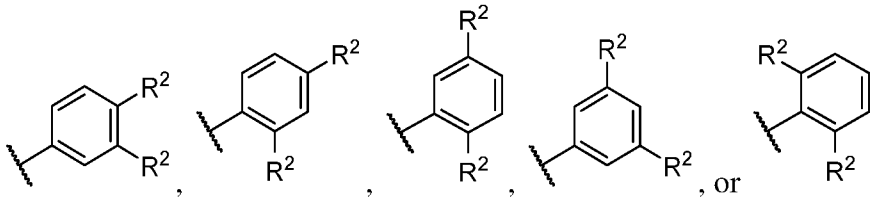
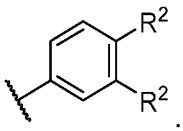
each occurrence of R^2 is independently halogen, substituted or unsubstituted amino, substituted or unsubstituted amido, cyano, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two occurrences of R^2 are joined with their intervening atoms to form substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

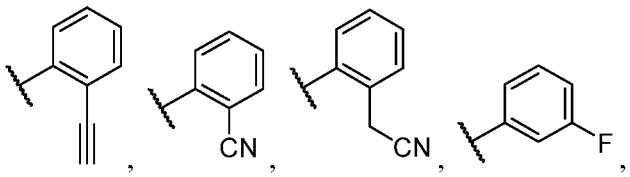
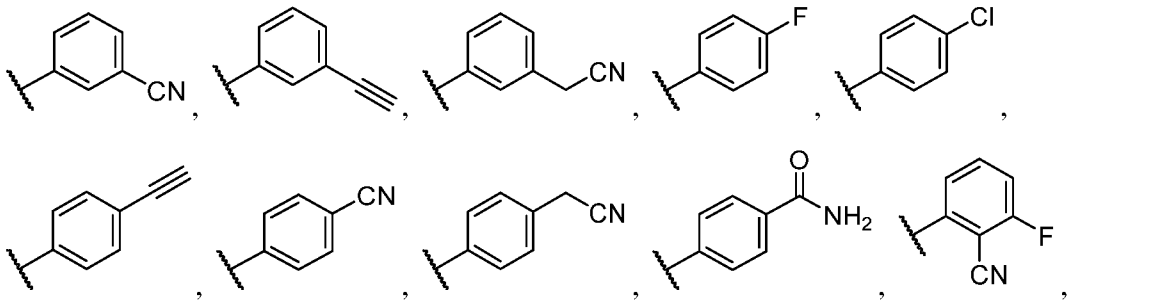
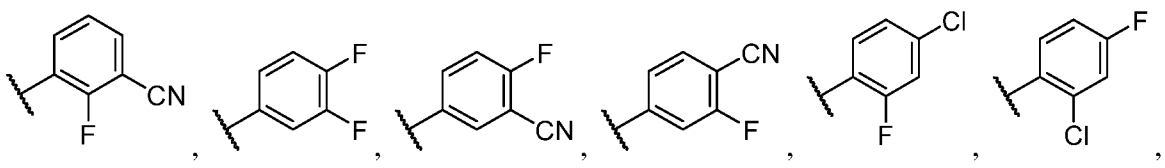
[0024] In certain embodiments, compounds of Formula (**I**) are compounds wherein X is N and Y is CH, CF or N. In certain embodiments, compounds of Formula (**I**) are compounds wherein R^a and R^b are each independently hydrogen or fluoro. In certain embodiments, compounds of Formula (**I**) are compounds wherein R^a and R^b are each independently hydrogen.

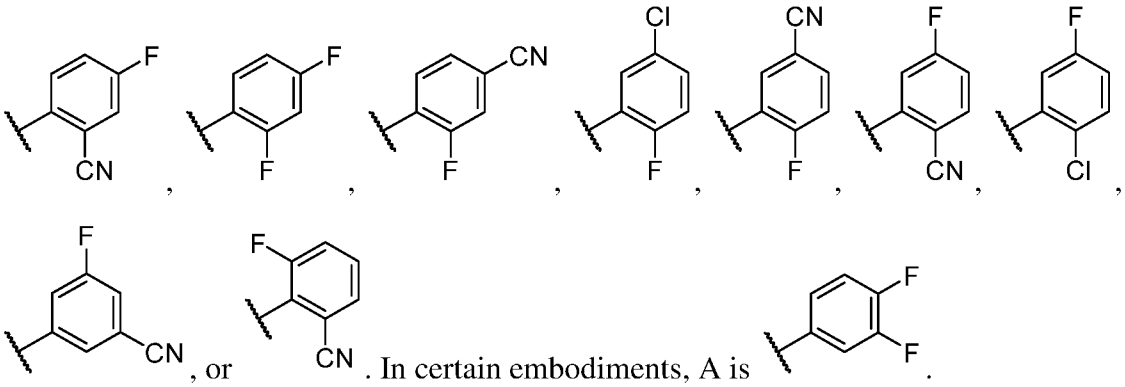
[0025] In certain embodiments, A is phenyl substituted with 1-3 independent substituents R^2, wherein each occurrence of R^2 is, independently, fluoro, chloro, cyano, cyclopropyl, C_{2-4} alkynyl, or C_{1-4} alkyl optionally substituted with one or more fluoro, cyano, or alkynyl. In certain embodiments, A is phenyl substituted with 1-3 independent substituents R^2, wherein each occurrence of R^2 is, independently, fluoro, chloro, cyano, methyl optionally substituted with one or more fluoro, or methyl optionally substituted with a cyano. In certain embodiments, A is phenyl substituted with 1-3 independent substituents R^2, wherein each occurrence of R^2 is, independently, fluoro, chloro, cyano, methyl optionally substituted with one or more fluoro, or methyl optionally substituted with a cyano.

[0026] In certain embodiments, A is phenyl substituted with 1-2 independent substituents R^2, wherein each occurrence of R^2 is, independently, fluoro, chloro, cyano, cyclopropyl, C_{2-4} alkynyl, or C_{1-4} alkyl optionally substituted with one or more fluoro, cyano, or alkynyl. In certain embodiments, A is phenyl substituted with 1-2 independent substituents R^2, wherein

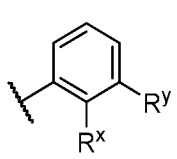
each occurrence of R^2 is, independently, fluoro, chloro, cyano, methyl optionally substituted with one or more fluoro, or methyl optionally substituted with a cyano. In certain embodiments, A is phenyl substituted with 1-2 independent substituents R^2, wherein each occurrence of R^2 is, independently, fluoro, chloro, cyano, methyl optionally substituted with one or more fluoro, or methyl optionally substituted with a cyano.

[0027] In certain embodiments, A is , . In certain embodiments, A is .

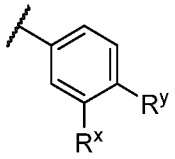
[0028] In certain embodiments, A is , , , .



. In certain embodiments, A is

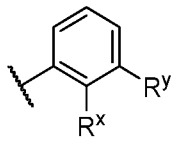


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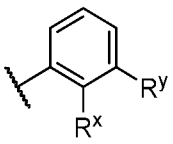


[0029] In certain embodiments, A is , wherein R^x and R^y join to form a 5-6 membered heteroaryl, a 4-6 membered heterocyclyl, or a C_{4-6} carbocyclyl ring, wherein A is optionally substituted with 1-3 independent substituents R^2. In certain embodiments, R^2 may be attached to the phenyl ring of A or to the 5-6 membered heteroaryl, 4-6 membered heterocyclyl, or C_{4-6} carbocyclyl ring formed by joining R^x and R^y.

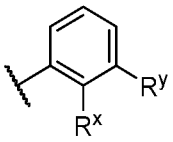
[0030] In certain embodiments, A is



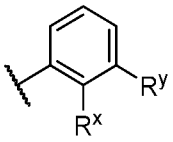
, wherein R^x and R^y join to form a 5-6 membered heteroaryl, a 4-6 membered heterocyclyl, or a C_{4-6} carbocyclyl ring, wherein A is optionally substituted with 1-3 independent substituents R^2. In certain embodiments, A is



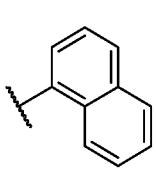
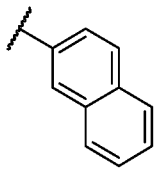
, wherein R^x and R^y join to form a 5-6 membered heteroaryl ring, wherein A is optionally substituted with 1-3 independent substituents R^2. In certain embodiments, A is

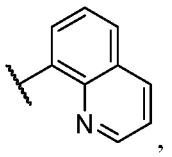
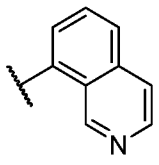
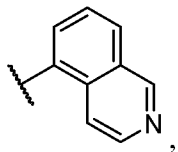
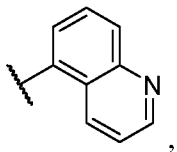
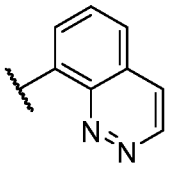
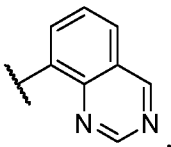
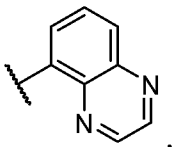
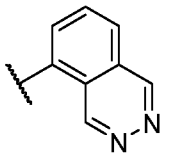
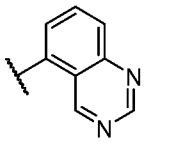
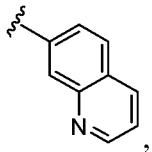
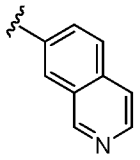
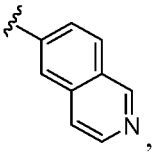
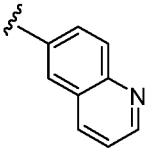
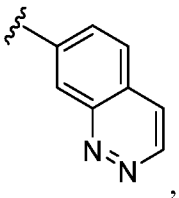
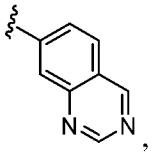
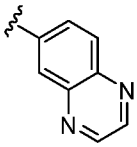
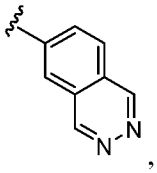
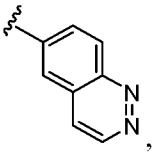


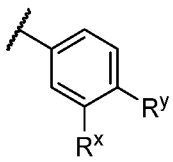
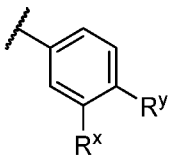
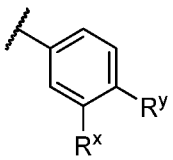
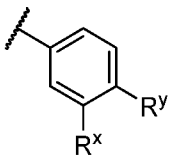
, wherein R^x and R^y join to form a 4-6 membered heterocyclyl ring, wherein A is optionally substituted with 1-3 independent substituents R^2. In certain embodiments, A is

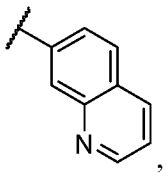
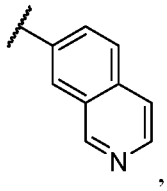
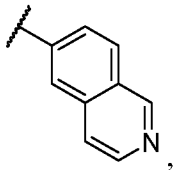
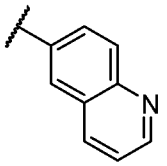
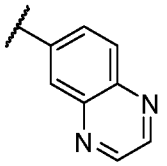
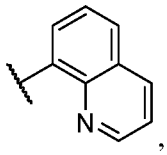
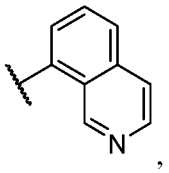
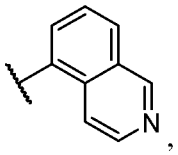
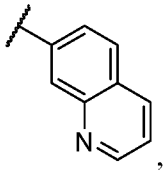
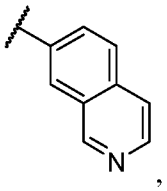
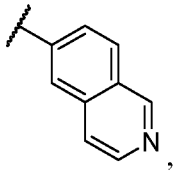
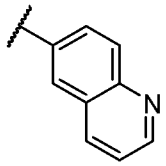
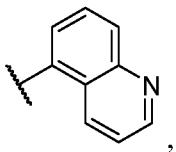
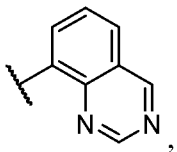
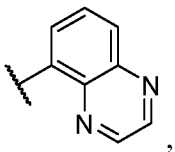
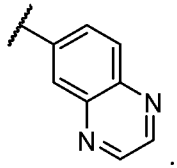


, wherein R^x and R^y join to form a C_{4-6} carbocyclyl ring, wherein A is optionally substituted with 1-3 independent substituents R^2.

[0031] In certain embodiments, A is  or .

[0032] In certain embodiments, A is , , , , , , , , , , , , , , , , , , or wherein A is optionally substituted with 1-3 independent substituents R^2.

[0033] In certain embodiments, A is , wherein R^x and R^y join to form a 5-6 membered heteroaryl, a 4-6 membered heterocyclyl, or a C_{4-6} carbocyclyl ring, wherein A is optionally substituted with 1-3 independent substituents R^2. In certain embodiments, A is , wherein R^x and R^y join to form a 5-6 membered heteroaryl ring, wherein A is optionally substituted with 1-3 independent substituents R^2. In certain embodiments, A is , wherein R^x and R^y join to form a 4-6 membered heterocyclyl ring, wherein A is optionally substituted with 1-3 independent substituents R^2. In certain embodiments, A is , wherein R^x and R^y join to form a C_{4-6} carbocyclyl ring, wherein A is optionally

substituted with 1-3 independent substituents R^2. In certain embodiments, A is , , , , or . In certain embodiments, A is , , , , , , , , , , .

[0034] As described herein, each occurrence of R^2 is independently halogen, substituted or unsubstituted amino, substituted or unsubstituted amido, cyano, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two occurrences of R^2 are joined with their intervening atoms to form substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In certain embodiments, each occurrence of R^2 is independently halogen, substituted or unsubstituted amido, cyano, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In certain embodiments, each occurrence of R^2 is independently halogen, substituted or unsubstituted amido, cyano, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl.

[0035] In certain embodiments, R^2 is substituted or unsubstituted aminoalkyl, substituted or unsubstituted amidoalkyl, amino optionally substituted with C_{1-4} alkyl, or amido optionally substituted with C_{1-4} alkyl. In certain embodiments, R^2 is amino or amido optionally substituted with C_{1-4} alkyl.

[0036] In certain embodiments, each occurrence of R^2 is independently halogen, cyano, -(C=O)NH_2, C_{1-6} alkyl, C_{3-6} cycloalkyl, 4-6 membered heterocyclyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with one or more halogen or cyano.

[0037] In certain embodiments, each occurrence of R^2 is independently fluoro, chloro, methyl, ethyl, isopropyl, trifluoromethyl, cyclopropyl, -(C=O)NH_2, cyano, cyanomethyl, ethynyl, or morpholinyl. In certain embodiments, each occurrence of R^2 is independently fluoro. In certain embodiments, each occurrence of R^2 is independently chloro. In certain embodiments, each occurrence of R^2 is independently methyl. In certain embodiments, each occurrence of R^2 is independently ethyl. In certain embodiments, each occurrence of R^2 is independently isopropyl. In certain embodiments, each occurrence of R^2 is independently trifluoromethyl. In certain embodiments, each occurrence of R^2 is independently cyclopropyl. In certain embodiments, each occurrence of R^2 is independently -(C=O)NH_2. In certain embodiments, each occurrence of R^2 is independently cyano. In certain embodiments, each occurrence of R^2 is independently cyanomethyl. In certain embodiments, each occurrence of R^2 is independently ethynyl. In certain embodiments, each occurrence of R^2 is independently morpholinyl.

[0038] In certain embodiments, each occurrence of R^2 is independently halogen. In certain embodiments, each occurrence of R^2 is independently fluoro or chloro. In certain embodiments, each occurrence of R^2 is fluoro.

[0039] In certain embodiments, A is substituted with 1 or 2 R^2 groups, wherein each occurrence of R^2 is independently halogen, cyano, -(C=O)NH_2, C_{1-6} alkyl, C_{3-6} cycloalkyl, 4-6 membered heterocyclyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with one or more halogen or cyano.

[0040] In certain embodiments, A is substituted with 1 or 2 R^2 groups, wherein each occurrence of R^2 is independently fluoro, chloro, methyl, ethyl, isopropyl, trifluoromethyl, cyclopropyl, -(C=O)NH_2, cyano, cyanomethyl, ethynyl, or morpholinyl.

[0041] In certain embodiments, A is substituted with 1 or 2 R^2 groups, wherein each occurrence of R^2 is independently fluoro, chloro, cyano, cyclopropyl, C_{2-4} alkynyl, or C_{1-4} alkyl optionally substituted with one or more fluoro, cyano, or alkynyl.

[0042] In certain embodiments, A is substituted with 1 or 2 R^2 groups, wherein each occurrence of R^2 is independently halogen. In certain embodiments, A is substituted with 1 or 2 R^2 groups, wherein each occurrence of R^2 is independently fluoro or chloro. In certain embodiments, A is substituted with 1 or 2 R^2 groups, wherein each occurrence of R^2 is fluoro.

[0043] In certain embodiments, A is C_{6-14} aryl, 5-11 membered heteroaryl, C_{3-10} cycloalkyl, or 4-11 membered heterocyclyl, wherein A is optionally substituted with 1-3 independent substituents R^2; each occurrence of R^1 is independently hydrogen, halogen, or C_{1-6} alkyl optionally substituted with one or more halogen or alkoxy; and each occurrence of R^2 is independently halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with one or more halogen or cyano.

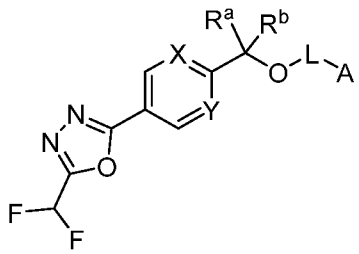
[0044] In certain embodiments, each occurrence of R^1 is independently hydrogen, halogen, or methyl optionally substituted with one or more halogen or alkoxy; and each occurrence of R^2 is independently halogen, cyano, methyl, cyclopropyl, C_{2-3} alkenyl, or C_{2-3} alkynyl, wherein each methyl, cyclopropyl, C_{2-3} alkenyl, or C_{2-3} alkynyl is optionally substituted with one or more halogen or cyano.

[0045] In certain embodiments, each halogen in R^1, R^2, R^a and R^b is fluoro or chloro. In certain embodiments, each halogen in R^1, R^2, R^a and R^b is fluoro.

[0046] In certain embodiments, the compound of Formula (**I**) is not one or more of the following compounds: 2-(difluoromethyl)-5-(2-((4-fluorophenoxy)methyl)pyrimidin-5-yl)-1,3,4-oxadiazole (1); 2-(6-((5-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (2); 2-(6-((4-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (3); 2-(6-((2-chloro-4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (4); 2-(difluoromethyl)-5-(6-((2,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (5); 2-(difluoromethyl)-5-(5-fluoro-6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (6); 2-(6-((2-chloro-5-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (7); 2-(6-((4-chlorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (8); 2-(difluoromethyl)-5-(6-((3,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (9); 2-(difluoromethyl)-5-(6-((quinolin-8-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (10); 2-(difluoromethyl)-5-(6-((naphthalen-1-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (11); 2-

(difluoromethyl)-5-(6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (12); 2-(6-(difluoro(quinolin-8-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (13); 2-(6-(difluoro(naphthalen-1-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (14); and 2-(6-(difluoro(4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (15).

[0047] In one aspect, disclosed is a compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof, wherein:

X is N, and Y is CH, CF or N;

R^a and R^b are each independently hydrogen;

L is a bond;

A is phenyl, phenyl fused to a 6-membered heteroaryl, or a 6,6 bicyclic aryl ring system, wherein A is optionally substituted with 1-3 independent substituents R^2;

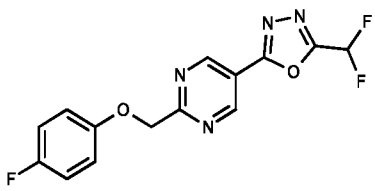
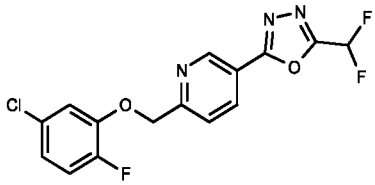
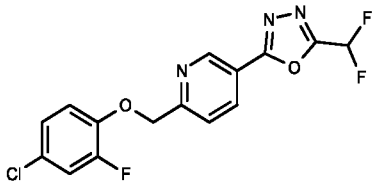
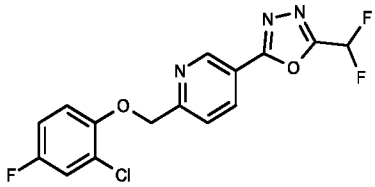
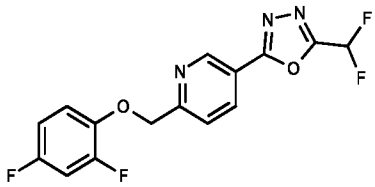
each occurrence of R^2 is independently halogen, substituted or unsubstituted amido, cyano, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two occurrences of R^2 are joined with their intervening atoms to form substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

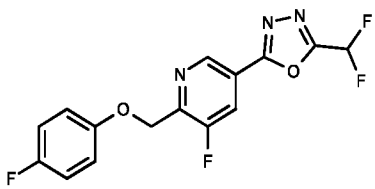
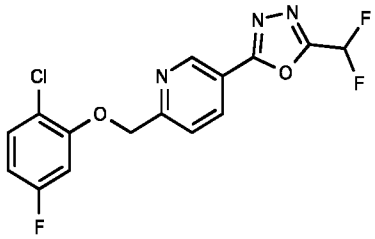
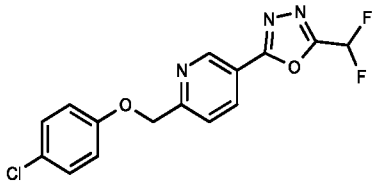
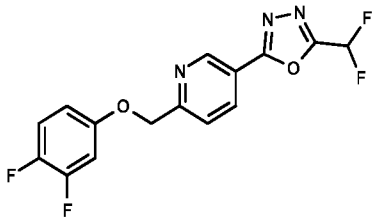
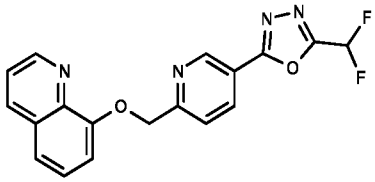
provided that the compound is not a compound selected from the group consisting of: 2-(difluoromethyl)-5-(2-((4-fluorophenoxy)methyl)pyrimidin-5-yl)-1,3,4-oxadiazole (1); 2-(6-((5-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (2); 2-(6-((4-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (3); 2-(6-((2-chloro-4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (4); 2-(difluoromethyl)-5-(6-((2,4-

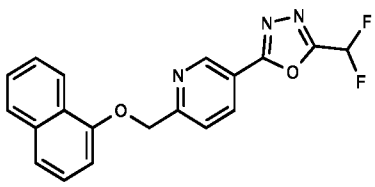
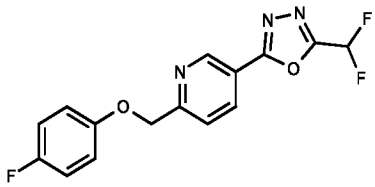
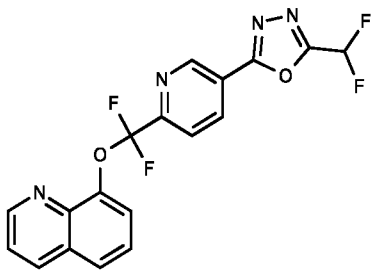
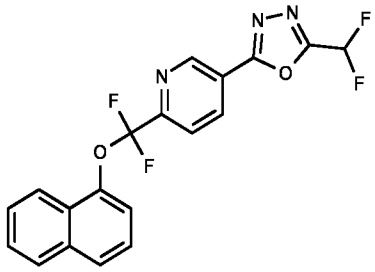
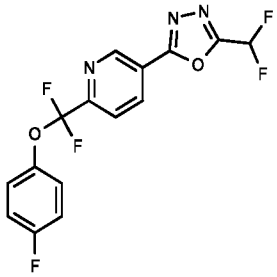
difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (5); 2-(difluoromethyl)-5-(5-fluoro-6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (6); 2-(6-((2-chloro-5-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (7); 2-(6-((4-chlorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (8); 2-(difluoromethyl)-5-(6-((3,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (9); 2-(difluoromethyl)-5-(6-((quinolin-8-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (10); 2-(difluoromethyl)-5-(6-((naphthalen-1-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (11); 2-(difluoromethyl)-5-(6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (12); 2-(6-(difluoro(quinolin-8-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (13); 2-(6-(difluoro(naphthalen-1-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (14); and 2-(6-(difluoro(4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (15).

[0048] In another aspect, provided are compounds selected from the group consisting of: 2-(difluoromethyl)-5-(2-((4-fluorophenoxy)methyl)pyrimidin-5-yl)-1,3,4-oxadiazole (1); 2-(6-((5-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (2); 2-(6-((4-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (3); 2-(6-((2-chloro-4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (4); 2-(difluoromethyl)-5-(6-((2,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (5); 2-(difluoromethyl)-5-(5-fluoro-6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (6); 2-(6-((2-chloro-5-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (7); 2-(6-((4-chlorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (8); 2-(difluoromethyl)-5-(6-((3,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (9); 2-(difluoromethyl)-5-(6-((quinolin-8-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (10); 2-(difluoromethyl)-5-(6-((naphthalen-1-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (11); 2-(difluoromethyl)-5-(6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (12); 2-(6-(difluoro(quinolin-8-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (13); 2-(6-(difluoro(naphthalen-1-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (14); and 2-(6-(difluoro(4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (15), or a pharmaceutically acceptable salt thereof.

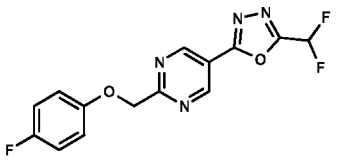
[0049] In certain embodiments, the compound is one of the following compounds, or a pharmaceutically acceptable salt thereof:

Compound	Compound Structure	Compound Name
1		2-(difluoromethyl)-5-(2-((4-fluorophenoxy)methyl)pyrimidin-5-yl)-1,3,4-oxadiazole
2		2-(6-((5-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole
3		2-(6-((4-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole
4		2-(6-((2-chloro-4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole
5		2-(difluoromethyl)-5-(6-((2,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole

Compound	Compound Structure	Compound Name
6		2-(difluoromethyl)-5-(5-fluoro-6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole
7		2-(6-((2-chloro-5-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole
8		2-(6-((4-chlorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole
9		2-(difluoromethyl)-5-(6-((3,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole
10		2-(difluoromethyl)-5-(6-((quinolin-8-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole

Compound	Compound Structure	Compound Name
11		2-(difluoromethyl)-5-(6-((naphthalen-1-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole
12		2-(difluoromethyl)-5-(6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole
13		2-(6-(difluoro(quinolin-8-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole
14		2-(6-(difluoro(naphthalen-1-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole
15		2-(6-(difluoro(4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole

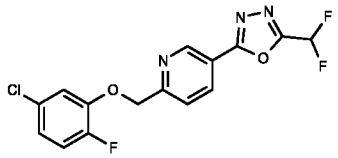
[0050] In certain embodiments, the compound is:



(1),

or a pharmaceutically acceptable salt thereof.

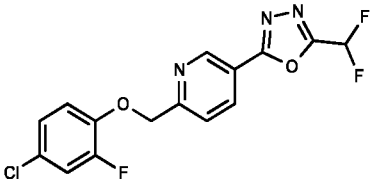
[0051] In certain embodiments, the compound is:



(2),

or a pharmaceutically acceptable salt thereof.

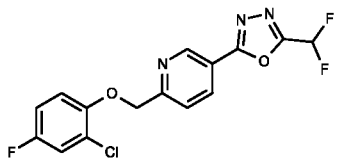
[0052] In certain embodiments, the compound is:



(3),

or a pharmaceutically acceptable salt thereof.

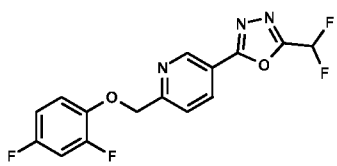
[0053] In certain embodiments, the compound is:



(4),

or a pharmaceutically acceptable salt thereof.

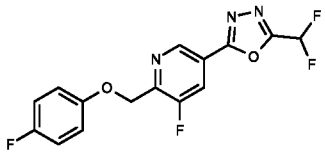
[0054] In certain embodiments, the compound is:



(5),

or a pharmaceutically acceptable salt thereof.

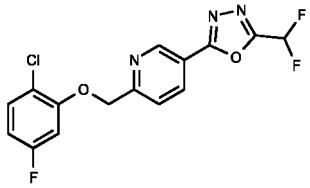
[0055] In certain embodiments, the compound is:



(6),

or a pharmaceutically acceptable salt thereof.

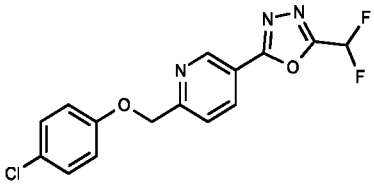
[0056] In certain embodiments, the compound is:



(7),

or a pharmaceutically acceptable salt thereof.

