BICYCLIC HETEROAROMATIC COMPOUNDS AS TRPML MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Application No. 63/564,383, filed March 12, 2024, the entirety of which is incorporated by reference.

BACKGROUND

[0002] Transient receptor potential (TRP) channels TRPML1, TRPML2, and TRPML3 are Ca^{2-} cation channels that are mostly localized to intracellular compartments. TRPML1, for example, otherwise referred to as MCOLN1 is a Ca^{2+} channel in the lysosome that regulates certain aspects of lysosome trafficking, including autophagy. *See* Wang, *et al.*, PNAS, E1373-E1381 (March 2, 2015). In particular, TRPML1 is an inwardly rectifying current channel that transports cations from the lumen of the lysosome to the cytosol. *See* Di Paolda, *et al.*, Cell Calcium 69:112-121 (2018). Release of Ca^{2+} from the lysosome via TRPML1 modulates transcription factor EB activity. *See* Medina, *et al.*, Nat. Cell. Biol., 17(3):288-299 (2015).

SUMMARY

[0003] It has recently been discovered that upregulation of autophagy is beneficial to patients suffering from a number of diseases and disorders. For example, it has been reported that inducing autophagy promotes clearance of hepatotoxic alpha-1-anti-trypsin (ATZ) in the liver. *See* Pastore, *et al.*, EMBO Mol. Med. 5(3): 397-412 (Mar. 2013). Moreover, autophagy was recently found to be useful in the treatment of neurodegenerative disorders, cancer, and heart disease. *See* Pierzynowska, *et al.*, Metab. Brain Dis., 33(4); 989-1008 (2018) (discussing neurodegenerative disorders); Nelson & Shacka, Curr. Pathobiol. Rep., 1(4): 239-245 (2013) (discussing cancer); Sciaretta, *et al.*, Annual Review of Physiology, 80:1-26 (2018) (discussing heart disease); Maiuri & Kroemer, Cell Death & Differentiation, 26: 680-689 (2019) (discussing therapeutic applications of autophagy, generally).

[0004] The present disclosure provides, among other things, technologies for regulating (e.g., up-regulating) autophagy. For example, in some embodiments, the present disclosure demonstrates effectiveness of certain approaches to TRPML modulation (e.g., TRPML agonism, including agonism of TRPML1, TPRML2, and/or TRPML3) in enhancing autophagy. Thus,

among other things, the present disclosure demonstrates that targeting a TRPML (e.g., TRPML1, TRPML2, and/or TRPML3) as described herein can enhance autophagy.

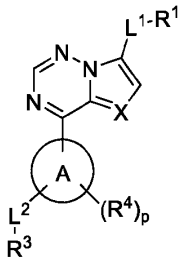
[0005] The present disclosure also provides certain technologies for use in medicine, and in particular for treating certain diseases, disorders or conditions and/or for identifying, characterizing, and/or manufacturing certain agents and/or compositions or that comprise or deliver them that are useful in treating such diseases, disorders or conditions.

[0006] In some embodiments, the present disclosure demonstrates that modulating (e.g., agonizing) a TRPML (e.g., TRPML1, TRPML2, and/or TRPML3) and/or otherwise enhancing autophagy is useful in the treatment of certain diseases, disorders or conditions.

[0007] It is, therefore, desirable to identify methods and modes of promoting autophagy. Given TRPML's role in autophagy, described herein are TRPML (e.g., TRPML1, TRPML2, and/or TRPML3) modulators useful for promoting autophagy and/or treating certain diseases, disorders, or conditions.

[0008] In particular, the present application provides technologies useful for modulating a TRPML (e.g., TRPML1, TRPML2, and/or TRPML3).

[0009] In some embodiments, the present disclosure provides a compound represented by Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein X, R^1, R^3, R^4, L^1, L^2, Ring A, and p are as defined in classes and subclasses herein, both singly and in combination.

[0010] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound represented by Formula I, or a pharmaceutically acceptable salt thereof.

[0011] In some embodiments, the present disclosure provides a method of modulating TRMPL in a subject comprising administering to the subject a compound described herein.

[0012] In some embodiments the present disclosure provides a method of treating a disease, disorder, or condition in a subject comprising administering to the subject a compound described herein.

BREIF DESCRIPTION OF THE DRAWINGS

[0013] Figure 1 presents a representative graph depicting abundance of alpha-synuclein present in the striata of rats following treatment with compounds of the present disclosure compared to control. Each dot represents an individual rat and the horizontal line is the median for each treatment group.

[0014] Figure 2 presents a representative graph depicting abundance of TH+ neurons in the injected hemisphere of the substantia nigra of rats following treatment with compounds of the present disclosure compared to control. Each dot represents an individual rat and the horizontal line is the median for each treatment group.