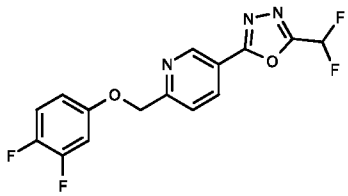
[0057] In certain embodiments, the compound is:



(8),

or a pharmaceutically acceptable salt thereof.

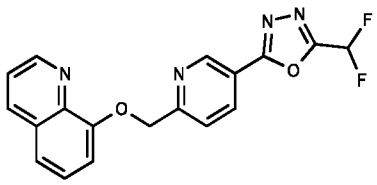
[0058] In certain embodiments, the compound is:



(9),

or a pharmaceutically acceptable salt thereof.

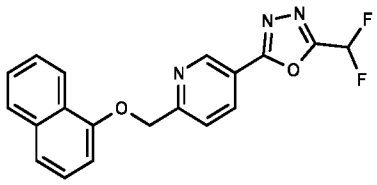
[0059] In certain embodiments, the compound is:



(10),

or a pharmaceutically acceptable salt thereof.

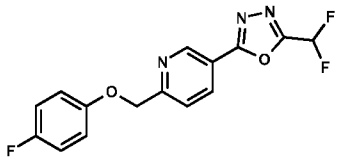
[0060] In certain embodiments, the compound is:



(11),

or a pharmaceutically acceptable salt thereof.

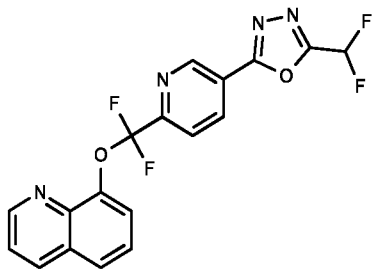
[0061] In certain embodiments, the compound is:



(12),

or a pharmaceutically acceptable salt thereof.

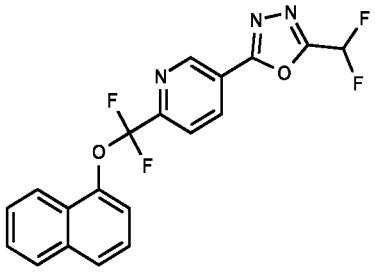
[0062] In certain embodiments, the compound is:



(13),

or a pharmaceutically acceptable salt thereof.

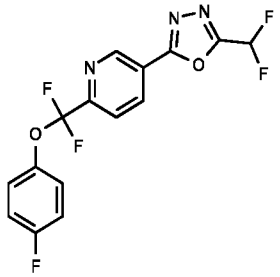
[0063] In certain embodiments, the compound is:



(14),

or a pharmaceutically acceptable salt thereof.

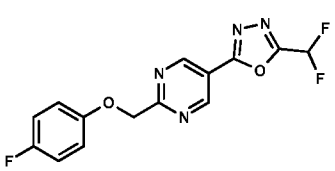
[0064] In certain embodiments, the compound is:



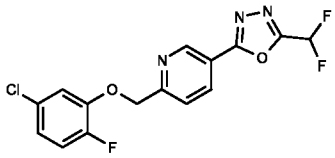
(15),

or a pharmaceutically acceptable salt thereof.

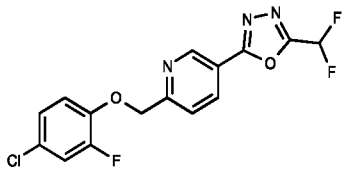
[0065] In certain embodiments, a pharmaceutical composition is provided comprising one or more of the following compounds, or a pharmaceutically acceptable salt thereof:



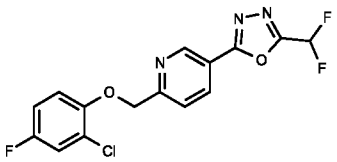
(1),



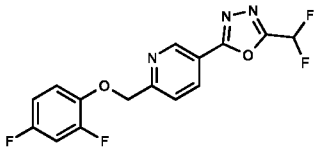
(2),



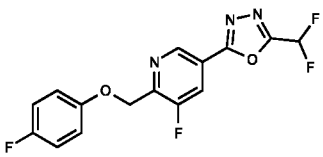
(3),



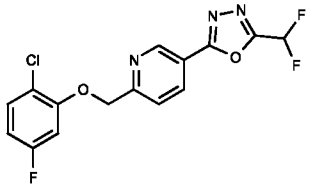
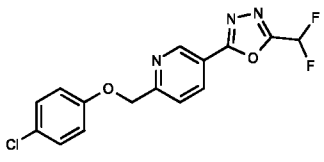
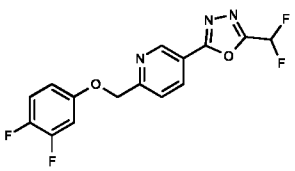
(4),

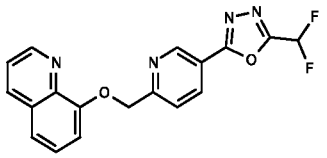
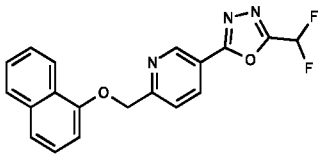
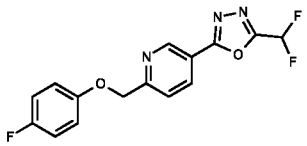


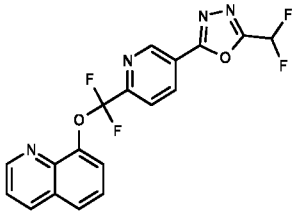
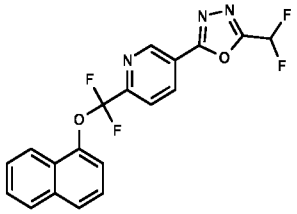
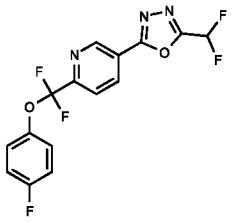
(5),



(6),


(7),

(8),

(9),


(10),

(11),

(12),


(13),

(14), or

(15).

Pharmaceutical Compositions

[0066] The present disclosure provides pharmaceutical compositions comprising a disclosed compound, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition described herein comprises a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0067] In certain embodiments, a compound disclosed herein is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount.

[0068] In certain embodiments, the effective amount is an amount effective for treating a cardiovascular disease in a subject in need thereof.

[0069] In certain embodiments, the effective amount is an amount effective for inhibiting the activity (*e.g.*, aberrant activity, such as increased activity) of HDAC6 in a subject, tissue, biological sample, or cell. The present disclosure provides pharmaceutical compositions comprising a compound that interacts with (*e.g.*, inhibits) HDAC6 for use in treating a HDAC6-related disease or disorder in a subject in need thereof. The present disclosure provides pharmaceutical compositions comprising a compound that interacts with (*e.g.*,

inhibits) HDAC6 for use in treating a disease or disorder associated with aberrant activity of HDAC6 in a subject in need thereof. The present disclosure provides pharmaceutical compositions comprising a compound that interacts with (*e.g.*, inhibits) HDAC6 for use in treating a disease or disorder associated with increased activity of HDAC6 in a subject in need thereof.

[0070] In certain embodiments, the effective amount is an amount effective for treating a neurological disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a neurological disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a neurodegenerative, neurodevelopmental, neuropsychiatric, or neuropathy disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a neurodegenerative, neurodevelopmental, neuropsychiatric, or neuropathy disease in a subject in need thereof. In certain embodiments, the composition is for use in treating Fragile-X syndrome, Charcot-Marie-Tooth disease, Alzheimer's disease, Parkinson's diseases, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, Lewy body dementia, vascular dementia, muscular atrophy, seizure induced memory loss, schizophrenia, Rubinstein Taybi syndrome, Rett Syndrome, attention deficit hyperactivity disorder, dyslexia, bipolar disorder, social, cognitive and learning disorders associated with autism, attention deficit disorder, schizophrenia, major depressive disorder, peripheral neuropathy, diabetic retinopathy, diabetic peripheral neuropathy, chemotherapy-induced peripheral neuropathy, chemotherapy-induced cognitive dysfunction, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), or a tauopathy. In certain embodiments, the composition is for use in treating primary age-related tauopathy (PART)/neurofibrillary tangle-predominant senile dementia, chronic traumatic encephalopathy, dementia pugilistica, progressive supranuclear palsy, corticobasal degeneration, Pick's disease, frontotemporal dementia, frontotemporal dementia and parkinsonism linked to chromosome 17, Lytico-Bodig disease, ganglioglioma, gangliocytoma, meningioangiomatosis, postencephalitic parkinsonism, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, lipofuscinosis, Alzheimer's disease, or argyrophilic grain disease.

[0071] In certain embodiments, the composition is for use in treating chemotherapy-induced peripheral neuropathy, diabetic peripheral neuropathy, peripheral neuropathy, diabetic retinopathy, obesity, autosomal dominant polycystic kidney disease,

cardiomyopathy, an auto-immune disease such as systemic lupus erythematosus (SLE), or cancer.

[0072] In certain embodiments, the composition is for use in treating a disease or disorder mediated by or linked to T-cell dysregulation. In certain embodiments, the composition is for use in treating arthritis, colitis, allograft rejection, lupus, asthma, psoriasis, inflammation, allergy, allergic encephalomyelitis, autoimmune lymphoproliferative disorder, autoimmune polyglandular syndrome type II, type I diabetes, lymphoma, Wiskott-Aldrich syndrome, or myasthenia gravis.

[0073] In certain embodiments, the compound or pharmaceutical composition is a solid. In certain embodiments, the compound or pharmaceutical composition is a powder. In certain embodiments, the compound or pharmaceutical composition can be dissolved in a liquid to make a solution. In certain embodiments, the compound or pharmaceutical composition is dissolved in water to make an aqueous solution. In certain embodiments, the pharmaceutical composition is a liquid for parental injection. In certain embodiments, the pharmaceutical composition is a liquid for oral administration (*e.g.*, ingestion). In certain embodiments, the pharmaceutical composition is a liquid (*e.g.*, aqueous solution) for intravenous injection. In certain embodiments, the pharmaceutical composition is a liquid (*e.g.*, aqueous solution) for subcutaneous injection.

[0074] After formulation with an appropriate pharmaceutically acceptable excipient in a desired dosage, the pharmaceutical compositions of the present dislcosure can be administered to humans and other animals orally, parenterally, intracisternally, intraperitoneally, topically, bucally, or the like, depending on the disease or condition being treated.

[0075] In certain embodiments, a pharmaceutical composition comprising a compound disclosed herein is administered, orally or parenterally, at dosage levels of each pharmaceutical composition sufficient to deliver from about 0.001 mg/kg to about 200 mg/kg in one or more dose administrations for one or several days (depending on the mode of administration). In certain embodiments, the effective amount per dose varies from about 0.001 mg/kg to about 200 mg/kg, about 0.001 mg/kg to about 100 mg/kg, about 0.01 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic and/or prophylactic effect. In certain embodiments, the compounds described herein may be at dosage levels

sufficient to deliver from about 0.001 mg/kg to about 200 mg/kg, from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic and/or prophylactic effect. The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage may be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). In certain embodiments, the composition described herein is administered at a dose that is below the dose at which the agent causes non-specific effects.

[0076] In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.001 mg to about 1000 mg per unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.01 mg to about 200 mg per unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.01 mg to about 100 mg per unit dose. In certain embodiments, pharmaceutical composition is administered at a dose of about 0.01 mg to about 50 mg per unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.01 mg to about 10 mg per unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.1 mg to about 10 mg per unit dose.

[0077] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the composition comprising a compound disclosed herein into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[0078] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a “unit dose” is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage, such as, for example, one-half or one-third of such a dosage.

[0079] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[0080] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition. Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof. Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof. Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.* bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.* polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan

(Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60), sorbitan tristearate (Span 65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (*e.g.* polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.* Cremophor™), polyoxyethylene ethers, (*e.g.* polyoxyethylene lauryl ether (Brij 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F-68, Poloxamer-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof. Exemplary binding agents include starch (*e.g.*, cornstarch and starch paste), gelatin, sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof. Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent. Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and

thimerosal. Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid. Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol. Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid. Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof. Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegive theable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof. Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazelnut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver,

walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[0081] Liquid dosage forms for oral and parenteral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active agents, 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 (in particular, 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, oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, agents of the invention are mixed with solubilizing agents such CREMOPHOR EL® (polyethoxylated castor oil), alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and combinations thereof.

[0082] 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. 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.

[0083] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0084] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is mixed with at least one inert,

pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0085] 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. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. 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.

[0086] The active agents 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 agent 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, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner.

Examples of embedding compositions which can be used include polymeric substances and waxes.

[0087] Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments, or pastes; or solutions or suspensions such as drops. Formulations for topical administration to the skin surface can be prepared by dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream, ointment, or soap. Useful carriers are capable of forming a film or layer over the skin to localize application and inhibit removal. For topical administration to internal tissue surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue-coating solutions, such as pectin-containing formulations can be used. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present disclosure contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of an agent to the body. Such dosage forms can be made by dissolving or dispensing the agent in the proper medium. Absorption enhancers can also be used to increase the flux of the agent across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the agent in a polymer matrix or gel.

[0088] Additionally, the carrier for a topical formulation can be in the form of a hydroalcoholic system (*e.g.*, liquids and gels), an anhydrous oil or silicone based system, or an emulsion system, including, but not limited to, oil-in-water, water-in-oil, water-in-oil-in-water, and oil-in-water-in-silicone emulsions. The emulsions can cover a broad range of consistencies including thin lotions (which can also be suitable for spray or aerosol delivery), creamy lotions, light creams, heavy creams, and the like. The emulsions can also include microemulsion systems. Other suitable topical carriers include anhydrous solids and semisolids (such as gels and sticks); and aqueous based mousse systems.

[0089] Also encompassed by the disclosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a pharmaceutical composition or compound described herein and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a pharmaceutical composition or compound described herein. In some embodiments, the

pharmaceutical composition or compound described herein provided in the first container and the second container are combined to form one unit dosage form.

In certain embodiments, a kit described herein further includes instructions for using the kit. A kit described herein may also include information as required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). In certain embodiments, the information included in the kits is prescribing information.

Methods of Treatment

[0090] The present disclosure provides methods of inhibiting the activity of HDAC. In certain embodiments, the application provides a method of inhibiting the activity of HDAC6. In certain embodiments, the application provides a method of inhibiting the activity of HDAC6 *in vitro*. In certain embodiments, the application provides a method of inhibiting the activity of HDAC6 *in vivo*. In certain embodiments, the application provides a method of inhibiting the activity of HDAC6 in a cell. In certain embodiments, the application provides a method of inhibiting the activity of HDAC6 in a human cell.

[0091] The present disclosure provides methods for treating HDAC6-related diseases and disorders. HDAC6 is unique in structure and function among all HDAC paralogs. In particular, it possesses two catalytic (deacetylase) domains and a zinc finger ubiquitin-binding domain. HDAC6 does not deacetylate histones, yet interacts with multiple substrates that affect disease-relevant pathways including microtubule stability, axonal and mitochondrial transport, protein aggregation, and autophagy. For example, HDAC6's direct substrates (*e.g.*, tau, tubulin, and HSP90) engage key mechanisms in Alzheimer's disease. As a result of its unique structure and function, selectively targive theing and inhibiting HDAC6 activity may avoid the side effects that are typical of existing FDA-approved HDAC inhibitors that result in clinical toxicity due to broad inhibition of multiple HDAC paralogs an/or inhibition of HDACs 1 and/or 2 (which has been shown to cause thrombocytopenia, a dose-limiting toxicity of most FDA-approved pan-HDAC inhibitors). Thus, treatment of HDAC6-related diseases with HDAC6-selective inhibitors may be particularly effective. In certain embodiments, the application provides a method of treating a neurological or peripheral disease or disorder.

[0092] In certain embodiments, the application provides a method of treating a neurological disease or disorder. In certain embodiments, the application provides a method of treating a neurodegenerative, neurodevelopmental, neuropsychiatric, or neuropathy disease or disorder. In certain embodiments, the application provides a method of treating Fragile-X syndrome,

Charcot-Marie-Tooth disease, Alzheimer's disease, Parkinson's diseases, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, Lewy body dementia, vascular dementia, muscular atrophy, seizure induced memory loss, schizophrenia, Rubinstein Taybi syndrome, Rett Syndrome, attention deficit hyperactivity disorder, dyslexia, bipolar disorder, social, cognitive and learning disorders associated with autism, attention deficit disorder, schizophrenia, major depressive disorder, peripheral neuropathy, diabetic retinopathy, diabetic peripheral neuropathy, chemotherapy-induced peripheral neuropathy, chemotherapy-induced cognitive dysfunction, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), or a tauopathy. In certain embodiments, the application provides a method of treating primary age-related tauopathy (PART)/neurofibrillary tangle-predominant senile dementia, chronic traumatic encephalopathy, dementia pugilistica, progressive supranuclear palsy, corticobasal degeneration, Pick's disease, frontotemporal dementia, frontotemporal dementia and parkinsonism linked to chromosome 17, Lytico-Bodig disease, ganglioglioma, gangliocytoma, meningioangiomatosis, postencephalitic parkinsonism, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, lipofuscinosis, Alzheimer's disease, or argyrophilic grain disease. In certain embodiments, the application provides a method of treating Alzheimer's disease.

[0093] In certain embodiments, the application provides a method of treating a neurodegenerative, neurodevelopmental, neuropsychiatric, or neuropathy disease or disorder. In certain embodiments, the application provides a method of treating a neurological disease or disorder, such as Alzheimer's disease, Fragile-X syndrome, Charcot-Marie-Tooth disease, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, Rett Syndrome, major depressive disorder, chemotherapy-induced cognitive dysfunction, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), brain cancer, or a tauopathy such as frontotemporal dementia, progressive supranuclear palsy, or corticobasal degeneration.

[0094] In certain embodiments, the application provides a method of treating a peripheral disease or disorder such as chemotherapy-induced peripheral neuropathy, diabetic peripheral neuropathy, peripheral neuropathy, diabetic retinopathy, obesity, autosomal dominant polycystic kidney disease, cardiomyopathy, an auto-immune disease such as systemic lupus erythematosus (SLE), or cancer.

[0095] In certain embodiments, the application provides a method of treating cystic fibrosis. In certain embodiments, the application provides a method of treating polycystic

kidney disease. In certain embodiments, the application provides a method of treating pulmonary hypertension. In certain embodiments, the application provides a method of treating cardiac dysfunction.

[0096] In certain embodiments, the methods comprise administering to a subject in need thereof (*e.g.*, a subject with a neurological disorder) a compound that interacts with HDAC6, for example, a compound that is an inhibitor of HDAC6, a modulator of HDAC6, a binder of HDAC6, or a compound that modifies HDAC6. In certain embodiments, the methods comprise administering a compound of the disclosure (*e.g.*, compounds (1) – (15)), or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug, or composition thereof, to a subject in need thereof. In some embodiments, the method comprises administering a pharmaceutical composition comprising a compound of the disclosure (*e.g.*, compounds (1) – (15)), or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug, or composition thereof, to a subject in need thereof.

[0097] In certain embodiments, the methods comprise administering an additional therapeutic agent.

DEFINITIONS

Chemical definitions

[0098] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0099] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers,

including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen *et al.*, Tetrahedron 33:2725 (1977); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S.H., Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[00100] In a formula, ~~~ is a single bond where the stereochemistry of the moieties immediately attached thereto is not specified, --- is absent or a single bond, and ═══ or ═══ is a single or double bond.

[00101] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, replacement of ^{19}F with ^{18}F, or the replacement of ^{12}C with ^{13}C or ^{14}C are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[00102] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[00103] The term "aliphatic" refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. Likewise, the term "heteroaliphatic" refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

[00104] The term "alkyl" refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group

has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), propyl (C_3) (*e.g.*, n-propyl, isopropyl), butyl (C_4) (*e.g.*, n-butyl, tert-butyl, sec-butyl, iso-butyl), pentyl (C_5) (*e.g.*, n-pentyl, 3-pentanyl, amyl, neopentyl, 3-methyl-2-butanyl, tertiary amyl), and hexyl (C_6) (*e.g.*, n-hexyl). Additional examples of alkyl groups include n-heptyl (C_7), n-octyl (C_8), and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents (*e.g.*, halogen, such as F). In certain embodiments, the alkyl group is an unsubstituted C_{1-10} alkyl (such as unsubstituted C_{1-6} alkyl, *e.g.*, $-CH_3$ (Me), unsubstituted ethyl (Et), unsubstituted propyl (Pr, *e.g.*, unsubstituted n-propyl (n-Pr), unsubstituted isopropyl (i-Pr)), unsubstituted butyl (Bu, *e.g.*, unsubstituted n-butyl (n-Bu), unsubstituted tert-butyl (tert-Bu or t-Bu), unsubstituted sec-butyl (sec-Bu), unsubstituted isobutyl (i-Bu)). In certain embodiments, the alkyl group is a substituted C_{1-10} alkyl (such as substituted C_{1-6} alkyl, *e.g.*, $-CF_3$, Bn).

[00105] The term "haloalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} haloalkyl"). Examples of haloalkyl groups include $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, and the like.

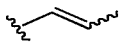
[00106] The term "alkoxy" refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. In some embodiments, the alkoxy moiety has 1 to 8 carbon atoms ("C_{1-8} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 6 carbon atoms ("C_{1-6} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 4 carbon atoms ("C_{1-4} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 3 carbon atoms ("C_{1-3} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 2 carbon atoms ("C_{1-2} alkoxy"). Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy and tert-butoxy.

[00107] The term "alkoxyalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by an alkoxy group, as defined herein. In some embodiments, the alkoxyalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} alkoxyalkyl"). In some

embodiments, the alkoxyalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} alkoxyalkyl").

[00108] The term "heteroalkyl" refers to an alkyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 20 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-20} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 18 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-18} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 16 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-16} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 14 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-14} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 12 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-12} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-3} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-2} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In some embodiments, the heteroalkyl group defined herein is a partially unsaturated group having 1 or more heteroatoms within the parent chain and at least one unsaturated carbon, such as a carbonyl group. For example, a heteroalkyl group may comprise an amide or ester functionality in its parent chain such that one or more carbon atoms are unsaturated carbonyl groups. Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an

"unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-20} alkyl. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-10} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-20} alkyl. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-10} alkyl.

[00109] The term "alkenyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is a substituted C_{2-10} alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is not specified (*e.g.*, $-CH=CHCH_3$ or ) may be an (E)- or (Z)-double bond.

[00110] The term "heteroalkenyl" refers to an alkenyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10} alkenyl"). In some embodiments, a heteroalkenyl group

has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-4} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC_{2-10} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{2-10} alkenyl.

[00111] The term "alkynyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon-carbon triple bonds can be internal (such as in 2-butynyl) or terminal (such as in 1-butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like.

Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is a substituted C_{2-10} alkynyl.

[00112] The term "heteroalkynyl" refers to an alkynyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1or 2 heteroatoms within the parent chain ("heteroC_{2-4} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC_{2-10} alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC_{2-10} alkynyl.

[00113] The term "carbocyclyl" or "carbocyclic" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl

group has 3 to 7 ring carbon atoms ("C_{3-7} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("C_{4-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 7 ring carbon atoms ("C_{4-7} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 8 ring carbon atoms ("C_{4-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 10 ring carbon atoms ("C_{4-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("C_{5-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1H-indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or polycyclic (*e.g.*, containing a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") or tricyclic system ("tricyclic carbocyclyl")) and can be saturated or can contain one or more carbon-carbon double or triple bonds. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C_{3-14} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-14} carbocyclyl.

[00114] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a

cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms ("C_{4-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C_{3-14} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_{3-14} cycloalkyl.

[00115] The term "heterocyclyl" or "heterocyclic" refers to a radical of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3-14 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or polycyclic (*e.g.*, a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl")), and can be saturated or can contain one or more carbon-carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3-14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3-14 membered heterocyclyl.

[00116] In some embodiments, a heterocyclyl group is a 5-10 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is

independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 6-10 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("6-10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-8 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-6 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heterocyclyl"). In some embodiments, the 5-6 membered heterocyclyl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

[00117] Exemplary 3-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazinyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl,

octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydrofuro[2,3-b]pyridinyl, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

[00118] The term "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has 6 ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("C_{14} aryl"; *e.g.*, anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is an unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is a substituted C_{6-14} aryl.

[00119] "Aralkyl" is a subset of "alkyl" and refers to an alkyl group substituted by an aryl group, wherein the point of attachment is on the alkyl moiety.

[00120] The term "heteroaryl" refers to a radical of a 5-14 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-14 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein

the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

[00121] In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-8 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5-14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5-14 membered heteroaryl.

[00122] Exemplary 5-membered heteroaryl groups containing 1 heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing 2 heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing 3 heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing 4 heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing 1 heteroatom include,

without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing 2 heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing 3 or 4 heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing 1 heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include, without limitation, phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, and phenazinyl.

[00123] "Heteroaralkyl" is a subset of "alkyl" and refers to an alkyl group substituted by a heteroaryl group, wherein the point of attachment is on the alkyl moiety.

[00124] The term "polycyclic spiro ring system" refers to ring systems having two or more rings linked by one common atom. The common atom is known as a spiro atom. The ring systems may be fully carbocyclic (all carbon) or heterocyclic (having one or more non-carbon atom). A ring system is considered heterocyclic if the spiro atom or any atom in either ring are not carbon atoms.

[00125] The term "bridged ring system" refers to ring systems having two or more rings that contain a bridge—a single atom or an unbranched chain of atoms (or even just a valence bond) that connect two "bridgehead" atoms. The bridgehead atoms are defined as any atom that is not a hydrogen, and that is part of the skeletal framework of the molecule that is bonded to three or more other skeletal atoms. The ring systems may be fully carbocyclic (all carbon) or heterocyclic (having one or more non-carbon atoms). A ring system is considered heterocyclic if any atom is not a carbon atom.

[00126] The term "unsaturated bond" refers to a double or triple bond.

[00127] The term "unsaturated" or "partially unsaturated" refers to a moiety that includes at least one double or triple bond.

[00128] The term "saturated" refers to a moiety that does not contain a double or triple bond, *i.e.*, the moiety only contains single bonds.

[00129] Affixing the suffix "-ene" to a group indicates the group is a divalent moiety, *e.g.*, alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl,

alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl, heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl. As one further example, haloalkylene is the divalent moiety of haloalkyl (*i.e.*, an alkylene group substituted with one or more halogens)

[00130] A group is optionally substituted unless expressly provided otherwise. The term "optionally substituted" refers to being substituted or unsubstituted. In certain embodiments, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are optionally substituted. "Optionally substituted" refers to a group which may be substituted or unsubstituted (*e.g.*, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" heteroalkyl, "substituted" or "unsubstituted" heteroalkenyl, "substituted" or "unsubstituted" heteroalkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted" means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, and includes any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety. The invention is not intended to be limited in any manner by the exemplary substituents described herein.

[00131] Exemplary carbon atom substituents include, but are not limited to, halogen, –CN, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, –OH, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3{}^+X^-$, $-N(OR^{cc})R^{bb}$, –SH, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, –CHO, $-C(OR^{cc})_3$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$,

$-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)(N(R^{bb})_2)_2$, $-OP(=O)(N(R^{bb})_2)_2$, $-NR^{bb}P(=O)(R^{aa})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(N(R^{bb})_2)_2$, $-P(R^{cc})_2$, $-P(OR^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_3{}^+X^-$, $-P(R^{cc})_4$, $-P(OR^{cc})_4$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3{}^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3{}^+X^-$, $-OP(R^{cc})_4$, $-OP(OR^{cc})_4$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^- is a counterion;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-CN$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)(N(R^{cc})_2)_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^- is a counterion;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)(OR^{ee})_2$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S; wherein X^- is a counterion;

each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl, or two R^{ff} groups are joined to form a 3-10 membered heterocyclyl or 5-10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1-6}$ alkyl, $–ON(C_{1-6}$ alkyl$)_2$, $–N(C_{1-6}$ alkyl$)_2$, $–N(C_{1-6}$ alkyl$)_3^+X^–$, $–NH(C_{1-6}$ alkyl$)_2^+X^–$, $–NH_2(C_{1-6}$ alkyl$)^+X^–$, $–NH_3^+X^–$, $–N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl), –N(OH)(C_{1-6} alkyl), –NH(OH), –SH, $–SC_{1-6}$ alkyl, $–SS(C_{1-6}$ alkyl), $–C(=O)(C_{1-6}$ alkyl), $–CO_2H$, $–CO_2(C_{1-6}$ alkyl), $–OC(=O)(C_{1-6}$ alkyl), $–OCO_2(C_{1-6}$ alkyl), $–C(=O)NH_2$, $–C(=O)N(C_{1-6}$ alkyl$)_2$, $–OC(=O)NH(C_{1-6}$ alkyl), $–NHC(=O)(C_{1-6}$ alkyl), $–N(C_{1-6}$ alkyl$)C(=O)($ C_{1-6} alkyl), $–NHCO_2(C_{1-6}$ alkyl), $–NHC(=O)N(C_{1-6}$ alkyl$)_2$, $–NHC(=O)NH(C_{1-6}$ alkyl), $–NHC(=O)NH_2$, $–C(=NH)O(C_{1-6}$ alkyl), $–OC(=NH)(C_{1-6}$ alkyl), $–OC(=NH)OC_{1-6}$ alkyl, $–C(=NH)N(C_{1-6}$ alkyl$)_2$, $–C(=NH)NH(C_{1-6}$ alkyl), $–C(=NH)NH_2$, $–OC(=NH)N(C_{1-6}$ alkyl$)_2$, $–OC(=NH)NH(C_{1-6}$ alkyl), $–OC(=NH)NH_2$, $–NHC(=NH)N(C_{1-6}$ alkyl$)_2$, $–NHC(=NH)NH_2$, $–NHSO_2(C_{1-6}$ alkyl), $–SO_2N(C_{1-6}$ alkyl$)_2$, $–SO_2NH(C_{1-6}$ alkyl), $–SO_2NH_2$, $–SO_2(C_{1-6}$ alkyl), $–SO_2O(C_{1-6}$ alkyl), $–OSO_2(C_{1-6}$ alkyl), $–SO(C_{1-6}$ alkyl), $–Si(C_{1-6}$ alkyl$)_3$, $–OSi(C_{1-6}$ alkyl$)_3$ $–C(=S)N(C_{1-6}$ alkyl$)_2$, C(=S)NH(C_{1-6} alkyl), $C(=S)NH_2$, $–C(=O)S(C_{1-6}$ alkyl), $–C(=S)SC_{1-6}$ alkyl, $–SC(=S)SC_{1-6}$ alkyl, $–P(=O)(OC_{1-6}$ alkyl$)_2$, $–P(=O)(C_{1-6}$ alkyl$)_2$, $–OP(=O)(C_{1-6}$ alkyl$)_2$, $–OP(=O)(OC_{1-6}$ alkyl$)_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein $X^–$ is a counterion.

[00132] The term “halo” or “halogen” refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[00133] The term “hydroxyl” or “hydroxy” refers to the group –OH. The term “substituted hydroxyl” or “substituted hydroxyl,” by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $–OR^{aa}$, $–ON(R^{bb})_2$, $–OC(=O)SR^{aa}$, $–OC(=O)R^{aa}$, $–OCO_2R^{aa}$, $–OC(=O)N(R^{bb})_2$, $–OC(=NR^{bb})R^{aa}$, $–OC(=NR^{bb})OR^{aa}$, $–OC(=NR^{bb})N(R^{bb})_2$, $–OS(=O)R^{aa}$, $–OSO_2R^{aa}$, $–OSi(R^{aa})_3$, $–OP(R^{cc})_2$, $–OP(R^{cc})_3^+X^–$, $–OP(OR^{cc})_2$, $–OP(OR^{cc})_3^+X^–$, $–OP(=O)(R^{aa})_2$, $–OP(=O)(OR^{cc})_2$, and $–OP(=O)(N(R^{bb})_2)_2$, wherein $X^–$, R^{aa}, R^{bb}, and R^{cc} are as defined herein.

[00134] The term “amino” refers to the group $–NH_2$. The term “substituted amino,” by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino. In certain embodiments, the “substituted amino” is a monosubstituted amino or a disubstituted amino group.

[00135] The term “monosubstituted amino” refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one hydrogen and one group

other than hydrogen, and includes groups selected from –NH(R^{bb}), –NHC(=O)R^{aa}, –NHCO_2R^{aa}, –NHC(=O)N(R^{bb})$_2$, –NHC(=NR^{bb})N(R^{bb})$_2$, –NHSO_2R^{aa}, –NHP(=O)(OR^{cc})$_2$, and –NHP(=O)(N(R^{bb})$_2$)$_2$, wherein R^{aa}, R^{bb} and R^{cc} are as defined herein, and wherein R^{bb} of the group –NH(R^{bb}) is not hydrogen.

[00136] The term "disubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than hydrogen, and includes groups selected from –N(R^{bb})$_2$, –NR^{bb}C(=O)R^{aa}, –NR^{bb}CO_2R^{aa}, –NR^{bb}C(=O)N(R^{bb})$_2$, –NR^{bb}C(=NR^{bb})N(R^{bb})$_2$, –NR^{bb}SO_2R^{aa}, –NR^{bb}P(=O)(OR^{cc})$_2$, and –NR^{bb}P(=O)(N(R^{bb})$_2$)$_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with hydrogen.

[00137] The term "trisubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three groups, and includes groups selected from –N(R^{bb})$_3$ and –N(R^{bb})$_3^+X^-$, wherein R^{bb} and X^- are as defined herein.

[00138] The term "sulfonyl" refers to a group selected from –SO_2N(R^{bb})$_2$, –SO_2R^{aa}, and –SO_2OR^{aa}, wherein R^{aa} and R^{bb} are as defined herein.

[00139] The term "sulfinyl" refers to the group –S(=O)R^{aa}, wherein R^{aa} is as defined herein.

[00140] The term "acyl" refers to a group having the general formula: –C(=O)R^{X1}, –C(=O)OR^{X1}, –C(=O)–O–C(=O)R^{X1}, –C(=O)SR^{X1}, –C(=O)N(R^{X1})$_2$, –C(=S)R^{X1}, –C(=S)N(R^{X1})$_2$, –C(=S)O(R^{X1}), –C(=S)S(R^{X1}), –C(=NR^{X1})R^{X1}, –C(=NR^{X1})OR^{X1}, –C(=NR^{X1})SR^{X1}, or –C(=NR^{X1})N(R^{X1})$_2$, wherein R^{X1} is hydrogen; halogen; substituted or unsubstituted hydroxyl; substituted or unsubstituted thiol; substituted or unsubstituted amino; substituted or unsubstituted acyl, cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkyl; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, mono- or di- aliphaticamino, mono- or di- heteroaliphaticamino, mono- or di- alkylamino, mono- or di- heteroalkylamino, mono- or di-arylamino, or mono- or di-heteroarylamino; or two R^{X1} groups taken togive theher form a 5- to 6-membered heterocyclic ring. Exemplary acyl groups include aldehydes (–CHO), carboxylic acids (–CO_2H), ketones, acyl halides, esters, amides, imines, carbonates, carbamates, and ureas. Acyl substituents include, but are not limited to, any of the substituents described herein, that

result in the formation of a stable moiety (*e.g.*, aliphatic, alkyl, alkenyl, alkynyl, heteroaliphatic, heterocyclic, aryl, heteroaryl, acyl, oxo, imino, thiooxo, cyano, isocyano, amino, azido, nitro, hydroxyl, thiol, halo, aliphaticamino, heteroaliphaticamino, alkylamino, heteroalkylamino, arylamino, heteroarylamino, alkylaryl, arylalkyl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, acyloxy, and the like, each of which may or may not be further substituted).

[00141] The term "oxo" refers to the group =O, and the term "thiooxo" refers to the group =S.

[00142] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, –OH, $-OR^{aa}$, $-N(R^{cc})_2$, –CN, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)(OR^{cc})_2$, $-P(=O)(R^{aa})_2$, $-P(=O)(N(R^{cc})_2)_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10}alkyl, heteroC_{2-10}alkenyl, heteroC_{2-10}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein.

[00143] In certain embodiments, the substituent present on the nitrogen atom is a nitrogen protecting group (also referred to herein as an "amino protecting group"). Nitrogen protecting groups include, but are not limited to, –OH, $-OR^{aa}$, $-N(R^{cc})_2$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, C_{1-10} alkyl (*e.g.*, aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[00144] For example, nitrogen protecting groups such as amide groups (*e.g.*, –C(=O)R^{aa}) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, N-benzoylphenylalanyl derivative, benzamide, p-phenylbenzamide, o-nitophenylacetamide, o-nitrophenoxyacetamide, acetoacetamide, (N'-dithiobenzyloxyacylamino)acetamide, 3-(p-hydroxyphenyl)propanamide, 3-(o-nitrophenyl)propanamide, 2-methyl-2-(o-nitrophenoxy)propanamide, 2-methyl-2-(o-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, o-nitrocinnamide, N-acetylmethionine derivative, o-nitrobenzamide and o-(benzoyloxymethyl)benzamide.

[00145] Nitrogen protecting groups such as carbamate groups (*e.g.*, –C(=O)OR^{aa}) include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluoroenylmethyl carbamate, 2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-t-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenylyl)ethyl carbamate (Bpoc), 1-(3,5-di-t-butylphenyl)-1-methylethyl carbamate (t-Bumeoc), 2-(2′- and 4′-pyridyl)ethyl carbamate (Pyoc), 2-(N,N-dicyclohexylcarboxamido)ethyl carbamate, t-butyl carbamate (BOC or Boc), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, N-hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), p-methoxybenzyl carbamate (Moz), p-nitobenzyl carbamate, p-bromobenzyl carbamate, p-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (Msz), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(p-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, m-chloro-p-acyloxybenzyl carbamate, p-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc),

m-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, o-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(o-nitrophenyl)methyl carbamate, t-amyl carbamate, S-benzyl thiocarbamate, p-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, p-decyloxybenzyl carbamate, 2,2-dimethoxyacylvinyl carbamate, o-(N,N-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(N,N-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, p-(p'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(p-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, p-(phenylazo)benzyl carbamate, 2,4,6-tri-t-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[00146] Nitrogen protecting groups such as sulfonamide groups (*e.g.*, $-S(=O)_2R^{aa}$) include, but are not limited to, p-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β-trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4′,8′-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[00147] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, N′-p-toluenesulfonylaminoacyl derivative, N′-phenylaminothioacyl derivative, N-benzoylphenylalanyl derivative, N-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, N-phthalimide, N-dithiasuccinimide (Dts), N-2,3-diphenylmaleimide, N-2,5-dimethylpyrrole, N-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, N-methylamine, N-allylamine, N-[2-(trimethylsilyl)ethoxy]methylamine (SEM), N-3-acetoxypropylamine, N-(1-isopropyl-4-nitro-2-oxo-3-pyroolin-3-yl)amine, quaternary ammonium salts, N-benzylamine, N-di(4-

methoxyphenyl)methylamine, N-5-dibenzosuberylamine, N-triphenylmethylamine (Tr), N-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), N-9-phenylfluorenylamine (PhF), N-2,7-dichloro-9-fluorenylmethyleneamine, N-ferrocenylmethylamino (Fcm), N-2-picolylamino N'-oxide, N-1,1-dimethylthiomethyleneamine, N-benzylideneamine, N-p-methoxybenzylideneamine, N-diphenylmethyleneamine, N-[(2-pyridyl)mesityl]methyleneamine, N-(N',N'-dimethylaminomethylene)amine, N,N'-isopropylidenediamine, N-p-nitrobenzylideneamine, N-salicylideneamine, N-5-chlorosalicylideneamine, N-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, N-cyclohexylideneamine, N-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, N-borane derivative, N-diphenylborinic acid derivative, N-[phenyl(pentaacylchromium- or tungsten)acyl]amine, N-copper chelate, N-zinc chelate, N-nitroamine, N-nitrosoamine, amine N-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, o-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys). In certain embodiments, a nitrogen protecting group is benzyl (Bn), tert-butyloxycarbonyl (BOC), carbobenzyloxy (Cbz), 9-flurenylmethyloxycarbonyl (Fmoc), trifluoroacetyl, triphenylmethyl, acetyl (Ac), benzoyl (Bz), p-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP), 2,2,2-trichloroethyloxycarbonyl (Troc), triphenylmethyl (Tr), tosyl (Ts), brosyl (Bs), nosyl (Ns), mesyl (Ms), triflyl (Tf), or dansyl (Ds).

[00148] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to herein as an "hydroxyl protecting group"). Oxygen protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[00149] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), t-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), p-

methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (p-AOM), guaiacolmethyl (GUM), t-butoxymethyl, 4-pentenyloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, t-butyl, allyl, p-chlorophenyl, p-methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn), p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, p-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl N-oxido, diphenylmethyl, p,p'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α-naphthyldiphenylmethyl, p-methoxyphenyldiphenylmethyl, di(p-methoxyphenyl)phenylmethyl, tri(p-methoxyphenyl)methyl, 4-(4'-bromophenacyloxyphenyl)diphenylmethyl, 4,4′,4″-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4′,4″-tris(levulinoyloxyphenyl)methyl, 4,4′,4″-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-yl)bis(4′,4″-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1′-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, benzisothiazolyl S,S-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, t-butyldimethylsilyl (TBDMS), t-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), t-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, p-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, t-butyl carbonate (BOC or Boc), p-

nitrophenyl carbonate, benzyl carbonate, p-methoxybenzyl carbonate, 3,4-dimethoxybenzyl carbonate, o-nitrobenzyl carbonate, p-nitrobenzyl carbonate, S-benzyl thiocarbonate, 4-ethoxy-1-napththyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, o-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (E)-2-methyl-2-butenoate, o-(methoxyacyl)benzoate, α-naphthoate, nitrate, alkyl N,N,N',N'-tetramethylphosphorodiamidate, alkyl N-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts). In certain embodiments, an oxygen protecting group is silyl. In certain embodiments, an oxygen protecting group is t-butyldiphenylsilyl (TBDPS), t-butyldimethylsilyl (TBDMS), triisoproylsilyl (TIPS), triphenylsilyl (TPS), triethylsilyl (TES), trimethylsilyl (TMS), triisopropylsiloxymethyl (TOM), acetyl (Ac), benzoyl (Bz), allyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-trimethylsilylethyl carbonate, methoxymethyl (MOM), 1-ethoxyethyl (EE), 2-methyoxy-2-propyl (MOP), 2,2,2-trichloroethoxyethyl, 2-methoxyethoxymethyl (MEM), 2-trimethylsilylethoxymethyl (SEM), methylthiomethyl (MTM), tetrahydropyranyl (THP), tetrahydrofuranyl (THF), p-methoxyphenyl (PMP), triphenylmethyl (Tr), methoxytrityl (MMT), dimethoxytrityl (DMT), allyl, p-methoxybenzyl (PMB), t-butyl, benzyl (Bn), allyl, or pivaloyl (Piv).

[00150] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a "thiol protecting group"). Sulfur protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference. In certain embodiments, a sulfur protecting group is acetamidomethyl, t-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl.

[00151] A "counterion" or "anionic counterion" is a negatively charged group associated with a positively charged group in order to maintain electronic neutrality. An anionic counterion may be monovalent (*i.e.*, including one formal negative charge). An anionic

counterion may also be multivalent (*i.e.*, including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (*e.g.*, F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HCO_3^-, HSO_4^-, sulfonate ions (*e.g.*, methansulfonate, trifluoromethanesulfonate, *p*–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), carboxylate ions (*e.g.*, acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like), BF_4^-, PF_4^-, PF_6^-, AsF_6^-, SbF_6^-, $B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$, $B(C_6F_5)_4^-$, BPh_4^-, $Al(OC(CF_3)_3)_4^-$, and carborane anions (*e.g.*, $CB_{11}H_{12}^-$ or $(HCB_{11}Me_5Br_6)^-$). Exemplary counterions which may be multivalent include CO_3^{2-}, HPO_4^{2-}, PO_4^{3-}, $B_4O_7^{2-}$, SO_4^{2-}, $S_2O_3^{2-}$, carboxylate anions (*e.g.*, tartrate, citrate, fumarate, maleate, malate, malonate, gluconate, succinate, glutarate, adipate, pimelate, suberate, azelate, sebacate, salicylate, phthalates, aspartate, glutamate, and the like), and carboranes.

[00152] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and Claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other definitions

[00153] The following definitions are more general terms used throughout the present application.

[00154] As used herein, the term "salt" refers to any and all salts, and encompasses pharmaceutically acceptable salts.

[00155] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and/or animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate,

ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}$ alkyl$)_4^-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[00156] The term "solvate" refers to forms of the compound, or a salt thereof, that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds described herein may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[00157] The term "hydrate" refers to a compound that is associated with water molecules. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x\ H_2O$, wherein R is the compound, and x is a number greater than 0. A given compound may form more than one type of hydrate, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \cdot 0.5\ H_2O$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2\ H_2O$) and hexahydrates ($R \cdot 6\ H_2O$)).

[00158] The term "tautomers" or "tautomeric" refers to two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a single bond, or vice versa). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

[00159] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

[00160] Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (−)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[00161] The term "polymorph" refers to a crystalline form of a compound (or a salt, hydrate, or solvate thereof). Many compounds can adopt a variety of different crystal forms (i.e., different polymorphs). Typically, such different crystalline forms have different X-ray diffraction patterns, infrared spectra, and/or can vary in some or all properties such as melting points, density, hardness, crystal shape, optical and electrical properties, stability, solubility, and bioavailability. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate a given preparation. Various polymorphs of a compound can be prepared by crystallization under different conditions.

[00162] The term "co-crystal" refers to a crystalline structure composed of at least two components. In certain embodiments, a co-crystal contains a compound of the present disclosure and one or more other component(s), including, but not limited to, atoms, ions, molecules, or solvent molecules. In certain embodiments, a co-crystal contains a compound of the present disclosure and one or more solvent molecules. In certain embodiments, a co-

crystal contains a compound of the present disclosure and one or more acid or base. In certain embodiments, a co-crystal contains a compound of the present disclosure and one or more components related to said compound, including, but not limited to, an isomer, tautomer, salt, solvate, hydrate, synthetic precursor, synthetic derivative, fragment, or impurity of said compound.

[00163] The term "prodrugs" refers to compounds that have cleavable groups that are removed, by solvolysis or under physiological conditions, to provide the compounds described herein, which are pharmaceutically active in vivo. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like. Other derivatives of the compounds described herein have activity in both their acid and acid derivative forms, but in the acid sensitive form often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides, and anhydrides derived from acidic groups pendant on the compounds described herein are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, C_{7-12} substituted aryl, and C_{7-12} arylalkyl esters of the compounds described herein may be preferred.

[00164] The terms "composition" and "formulation" are used interchangeably.

[00165] A "subject" to which administration is contemplated refers to a human (*i.e.*, male or female of any age group, *e.g.*, pediatric subject (*e.g.*, infant, child, or adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) or non-human animal. In certain embodiments, the non-human animal is a mammal (*e.g.*, primate (*e.g.*, cynomolgus monkey or rhesus monkey), commercially relevant mammal (*e.g.*, cattle, pig, horse, sheep, goat, cat, or dog), or bird (*e.g.*, commercially relevant bird, such as chicken, duck, goose, or turkey)). In certain embodiments, the non-human animal is a fish, reptile, or amphibian. The non-human animal may be a male or female at any stage of development. The non-human animal may be a transgenic animal or genetically engineered animal. The term "patient" refers to a human subject in need of treatment of a disease. The subject may also be a plant. In certain embodiments, the plant is a land plant. In certain embodiments, the plant is a non-vascular land plant. In certain embodiments, the plant is a vascular land plant. In certain

embodiments, the plant is a seed plant. In certain embodiments, the plant is a cultivated plant. In certain embodiments, the plant is a dicot. In certain embodiments, the plant is a monocot. In certain embodiments, the plant is a flowering plant. In some embodiments, the plant is a cereal plant, *e.g.*, maize, corn, wheat, rice, oat, barley, rye, or millet. In some embodiments, the plant is a legume, *e.g.*, a bean plant, *e.g.*, soybean plant. In some embodiments, the plant is a tree or shrub.

[00166] The term "biological sample" refers to any sample including tissue samples (such as tissue sections and needle biopsies of a tissue); cell samples (*e.g.*, cytological smears (such as Pap or blood smears) or samples of cells obtained by microdissection); samples of whole organisms (such as samples of yeasts or bacteria); or cell fractions, fragments or organelles (such as obtained by lysing cells and separating the components thereof by centrifugation or otherwise). Other examples of biological samples include blood, serum, urine, semen, fecal matter, cerebrospinal fluid, interstitial fluid, mucous, tears, sweat, pus, biopsied tissue (*e.g.*, obtained by a surgical biopsy or needle biopsy), nipple aspirates, milk, vaginal fluid, saliva, swabs (such as buccal swabs), or any material containing biomolecules that is derived from a first biological sample.

[00167] The term "administer," "administering," or "administration" refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound described herein, or a composition thereof, in or on a subject.

[00168] The terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*e.g.*, in light of a history of symptoms). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[00169] The terms "condition," "disease," and "disorder" are used interchangeably.

[00170] An "effective amount" of a compound described herein refers to an amount sufficient to elicit the desired biological response. An effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. In certain embodiments, an effective amount is a therapeutically effective amount. In certain embodiments, an effective amount is a

prophylactic treatment. For example, in treating cancer, an effective amount of an inventive composition may prevent tumor regrowth, reduce the tumor burden, or stop the growth or spread of a tumor. In certain embodiments, an effective amount is the amount of a compound described herein in a single dose. In certain embodiments, an effective amount is the combined amounts of a compound described herein in multiple doses.

[00171] A "therapeutically effective amount" of a compound described herein is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent. In certain embodiments, a therapeutically effective amount is an amount sufficient for HDAC6 inhibition (*e.g.*, at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% inhibition of the activity of HDAC6). In certain embodiments, a therapeutically effective amount is an amount sufficient for treating a disease or disorder (*e.g.*, neurological disorder, cancer). In certain embodiments, a therapeutically effective amount is an amount sufficient for HDAC6 inhibition and treating a disease or disorder (*e.g.*, neurological disorder, cancer).

[00172] A "prophylactically effective amount" of a compound described herein is an amount sufficient to prevent a condition, or one or more signs or symptoms associated with the condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent. In certain embodiments, a prophylactically effective amount is an amount sufficient for HDAC6 inhibition. In certain embodiments, a prophylactically effective amount is an amount sufficient for treating a disease or disorder (*e.g.*, neurological disorder, cancer). In certain embodiments, a prophylactically effective amount is an amount sufficient for HDAC6 inhibition and treating a disease or disorder (*e.g.*, neurological disorder, cancer).

[00173] As used herein, the term "inhibit" or "inhibition" in the context of enzymes, for example, in the context of HDAC6, refers to a reduction in the activity of the enzyme. In

some embodiments, the term refers to a reduction of the level of enzyme activity, *e.g.*, HDAC6 activity, to a level that is statistically significantly lower than an initial level, which may, for example, be a baseline level of enzyme activity. In some embodiments, the term refers to a reduction of the level of enzyme activity, *e.g.*, HDAC6 activity, to a level that is less than 75%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.1%, less than 0.01%, less than 0.001%, or less than 0.0001% of an initial level, which may, for example, be a baseline level of enzyme activity.

[00174] A "proliferative disease" refers to a disease that occurs due to abnormal growth or extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be associated with: 1) the pathological proliferation of normally quiescent cells; 2) the pathological migration of cells from their normal location (*e.g.*, metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes such as matrix metalloproteinases (*e.g.*, collagenases, gelatinases, and elastases); or 4) pathological angiogenesis as in proliferative retinopathy and tumor metastasis. Exemplary proliferative diseases include cancers (*i.e.*, "malignant neoplasms"), benign neoplasms, angiogenesis or diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases.

[00175] The terms "neoplasm" and "tumor" are used herein interchangeably and refer to an abnormal mass of tissue wherein the growth of the mass surpasses and is not coordinated with the growth of a normal tissue. A neoplasm or tumor may be "benign" or "malignant," depending on the following characteristics: degree of cellular differentiation (including morphology and functionality), rate of growth, local invasion, and metastasis. A "benign neoplasm" is generally well differentiated, has characteristically slower growth than a malignant neoplasm, and remains localized to the site of origin. In addition, a benign neoplasm does not have the capacity to infiltrate, invade, or metastasize to distant sites. Exemplary benign neoplasms include, but are not limited to, lipoma, chondroma, adenomas, acrochordon, senile angiomas, seborrheic keratoses, lentigos, and sebaceous hyperplasias. In some cases, certain "benign" tumors may later give rise to malignant neoplasms, which may result from additional genetic changes in a subpopulation of the tumor's neoplastic cells, and these tumors are referred to as "pre-malignant neoplasms." An example of a pre-malignant neoplasm is a teratoma. In contrast, a "malignant neoplasm" is generally poorly differentiated

(anaplasia) and has characteristically rapid growth accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue. Furthermore, a malignant neoplasm generally has the capacity to metastasize to distant sites.

[00176] The term "metastasis," "metastatic," or "metastasize" refers to the spread or migration of cancerous cells from a primary or original tumor to another organ or tissue and is typically identifiable by the presence of a "secondary tumor" or "secondary cell mass" of the tissue type of the primary or original tumor and not of that of the organ or tissue in which the secondary (metastatic) tumor is located. For example, a prostate cancer that has migrated to bone is said to be metastasized prostate cancer and includes cancerous prostate cancer cells growing in bone tissue.

[00177] The term "cancer" refers to a malignant neoplasm (*Stedman's Medical Dictionary*, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990). Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.*, cholangiocarcinoma); bladder cancer; breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (*e.g.*,meningioma, glioblastomas, glioma (*e.g.*, astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.*, cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.*, Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma); esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett's adenocarcinoma); Ewing's sarcoma; eye cancer (*e.g.*, intraocular melanoma, retinoblastoma); familiar hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.*, stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematological cancers (*e.g.*, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, diffuse large B-cell lymphoma (DLBCL)), follicular

lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.*, Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.*, cutaneous T-cell lymphoma (CTCL) (*e.g.*, mycosis fungiodes, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (*e.g.*, nephroblastoma a.k.a. Wilms' tumor, renal cell carcinoma); liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma); lung cancer (*e.g.*, bronchogenic carcinoma,small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (*e.g.*, systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) a.k.a. myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.*, bone cancer); ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.*, pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.*, Pagive the's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (*e.g.*, prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (*e.g.*, appendix cancer); soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH),

liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma; testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma); thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (*e.g.*, Pagive the's disease of the vulva).

[00178] The term "immunotherapy" refers to a therapeutic agent that promotes the treatment of disease by inducing, enhancing, or suppressing an immune response. Immunotherapies designed to elicit or amplify an immune response are classified as activation immunotherapies, while immunotherapies that reduce or suppress are classified as suppression immunotherapies. Immunotherapies are typically, but not always, biotherapeutic agents. Numerous immunotherapies are used to treat cancer. These include, but are not limited to, monoclonal antibodies, adoptive cell transfer, cytokines, chemokines, vaccines, and small molecule inhibitors.

[00179] The terms "biologic," "biologic drug," and "biological product" refer to a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, nucleic acids, and proteins. Biologics may include sugars, proteins, or nucleic acids, or complex combinations of these substances, or may be living entities, such as cells and tissues. Biologics may be isolated from a variety of natural sources (*e.g.*, human, animal, microorganism) and may be produced by biotechnological methods and other technologies.

[00180] The term "small molecule" or "small molecule therapeutic" refers to molecules, whether naturally occurring or artificially created (*e.g.*, via chemical synthesis) that have a relatively low molecular weight. Typically, a small molecule is an organic compound (*i.e.*, it contains carbon). The small molecule may contain multiple carbon-carbon bonds, stereocenters, and other functional groups (*e.g.*, amines, hydroxyl, carbonyls, and heterocyclic rings, etc.). In certain embodiments, the molecular weight of a small molecule is not more than about 1,000 g/mol, not more than about 900 g/mol, not more than about 800 g/mol, not more than about 700 g/mol, not more than about 600 g/mol, not more than about 500 g/mol, not more than about 400 g/mol, not more than about 300 g/mol, not more than about 200 g/mol, or not more than about 100 g/mol. In certain embodiments, the molecular weight of a small molecule is at least about 100 g/mol, at least about 200 g/mol, at least about 300 g/mol, at least about 400 g/mol, at least about 500 g/mol, at least about 600 g/mol, at least about 700 g/mol, at least about 800 g/mol, or at least about 900 g/mol, or at least about

1,000 g/mol. Combinations of the above ranges (*e.g.*, at least about 200 g/mol and not more than about 500 g/mol) are also possible. In certain embodiments, the small molecule is a therapeutically active agent such as a drug (*e.g.*, a molecule approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (C.F.R.)). The small molecule may also be complexed with one or more metal atoms and/or metal ions. In this instance, the small molecule is also referred to as a "small organometallic molecule." Preferred small molecules are biologically active in that they produce a biological effect in animals, preferably mammals, more preferably humans. Small molecules include, but are not limited to, radionuclides and imaging agents. In certain embodiments, the small molecule is a drug. Preferably, though not necessarily, the drug is one that has already been deemed safe and effective for use in humans or animals by the appropriate governmental agency or regulatory body. For example, drugs approved for human use are listed by the FDA under 21 C.F.R. §§ 330.5, 331 through 361, and 440 through 460, incorporated herein by reference; drugs for veterinary use are listed by the FDA under 21 C.F.R. §§ 500 through 589, incorporated herein by reference. All listed drugs are considered acceptable for use in accordance with the present invention.

[00181] The term "therapeutic agent" refers to any substance having therapeutic properties that produce a desired, usually beneficial, effect. For example, therapeutic agents may treat, ameliorate, and/or prevent disease. Therapeutic agents, as disclosed herein, may be biologics or small molecule therapeutics, or combinations thereof.

[00182] The term "chemotherapeutic agent" refers to a therapeutic agent known to be of use in chemotherapy for cancer.

[00183] A "hematological cancer" includes a cancer which affects a hematopoietic cell or tissue. Hematological cancers include cancers associated with aberrant hematological content and/or function. Examples of hematological cancers include, but are nor limited to, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL)), lymphoma such as Hodgkin's lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL), non-Hodgkin's lymphoma (NHL) (*e.g.*, diffuse large B-cell lymphoma (DLBCL)), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma,

lymphoplasmacytic lymphoma (*i.e.*, Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, primary central nervous system (CNS) lymphoma, T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.*, cutaneous T-cell lymphoma (CTCL) (*e.g.*, mycosis fungiodes, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma), a mixture of one or more leukemia/lymphoma as described above, multiple myeloma, heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease) acute non-lymphocytic leukemia (ANLL), acute promyelocytic leukemia (APL), acute myelomonocytic leukemia (AMMoL), polycythemia vera, Wilm's tumor, and Ewing's sarcoma.