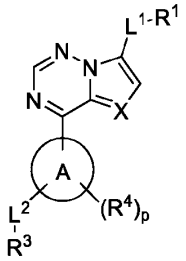
[0015] Figure 3 presents a visualization of rat brain slice images with TH+ (tyrosine hydrolase) neuron staining to depict abundance of neurons following treatment with compounds of the present disclosure compared to control. The boxed region denotes the substantia nigra of the injected hemisphere.

[0016] Figure 4 presents a representative diagram depicting percentage survival of mice co-treated with compounds of the present disclosure and Conduritol-β-epoxide (CBE) compared to control and CBE alone.

[0017] Figure 5 presents a representative graph depicting abundance of neurofilament light chain (NfL) in the cerebrospinal fluid of mice following co-treatment with compounds of the present disclosure and CBE compared to control and CBE alone.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0018] The present disclosure provides, among other things, compounds and compositions that are modulators of TRPML (e.g., TRPML1, TRPML2, and/or TRPML3). In some embodiments, modulators of TRPML are agonists of TRPML. In some embodiments, a modulator of TRPML is a compound represented by Formula I:



I

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

Compounds and Definitions

[0019] Compounds of this disclosure include those described generally above and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0020] Unless otherwise stated, structures depicted herein are meant to include all stereoisomeric (e.g., enantiomeric or diastereomeric) forms of the structure, as well as all geometric or conformational isomeric forms of the structure. For example, the R and S configurations of each stereocenter are contemplated as part of the disclosure. Therefore, single stereochemical isomers, as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of provided compounds are within the scope of the disclosure. For example, in some cases, Table 1 shows one or more stereoisomers of a compound, and unless otherwise indicated, represents each stereoisomer alone and/or as a mixture. Unless otherwise stated, all tautomeric forms of provided compounds are within the scope of the disclosure.

[0021] Unless otherwise indicated, structures depicted herein are meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example,

compounds having the present structures including replacement of hydrogen by deuterium or tritium, or replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure.

[0022] ***About or approximately:*** As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In general, those skilled in the art, familiar within the context, will appreciate the relevant degree of variance encompassed by "about" or "approximately" in that context. For example, in some embodiments, the term "approximately" or "about" may encompass a range of values that are within (i.e., ±) 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less of the referred value.

[0023] ***Administering:*** As used herein, the term "administering" or "administration" typically refers to the administration of a composition to a subject to achieve delivery of an agent that is, or is included in, a composition to a target site or a site to be treated. Those of ordinary skill in the art will be aware of a variety of routes that may, in appropriate circumstances, be utilized for administration to a subject, for example a human. For example, in some embodiments, administration may be ocular, oral, parenteral, topical, *etc.* In some particular embodiments, administration may be bronchial (*e.g.*, by bronchial instillation), buccal, dermal (which may be or comprise, for example, one or more of topical to the dermis, intradermal, interdermal, transdermal, *etc.*), enteral, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, within a specific organ (*e.g.*, intrahepatic), mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (*e.g.*, by intratracheal instillation), vaginal, vitreal, *etc.* In some embodiments, administration may be parenteral. In some embodiments, administration may be oral. In some particular embodiments, administration may be intravenous. In some particular embodiments, administration may be subcutaneous. In some embodiments, administration may involve only a single dose. In some embodiments, administration may involve application of a fixed number of doses. In some embodiments, administration may involve dosing that is intermittent (*e.g.*, a plurality of doses separated in time) and/or periodic (*e.g.*, individual doses separated by a common period of time) dosing. In some embodiments, administration may involve continuous dosing (*e.g.*, perfusion) for at least a selected period of time. In some embodiments, administration may comprise a prime-and-boost protocol. A prime-and-boost protocol can include administration of a first dose of a

pharmaceutical composition (e.g., an immunogenic composition, e.g., a vaccine) followed by, after an interval of time, administration of a second or subsequent dose of a pharmaceutical composition (e.g., an immunogenic composition, e.g., a vaccine). In the case of an immunogenic composition, a prime-and-boost protocol can result in an increased immune response in a patient.

[0024] ***Agonist***: As used herein, the term "agonist" generally refers to an agent whose presence or level correlates with elevated level or activity of a target, as compared with that observed absent the agent (or with the agent at a different level). In some embodiments, an agonist is one whose presence or level correlates with a target level or activity that is comparable to or greater than a particular reference level or activity (e.g., that observed under appropriate reference conditions, such as presence of a known agonist, e.g., a positive control). In some embodiments, an agonist may be a direct agonist in that it exerts its influence directly on (e.g., interacts directly with) the target; in some embodiments, an agonist may be an indirect agonist in that it exerts its influence indirectly (e.g., by acting on, such as interacting with, a regulator of the target, or with some other component or entity).