[00184] The term "heteroimmune disease" refers to a state in which an immune response to an exogenous antigen (*e.g.*, drug, pathogen) results in immunopathological changes. The immune response is triggered by an antigen from a different species (heteroimmune), thus it differs from an infectious disease because the emphasis is on the immune response, not the foreign species (infectious pathogen) causing the disease.

EXAMPLES

[00185] In order that the invention described herein may be more fully understood, the following examples are set forth. The examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

Synthetic Methods

[00186] Compounds disclosed herein were prepared following the synthetic schemes and procedures described in detail below. The examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope. Compounds of the disclosure that are not explicitly described in the following procedures may be prepared by analogous methods. Those having ordinary skill in the art would understand how to make such compounds from the disclosure provided herein and by means known in the art of organic synthesis. For example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups

in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and subsequent editions thereof are representative and instructive. Methods for optimizing reaction conditions, if necessary minimizing competing by products, are known in the art.

[00187] General details. All oxygen and/or moisture-sensitive reactions were carried out under nitrogen (N_2) atmosphere in glassware that had been flame-dried under vacuum (approximately 0.5 mm Hg) and purged with N_2 prior to use. All reagents and solvents were purchased from commercial vendors and used as received or synthesized according to methods already reported. NMR spectra were recorded on a Bruker 300 (300 MHz ^{1}H, 75 MHz ^{13}C) or Varian UNITY INOVA 500 (500 MHz ^{1}H, 125 MHz ^{13}C) spectrometer. Proton and carbon chemical shifts are reported in ppm (δ) referenced to the NMR solvent. Data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz). Unless otherwise indicated, NMR data were collected at 25 °C. Flash chromatography was performed using 40-60 μm Silica Gel (60 Å mesh) on a Teledyne Isco Combiflash R_f. Tandem Liquid Chromatography/Mass Spectrometry (LC/MS) was performed on a Waters 2795 separations module and 3100 mass detector. Analytical thin layer chromatography (TLC) was performed on EM Reagent 0.25 mm silica gel 60-F plates.

[00188] LCMS_Condition_01: Column: X-Bridge BEH C-18 (3.0X50 mm, 2.5 μm), Mobile Phase: A-0.025% FA in Water, Mobile Phase: B-ACN, Flow Rate: 1.2 mL/min (Gradient).

[00189] LCMS Condition_02: Column: X-Select CSH C-18 (150 X 4.6 mm, 3.5 μm), Mobile Phase: A-0.025% Aq FORMIC ACID, Mobile Phase: B-ACN, Flow Rate: 1.0 mL/min (Gradient).

[00190] HPCL_Condition_01: Column: XSELECT CSH C18 (150 X 4.6mm, 3.5μ), Mobile Phase-A: 0.05% TFA: ACETONITRILE (95:05), Mobile Phase-B: ACETONITRILE: 0.05% TFA (95:05), Flow: 1.0 mL/min, Diluent: ACN: Water.

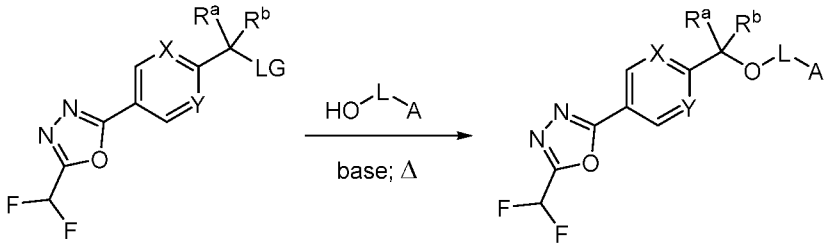
[00191] HPLC_Condition_02: Column: XSELECT CSH C18 (150 X 4.6mm, 3.5μ), Mobile Phase-A: 5mM Ammonium acetate, Mobile Phase- ACN, Flow: 1.0 mL/min, Diluent: ACN: Water.

[00192] Reverse phase PREP Purification methods: Preparative Column X-SELECT (250*30mm), 5u Mobile Phase A 10mm ABC in Water Mobile Phase B ACN Flow rate 25

mL, Instrument ID Prep-14 Gradient (Time/%B) 0/10, 3/10, 10/25, 20/40, 30/55, 40/60, 50/75, 60/95.

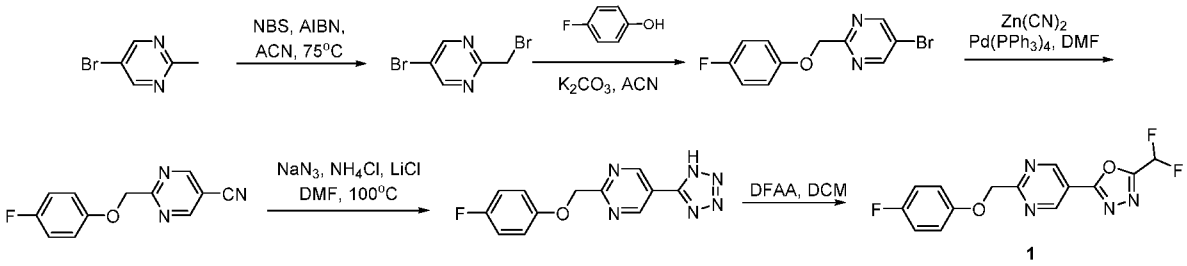
[00193] Compounds (1) – (15) were prepared following the synthetic schemes and procedures are described in detail below.

General Scheme –



[00194] In general, compounds can be prepared via nucleophilic displacement of a leaving group (LG) in the presence of a base (e.g., K_2CO_3 or Ag_2CO_3) at a temperature above room temperature. Other synthetic strategies may be employed according to the syntheses described below. Synthesis of the disclosed compounds employ reaction methods known to one of ordinary skill in the art.

2-(Difluoromethyl)-5-(2-((4-fluorophenoxy)methyl)pyrimidin-5-yl)-1,3,4-oxadiazole (Compound **1**)



[00195] Step-1: 5-Bromo-2-(bromomethyl)pyrimidine: To a stirred solution of 5-bromo-2-methylpyrimidine (5.0 g, 2.89 mmol) in ACN (500 mL) was added portion wise NBS (6.4 g, 3.61 mmol) for 15-20 mins at 0 °C, followed by AIBN (0.76 g, 0.29 mmol) at room temperature. The reaction mixture was stirred at same temperature for 30 mins, then heated at 75 °C for 48 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water (100 mL) and extracted with DCM (200 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give a light brown thick crude product. The crude product was purified by using 100-200 mesh silica gel column

chromatography by eluting with 0-50% DCM in hexane to give the product (1.5 g, 20% yield) as light brown solid.

[00196] Step-2: 5-Bromo-2-((4-fluorophenoxy)methyl)pyrimidine: To a stirred solution of 5-bromo-2-(bromomethyl)pyrimidine (0.7 g, 2.78 mmol) and 4-fluorophenol (0.374 g, 3.34 mmol) in acetonitrile (10 mL) was added K_2CO_3 (1.15 g, 8.34 mmol) and the reaction mixture was stirred at 80 °C for 12 hours. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-30% ethyl acetate in hexane to give the product (0.7 g, 89% yield) as an off white solid.

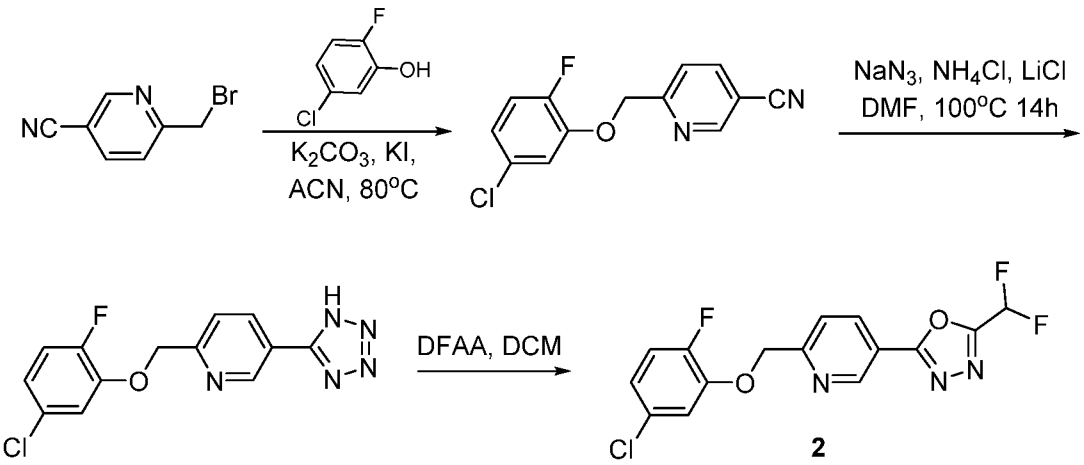
[00197] Step-3: 2-((4-Fluorophenoxy)methyl)pyrimidine-5-carbonitrile: To a stirred solution of 5-bromo-2-((4-fluorophenoxy)methyl)pyrimidine (0.5 g, 1.77 mmol) in DMF (20 mL), was added $Zn(CN)_2$ (0.622 g, 5.31 mmol) at RT, the reaction mixture was purged with argon for 30 mins and was added $Pd(PPh_3)_4$ (0.2 g, 0.177 mmol) and again it was purged with argon for 10 mins. The reaction mixture was stirred at 100 °C for 12h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite and the filtrate was concentrated to give the crude product. The crude product was purified by using 230-400 mesh silica gel column chromatography by eluting with 0-20% ethyl acetate in hexane to give the product (0.25 g, 61.75% yield) as an off white solid. LC-MS: m/z 248.8 $[M-H]^-$.

[00198] Step-4: 2-((4-Fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyrimidine: To a stirred solution of 2-((4-fluorophenoxy)methyl)pyrimidine-5-carbonitrile (0.25 g, 1.09 mmol) in DMF (20 mL) was added sodium azide (0.212 g, 3.27 mmol), NH_4Cl (0.176 g, 3.27 mmol) and LiCl (0.045 g, 1.09 mmol) at room temperature and the reaction mixture was stirred at 100 °C for 12h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl and the precipitated solid was filtered and dried to give the product (0.25 g, 84.45% yield) as an off white solid. LC-MS: m/z 273.0 $[M+H]^+$.

[00199] Step-5: 2-(Difluoromethyl)-5-(2-((4-fluorophenoxy)methyl)pyrimidin-5-yl)-1,3,4-oxadiazole (**1**): To a stirred solution of 2-((4-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyrimidine (0.25 g, 0.92 mmol) in DCM (25 mL) was added difluoro acetic anhydride (0.4 mL, 3.67 mmol) at 0°C and the reaction mixture was stirred at RT for 12h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL) and extracted with DCM (100 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was

purified by using 230-400 mesh silica gel column chromatography by eluting with 30% ethyl acetate in hexane to give the product (0.11 g, 37.28% yield) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.44 (s, 2H), 7.77 - 7.43 (m, 1H), 7.16 - 7.07 (m, 2H), 7.07 - 6.98 (m, 2H), 5.42 (s, 2H);^{19}F NMR (400 MHz, DMSO-*d$_6$*): -120, -123. LC-MS: m/z 323.00 $[M+H]^+$

2-(6-((5-Chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Compound **2**)



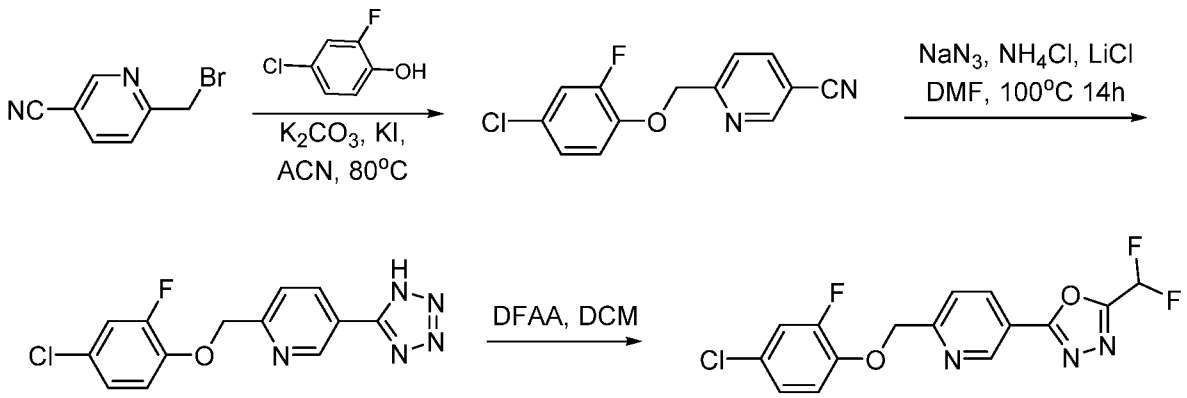
[00200] Step-1: 6-((5-Chloro-2-fluorophenoxy)methyl)nicotinonitrile: To a stirred solution of 6-(bromomethyl)nicotinonitrile (0.5 g, 2.55 mmol) and 2-fluoro-5-chlorophenol (0.521 g, 3.57 mmol) in acetonitrile (10 mL), K_2CO_3 (0.528 g, 3.72 mmol) and KI (0.083 g, 0.51 mmol) were added and the reaction mixture was stirred at 80°C for 12 hours. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite bed and filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-10% ethyl acetate in hexane to give the product (0.600 g, 89.82% yield) as an off white solid. LC-MS: m/z 263.00 $[M+H]^+$.

[00201] Step-2: 2-((5-Chloro-2-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine: To a stirred solution of 6-((5-chloro-2-fluorophenoxy)methyl)nicotinonitrile (0.6 g, 2.29 mmol) in DMF (10 mL), sodium azide (0.744 g, 11.4 mmol), NH_4Cl (0.6 g, 11.4 mmol) and LiCl (0.060 g) were added and the reaction mixture was stirred at 100°C for 16h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl, extracted with ethyl acetate (2 X 50 mL). The organic layer was dried over sodium sulphate and concentrated to give the crude product. The

crude product was washed with hexane (2 x 10 mL) to give the product (0.65 g, 92.85% yield) as an off white solid. LC-MS: m/z 306.00 $[M+H]^+$.

[00202] Step-3: 2-(6-((5-Chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (**2**): To a stirred solution of 2-((5-chloro-2-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine (0.350 g, 1.14 mmol) in DCM (15 mL) at 0°C, difluoroacetic anhydride (0.4 mL, 3.42 mmol) was added and the reaction mixture was stirred at RT for 16 hours. After completion of reaction (monitored by TLC), the reaction mixture was diluted with DCM (20 mL) and basified with saturated sodium bicarbonate solution and extracted with DCM (50 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-10% ethyl acetate in hexane to give the product (0.170 g, 41.76% yield) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, J = 2.0 Hz, 1H), 8.56 - 8.49 (m, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.74 - 7.45 (m, 2H), 7.45 - 7.39 (m, 1H), 7.10 - 7.02 (m, 1H), 5.44 (s, 2H); ^{19}F NMR (400 MHz, DMSO-d_6) δ -121, -138; LC-MS: m/z 356.00 [M+H]+

2-(6-((4-Chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Compound **3**)



3

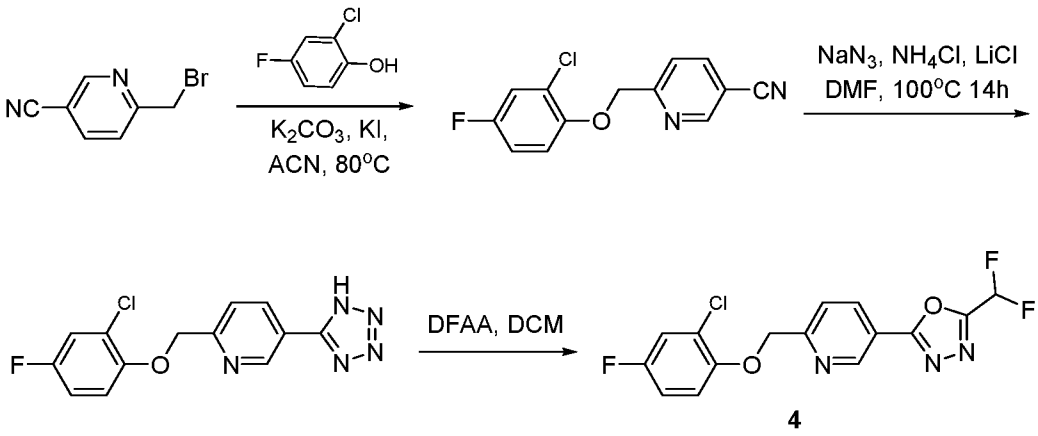
[00203] Step-1: 6-((4-Chloro-2-fluorophenoxy)methyl)nicotinonitrile: To a stirred solution of 6-(bromomethyl)nicotinonitrile (0.5 g, 2.55 mmol) and 2-fluoro-4-chlorophenol (0.521 g, 3.57 mmol) in acetonitrile (10 mL), K_2CO_3 (0.528 g, 3.82 mmol) and KI (0.084 g, 0.51 mmol) were added and the reaction mixture was stirred at 80°C for 12 hours. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite bed and filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting

with 0-10% ethyl acetate in hexane to give the product (0.400 g, 59.88% yield) as an off white solid. LC-MS: m/z 262.8 $[M+H]^+$.

[00204] Step-2: 2-((4-chloro-2-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine: To a stirred solution of 6-((4-chloro-2-fluorophenoxy)methyl)nicotinonitrile (0.4 g, 1.52 mmol) in DMF (10 mL), sodium azide (0.297 g, 4.58 mmol), NH_4Cl (0.247 g, 4.58 mmol) and LiCl (0.064 g, 1.52 mmol) were added, and the reaction mixture was stirred at 100°C for 16h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl, extracted with ethyl acetate (2 X 50 mL). The organic layer was dried over sodium sulphate and concentrated to give the crude product. The crude product was washed with hexane (2 x 10 mL) to give the product (0.300 g, 64.51% yield) as light brown liquid. LC-MS: m/z 306.05 $[M+H]^+$.

[00205] Step-3: 2-(6-((4-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (**3**): To a stirred solution of 2-((4-chloro-2-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine (0.300 g, 0.98 mmol) in DCM (10 mL) at 0°C, difluoro acetic anhydride (0.342 g, 1.96 mmol) was added and the reaction mixture was stirred at RT for 15 hours. After completion of reaction (monitored by TLC), the reaction mixture was diluted with DCM (20 mL) and basified with saturated sodium bicarbonate solution and extracted with ethyl acetate (50 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-20% ethyl acetate in hexane to give the product (0.120 g, 34.38% yield) as an off white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.23 (d, J = 2.0 Hz, 1H), 8.51 (dd, J = 2.4, 8.3 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.73 - 7.44 (m, 2H), 7.30 (t, J = 9.0 Hz, 1H), 7.26 - 7.20 (m, 1H), 5.41 (s, 2H); LC-MS: m/z 355.9 [M+H]+

2-(6-((2-Chloro-4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Compound **4**)



4

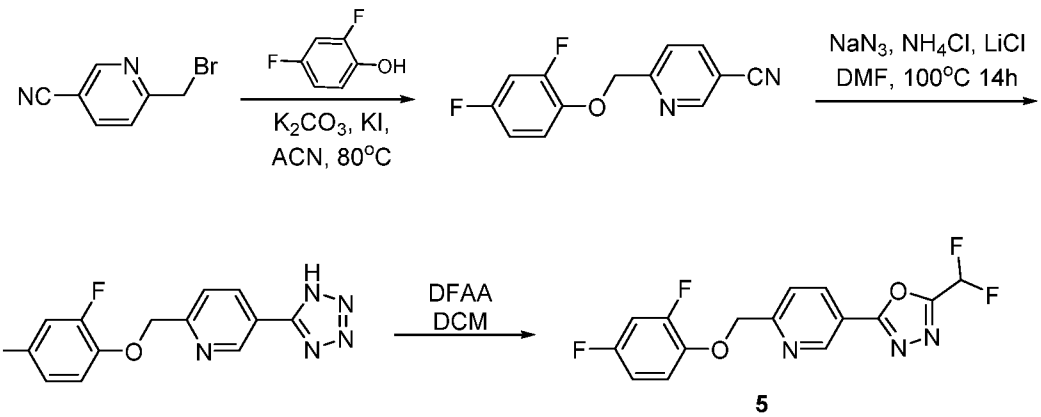
[00206] Step-1: 6-((2-Chloro-4-fluorophenoxy)methyl)nicotinonitrile: To a stirred solution of 6-(bromomethyl)nicotinonitrile (0.5 g, 2.55 mmol) and 2-chloro-4-fluorophenol (0.524 g, 3.57 mmol) in acetonitrile (10 mL), K_2CO_3 (0.520 g, 3.72 mmol) and KI (0.083 g, 0.51 mmol) were added, and the reaction mixture was stirred at 80°C for 12 hours. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite bed and filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-10% ethyl acetate in hexane to give the product (0.35 g, 52.39% yield) as an off white solid. LC-MS: m/z 262.9 $[M+H]^+$

[00207] Step-2: 2-((2-Chloro-4-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine: To a stirred solution of 6-((2-chloro-4-fluorophenoxy)methyl)nicotinonitrile (0.35 g, 1.33 mmol) in DMF (10 mL), sodium azide (0.434 g, 6.67 mmol), NH_4Cl (0.35 g, 6.67 mmol) and LiCl (0.035 g, 1.33 mmol) were added, and the reaction mixture was stirred at 100°C for 16h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl, solid precipitated out was filtered and was dried to give the product (0.370 g, 90.68% yield) as an off white solid. LC-MS: m/z 306.05 $[M+H]^+$

[00208] Step-3: 2-(6-((2-Chloro-4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (**4**): To a stirred solution of 2-((2-chloro-4-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine (0.37 g, 1.21 mmol) in DCM (10 mL) at 0°C, difluoro acetic anhydride (0.43 mL, 3.63 mmol) was added and the reaction mixture was stirred at RT for 15 hours. After completion of reaction (monitored by TLC), the reaction mixture was diluted with DCM (20 mL) and washed with water (20 mL). The organic layer was dried over sodium

sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-20% ethyl acetate in hexane to give the product (0.160 g, 37.20% yield) as an off white solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (d, J = 2.0 Hz, 1H), 8.63 - 8.44 (m, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.73 - 7.44 (m, 2H), 7.33 - 7.25 (m, 1H), 7.21 (dt, J = 2.9, 8.6 Hz, 1H), 5.41 (s, 2H). ^{19}F NMR (400 MHz, DMSO-d_6) δ -121. LC-MS: m/z 356.05 [M+H]+

2-(Difluoromethyl)-5-(6-((2,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (Compound **5**)



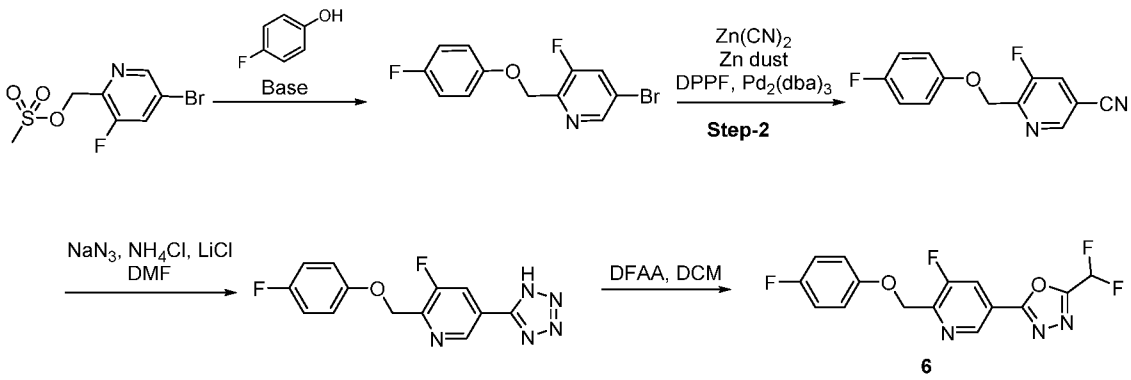
5

[00209] Step-1: 6-((2,4-Difluorophenoxy)methyl)nicotinonitrile: To a stirred solution of 6-(bromomethyl)nicotinonitrile (0.5 g, 2.55 mmol) and 2,4-difluorophenol (0.455 g, 3.57 mmol) in acetonitrile (10 mL), K_2CO_3 (0.520 g, 3.72 mmol) and KI (0.083 g, 0.51 mmol) were added, and the reaction mixture was stirred at 80°C for 12 hours. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite bed and filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by using 230-400 mesh silica gel column chromatography by eluting with 0-30% ethyl acetate in hexane to give the product (0.474 g, 76.82% yield) as an off white solid. LC-MS: m/z 246.9 $[M+H]^+$.

[00210] Step-2: 2-((2,4-Difluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine: To a stirred solution of 6-((2,4-difluorophenoxy)methyl)nicotinonitrile (0.4 g, 1.65 mmol) in DMF (10 mL), sodium azide (0.573 g, 8.26 mmol), NH_4Cl (0.438 g, 8.26 mmol) and LiCl (0.040 g, 1.65 mmol) were added and the reaction mixture was stirred at 100°C for 16h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl, solid precipitated out was filtered and was dried to give the product (0.429 g, 89.93% yield) as an off white solid. LC-MS: m/z 289.9 $[M+H]^+$.

[00211] Step-3: 2-(Difluoromethyl)-5-(6-((2,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (**5**): To a stirred solution of 2-((2,4-difluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine (0.4 g, 1.38 mmol) in DCM (10 mL) at 0°C, difluoro acetic anhydride (0.484 g, 2.76 mmol) was added and the reaction mixture was stirred at RT for 14 hours. After completion of reaction (monitored by TLC), the reaction mixture was diluted with DCM (20 mL) and washed with water (20 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 230-400 mesh silica gel column chromatography by eluting with 0-30% ethyl acetate in hexane to give the product (0.100 g, 21.32% yield) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.23 (d, *J* = 2.0 Hz, 1H), 8.51 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.82 - 7.74 (m, 1H), 7.72 - 7.43 (m, 1H), 7.42 - 7.24 (m, 2H), 7.10 - 6.97 (m, 1H), 5.38 (s, 2H); ^{19}F NMR (400 MHz, DMSO-*d*$_6$) *δ:* -119, -121, -130. LC-MS: m/z 340.00 [M+H]+

2-(Difluoromethyl)-5-(5-fluoro-6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (Compound **6**)



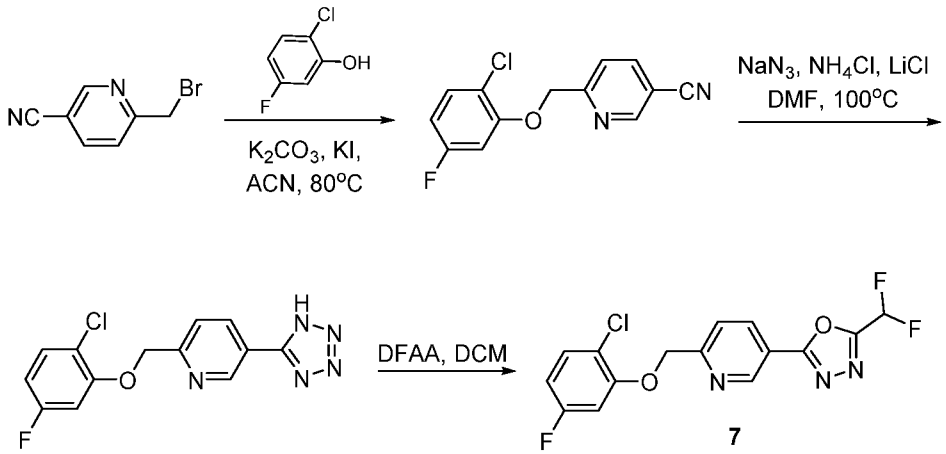
[00212] Step-1: 5-Bromo-3-fluoro-2-((4-fluorophenoxy)methyl)pyridine: To a stirred solution of (5-bromo-3-fluoropyridin-2-yl)methyl methanesulfonate (0.5 g, 1.76 mmol) in DMF (7 mL), was added NaH (0.063 g, 2.64 mmol) at 0°C, then stirred it for 5min at 0°C. 4-Fluorophenol (0.197 g, 1.76 mmol) dissolved in DMF (2 mL) was slowly added at 0°C. Then the reaction mixture was stirred at room temperature for 45mins. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water (100 mL) and extracted with ethyl acetate (150 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-10% ethyl acetate in hexane to give the product (0.4 g, 76.05% yield) as an off white solid. LC-MS: m/z 299.8 [M+H]+.

[00213] Step-2: 5-fluoro-6-((4-fluorophenoxy)methyl)nicotinonitrile: To a stirred solution of 5-bromo-3-fluoro-2-((4-fluorophenoxy)methyl)pyridine (0.4 g, 1.36 mmol) in DMA (10 mL), was added $Zn(CN)_2$ (0.393 g, 3.40 mmol) and Zn dust (0.061 g, 0.95 mmol) at RT, the reaction mixture was purged with argon for 45 mins and the $Pd_2(dba)_3$ (0.138 g, 0.13 mmol) and dppf (0.222 g, 0.40 mmol) was added and again it was purged with argon for 20 mins. The reaction mixture was stirred at 100°C for 16h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite and the filtrated was diluted with ethyl acetate (100 mL) and washed with water (2 x 50 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-25% ethyl acetate in hexane to give the product (0.2 g, 60.79% yield) as a brown sticky solid. LC-MS: m/z 246.8 [M+H]+.

[00214] Step-3: 3-fluoro-2-((4-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine: To a stirred solution of 5-fluoro-6-((4-fluorophenoxy)methyl)nicotinonitrile (0.2 g, 0.81 mmol) in DMF (10 mL), sodium azide (0.264 g, 4.06 mmol), NH_4Cl (0.22 g, 4.06 mmol) and LiCl (0.060 g, 0.81 mmol) were added and the reaction mixture was stirred at 100°C for 16h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl and extracted with ethyl acetate (2 x 50 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the product (0.21 g, 89.36% yield) as a brown sticky solid which was used as such for further step.

[00215] Step-4: 2-(difluoromethyl)-5-(5-fluoro-6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (**6**): To a stirred solution of 3-fluoro-2-((4-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine (0.21 g, 0.73 mmol) in DCM (10 mL) was added difluoro acetic anhydride (0.253 g, 1.5 mmol) at 0 °C. The reaction mixture was stirred at RT for 16 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL) and extracted with DCM (100 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 30% ethyl acetate in hexane to give the product (60 mg, 24.39% yield) as light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H), 8.46 (dd, J = 1.5, 10.3 Hz, 1H), 7.77 - 7.41 (m, 1H), 7.17 - 7.11 (m, 2H), 7.11 - 7.05 (m, 2H), 5.33 (s, 2H); ^{19}F NMR (400 MHz, DMSO-d_6): δ -122. LC-MS: m/z 340.05 [M+H]+

2-(6-((2-Chloro-5-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Compound **7**)



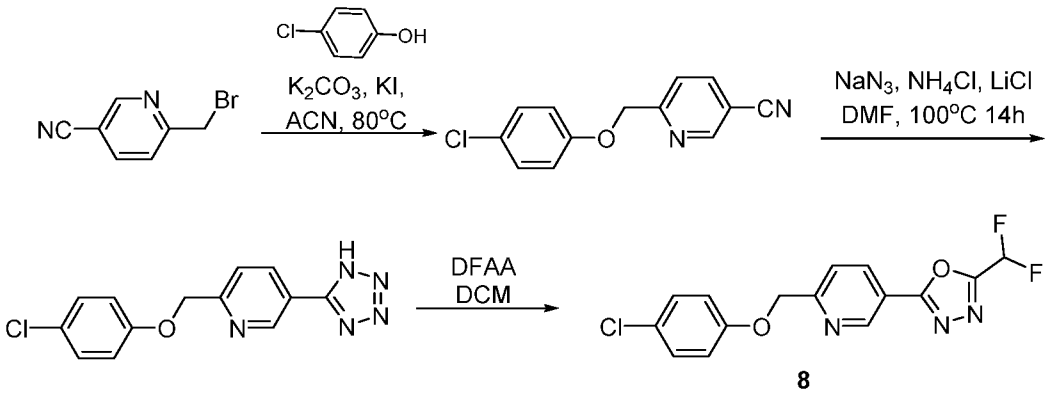
[00216] Step-1: 6-((2-Chloro-5-fluorophenoxy)methyl)nicotinonitrile: To a stirred solution of 6-(bromomethyl)nicotinonitrile (0.5 g, 2.55 mmol) and 2-chloro-5-fluorophenol (0.521 g, 3.57 mmol) in acetonitrile (10 mL), K_2CO_3 (0.528 g, 3.72 mmol) and KI (0.083 g, 0.51 mmol) were added, and the reaction mixture was stirred at 80°C for 16 hours. After completion of reaction (monitored by TLC), the reaction mixture was quenched with ice cold water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-10% ethyl acetate in hexane to give the product (0.5 g, 74.85% yield) as an off white solid. LC-MS: m/z 263.05 $[M+H]^+$.

[00217] Step-2: 2-((2-Chloro-5-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine: To a stirred solution of 6-((2-chloro-5-fluorophenoxy)methyl)nicotinonitrile (0.9 g, 1.91 mmol) in DMF (15 mL), sodium azide (0.62 g, 9.59 mmol), NH_4Cl (0.513 g, 9.59 mmol) and LiCl (0.050 g) were added, and the reaction mixture was stirred at 100°C for 16h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl, the precipitated solid was filtered and washed with ice cold water and hexane. The product was dried under reduced pressure to give the product (0.45 g, 77.18% yield) as an off white solid. LC-MS: m/z 306.0 $[M+H]^+$.

[00218] Step-3: 2-(6-((2-Chloro-5-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazolee (**7**): To a stirred solution of 2-((2-chloro-5-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine (0.3 g, 0.98 mmol) in DCM (9 mL) at 0°C, difluoro acetic anhydride (0.34 mL, 2.94 mmol) was added and the reaction mixture was stirred at RT for 16h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with ice cold

water (20 mL) and extracted with DCM (50 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-30% ethyl acetate in hexane to give the product (0.160 g, 45.84% yield) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, J = 2.0 Hz, 1H), 8.54 (dd, J = 2.0, 8.3 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.73 - 7.43 (m, 2H), 7.36 - 7.17 (m, 1H), 6.89 (dt, J = 2.9, 8.6 Hz, 1H), 5.44 (s, 2H); ^{19}F NMR (400 MHz, DMSO-d_6) δ -112, -120; LC-MS: m/z 355.9 [M+H]+

2-(6-((4-Chlorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Compound **8**)



8

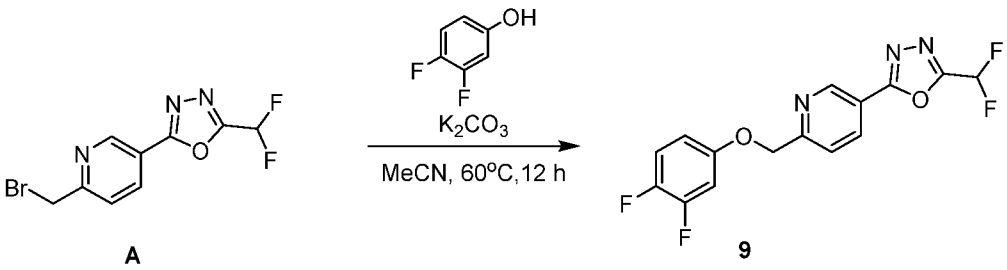
[00219] Step-1: 6-((4-Chlorophenoxy)methyl)nicotinonitrile: To a stirred solution of 6-(bromomethyl)nicotinonitrile (0.5 g, 2.55 mmol) and 4-chlorphenol (0.393 g, 3.06 mmol) in acetonitrile (20 mL), K_2CO_3 (0.528 g, 3.82 mmol) and KI (0.084 g, 0.51 mmol) were added, and the reaction mixture was stirred at 80°C for 12 hours. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite bed and filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by using 230-400 mesh silica gel column chromatography by eluting with 0-30% ethyl acetate in hexane to give the product (0.4 g, 64.3% yield) as an off white solid. LC-MS: m/z 244.9$[M+H]^+$.

[00220] Step-2: 2-((4-Chlorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine: To a stirred solution of 6-((4-chlorophenoxy)methyl)nicotinonitrile (0.4 g, 1.63 mmol) in DMF (20 mL), sodium azide (0.319 g, 4.91 mmol), NH_4Cl (0.265 g, 4.91 mmol) and LiCl (0.068 g, 1.63 mmol) were added and the reaction mixture was stirred at 100°C for 12h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure

and was acidified with 6N HCl, solid precipitated out was filtered and was dried to give the product (0.3 g, 63.82% yield) as an off white solid. LC-MS: m/z 287.95 $[M+H]^+$.

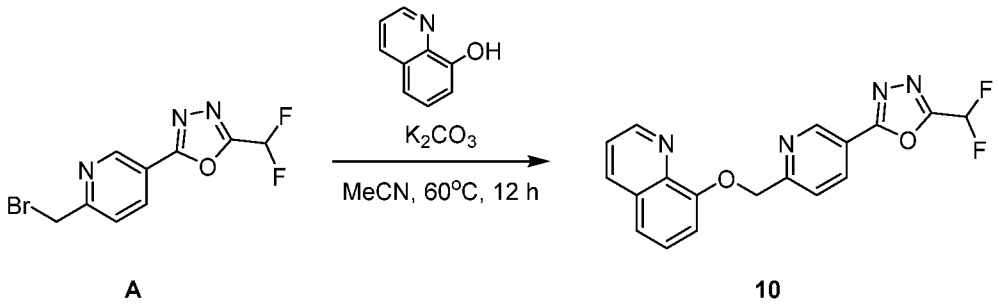
[00221] Step-3: 2-(6-((4-Chlorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (**8**): To a stirred solution of 2-((4-chlorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine (0.3 g, 1.04 mmol) in DCM (20 mL) at 0°C, difluoro acetic anhydride (0.45 mL, 4.18 mmol) was added and the reaction mixture was stirred at RT for 12 hours. After completion of reaction (monitored by TLC), the reaction mixture was diluted with DCM (20 mL) and washed with water (20 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 230-400 mesh silica gel column chromatography by eluting with 0-30% ethyl acetate in hexane to give the product (0.070 g, 19.88% yield) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 - 9.14 (m, 1H), 8.48 (dd, J = 2.2, 8.1 Hz, 1H), 7.77 (br d, J = 7.8 Hz, 1H), 7.73 - 7.43 (m, 1H), 7.43 - 7.29 (m, 2H), 7.09 (br d, J = 8.8 Hz, 2H), 5.32 (s, 2H); ^{19}F NMR (400 MHz, DMSO-d_6) δ -122; LC-MS: m/z 338.05 $[M+H]^+$

2-(Difluoromethyl)-5-[6-[(3,4-difluorophenoxy)methyl]-3-pyridyl]-1,3,4-oxadiazole (Compound **9**)



[00222] To a solution of 2-[6-(bromomethyl)-3-pyridyl]-5-(difluoromethyl)-1,3,4-oxadiazole (500 mg, 1.72 mmol, 1 *eq*) and 3,4-difluorophenol (224.25 mg, 1.72 mmol, 1 *eq*) in MeCN (8 mL) was added K_2CO_3 (476.47 mg, 3.45 mmol, 2 *eq*) at 25 °C. The mixture was stirred at 60 °C for 12 hr. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (neutral) to obtain 2-(difluoromethyl)-5-[6-[(3,4-difluorophenoxy)methyl]-3-pyridyl]-1,3,4-oxadiazole (165.39 mg, 486.50 umol, 28.22% yield, 99.8% purity) as an off-white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.28 (d, J = 1.8 Hz, 1H), 8.55 (dd, J = 2.3, 8.3 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.28 - 7.14 (m, 2H), 7.04 (ddd, J = 3.1, 6.6, 12.2 Hz, 1H), 6.89 - 6.84 (m, 1H), 5.30 (s, 2H). MS(ESI): 319.2$[M+H]^+$.

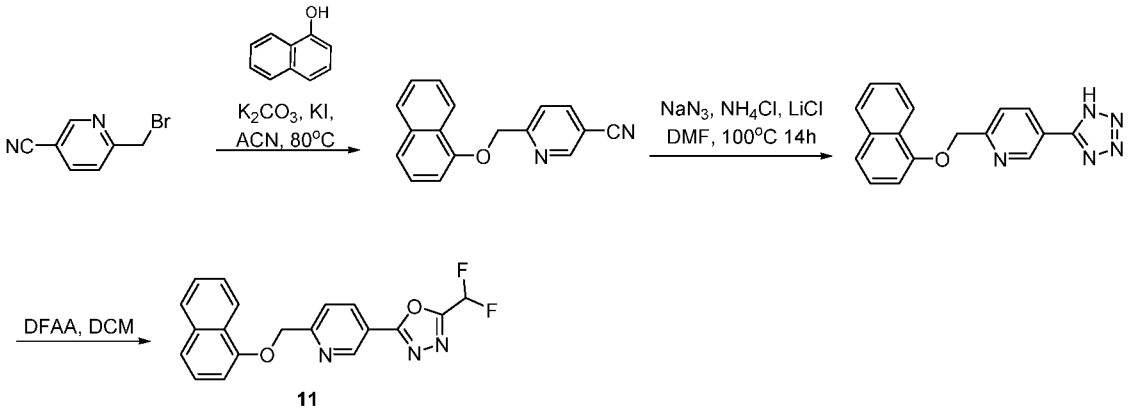
2-(Difluoromethyl)-5-[6-(8-quinolyloxymethyl)-3-pyridyl]-1,3,4-oxadiazole (Compound **10**)



A 10

[00223] To a solution of 2-[6-(bromomethyl)-3-pyridyl]-5-(difluoromethyl)-1,3,4-oxadiazole (150 mg, 517.13 umol, 1 *eq*) and quinolin-8-ol (75.07 mg, 517.13 umol, 89.36 µL, 1 *eq*) in MeCN (4 mL) was added K_2CO_3 (142.94 mg, 1.03 mmol, 2 *eq*) at 25 °C. Then the mixture was stirred at 60 °C for 12 hr. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (neutral) to obtain 2-(difluoromethyl)-5-[6-(8-quinolyloxymethyl)-3-pyridyl]-1,3,4-oxadiazole (18.0 mg, 50.24 umol, 9.72% yield, 98.9% purity) as a white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.31 (d, *J* = 1.6 Hz, 1H), 8.90 (dd, *J* = 1.6, 4.3 Hz, 1H), 8.52 (dd, *J* = 2.1, 8.3 Hz, 1H), 8.38 (dd, *J* = 1.6, 8.3 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.62 (dd, *J* = 4.3, 8.4 Hz, 1H), 7.58 - 7.55 (m, 1H), 7.54 - 7.50 (m, 1H), 7.40 - 7.13 (m, 2H), 5.62 (s, 2H). MS(ESI): 355.0 [M+H]+

2-(Difluoromethyl)-5-(6-((naphthalen-1-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (Compound **11**)



11

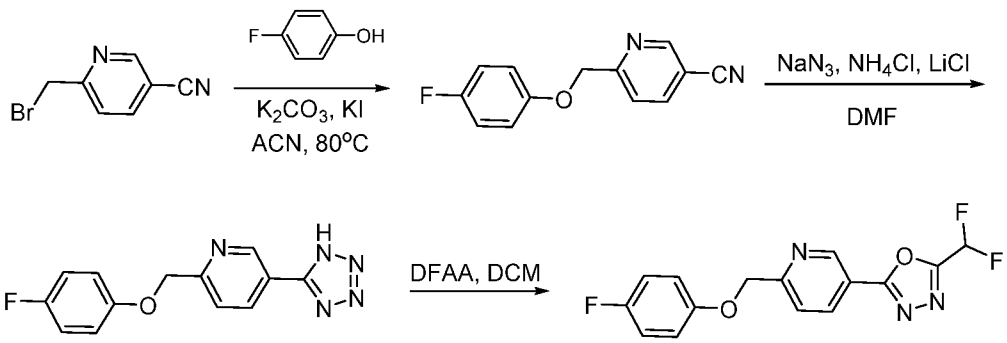
[00224] Step-1: 6-((Naphthalen-1-yloxy)methyl)nicotinonitrile: To a stirred solution of 6-(bromomethyl)nicotinonitrile (0.5 g, 2.55 mmol) and naphthalen-1-ol (0.477 g, 3.31 mmol) in acetonitrile (20 mL), was added K_2CO_3 (0.528 g, 3.82 mmol) and KI (0.084 g, 0.51 mmol) and the reaction mixture was stirred at 80 °C for 12 hours. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite bed and filtrate was

concentrated under reduced pressure to give the crude product. The crude product was purified by using 230-400 mesh silica gel column chromatography by eluting with 0-15% ethyl acetate in hexane to give the product (0.35 g, 52.79% yield) as a light yellow solid. LC-MS: m/z 260.95[M+H]$^+$.

[00225] Step-2: 2-((Naphthalen-1-yloxy)methyl)-5-(1H-tetrazol-5-yl)pyridine: To a stirred solution of 6-((naphthalen-1-yloxy)methyl)nicotinonitrile (0.35 g, 1.34 mmol) in DMF (10 mL) was added sodium azide (0.262 g, 4.03 mmol), NH_4Cl (0.218 g, 4.03 mmol) and LiCl (0.056 g, 1.34 mmol) and the reaction mixture was stirred at 100°C for 12h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl, solid precipitated out was filtered and was dried to give the product (0.3 g, 73.71% yield) as an off white solid. LC-MS: m/z 303.9 [M+H]$^+$.

[00226] Step-3: 2-(Difluoromethyl)-5-(6-((naphthalen-1-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (**11**): To a stirred solution of 2-((naphthalen-1-yloxy)methyl)-5-(1H-tetrazol-5-yl)pyridine (0.3 g, 0.99 mmol) in DCM (20 mL) was added difluoroacetic anhydride (0.34 mL, 1.98 mmol) at 0 °C and the reaction mixture was stirred at RT for 12 hours. After completion of reaction (monitored by TLC), the reaction mixture was diluted with DCM (20 mL) and washed with water (20 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 230-400 mesh silica gel column chromatography by eluting with 0-40% ethyl acetate in hexane to give the product (0.11 g, 31.51% yield) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.59 - 8.45 (m, 1H), 8.41 - 8.24 (m, 1H), 8.03 - 7.82 (m, 2H), 7.76 - 7.68 (m, 1H), 7.63 - 7.50 (m, 3H), 7.50 - 7.38 (m, 1H), 7.08 (br d, J = 7.3 Hz, 1H), 5.53 (s, 2H); ^{19}F NMR (400 MHz, DMSO-d_6) δ -122. LC-MS: m/z 354.05 [M+H]$^+$

2-(Difluoromethyl)-5-(6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (Compound **12**)



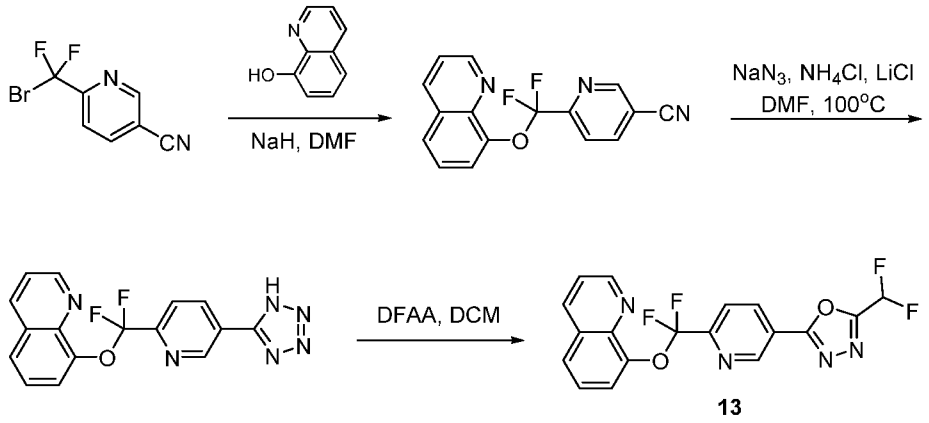
12

[00227] Step-1: 6-((4-Fluorophenoxy)methyl)nicotinonitrile: To a stirred solution of 6-(bromomethyl)nicotinonitrile (0.3 g, 1.53 mmol) and 4-fluorophenol (0.222 g, 1.98 mmol) in acetonitrile (10 mL), K_2CO_3 (0.316 g, 2.29 mmol) and KI (0.050 g, 0.306 mmol) were added, and the reaction mixture was stirred at 80°C for 12 hours. After completion of reaction (monitored by TLC), the reaction mixture was quenched with ice cold water (50 mL) and extracted with DCM (2 x 50 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 230-400 mesh silica gel column chromatography by eluting with 0-30% ethyl acetate in hexane to give the product (0.25 g, 71.83% yield) as a white solid. LC-MS: m/z 228.90 $[M+H]^+$.

[00228] Step-2: 2-((4-Fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine: To a stirred solution of 6-((4-fluorophenoxy)methyl)nicotinonitrile (0.25 g, 1.09 mmol) in DMF (10 mL), sodium azide (0.213 g, 3.28 mmol), NH_4Cl (0.177 g, 3.28 mmol) and LiCl (0.046 g) were added and the reaction mixture was stirred at 100°C for 12h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl, the precipitated solid was filtered and washed with ice cold water and hexane. The product was dried under reduced pressure to give the product (0.2 g, 67.34% yield) as an off-white solid which was used as such for further step. LC-MS: m/z 272.05 $[M+H]^+$.

[00229] Step-3: 2-(Difluoromethyl)-5-(6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (**12**): To a stirred solution of 2-((4-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine (0.2 g, 0.74 mmol) in DCM (20 mL) at 0°C, difluoro acetic anhydride (0.16 mL, 1.47 mmol) was added and the reaction mixture was stirred at RT for 12h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with ice cold water (20 mL) and extracted with DCM (50 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 230-400 mesh silica gel column chromatography by eluting with 0-30% ethyl acetate in hexane to give the product (0.110 g, 46.61% yield) as an off white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 9.22 (d, J = 2.0 Hz, 1H), 8.48 (dd, J = 2.0, 8.3 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.71 - 7.45 (m, 1H), 7.17 - 7.06 (m, 4H), 5.30 (s, 2H); ^{19}F NMR (400 MHz, DMSO-d_6): δ -120, -123. LC-MS: m/z 322.05 $[M+H]^+$

2-(6-(Difluoro(quinolin-8-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Compound **13**)



13

[00230] Step-1: 6-(Difluoro(quinolin-8-yloxy)methyl)nicotinonitrile: To a stirred solution of 6-(bromodifluoromethyl)nicotinonitrile (0.48 g, 2.06 mmol) in DMF (5 mL), was added NaH (60%, 0.099 g, 2.48 mmol) at 0°C, then stirred it for 5 min at 0°C. Quinolin-8-ol (0.3 g, 2.06 mmol) dissolved in DMF (2 mL) was slowly added at 0°C. Then the reaction mixture was stirred at room temperature for 30 mins. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-10% ethyl acetate in hexane to give the product (0.22 g, 35.83% yield) as an off white solid. LC-MS: m/z 298.1 [M+H]+.

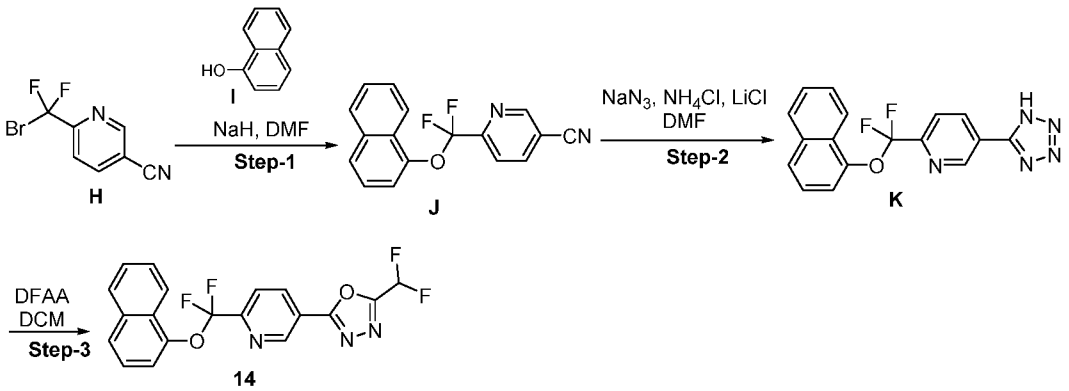
[00231] Step-2: 8-((5-(1H-Tetrazol-5-yl)pyridin-2-yl)difluoromethoxy)quinoline: To a stirred solution of 6-(difluoro(quinolin-8-yloxy)methyl)nicotinonitrile (0.22 g, 0.74 mmol) in DMF (7 mL), sodium azide (0.144 g, 2.22 mmol), NH_4Cl (0.124 g, 2.22 mmol) and LiCl (0.030 g) were added, and the reaction mixture was stirred at 100°C for 8h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl, extracted with ethyl acetate (2 X 50 mL). The organic layer was dried over sodium sulphate and concentrated to give the product (0.220 g, 87.64%) as an off white solid which was used as such for further step.

[00232] Step-3: 2-(6-(Difluoro(quinolin-8-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (**13**): To a stirred solution of 8-((5-(1H-tetrazol-5-yl)pyridin-2-yl)difluoromethoxy)quinoline (0.220 g, 0.64 mmol) in DCM (10 mL) at 0°C, difluoro acetic anhydride (0.225 g, 1.29 mmol) was added and the reaction mixture was stirred at RT for 16 hours. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (20 mL) and extracted with DCM (50 mL). The organic layer was dried over

sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-10% ethyl acetate in hexane to give the product (0.080 g, 31.74% yield) as an off white solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 9.09 - 8.89 (m, 1H), 8.86 - 8.64 (m, 1H), 8.48 (s, 1H), 8.44 - 8.35 (m, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.82 (br d, J = 7.5 Hz, 1H), 7.77 - 7.47 (m, 3H); ^{19}F NMR (400 MHz, DMSO-d_6) δ -78, -121. LC-MS: m/z 391.20 [M+H]+

[00233]

2-(6-(difluoro(naphthalen-1-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Compound **14**)**:**



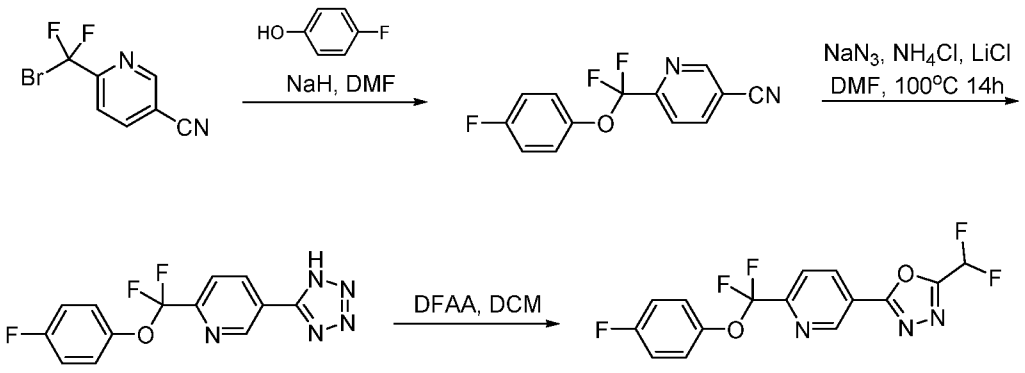
[00234] Step-1: 6-(difluoro(naphthalen-1-yloxy)methyl)nicotinonitrile (**J**): To a stirred solution of compound **I** (0.19 g, 1.30 mmol) in DMF (2 mL) was added NaH (60%, 0.08 g, 2.00 mmol) at 0 °C and the reaction mixture was stirred for 20 min at the same temperature. To the resulting reaction mixture, Compound **H** (0.3 g, 1.30 mmol) dissolved in DMF (1 mL) was slowly added at 0 °C and the reaction mixture was stirred at room temperature for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with cold water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by 100-200 mesh silica gel column chromatography by eluting with 0-10% ethyl acetate in hexane to give the compound **J** (0.32 g, 84.0%) as brown liquid. LC-MS: m/z 296.9 $[M+H]^+$.

[00235] Step-2: 2-(difluoro(naphthalen-1-yloxy)methyl)-5-(1*H*-tetrazol-5-yl)pyridine (**K**): To a stirred solution of compound **J** (0.32 g, 1.00 mmol) in DMF (5 mL), sodium azide (0.35 g, 5.40 mmol) was added followed by NH_4Cl (0.27 g, 5.40 mmol) and LiCl (0.03 g) and the reaction mixture was stirred at 100 °C for 5 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with

6N HCl. Product was extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford compound **K** (0.30 g, 82.0%) as light brown thick liquid which was used as such for the next reaction. LC-MS: m/z 339.9 $[M+H]^+$.

[00236] Step-3: 2-(6-(difluoro(naphthalen-1-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (14): To a stirred solution of compound **K** (0.30 g, 0.88 mmol) in DCM (6 mL), difluoroacetic anhydride (0.5 mL, 4.40 mmol) was added at 0 °C and the reaction mixture was stirred at RT for 16 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with cold water (20 mL) and extracted with DCM (50 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by 100-200 mesh silica gel column chromatography by eluting with 0-7% ethyl acetate in hexane to give **(14)** (0.10 g, 29.0% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.43 (d, J = 1.48 Hz, 1H), 8.72 (dd, J = 8.37, 1.97 Hz, 1H), 8.30 (s, 1H), 8.20 (d, J = 7.88 Hz, 1H), 8.00 - 8.05 (m, 1H), 7.90 - 7.95 (m, 1H), 7.46 - 7.79 (m, 5H). ^{19}F NMR (400 MHz, DMSO-d_6) δ ppm -68 (s, 2F), -122 (s, 2F). LC-MS: m/z 390.15 $[M+H]^+$.