[0025] ***Aliphatic:*** The term "aliphatic" refers to a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "cycloaliphatic"), that has a single point or more than one points of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-12 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms (e.g., C_{1-6}). In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms (e.g., C_{1-5}). In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms (e.g., C_{1-4}). In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms (e.g., C_{1-3}), and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms (e.g., C_{1-2}). Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups and hybrids thereof. A preferred aliphatic group is C_{1-6} alkyl. In some embodiments, an aliphatic is a bivalent group, such as an alkylene, alkenylene, or alkynylene.

[0026] ***Alkyl:*** The term "alkyl", used alone or as part of a larger moiety, refers to a saturated, optionally substituted straight or branched chain hydrocarbon group having (unless otherwise

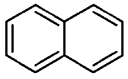
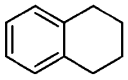
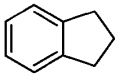
specified) 1-12, 1-10, 1-8, 1-6, 1-4, 1-3, or 1-2 carbon atoms (e.g., C_{1-12}, C_{1-10}, C_{1-8}, C_{1-6}, C_{1-4}, C_{1-3}, or C_{1-2}). Exemplary alkyl groups include methyl, ethyl, propyl, butyl, pentyl, hexyl, and heptyl.

[0027] ***Alkylene:*** The term "alkylene" refers to a bivalent alkyl group. In some embodiments, "alkylene" is a bivalent straight or branched alkyl group. In some embodiments, an "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, e.g., from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. An optionally substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms is optionally replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group and also include those described in the specification herein. It will be appreciated that two substituents of the alkylene group may be taken together to form a ring system. In certain embodiments, two substituents can be taken together to form a 3- to 7-membered ring. The substituents can be on the same or different atoms. The suffix "-ene" or "-enyl" when appended to certain groups herein are intended to refer to a bifunctional moiety of said group. For example, "-ene" or "-enyl", when appended to "cyclopropyl" becomes "cyclopropylene" or "cyclopropylenyl" and is intended to refer to a bifunctional cyclopropyl group, e.g., .

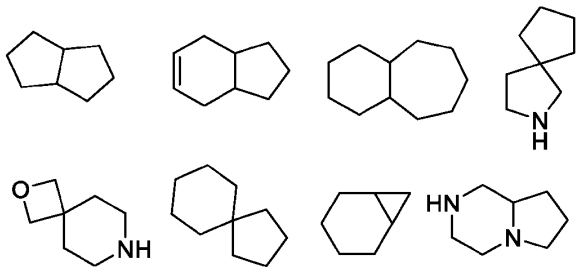
[0028] ***Alkenyl:*** The term "alkenyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain or cyclic hydrocarbon group having at least one double bond and having (unless otherwise specified) 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms (e.g., C_{2-12}, C_{2-10}, C_{2-8}, C_{2-6}, C_{2-4}, or C_{2-3}). Exemplary alkenyl groups include ethenyl, propenyl, butenyl, pentenyl, hexenyl, and heptenyl. The term "cycloalkenyl" refers to an optionally substituted non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and having about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[0029] ***Alkynyl:*** The term "alkynyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one triple bond and having (unless otherwise specified) 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms (e.g., C_{2-12}, C_{2-10}, C_{2-8}, C_{2-6}, C_{2-4}, or C_{2-3}). Exemplary alkynyl groups include ethynyl, propynyl, butynyl, pentynyl, hexynyl, and heptynyl.

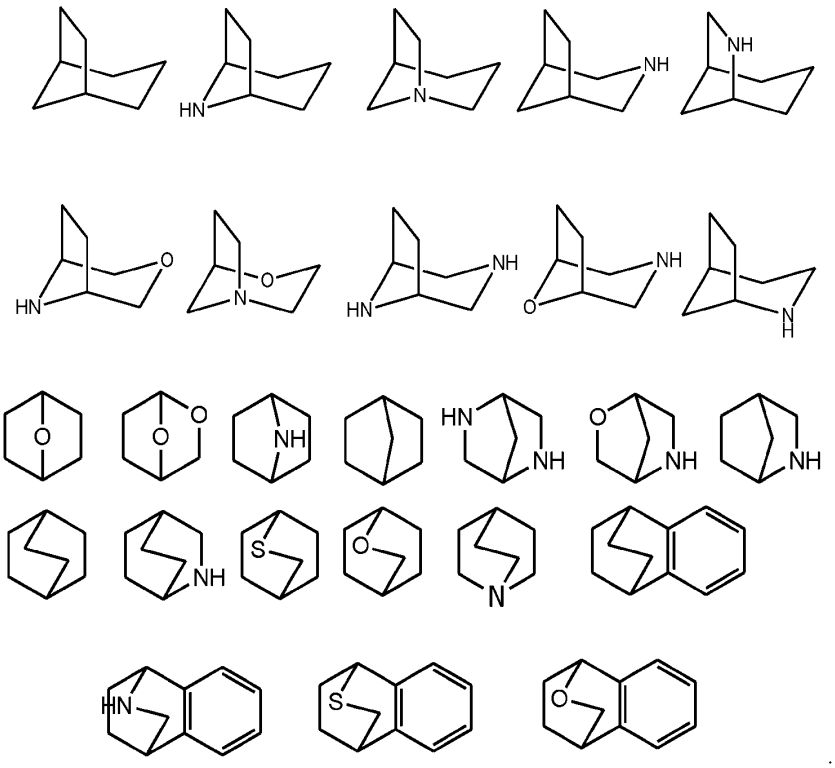
[0030] ***Aryl:*** The term "aryl" refers to monocyclic and bicyclic ring systems having a total of six to fourteen ring members (e.g., C_6-C_{14}), wherein at least one ring in the system is aromatic and