2-(6-(Difluoro(4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Compound **15**)



15

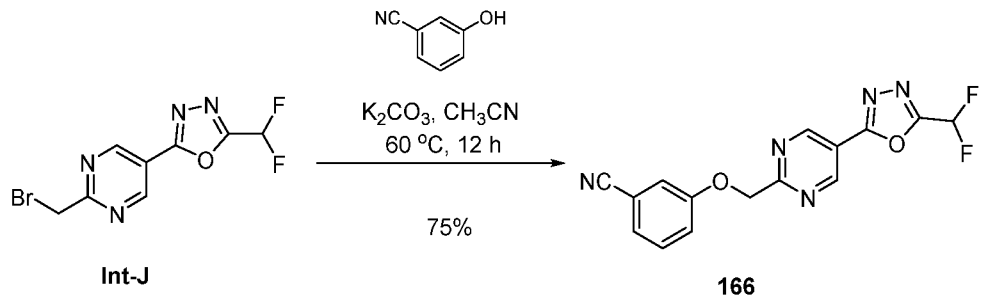
[00237] Step-1: 6-(Difluoro(4-fluorophenoxy)methyl)nicotinonitrile: To a stirred solution of 6-(bromodifluoromethyl)nicotinonitrile (0.3 g, 1.28 mmol) in DMF (5 mL), was added NaH (60%, 0.062 g, 1.54 mmol) at 0°C, then stirred it for 5min at 0°C. 4-fluorophenol (0.144 g, 1.28 mmol) dissolved in DMF (2 mL) was slowly added at 0°C. Then the reaction mixture was stirred at room temperature for 45 mins. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200

mesh silica gel column chromatography by eluting with 0-10% ethyl acetate in hexane to give the product (0.2 g, 58.8% yield) as an off white solid. LC-MS: m/z 265.20 [M+H]+.

[00238] Step-2: 2-(Difluoro(4-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine: To a stirred solution of 6-(difluoro(4-fluorophenoxy)methyl)nicotinonitrile (0.2 g, 0.75 mmol) in DMF (5 mL), sodium azide (0.148 g, 2.27 mmol), NH_4Cl (0.127 g, 2.27 mmol) and LiCl (0.020 g) were added and the reaction mixture was stirred at 100°C for 16h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl, extracted with ethyl acetate (2 X 50 mL). The organic layer was dried over sodium sulphate and concentrated to give the crude product. The crude product was washed with hexane (2 x 10 mL) to give the product (0.2 g of crude product) as an off white solid which was used as such for further step.

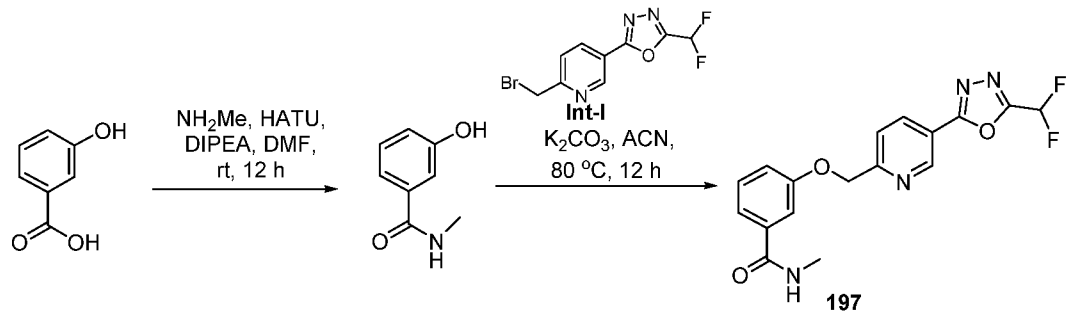
Step-3: 2-(6-(Difluoro(4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (**15**): To a stirred solution of 2-(difluoro(4-fluorophenoxy)methyl)-5-(1H-tetrazol-5-yl)pyridine (0.200 g, 0.65 mmol) in DCM (10 mL) at 0°C, difluoro acetic anhydride (1.2 mL, 6.5 mmol) was added and the reaction mixture was stirred at RT for 16 hours. After completion of reaction (monitored by TLC), the reaction mixture was diluted with DCM (20 mL) and basified with saturated sodium bicarbonate solution and extracted with DCM (50 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-10% ethyl acetate in hexane to give the product (0.120 g, 51.72% yield) as an off white solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (d, J = 1.5 Hz, 1H), 8.69 (dd, J = 2.0, 8.3 Hz, 1H), 8.17 (d, J = 8.3 Hz, 1H), 7.76 - 7.47 (m, 1H), 7.43 - 7.35 (m, 2H), 7.35 - 7.26 (m, 2H); ^{19}F NMR (400 MHz, DMSO-d_6) δ -70, -116, -121; LC-MS: m/z 358.15 [M+H]+.

2-(difluoromethyl)-5-(2-((4-fluorophenoxy)methyl)pyrimidin-5-yl)-1,3,4-oxadiazole (166)



[00239] Synthesis of 2-(difluoromethyl)-5-(2-((4-fluorophenoxy)methyl)pyrimidin-5-yl)-1,3,4-oxadiazole (**166**): To a stirred solution of 3-hydroxybenzonitrile (411 mg, 3.45 mmol) in acetonitrile (20 mL, 381 mmol) were added K_2CO_3 (1.427 g, 10.33 mmol) and 2-[2-(bromomethyl)pyrimidin-5-yl]-5-(difluoromethyl)-1,3,4-oxadiazole (**Int-J**, 1.0 g, 3.43 mmol) at room temperature. The reaction mixture was heated at 60 °C and stirred for 12 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with water (20 mL) and aqueous layer extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified by CombiFlash column chromatography using ethyl acetate: *n*-hexane (30%) to afford 2-(difluoromethyl)-5-(2-((4-fluorophenoxy)methyl)pyrimidin-5-yl)-1,3,4-oxadiazole (**166**, 830 mg, 75%) as an yellow solid. LC-MS: m/ z 330.15 [M+H]. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.44 (s, 2H), 7.47 - 7.74 (m, 3H), 7.41 - 7.45 (m, 1H), 7.37 (dd, J = 2.8, 9.2 Hz, 1H), 5.54 (s, 2H). HPLC = 98.09%, RT = 7.863 min.

3-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methoxy)-*N*-methylbenzamide (197)

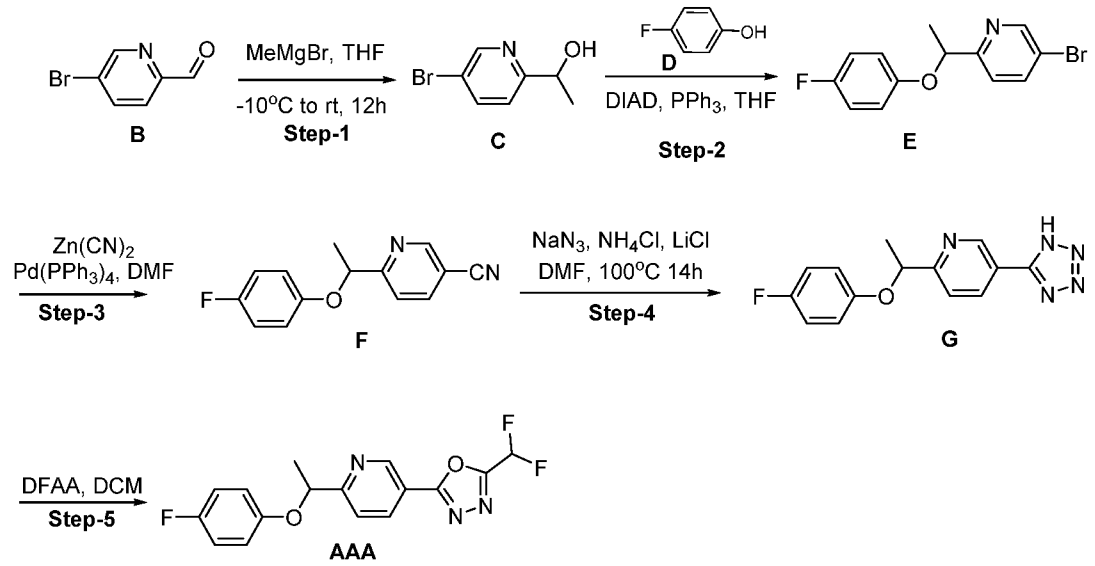


[00240] Synthesis of 3-hydroxy-*N*-methylbenzamide: To a stirred solution of 3-hydroxybenzoic acid (500 mg, 3.620 mmol, 1.0 equiv.) in DMF (5 mL) was added DIPEA (3.14 mL, 18.10 mmol, 5.0 equiv.) followed by HATU (2.06 g, 5.430 mmol, 1.5 equiv.) and methyl amine (488 mg, 7.24 mmol, 2.0 equiv.) at room temperature and stirred for 12 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (10 mLx3). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified

by Combi Flash column chromatography using ethyl acetate: *n*-heptane (50%) to afford 3-hydroxy-*N*-methylbenzamide (**2**, 546 mg, 98%) as a yellow solid.

[00241] Synthesis of 3-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methoxy)-*N*-methylbenzamide (197): To a stirred solution of 3-hydroxy-*N*-methylbenzamide (99 mg, 0.655 mmol, 1.5 equiv.) in acetonitrile (5 mL) was added K_2CO_3 (180 mg, 1.310 mmol, 3.0 equiv.) followed by 2-(6-(bromomethyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (**Int-I**, 100 mg, 0.436 mmol, 1.0 equiv.) at room temperature. The reaction mixture was heated at 80 °C and stirred for 12 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was cooled to room temperature and quenched with water (10 mL) and extracted with ethyl acetate (3X10 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified by Combi Flash column chromatography using ethyl acetate: *n*-heptane (20%) to afford 3-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methoxy)-N-methylbenzamide (**197**, 20 mg, 13%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (s, 1H), 8.40 - 8.52 (m, 2H), 7.70 - 7.81 (m, 1H), 7.36 - 7.60 (m, 4H), 7.21 (d, J = 8.31 Hz, 1H), 5.37 (s, 2H), 2.77 (d, J = 4.40 Hz, 3H). ^{19}F NMR (400 MHz, DMSO-d_6): δ - 121.780; -121.917. LC-MS: m/ z 360.8 [M+H]. HPLC: 95.83% at 6.995 min.

2-(Difluoromethyl)-5-(6-(1-(4-fluorophenoxy)ethyl)pyridin-3-yl)-1,3,4-oxadiazole (AAA)



[00242] Step-1: Synthesis of 1-(5-Bromopyridin-2-yl)ethan-1-ol (**C**): To a stirred solution of compound **B** (0.5 g, 2.68 mmol) in dry THF (10 mL), methyl magnesium bromide (1.79

mL, 5.37 mmol) was added at -10 °C, and then reaction mixture was stirred at room temperature for 12h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with aq. ammonium chloride (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography to give the product **C** (0.3 g, 55.24% yield) as colourless thick oil. LC-MS: m/z 203.90 $[M+H]^+$.

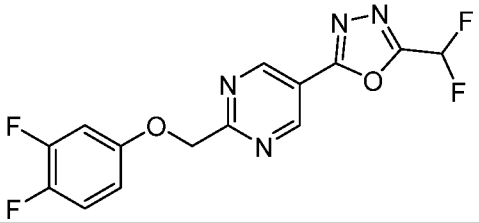
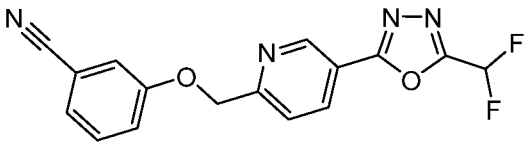
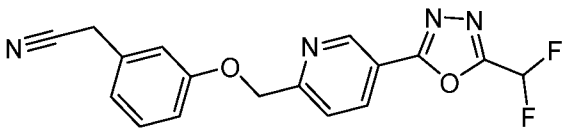
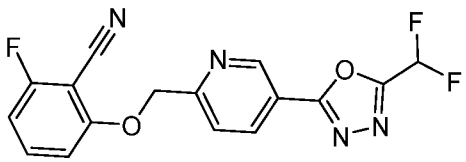
[00243] Step-2: Synthesis of 5-Bromo-2-(1-(4-fluorophenoxy)ethyl)pyridine (**E**): To a stirred solution of compound **C** (0.3 g, 1.48 mmol) in THF (5 mL), compound **D** (0.299 g, 2.67 mmol), PPh_3 (0.544 g, 2.07 mmol) were added under cooling, reaction mixture was stirred for 15 mins, then added DIAD (0.419 g, 2.07 mmol) at 0°C, then stirred at RT for 2h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography to give the product **E** (0.2 g, 45.66% yield) as light brown liquid. LC-MS: m/z 296.00 $[M+H]^+$.

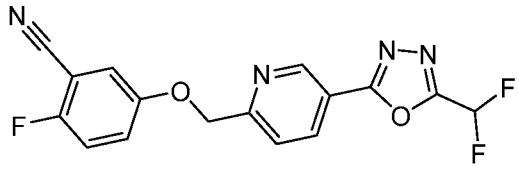
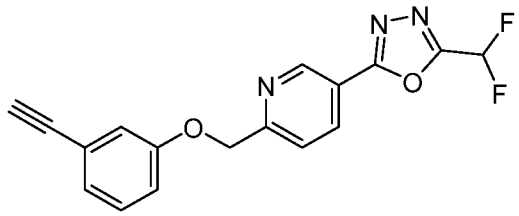
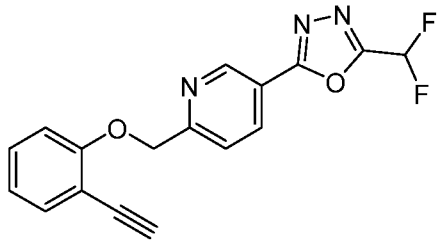
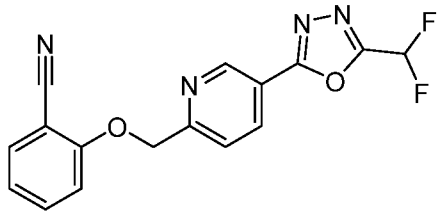
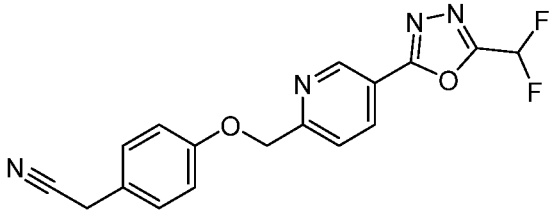
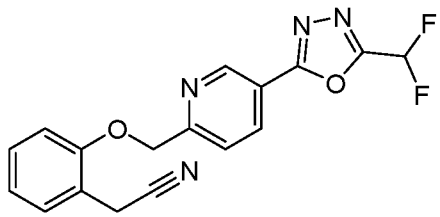
[00244] Step-3: Synthesis of 6-(1-(4-Fluorophenoxy)ethyl)nicotinonitrile (**F**): To a stirred solution of compound **E** (0.2 g, 0.677 mmol) in DMA (5 mL), were added $Zn(CN)_2$ (0.198 g, 1.69 mmol) and Zn dust (0.030 g, 0.474 mmol) at RT, the reaction mixture was purged with argon for 30 mins and the $Pd_2(dba)_3$ (0.070 g, 0.067 mmol) and dppf (0.112 g, 0.203 mmol) were added and again it was purged with argon for 15 mins. The reaction mixture was stirred at 100°C for 12h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite® and washed with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by using 100-200 mesh silica gel column chromatography by eluting with 0-20% ethyl acetate in hexane to give the product **F** (0.110 g, 67.07% yield) as an off-white solid. LC-MS: m/z 243.05 $[M+H]^+$.

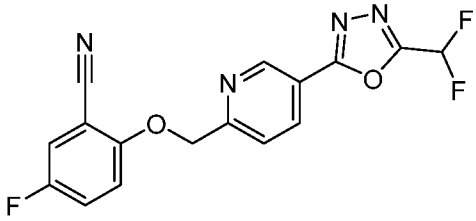
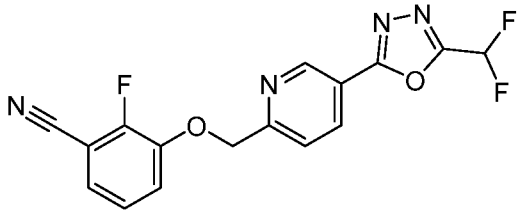
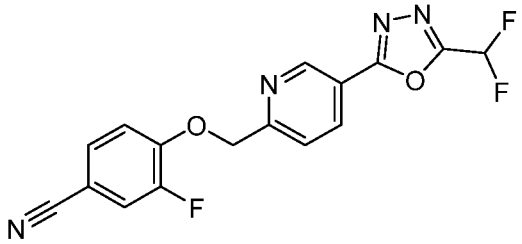
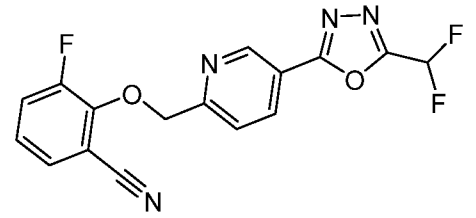
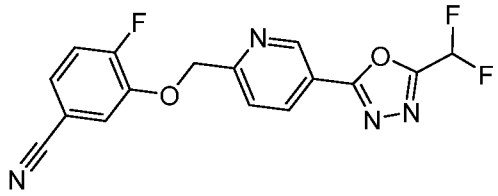
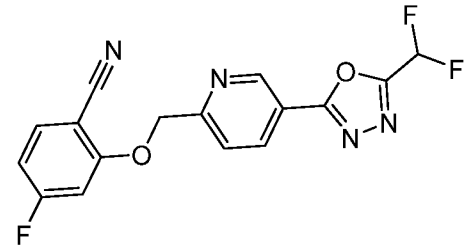
[00245] Step-4: Synthesis of 2-(1-(4-fluorophenoxy)ethyl)-5-(1*H*-tetrazol-5-yl)pyridine (**G**): To a stirred solution of compound **F** (0.11 g, 0.454 mmol) in DMF (10 mL), sodium azide (0.088 g, 1.36 mmol), NH_4Cl (0.073 g, 1.36 mmol) and LiCl (0.019 g, 0.454 mmol) were added and the reaction mixture was stirred at 100°C for 12h. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and was acidified with 6N HCl and the precipitated solid was filtered and dried to give product **G** (0.100 g, 77.51% yield) as light brown solid. LC-MS: m/z 286.05 $[M+H]^+$.

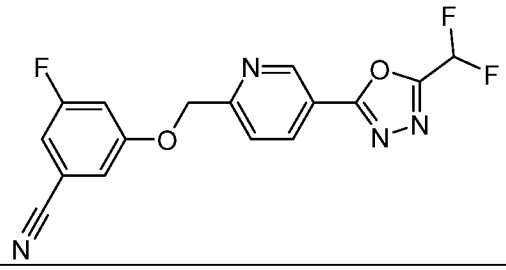
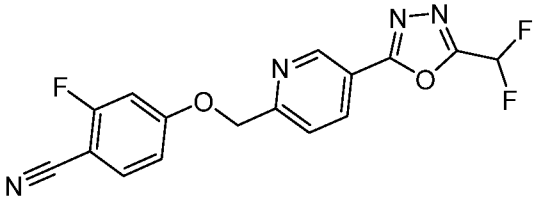
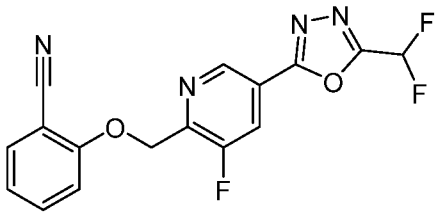
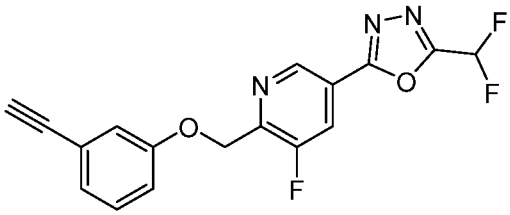
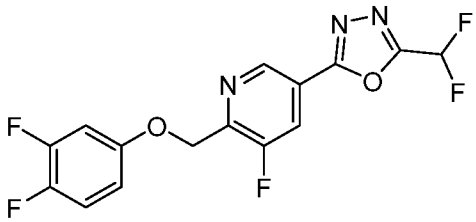
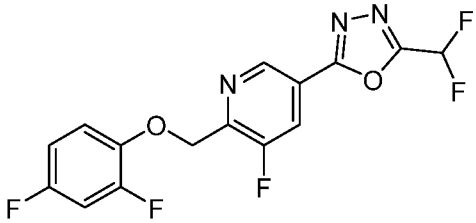
[00246] Step-5: Synthesis of 2-(Difluoromethyl)-5-(6-(1-(4-fluorophenoxy)ethyl)pyridin-3-yl)-1,3,4-oxadiazole (AAA): To a stirred solution of compound **G** (0.1 g, 0.35 mmol) in DCM (5 mL) at 0°C, difluoroacetic anhydride (0.122 g, 0.701 mmol) was added and the reaction mixture was stirred at RT for 12h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL) and basified with saturated sodium bicarbonate solution (20 mL), extracted with 5% methanol in DCM (50 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give crude product. The crude product was purified by using 230-400 mesh silica gel comlumn chromatography by eluting with 30% ethyl acetate in hexane to give the product (**AAA**) (0.060 g, 51.28% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.20 (s, 1H), 8.43 (dd, J = 2.0, 8.3 Hz, 1H), 7.78 - 7.38 (m, 2H), 7.13 - 7.01 (m, 2H), 7.00 - 6.89 (m, 2H), 5.56 (q, J = 6.4 Hz, 1H), 1.62 (d, J = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm = -120.70 (s, 1F), -120.83 (s, 1F), -123.28 (td, J = 4.2, 8.2 Hz, 1F). LC-MS: m/z 336.05 $[M+H]^+$.

[00247] The following compounds were also prepared.

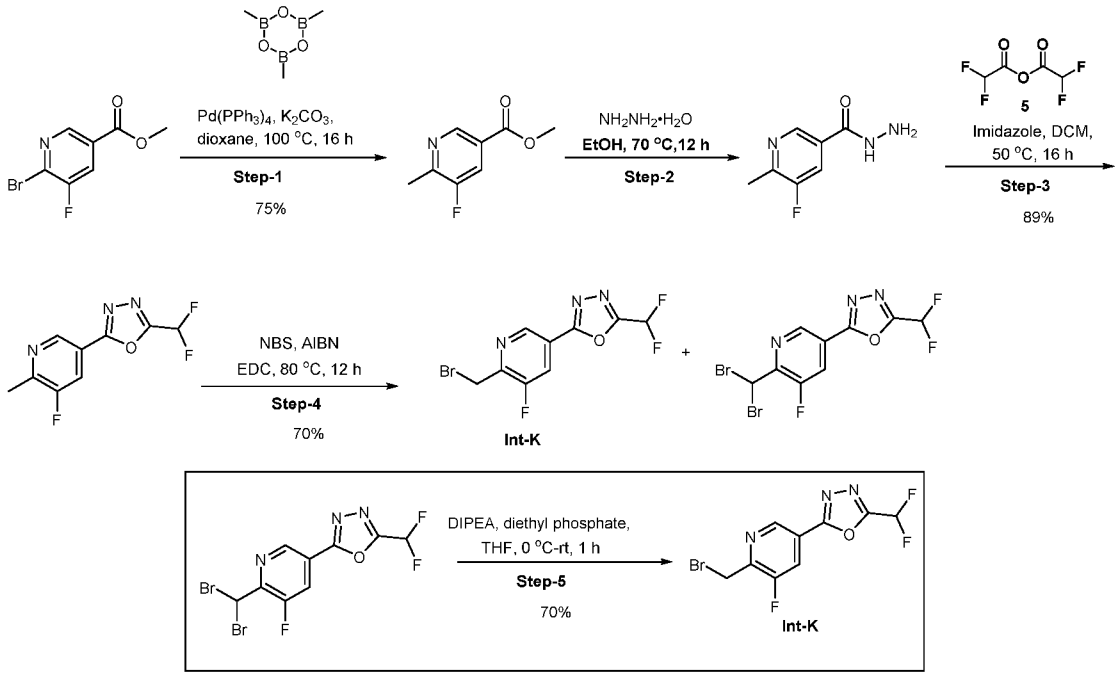
Compound	Structure/Name	Characterization
22		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.47 (s, 2H), 7.44 - 7.14 (m, 2H), 7.01-6.98 (m, 1H), 6.86 - 6.80 (m, 1H), 5.42 (s, 2H) MS(ESI): 341.0 [M+H]+
26		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.30 (s, 1H), 8.56 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.45 (s, 1H), 7.43 - 7.38 (m, 2H), 7.37 - 7.14 (m, 1H), 5.39 (s, 2H). MS(ESI):329.0$[M+H]^+$
27	 2-[3-[[5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-2-pyridyl]methoxy]phenyl]acetonitrile	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.28 (d, J = 2.0 Hz, 1H), 8.55 (d, J = 2.2, 8.3 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.28 - 7.14 (m, 1H), 7.09 (s, 1H), 7.05 - 7.00 (m, 2H), 5.34 (s, 2H), 3.91 (s, 2H). MS(ESI): 343.0 [M+H]+
29		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.31 (s, 1H), 8.62 - 8.56 (m, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.72 - 7.64 (m, 1H), 7.41 - 7.12 (m, 2H), 7.00 (t, J = 8.5 Hz, 1H), 5.51 (s, 2H). MS(ESI):347.0[M+H]+

30	 5-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methoxy)-2-fluorobenzonitrile	^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 9.29 (d, *J*=1.75 Hz, 1 H) 8.56-8.45 (m, 1 H) 7.86-7.71 (m, 1 H) 7.12 - 7.51 (m, 4 H) 5.36 (s, 2 H) MS (ESI):347.2 $[M+H]^+$
39		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.28 (d, *J* = 1.9 Hz, 1H), 8.54 (d, *J* = 2.0, 8.3 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.40 - 7.26 (m, 2H), 7.15 (d, *J* = 1.3 Hz, 1H), 7.12 - 7.08 (m, 2H), 5.33 (s, 2H), 3.50 (s, 1H). MS(ESI):328.1$[M+H]^+$
41		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.28 (d, *J* = 1.5 Hz, 1H), 8.56 (d, *J* = 2.3, 8.3 Hz, 1H), 7.99 (d, *J* = 0.6, 8.3 Hz, 1H), 7.48 (d, *J* = 1.7, 7.6 Hz, 1H), 7.39 - 7.34 (m, 1H), 7.28 - 7.13 (m, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.00 (t, *J* = 0.9, 7.5 Hz, 1H), 5.38 (s, 2H), 3.73 (s, 1H). MS(ESI): 328.0 [M+H]+
42		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.30 (d, *J* = 2.1 Hz, 1H), 8.59 (d, *J* = 2.2, 8.2 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 1.6, 7.8 Hz, 1H), 7.69 - 7.64 (m, 1H), 7.40 - 7.18 (m, 2H), 7.15 (d, *J* = 6.4 Hz, 1H), 5.48 (s, 2H). MS(ESI):329.1$[M+H]^+$
43		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.28 (d, *J* = 1.8 Hz, 1H), 8.54 (d, *J* = 2.3, 8.3 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.40 - 7.14 (m, 3H), 7.11 - 7.07 (m, 2H), 5.33 (s, 2H), 3.85 (s, 2H). MS(ESI): 343.0 [M+H]+
44		^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 9.29 (d, *J*=1.50 Hz, 1 H) 8.55 (dd, *J*=8.19, 2.06 Hz, 1 H) 7.95 (d, *J*=8.13 Hz, 1 H) 7.35 - 7.44 (m, 2 H) 7.33 (s, 1 H) 7.11 - 7.08 (m, 1 H) 7.04 (t, *J*=7.63 Hz, 1 H) 5.42 (s, 2 H) 3.95 (s, 2 H). MS (ESI):343.2 $[M+H]^+$

45		^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 9.30 (d, *J*=1.50 Hz, 1 H) 8.59 (dd, *J*=8.25, 2.13 Hz, 1 H) 7.93 (d, *J*=8.25 Hz, 1 H) 7.54 (dd, *J*=7.75, 3.13 Hz, 1 H) 7.41 - 7.47 (m, 1 H) 7.14 - 7.41 (m, 2 H) 5.46 (s, 2 H). MS (ESI):347.2 $[M+H]^+$
46		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.30 (d, *J* = 1.6 Hz, 1H), 8.58 (d, *J* = 2.3, 8.3 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 1.8, 8.2 Hz, 1H), 7.37 - 7.33 (m, 1H), 7.31 (d, *J* = 1.0, 8.0 Hz, 1H), 7.28 - 7.14 (m, 1H), 5.45 (s, 2H). MS(ESI): 347.0 [M+H]+
47		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.30 (d, *J* = 1.5 Hz, 1H), 8.57 (d, *J* = 2.2, 8.2 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 1.9, 10.8 Hz, 1H), 7.57 (d, *J* = 1.6, 8.6 Hz, 1H), 7.41 - 7.14 (m, 2H), 5.48 (s, 2H). MS(ESI):347.2$[M+H]^+$
48		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.27 (d, *J* = 2.0 Hz, 1H), 8.60 (d, *J* = 2.1, 8.3 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.59 - 7.52 (m, 2H), 7.40 - 7.14 (m, 2H), 5.56 (s, 2H). MS(ESI):347.0$[M+H]^+$
49		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.31 (d, *J* = 1.6 Hz, 1H), 8.58 (d, *J* = 2.3, 8.1 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 1.9, 7.8 Hz, 1H), 7.46 - 7.42 (m, 1H), 7.40 - 7.37 (m, 1H), 7.35 - 7.14 (m, 1H), 5.44 (s, 2H). MS(ESI):347.2$[M+H]^+$
50		^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 9.31 (d, *J*=1.75 Hz, 1 H) 8.59 (dd, *J*=8.25, 2.25 Hz, 1 H) 7.93 (d, *J*=8.25 Hz, 1 H) 7.77 (dd, *J*=8.63, 6.13 Hz, 1 H) 7.14 - 7.42 (m, 2 H) 6.93 (td, *J*=8.41, 2.31 Hz, 1 H) 5.48 (s, 2 H). MS (ESI):347.2 $[M+H]^+$

51		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.30 (d, *J* = 2.1 Hz, 1H), 8.56 (d, *J* = 2.3, 8.3 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.40 - 7.14 (m, 4H), 5.40 (s, 2H). MS(ESI):347.2[M+H]$^+$
52		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.30 (d, *J* = 1.5 Hz, 1H), 8.56 (d, *J* = 2.3, 8.3 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 7.7, 8.7 Hz, 1H), 7.48 - 7.22 (m, 1H), 7.16 - 7.12 (m, 1H), 7.08 (d, *J* = 2.3, 8.8 Hz, 1H), 5.43 (s, 2H). MS(ESI): 347.0 [M+H]+
127		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.15 (s, 1H), 8.39 (d, *J* = 1.8, 9.6 Hz, 1H), 7.68 - 7.63 (m, 2H), 7.41 - 7.12 (m, 3H), 5.55 (d, *J* = 1.9 Hz, 2H) MS(ESI): 347.2 [M+H]+
128		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.14 (s, 1H), 8.36 (d, *J* = 1.8, 9.6 Hz, 1H), 7.41 - 7.15 (m, 3H), 7.11 - 7.08 (m, 2H), 5.37 (d, *J* = 1.9 Hz, 2H), 3.50 (s, 1H) MS(ESI): 346.1 [M+H]+
129		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.13 (d, *J* = 0.6 Hz, 1H), 8.36 (d, *J* = 1.8, 9.6 Hz, 1H), 7.41 - 7.15 (m, 2H), 7.03-6.99 (m, 1H), 6.88 - 6.84 (m, 1H), 5.34 (d, *J* = 1.8 Hz, 2H) MS(ESI): 358.0 [M+H]+
131		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.14 (d, *J* = 0.6 Hz, 1H), 8.37 (d, *J* = 1.8, 9.6 Hz, 1H), 7.41 - 7.15 (m, 2H), 7.01-6.98 (m, 1H), 6.93 - 6.86 (m, 1H), 5.39 (d, *J* = 1.9 Hz, 2H) MS(ESI): 358.1 [M+H]+

2-(6-(bromomethyl)-5-fluoropyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Int-K)



[00248] Step-1: Synthesis of methyl 5-fluoro-6-methylnicotinate: To a stirred solution of methyl 6-bromo-5-fluoronicotinate (**1,** 5.0 g, 21.36 mmol, 1.0 equiv.) in 1,4 dioxane (75 mL) was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (13.41 g, 106.8 mmol, 5.0 equiv.) followed by K_2CO_3 (4.429 g, 32.00 mmol, 1.5 equiv.) at room temperature and degassed the reaction mixture with argon for 15 min. To the resulting reaction mixture was added $Pd(PPh_3)_4$ (2.77 g, 0.235 mmol, 0.11 eq.). The reaction mixture was heated at 100 °C and stirred for 16 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was diluted with water (100 mL) and extracted with DCM (2 x 100 mL). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified by CombiFlash column chromatography using ethyl acetate: *n*-hexane (20%) to afford methyl 5-fluoro-6-methylnicotinate (2.70 g, 75%) as an off white solid.

[00249] Step-2: Synthesis of 5-fluoro-6-methylnicotinohydrazide: To a stirred solution of methyl 5-fluoro-6-methylnicotinate (0.740 g, 4.374 mmol, 1.0 equiv.) in EtOH (10 mL) was added hydrazine hydrate (1.402 g, 43.74 mmol, 5.0 equiv.) at room temperature. The reaction mixture was heated at 70 °C and stirred for 12 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was concentrated under reduced pressure to obtain crude product (0.740 g, crude). The crude product was as such used for next reaction without carried out further purification.

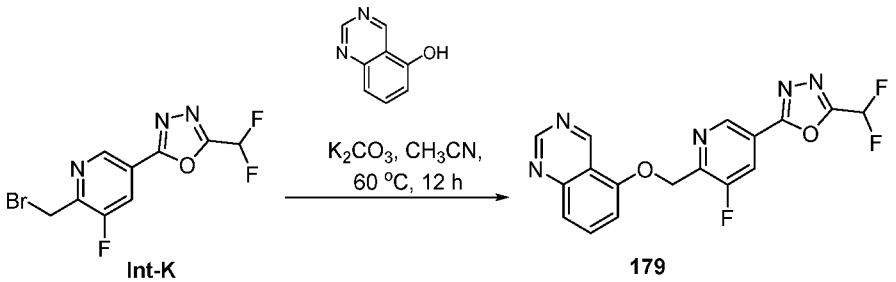
[00250] Step-3: Synthesis of 2-(difluoromethyl)-5-(5-fluoro-6-methylpyridin-3-yl)-1,3,4-oxadiazole: To a stirred solution of methyl 5-fluoro-6-methylnicotinohydrazide (0.740 g, 4.374 mmol, 1.0 equiv.) in DCM (50 mL) was added imidazole (0.893 g, 13.12 mmol, 3.0 equiv.) at room temperature for 15 min. To the resulting reaction mixture was added DFAA (2.28 g, 13.12 mmol) at 0 °C temperature. The reaction mixture was heated at 50 °C and stirred for 16 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was diluted with water (10 mL) and extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified by Combi Flash column chromatography using ethyl acetate: *n*-heptane (30%) to afford 2-(difluoromethyl)-5-(5-fluoro-6-methylpyridin-3-yl)-1,3,4-oxadiazole (1.788 g, 89.4%, from 2 steps) as an off white solid.

[00251] Step-4: Synthesis of 2-(6-(bromomethyl)-5-fluoropyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Int-K): To a stirred solution of methyl 5-fluoro-6-methylnicotinohydrazide 2-(difluoromethyl)-5-(5-fluoro-6-methylpyridin-3-yl)-1,3,4-oxadiazole (0.900 g, 3.927 mmol, 1.0 equiv.) in DCE (18 mL) was added NBS (2.10 g, 23.56 mmol, 6.0 equiv.) followed by AIBN (0.322 g, 1.963 mmol, 0.5 equiv.) at room temperature for 15 min. The reaction mixture was heated at 80 °C and stirred for 12 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine solution (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified by CombiFlash column chromatography using ethyl acetate: *n*-heptane (30%) to afford 2-(6-(bromomethyl)-5-fluoropyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole **(Int-K,** 0.600 g, 44%, **7**, 550 mg, 35%) as an off white solid. LC-MS: m/ z = 309.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.12 (s, 1H), 8.13 (br. d, J = 8.80 Hz, 1H), 6.76 - 7.10 (m, 1H), 4.66 (s, 3H).

Step-5: Synthesis of 2-(6-(bromomethyl)-5-fluoropyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Int-K): To a stirred solution of 2-(6-(dibromomethyl)-5-fluoropyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (0.370 g, 0.953 mmol, 1.0 equiv.) in THF (10 mL) was added DIPEA (0.246 g, 1.907 mmol, 2.0 equiv.) followed by Diethyl phosphate (263.1 g, 1.907 mmol, 1.907 equiv.) at 0 °C temperature. The resulting reaction mixture was allowed to attain room temperature and stirred for 1 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). Organic layer was washed with brine solution (10

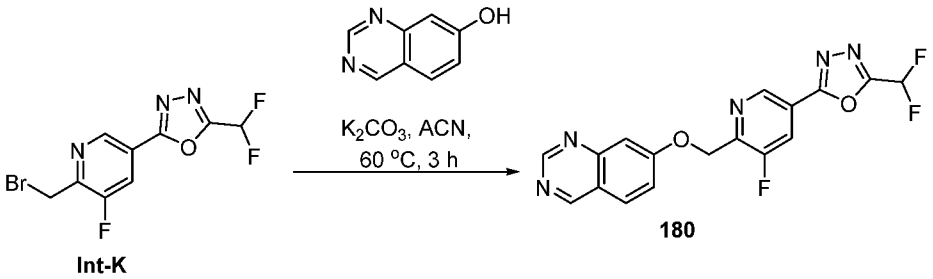
mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified by CombiFlash column chromatography using ethyl acetate: *n*-heptane (30%) to afford 2-(6-(bromomethyl)-5-fluoropyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole **(Int-K,** 0.687 g, 72.3%) as an off white solid. LC-MS: m/ z = 310.11; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.12 (s, 1H), 8.13 (d, J = 8.80 Hz, 1H), 6.76 - 7.10 (m, 1H), 4.66 (s, 3H).

2-(Difluoromethyl)-5-(5-fluoro-6-((quinazolin-5-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (179)



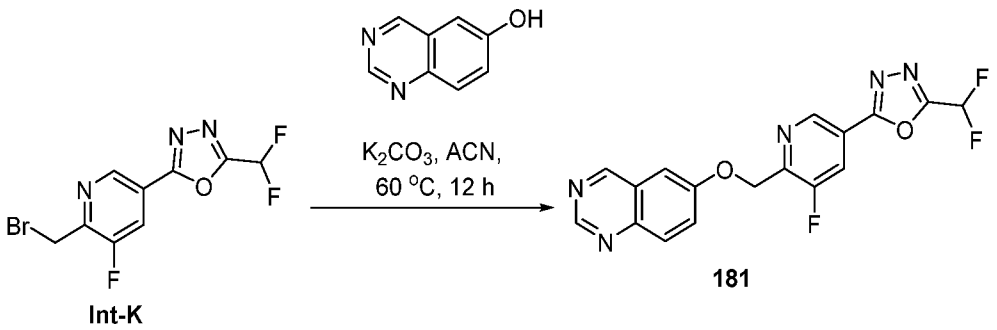
[00252] Synthesis of 2-(difluoromethyl)-5-(5-fluoro-6-((quinazolin-5-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (179): To a stirred solution of quinazolin-5-ol (47 mg, 0.321 mmol, 1.0 equiv.) in acetonitrile (5 mL) was added K_2CO_3 (112 mg, 0.817 mmol, 2.5 equiv.) followed by 2-(6-(bromomethyl)-5-fluoropyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (**Int-K**, 100 mg, 0.324 mmol, 1.0 equiv.) at room temperature. The reaction mixture was heated at 60 °C and stirred for 12 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue obtained was diluted with water (10 mL) and aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified by Combi Flash column chromatography using ethyl acetate: *n*-hexane (30%) to afford 2-(difluoromethyl)-5-(5-fluoro-6-((quinazolin-5-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (**179**, 37 mg, 30%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.67 (s, 1H), 9.30 (s, 1H), 9.11 (s, 1H), 8.52 (t, J = 32.6, 1H), 8.52 (dd, J = 9.82, 1.69 Hz, 1H), 7.47 – 7.72 (m, 2H), 7.41 (d, J = 7.6 Hz, 1H), 5.69 (br. s, 2H). ^{19}F NMR (400 MHz, DMSO-d_6): δ - 120.76; -123.10. LC-MS: m/ z 374.4 [M+H]. HPLC: 98.83% at 5.611 min.

2-(difluoromethyl)-5-(5-fluoro-6-((quinazolin-7-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (180)



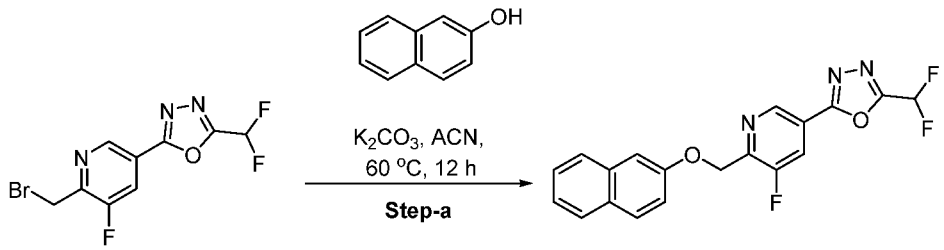
[00253] Synthesis of 2-(difluoromethyl)-5-(5-fluoro-6-((quinazolin-7-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (180): To a stirred solution of quinazolin-7-ol (47 mg, 0.321 mmol, 1.0 equiv.) in acetonitrile (5 mL) was added K_2CO_3 (113 mg, 0.817 mmol, 2.5 equiv.) followed by 2-(6-(bromomethyl)-5-fluoropyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (**Int-K**, 100 mg, 0.324 mmol, 1.0 equiv.) at room temperature. The reaction mixture was heated at 60 °C and stirred for 12 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue obtained was diluted with water (10 mL) and aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified by Combi Flash column chromatography using ethyl acetate: *n*-hexane (30%) to afford 2-(difluoromethyl)-5-(5-fluoro-6-((quinazolin-7-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (**180**, 65 mg, 55%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.44 (s, 1H), 9.18 (s, 1H), 9.12 (s, 1H), 8.51 (dd, J = 9.82, 1.69 Hz, 1H), 8.10 (d, J = 9.01 Hz, 1H), 7.55 – 7.75 (m, 2H), 7.40 – 7.50 (m, 1H), 5.62 (br. s, 2H). ^{19}F NMR (400 MHz, DMSO-d$_6$): δ - 120.75; -123.29. LC-MS: m/ z 374.4 [M+H]. HPLC: 97.51% at 9.483 min

2-(Difluoromethyl)-5-(5-fluoro-6-((quinazolin-6-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (181)



[00254] Synthesis of 2-(difluoromethyl)-5-(5-fluoro-6-((quinazolin-6-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (181): To a stirred solution of quinazolin-6-ol (47 mg, 0.321 mmol, 1.0 equiv.) in acetonitrile (5 mL) was added K_2CO_3 (112 mg, 0.400 mmol, 1.20 equiv.) followed by 2-(6-(bromomethyl)-5-fluoropyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (**Int-K**, 100 mg, 0.324 mmol, 1.0 equiv.) at room temperature. The reaction mixture was heated at 60 °C and stirred for 12 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue obtained was diluted with water (10 mL) and aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified by CombiFlash column chromatography using ethyl acetate: *n*-hexane (30%) to afford 2-(difluoromethyl)-5-(5-fluoro-6-((quinazolin-6-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (**181**, 57 mg, 30%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (s, 1H), 9.19 (s, 1H), 9.12 (s, 1H), 8.50 (dd, J = 10.1, 2.0 Hz, 1H), 7.98 (d, J = 9.01 Hz, 1H), 7.46 - 7.80 (m, 3H), 5.56 (d, J = 1.50 Hz, 2H). ^{19}F NMR (400 MHz, DMSO-d$_6$): δ -120.75; -123.29. LC-MS: m/z 371.9 [M+H]. HPLC: 99.56% at 9.207 min.

2-(Difluoromethyl)-5-(5-fluoro-6-((naphthalen-2-yloxy) methyl) pyridin-3-yl)-1,3,4-oxadiazole (182)

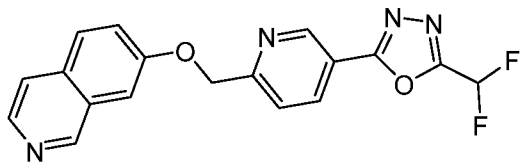
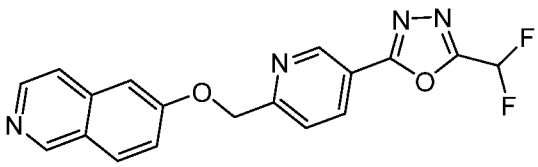
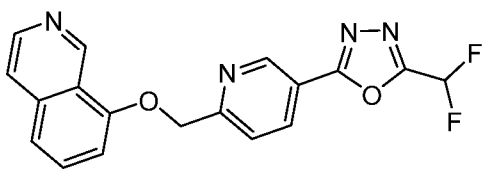
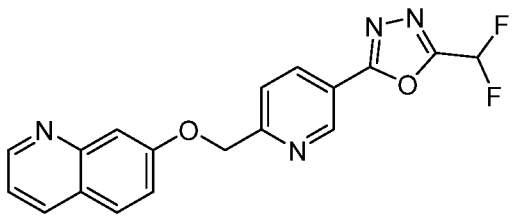


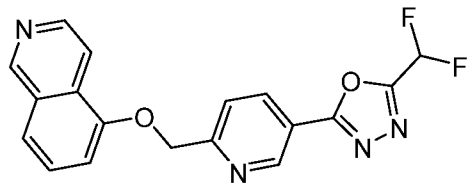
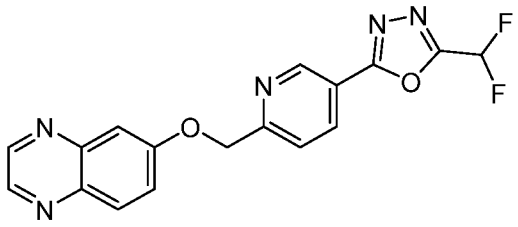
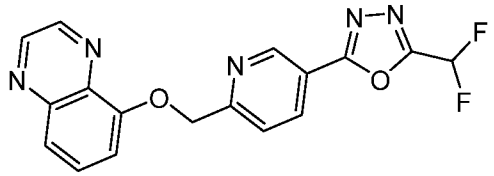
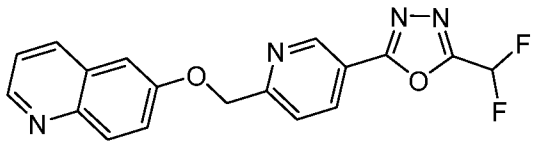
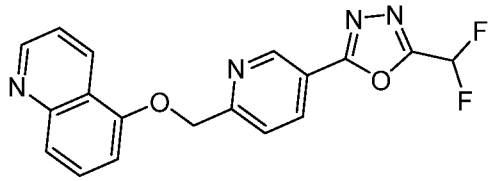
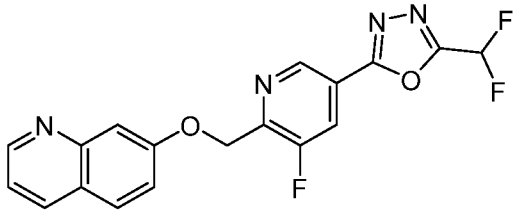
Int-K **182**

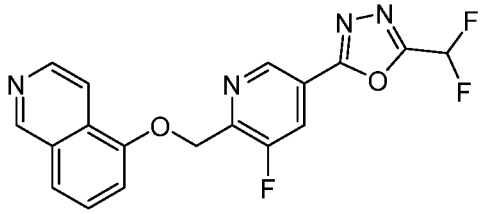
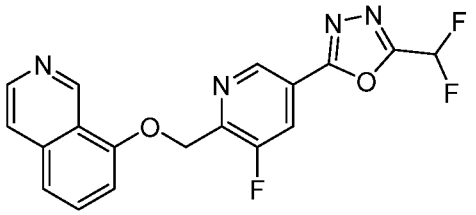
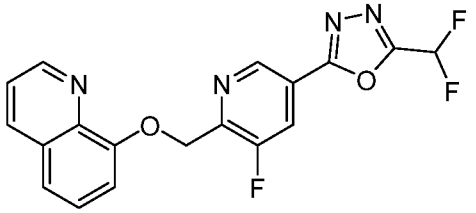
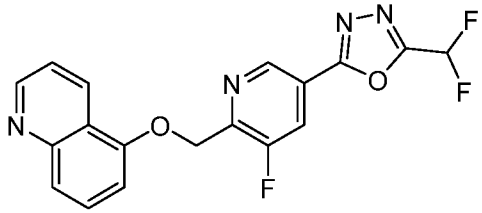
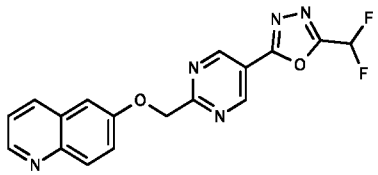
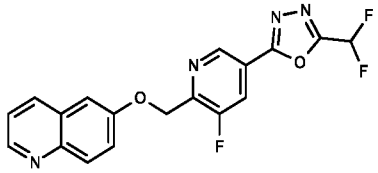
[00255] 2-(difluoromethyl)-5-(5-fluoro-6-((naphthalen-2-yloxy) methyl) pyridin-3-yl)-1,3,4-oxadiazole (182): To a stirred solution of naphthalen-2-ol (47 mg, 0.324 mmol, 1.0 equiv.) in acetonitrile (5 mL) was added K_2CO_3 (113 mg, 0.817 mmol, 2.5 equiv.) followed by 2-(difluoromethyl)-5-(5-fluoro-6-((naphthalen-2-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (**Int-K**, 100 mg, 0.324 mmol, 1.0 equiv.) at room temperature. The reaction mixture was heated at 60 °C and stirred for 12 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue obtained was diluted with water (10 mL)

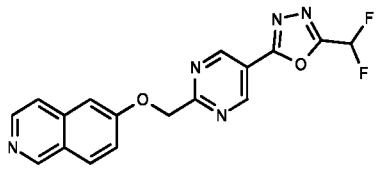
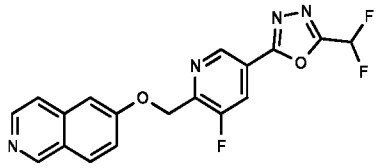
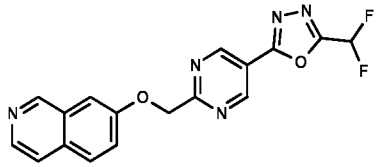
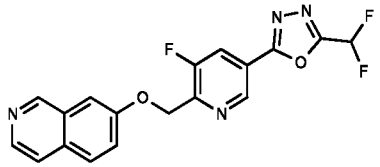
and aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified by CombiFlash column chromatography using ethyl acetate: *n*-hexane (30%) to afford 2-(difluoromethyl)-5-[5-fluoro-6-(2-naphthyloxymethyl)-3-pyridyl]-1,3,4-oxadiazole (**182**, 70.0 mg, 40%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 (d, J = 1.13 Hz, 1H), 8.45 - 8.51 (m, 1H), 7.79 - 7.88 (m, 3H), 7.44 - 7.73 (m, 3H), 7.34 - 7.40 (m, 1H), 7.25 (dd, J = 8.80, 2.40 Hz, 1H), 5.48 (br. s, 2H). ^{19}F NMR (400 MHz, DMSO-d_6): δ - 120.75; -123.29. LC-MS: m/ z = 371.9 [M+H]. HPLC: 99.56% at 9.207 min.

[00256] The following compounds were prepared in a manner analogous to that used for preparing compounds of Formula (**I**), above.

Compound	Structure/Name	Characterization
31		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.32 (d, J = 1.5 Hz, 1H), 9.16 (s, 1H), 8.57 (d, J = 2.2, 8.3 Hz, 1H), 8.35 (d, J = 5.8 Hz, 1H), 7.94 (m,2H), 7.80 (d, J = 5.8 Hz, 1H), 7.65 - 7.61 (m, 2H), 7.40 - 7.14 (m, 1H), 5.51 (s, 2H) MS(ESI): 355.0 [M+H]+
32		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.32 (d, J = 1.8 Hz, 1H), 9.12 (s, 1H), 8.57 (d, J = 2.3, 8.3 Hz, 1H), 8.36 (d, J = 6.0 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 5.9 Hz, 1H), 7.50 (d, J = 2.4, 9.0 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.40 - 7.14 (m, 1H), 5.52 (s, 2H). MS(ESI): 355.0 [M+H]+
33		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.69 (s, 1H), 9.34 (d, J = 1.6 Hz, 1H), 8.59 (d, J = 2.1, 8.3 Hz, 1H), 8.50 (d, J = 5.9 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 5.4 Hz, 1H), 7.75 - 7.70 (m, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.41 - 7.14 (m, 2H), 5.61 (s, 2H). MS(ESI):355.0[M+H]$^+$
34		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.32 (d, J = 1.6 Hz, 1H), 8.77 (d, J = 1.7, 4.4 Hz, 1H), 8.56 (d, J = 2.3, 8.3 Hz, 1H), 8.32 (d, J = 1.4, 8.3 Hz, 1H), 7.93 (t, J = 8.4 Hz, 2H), 7.48 - 7.41 (m, 3H), 7.40 - 7.14 (m, 1H), 5.52 (s, 2H). MS(ESI): 355.0 [M+H]+

35		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.33 (d, *J* = 2.0 Hz, 1H), 9.24 (s, 1H), 8.59 (d, *J* = 2.2, 8.2 Hz, 1H), 8.51 (d, *J* = 5.9 Hz, 1H), 8.28 (d, *J* = 6.0 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.29 - 7.14 (m, 1H), 5.57 (s, 2H). MS(ESI):355.1[M+H]$^+$
36		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.33 (d, *J* = 1.6 Hz, 1H), 8.83 (d, *J* = 2.0 Hz, 1H), 8.77 (d, *J* = 1.9 Hz, 1H), 8.57 (d, *J* = 2.3, 8.3 Hz, 1H), 8.08 (d, *J* = 9.3 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 2.8, 9.3 Hz, 1H), 7.56 (d, *J* = 2.8 Hz, 1H), 7.27 (t, *J* = 51.6 Hz, 1H), 5.55 (s, 2H). MS(ESI):356.2[M+H]$^+$
55		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.31 (d, *J* = 2.1 Hz, 1H), 8.97 (d, *J* = 1.9 Hz, 1H), 8.92 (d, *J* = 1.8 Hz, 1H), 8.55 (dd, *J* = 2.1, 8.3 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.82 - 7.74 (m, 2H), 7.43 - 7.14 (m, 2H), 5.63 (s, 2H). MS(ESI): 356.0 [M+H]+
62		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.32 (d, *J* = 1.5 Hz, 1H), 8.73 (dd, *J* = 1.6, 4.3 Hz, 1H), 8.57 (dd, *J* = 2.3, 8.3 Hz, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 8.01 (d, *J* = 9.3 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.62 (dd, *J* = 2.8, 9.2 Hz, 1H), 7.51 (dd, *J* = 4.3, 8.3 Hz, 1H), 7.46 (d, *J* = 2.8 Hz, 1H), 7.40 - 7.14 (m, 1H), 5.49 (s, 2H). MS(ESI):355.0[M+H]$^+$
63		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.32 (d, *J* = 1.8 Hz, 1H), 8.90 - 8.85 (m, 2H), 8.58 (dd, *J* = 2.3, 8.3 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.73 - 7.67 (m, 2H), 7.60 (d, *J* = 4.4, 8.4 Hz, 1H), 7.41 - 7.14 (m, 2H), 5.57 (s, 2H). MS(ESI):355.1[M+H]$^+$
124		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.17 (d, *J* = 0.6 Hz, 1H), 8.79 (d, *J* = 1.7, 4.4 Hz, 1H), 8.39 (d, *J* = 1.8, 9.6 Hz, 1H), 8.32 (d, *J* = 1.0, 8.3 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.45 - 7.15 (m, 3H), 5.57 (d, *J* = 1.8 Hz, 2H) MS(ESI): 373.0 [M+H]+

125		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.20 (s, 1H), 9.17 (s, 1H), 8.43 (d, *J* = 6.0 Hz, 1H), 8.40 (d, *J* = 1.7, 9.7 Hz, 1H), 8.10 (d, *J* = 5.9 Hz, 1H), 7.74 - 7.70 (m, 1H), 7.66 - 7.62 (m, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.28 (s, 1H), 5.63 (d, *J* = 1.6 Hz, 2H) MS(ESI): 373.0 [M+H]+
126		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.52 (s, 1H), 9.19 (s, 1H), 8.46 (d, *J* = 5.8 Hz, 1H), 8.41 (d, *J* = 1.7, 9.7 Hz, 1H), 7.81 - 7.79 (m, 1H), 7.76 - 7.72 (m, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.42 - 7.16 (m, 2H), 5.67 (d, *J* = 1.8 Hz, 2H) MS(ESI): 373.0 [M+H]+
130		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.15 (s, 1H), 8.80 (d, *J* = 1.5, 4.3 Hz, 1H), 8.36-8.20 (m, 2H), 7.59 - 7.54 (m, 3H), 7.44 - 7.15 (m, 2H), 5.63 (d, *J* = 1.4 Hz, 2H) MS(ESI): 373.0 [M+H]+
132		^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.18 (s, 1H), 8.85 (d, *J* = 1.6, 4.3 Hz, 1H), 8.70 (d, *J* = 0.9, 8.4 Hz, 1H), 8.40 (d, *J* = 1.7, 9.7 Hz, 1H), 7.75 - 7.70 (m, 1H), 7.69 - 7.66 (m, 1H), 7.53 (d, *J* = 4.4, 8.5 Hz, 1H), 7.42 - 7.16 (m, 2H), 5.63 (d, *J* = 1.6 Hz, 2H) MS(ESI): 373.2 [M+H]+
152		MS(ESI): 356.2[M+H]$^+$ ^{1}HNMR (400 MHz, DMSO-d6) δ = 9.47 (s, 2H), 8.75 (dd, J = 1.6, 4.2 Hz, 1H), 8.21 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 9.1 Hz, 1H), 7.75 - 7.52 (m, 2H), 7.49 - 7.45 (m, 1H), 7.43 (d, J = 2.9 Hz, 1H), 5.61 (s, 2H) ^{19}F NMR (377 MHz, DMSO-d6) δ = -120.69 (s, 2F)
153		^{1}HNMR (400 MHz, DMSO-d6) δ ppm 9.58 (br. s, 1H), 9.25 (s, 1H), 9.11 (s, 1H), 8.51 (dd, J = 1.6 Hz, J = 11.2 Hz, 1H), 8.26 (d, J = 7.2 Hz, 1H), 7.47 - 7.75 (m, 4H), 5.60 (br. s, 2H). LC-MS: m/z 373.2 [M+H].

154		MS(ESI): 356.0 $[M+H]^+$ ^{1}HNMR (400 MHz, DMSO-d6) δ = 9.47 (s, 2H), 9.17 (s, 1H), 8.39 (d, J = 5.8 Hz, 1H), 8.07 (d, J = 8.9 Hz, 1H), 7.74 - 7.61 (m, 2H), 7.45 - 7.39 (m, 2H), 5.64 (s, 2H) ^{19}F NMR (377 MHz, DMSO-d6) δ = -119.99 - -121.36 (m, 2F)
155		^{1}HNMR (400 MHz, DMSO-d6) δ ppm 9.08 - 9.21 (m, 2H), 8.36 - 8.53 (m, 2H), 8.06 (d, J = 9.01 Hz, 1H), 7.68 - 7.75 (m, 1H), 7.50 - 7.61 (m, 2H), 7.31 - 7.47 (m, 1H), 5.49 - 5.59 (m, 2H). LC-MS: m/z 373.2 $[M+H]$.
156		MS(ESI): 356.0 $[M+H]^+$ ^{1}HNMR (400 MHz, DMSO-d6) δ = 9.47 (s, 2H), 9.15 (s, 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.96 - 7.93 (m, 1H), 7.78 - 7.75 (m, 1H), 7.62 - 7.56 (m, 3H), 5.64 (s, 2H) ^{19}F NMR (377 MHz, DMSO-d6) δ = -120.69 (s, 2F)
157		^{1}HNMR (400 MHz, DMSO-d6) δ ppm 9.21 - 9.21 (m, 1H), 9.12 (s, 1H), 8.49 (dd, J = 9.82, 1.69 Hz, 1H), 8.39 (d, J = 5.63 Hz, 1H), 7.93 (d, J = 9.01 Hz, 1H), 7.77 (d, J = 5.63 Hz, 1H), 7.69 - 7.72 (m, 1H), 7.60 (s, 1H), 7.46 - 7.54 (m, 1H), 5.54 (d, J = 1.50 Hz, 2H). LC-MS: m/z: 373.2 $[M+H]^+$

Biological assay data and procedures

[00257] Enzymatic activity of compounds of the disclosure were determined in one of the two biochemical assays described below. Both follow the same protocol. The first relies on a caliper chip readout, while the second relies on a fluorogenic readout.

Caliper Endpoint Assay for HDAC Enzymatic Activity

[00258] HDAC reactions were assembled in 384 well plates (Greiner) in a total volume of 20 µL as follows: HDAC proteins (and their regulatory subunit, if applicable) were pre-diluted in the assay buffer comprising: 100 mM HEPES, pH 7.5, 0.1% BSA, 0.01% Triton X-100, 25mM KCl and dispensed into a 384 well plate (10 µL per well). An example of enzyme concentrations used in each assay is listed in the table below.

Assay	Expression Construct	Regulatory subunit	[Enzyme] nM	Substrate Peptide	Substrate Conc (μM)	Incubation Time (hr)
HDAC6	Full length Human HDAC6 with C-terminal FLAG-tag, expressed in baculovirus expression system.	None	6	FAM-RHKK(Ac)-NH2	1	5
HDAC8	Full length Human HDAC8 with N-terminal HIS-tag, expressed in baculovirus expression system.	None	5	FAM-RHKK(TFAc)-NH2	1	3

[00259] Test compounds were serially pre-diluted in 100% DMSO using 3-fold dilution steps and added to the protein samples by acoustic dispensing (Labcyte Echo). Concentration of DMSO was equalized to 1% in all samples. Final compound concentration in assays typically ranged from 100 μM to 0.00056 μM for a 12-point concentration-response format.

[00260] Control samples (0%-inhibition in the absence of inhibitor, DMSO only) and 100%-inhibition (in the absence of enzyme) were assembled in replicates of four (for each caliper sipper) and used to calculate the %-inhibition in the presence of compounds. At this step compounds were pre-incubated with enzyme for 30 minutes at room temperature (20-23 ºC). The reactions were initiated by addition of 10 μL of the FAM-labeled substrate peptide (see table above) pre-diluted in the same assay buffer. Final concentration of substrate peptide was 1 μM. The reactions were allowed to proceed at room temperature (20-23 ºC). Typical incubation times for each HDAC, based on pre-determined enzyme progress curves, vary and are listed in table above.

[00261] Following incubation, the reactions were quenched by addition of 50 μL of termination buffer (100 mM HEPES, pH7.5, 0.01% Triton X-100, 0.05% SDS). Terminated plates were analyzed on a microfluidic electrophoresis instrument (Caliper LabChip® 3000, Caliper Life Sciences/Perkin Elmer) which enables electrophoretic separation of deacetylated product from acetylated substrate. A change in the relative intensity of the peptide substrate and product is the parameter measured. Activity in each test sample was determined as the product to sum ratio (PSR): P/(S+P), where P is the peak height of the product, and S is the peak height of the substrate. Percent inhibition (P_{inh}) is determined using the following equation:

$P_{inh} = (PSR_{0\%inh} - PSR_{compound})/(PSR_{0\%inh} - PSR_{100\%inh})*100$, in which: $PSR_{compound}$ is the product/sum ratio in the presence of compound, $PSR_{0\%inh}$ is the product/sum ratio in the absence of compound and the $PSR_{100\%inh}$ is the product/sum ratio in the absence of the enzyme. To determine the IC_{50} of compounds (50%-inhibition) the %-inh data (P_{inh} versus

compound concentration) were fitted by a 4 parameter sigmoid dose-response model using XLfit software (IDBS).

Nanosyn Biochemical HDAC6 assay (fluorogenic format)

[00262] HDAC protein composition and respective substrate peptides are summarized in table below:

Assay name	Expression Construct	Regulatory subunit	Substrate peptide
hHDAC6	Full length Human HDAC6 with C-terminal FLAG-tag, expressed in baculovirus expression system.	None	LGK(Ac)-AMC
mHDAC6	Full length Mouse HDAC6, a.a. 2-1149 (end) with N-terminal GST-Tag, expressed in baculovirus expression system.	None	LGK(Ac)-AMC

[00263] The biochemical HDAC6 assay was performed using fluorescence detection (Fluor-De-Lys assay). In this assay, deacetylation of the Lysine residue in the LGK(Ac)-AMC peptide substrate, results in a cleavable bond between the fluorescent moiety of amino-methyl coumarin (AMC) and lysine. The AMC is released by the auxiliary treatment with trypsin, which is added to the termination buffer. The cleaved AMC generates strong fluorescent signal which is being detected (360nm excitation and 460nm emission).

[00264] HDAC reactions are assembled in black low binding 384 well plates (Corning) in a total volume of 20 mL as following:

HDAC6 protein is pre-diluted in the assay buffer comprising of: 100mM HEPES, pH 7.5, 0.01% BSA, 0.01% Triton X-100, 25mM KCl and dispensed into 384 well plate (10uL per well).

Test compounds are serially pre-diluted in DMSO and added to the protein samples by acoustic dispensing (Labcyte Echo). Concentration of DMSO is equalized to 1% in all samples.

Control samples (0%-inhibition in the absence of inhibitor, DMSO only) and 100%-inhibition (in the absence of enzyme) are assembled in the same plate and used to calculate the %-inhibition in the presence of compounds.

At this step compounds are pre-incubated with enzyme for 30 min.

The reactions are initiated by addition of 10uL of the LGK(Ac)-AMC substrate peptide pre-diluted in the same assay buffer.

Final concentration of hHDAC6 enzyme is 0.5 nM. Final concentration of mHDAC6 enzyme is 1nM. Final concentration of substrate peptide is 1.25 uM.

The reactions are allowed to proceed at room temperature for 1h.

Following incubation, the reactions are quenched by addition of 20 mL of termination buffer comprising of Trichostatin A (included as a termination agent) and trypsin (BPS catalog #50030). Terminated plates are read on Synergy Neo2 luminometer. A change in the relative luminescence intensity (RLUs) is the parameter measured. Percent inhibition (P_{inh}) is determined using the following equation:

$P_{inh} = (RLU_{0\%inh} - RLU_{compound})/(RLU_{0\%inh} - RLU_{100\%inh})*100$, in which: $RLU_{compound}$ is the sample luminescence in the presence of compound, $RLU_{0\%inh}$ is the sample luminescence in the absence of compound and the $RLU_{100\%inh}$ is the sample luminescence in the absence of the enzyme. To determine IC50 of compounds (50%-inhibition) the %-inh data (P_{inh} versus compound concentration) are fitted by a 4 parameter sigmoid dose-response model using XLfit software (IDBS)

[00265] Exemplary compounds were evaluated for inhibitory activity of a panel of HDAC paralogs. The results in Table 1 demonstrate that compounds of the disclosure have potent activity against HDAC6, and many compounds selectively inhibit HDAC6 over the Class I HDAC paralog HDAC8.

[00266] IC_{50} ranges: A: 0.001-0.1 μM; B: >0.1-1 μM; C: >1-10 μM; D: >10-100 μM; E: >100 μM.

[00267] Selectivity ranges (ratio of HDAC8 IC_{50}/HDAC6 IC_{50}): I: 0.1-1; II: >1-10; III: >10-100; IV: >100-1000; V: >1000

Table 1. In Vitro Enzymatic IC_{50} values for exemplary compounds

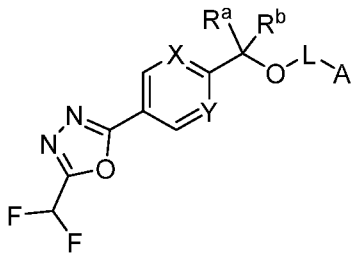
Compound	HDAC6 IC50	HDAC8 IC50	Selectivity (6 v 8) (fold)	Compound	HDAC6 IC50	HDAC8 IC50	Selectivity (6 v 8) (fold)
1	A	E	V	55	A	E	V
2	A	E	V	56	A	E	V
3	A	E	V	62	A	D	V
4	A	E	V	63	A	E	V
5	A	E	V	118	A	D	V
6	A	E	V	122	E	E	V
7	A	E	V	124	A		
8	A	E	V	125	A		
9	A	E	V	126	A		
10	A	E	V	127	A		

Compound	HDAC6 IC50	HDAC8 IC50	Selectivity (6 v 8) (fold)	Compound	HDAC6 IC50	HDAC8 IC50	Selectivity (6 v 8) (fold)
11	A	E	V	128	A		
12	A	E	V	129	A		
13	A	E	V	130	A		
14	B			131	A		
15	B	E	V	132	A		
22	A			150	A		
26	A	E	V	151	A		
27	A	E	V	152	A		
29	A	D	IV	153	A		
30	A	E	IV	154	A		
31	A	C	IV	155	A		
32	A	D	V	156	A		
33	A			157	A		
34	A	E	V	158	A		
35	A	E	V	159	A		
36	A	E	V	160	A		
39	A	E	V	161	A		
41	A	E	V	164	A		
42	A	E	V	165	A		
43	A	D	IV	166	A		
44	A	E	V	167	A		
45	A	E	V	168	A		
46	A	E	V	179	A		
47	A	D	V	180	A		
48	A	E	V	181	A		
49	A	D	IV	182	A		
50	A	E	V	197	A		
51	A	E	V	AAA	C		
52	A	E	V	trichostatin A (TSA)	A	B	IV

CLAIMS

What is claimed is:

1. A compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof,

wherein:

X is N or CR^1; Y is N or CR^1; provided that at least one of X and Y is N;

R^1 is hydrogen or halogen;

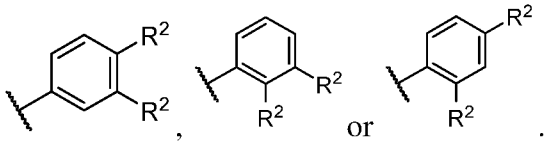
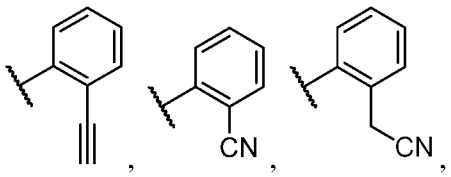
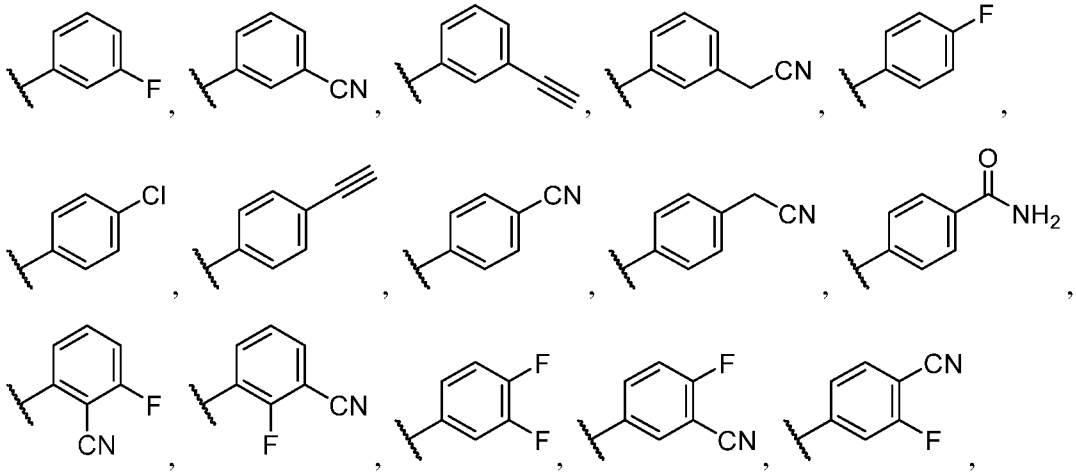
R^a and R^b are each independently hydrogen or halogen;

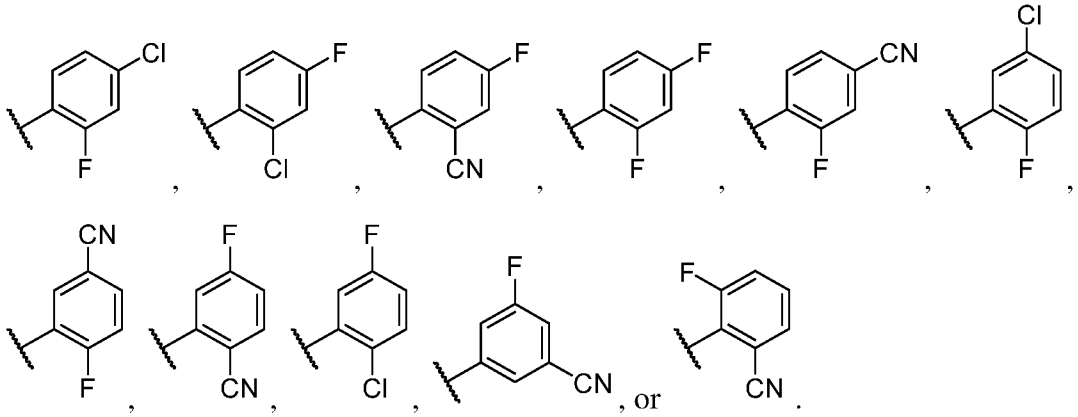
L is a bond;

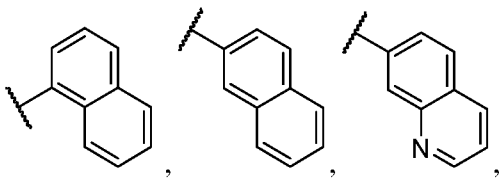
A is phenyl, phenyl fused to a 6-membered heteroaryl, or a 6,6 bicyclic aryl ring system, wherein A is optionally substituted with 1-3 independent substituents R^2;

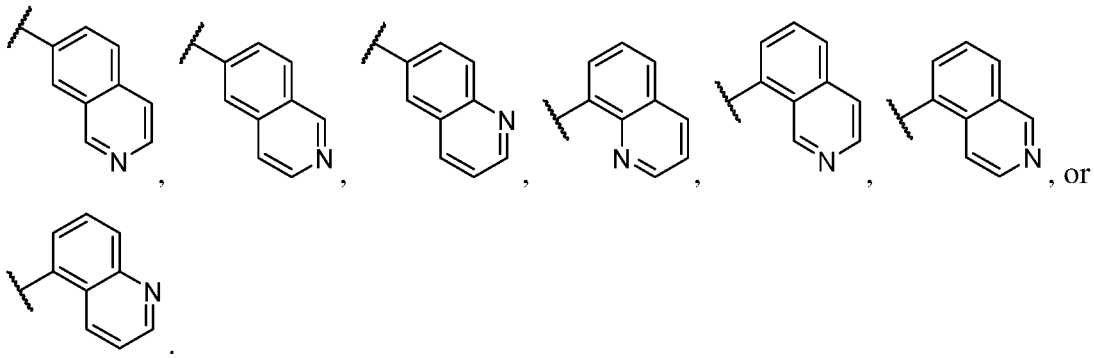
each occurrence of R^2 is independently halogen, cyano, substituted or unsubstituted amino, substituted or unsubstituted amido, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with one or more halogen or cyano.

2. The compound of claim 1, wherein R^1 is hydrogen or fluoro.
3. The compound of claim 2, wherein R^a and R^b are each independently hydrogen or fluoro.
4. The compound of claim 3, wherein each occurrence of R^2 is independently halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, cyclopropyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amidoalkyl, amino optionally substituted with C_{1-4} alkyl, or amido optionally substituted with C_{1-4} alkyl; wherein C_{1-4} alkyl is optionally substituted with halogen, cyano, amido, amino or aminoalkyl.
5. The compound of claim 4, wherein R^2 is independently chloro, fluoro, cyano, C_{1-4} alkyl, -(CH_2)CN, -NH_2, -$NH(CH_3)$, -$N(CH_3)_2$, -$C(O)NH_2$, -$C(O)NH(CH_3)$, or -$C(O)N(CH_3)_2$.

6. The compound of claim 4, wherein A is phenyl.
7. The compound of claim 6, wherein each occurrence of R^2 is independently fluoro, chloro, CN, or -CH_2-CN.
8. The compound of claim 6, wherein A is .
9. The compound of any one of claims 6-8, wherein R^a and R^b are each independently hydrogen.
10. The compound of claim 9, wherein A is substituted with 1-3 R^2 and at least one R^2 is not fluoro or chloro.
11. The compound of claim 3, wherein A is phenyl fused to a 6-member heteraryl or a 6,6 bicyclic aryl ring system.
12. The compound of claim 11, wherein A is isoquinolinyl.
13. The compound of claim 11, wherein A is naphthalenyl.
14. The compound of claim 11, wherein A is quinoxalinyl.
15. The compound of any one of claims 11-14, wherein A is unsubstituted.
16. The compound of claim 15, wherein R^a and R^b are each independently hydrogen.
17. The compound of claim 3, wherein A is , .



18. The compound of claim 1 or 3, wherein A is 

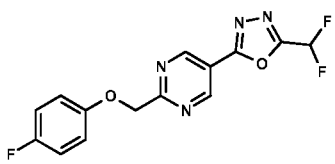
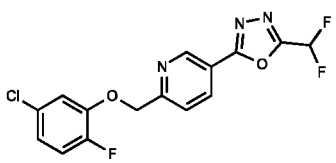
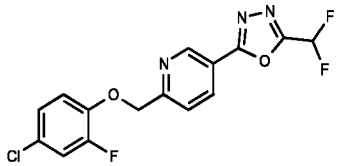


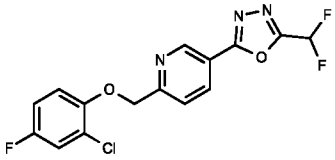
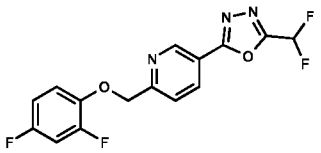
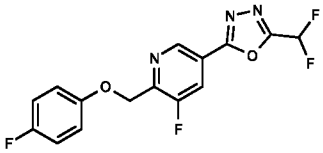
19. The compound of any one of claims 1-18, wherein X is N and Y is CH, CF or N.
20. The compound of claim 19, wherein Y is CH.
21. The compound of claim 19, wherein Y is CF.
22. The compound of claim 19, wherein Y is N.
23. The compound of claim 1, wherein the compound is 2-(difluoromethyl)-5-(2-((4-fluorophenoxy)methyl)pyrimidin-5-yl)-1,3,4-oxadiazole (1), or a pharmaceutically acceptable salt thereof.
24. The compound of claim 1, wherein the compound is 2-(6-((5-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (2), or a pharmaceutically acceptable salt thereof.
25. The compound of claim 1, wherein the compound is 2-(6-((4-chloro-2-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (3), or a pharmaceutically acceptable salt thereof.

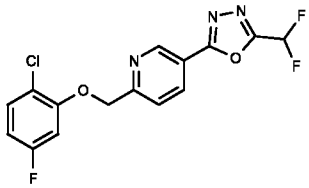
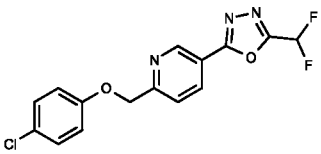
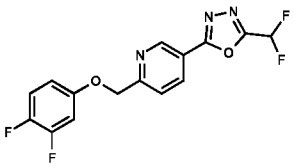
26. The compound of claim 1, wherein the compound is 2-(6-((2-chloro-4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (4), or a pharmaceutically acceptable salt thereof.
27. The compound of claim 1, wherein the compound is 2-(difluoromethyl)-5-(6-((2,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (5), or a pharmaceutically acceptable salt thereof.
28. The compound of claim 1, wherein the compound is 2-(difluoromethyl)-5-(5-fluoro-6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (6) , or a pharmaceutically acceptable salt thereof.
29. The compound of claim 1, wherein the compound is 2-(6-((2-chloro-5-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (7), or a pharmaceutically acceptable salt thereof.
30. The compound of claim 1, wherein the compound is 2-(6-((4-chlorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (8), or a pharmaceutically acceptable salt thereof.
31. The compound of claim 1, wherein the compound is 2-(difluoromethyl)-5-(6-((3,4-difluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (9), or a pharmaceutically acceptable salt thereof.
32. The compound of claim 1, wherein the compound is 2-(difluoromethyl)-5-(6-((quinolin-8-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (10), or a pharmaceutically acceptable salt thereof.
33. The compound of claim 1, wherein the compound is 2-(difluoromethyl)-5-(6-((naphthalen-1-yloxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (11), or a pharmaceutically acceptable salt thereof.
34. The compound of claim 1, wherein the compound is 2-(difluoromethyl)-5-(6-((4-fluorophenoxy)methyl)pyridin-3-yl)-1,3,4-oxadiazole (12), or a pharmaceutically acceptable salt thereof.
35. The compound of claim 1, wherein the compound is 2-(6-(difluoro(quinolin-8-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (13), or a pharmaceutically acceptable salt thereof.
36. The compound of claim 1, wherein the compound is 2-(6-(difluoro(naphthalen-1-yloxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (14), or a pharmaceutically acceptable salt thereof.

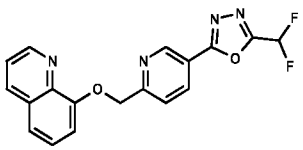
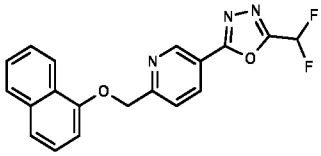
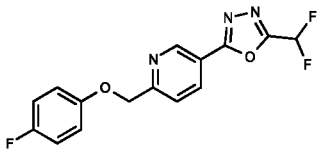
37. The compound of claim 1, wherein the compound is 2-(6-(difluoro(4-fluorophenoxy)methyl)pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (15), or a pharmaceutically acceptable salt thereof.

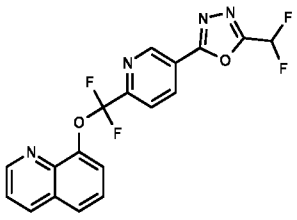
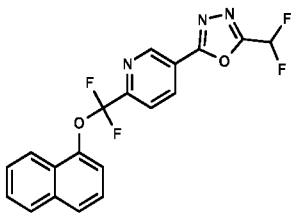
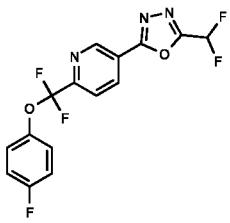
38. A pharmaceutical composition comprising a compound selected from the group consisting of:


(1),

(2),

(3),


(4),

(5),

(6),


(7),

(8),

(9),


(10),

(11),

(12),


(13),

(14), or

(15),

or a pharmaceutically acceptable salt thereof.

39. A method of treating a neurological disorder in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a

compound of any one of claims 1-38 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 38.

40. The method of claim 39, wherein the neurological disorder is amyotrophic lateral sclerosis.
41. The method of claim 39, wherein the neurological disorder is a tauopathy.
42. A method of treating autosomal dominant polycystic kidney disease in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-38 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 39.
43. A method of treating chemotherapy-induced peripheral neuropathy or chemotherapy-induced cognitive dysfunction in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-38 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 39.
44. The method of claim 43, wherein the subject is diagnosed with chemotherapy-induced peripheral neuropathy.
45. A method of treating cardiac dysfunction in a human comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-38 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 39.
46. The method of claim 45, wherein the subject is diagnosed with cardiomyopathy or cardiovascular disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 23/17900

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/44, A61K 31/381, A61K 31/443, A61K 31/395 (2023.01)
ADD. A61K 31/33, A61K 31/352 (2023.01)

CPC - INV. A61K 31/44, A61K 31/381, A61K 31/443, A61K 31/395
ADD. A61K 31/33, A61K 31/352

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"Pubchem CID 162351258", Create date: 13 December 2021 (13.12.2021), entire document, especially page 2, compound listed	1
Y	"Pubchem CID 19371420", Create date: 04 December 2007 (04.12.2007), entire document, especially page 2, compound listed	1
A	WO 2020/127974 A1 (Bayer Aktiengesellschaft), 25 June 2020 (25.06.2020), entire document, especially page 2, ln 1-10; page 9, ln 1-32; page 10, ln 1-38	1
A	US 2018/0256572 A1 (Yates, C., M.), 13 September 2018 (13.09.2018), entire document, especially para[0010]-[0024], [0695]	1
A	US 2018/0273495 A1 (Chong Kun Dang Pharmaceutical Corp.), 27 September 2018 (27.09.2018), entire document, especially para[0024]-[]	1
A	WO 2022/029041 A1 (Italfarmaco S.P.A.), 10 February 2022 (10.02.2022), entire document, especially page 8, para 3; page 9, para 2; page 10, para 1; page 12, row 1, third compound listed	1
A	US 2022/0098180 A1 (Takeda Pharmaceutical Company Limited), 31 March 2022 (31.03.2022), entire document, especially para[0021]-[0041]	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 June 2023	AUG 23 2023
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 23/17900

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 19-22, 39-46
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
----see supplemental box----

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/17900

Box III: lack of unity

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-18 and 23-38 are directed to a compound having a structure of Formula (I) as seen in instant claim 1. Claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by a compound of Formula (I) wherein X is N; Y is N; provided that at least one of X and Y is N; Ra and Rb are each independently hydrogen; L is a bond; A is phenyl. It is believed that claim 1 read on this first named invention, and thus these claims will be searched without fee. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of Formula (I) wherein X is N; Y is N; provided that at least one of X and Y is N; Ra is halogen; Rb is hydrogen; L is a bond; A is phenyl (i.e., claim 1).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Each invention in Group I+ includes the technical feature of a unique compound of Formula (I), which is not required by any other invention of Group I+.

Common Technical Features:

The inventions of Groups I+ share the technical feature of a compound of Formula (I).

These shared technical features, however, do not provide a contribution over the prior art as being obvious over a document entitled "Pubchem CID 162351258" (hereinafter 'Pubchem-258') in view of a document entitled "Pubchem CID 19371420" (hereinafter 'Pubchem -420'). Pubchem-258 teaches a compound analogous to a compound of Formula (I) as seen in instant claim 1 or a pharmaceutically acceptable salt thereof, wherein: X is N; Y is N; L is a bond; A is phenyl (see page 2, compound listed) but does not teach wherein a -CRaRb- moiety is between the pyrimidine ring and the phenoxy group wherein Ra and Rb are each independently hydrogen. However, Pubchem-420 does teach a compound analogous to a compound of Formula (I) as seen in instant claim 1 wherein Ra and Rb are each independently hydrogen (see page 2, compound listed). Therefore, based on the structural similarities between the two compounds, it would have been obvious to a person of ordinary skill in the art to combine these references and incorporate a -CRaRb- moiety is between the pyrimidine ring and the phenoxy group wherein Ra and Rb are each independently hydrogen Pubchem-420's compound into Pubchem-258's compound in order to isolate all possible derivatives of Pubchem-258's compounds by routine experimentation.

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+. The inventions of Group I+ thus lack unity under PCT Rule 13.

Note:
Claims 19-22 and 39-46 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).