wherein each ring in the system contains three to seven ring members. In some embodiments, an "aryl" group contains between six and twelve total ring members (e.g., C_6-C_{12}). The term "aryl" may be used interchangeably with the term "aryl ring". In certain embodiments, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Unless otherwise specified, "aryl" groups are hydrocarbons. In some embodiments, an "aryl" ring system is an aromatic ring (e.g., phenyl) that is fused to a non-aromatic ring (e.g., cycloalkyl). Examples of aryl rings include that are fused include , , and .

[0031] ***Bicyclic***: The term "bicyclic ring" or "bicyclic ring system" refers to any bicyclic ring system, *i.e.*, carbocyclic or heterocyclic, saturated or having one or more units of unsaturation, having one or more atoms in common between the two rings of the ring system. Thus, the term includes any permissible ring fusion, such as *ortho*-fused or spirocyclic. As used herein, the term "heterobicyclic" is a subset of "bicyclic" that requires that one or more heteroatoms are present in one or both rings of the bicycle. Such heteroatoms may be present at ring junctions and are optionally substituted, and may be selected from nitrogen (including N-oxides), oxygen, sulfur (including oxidized forms such as sulfones and sulfonates), phosphorus (including oxidized forms such as phosphates), boron, etc. In some embodiments, a bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, *i.e.*, carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a "bridge" is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a "bridgehead" is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bicyclic rings include:



Exemplary bridged bicyclics include:



[0032] ***Biological sample:*** As used herein, the term "biological sample" typically refers to a sample obtained or derived from a biological source (e.g., a tissue or organism or cell culture) of interest, as described herein. In some embodiments, a source of interest comprises an organism, such as an animal or human. In some embodiments, a biological sample is or comprises biological tissue or fluid. In some embodiments, a biological sample may be or comprise bone marrow; blood; blood cells; ascites; tissue or fine needle biopsy samples; cell-containing body fluids; free

floating nucleic acids; sputum; saliva; urine; cerebrospinal fluid, peritoneal fluid; pleural fluid; feces; lymph; gynecological fluids; skin swabs; vaginal swabs; oral swabs; nasal swabs; washings or lavages such as a ductal lavages or broncheoalveolar lavages; aspirates; scrapings; bone marrow specimens; tissue biopsy specimens; surgical specimens; feces, other body fluids, secretions, and/or excretions; and/or cells therefrom, etc. In some embodiments, a biological sample is or comprises cells obtained from an individual. In some embodiments, obtained cells are or include cells from an individual from whom the sample is obtained. In some embodiments, a sample is a "primary sample" obtained directly from a source of interest by any appropriate means. For example, in some embodiments, a primary biological sample is obtained by methods selected from the group consisting of biopsy (e.g., fine needle aspiration or tissue biopsy), surgery, collection of body fluid (e.g., blood, lymph, feces etc.), etc. In some embodiments, as will be clear from context, the term "sample" refers to a preparation that is obtained by processing (e.g., by removing one or more components of and/or by adding one or more agents to) a primary sample. For example, filtering using a semi-permeable membrane. Such a "processed sample" may comprise, for example, nucleic acids or proteins extracted from a sample or obtained by subjecting a primary sample to techniques such as amplification or reverse transcription of mRNA, isolation and/or purification of certain components, etc.

[0033] ***Carrier:*** As used herein, the term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which a composition is administered. In some exemplary embodiments, carriers can include sterile liquids, such as, for example, water and oils, including oils of petroleum, animal, vegetable of synthetic origin, such as, for example, peanut oil, soybean oil, mineral oil, sesame oil and the like. In some embodiments, carriers are or include one or more solid components.

[0034] ***Composition:*** Those skilled in the art will appreciate that the term "composition" may be used to refer to a discrete physical entity that comprises one or more specified components. In general, unless otherwise specified, a composition may be of any form – e.g., gas, gel, liquid, solid, etc.

[0035] ***Cycloaliphatic***: As used herein, the term "cycloaliphatic" refers to a monocyclic C_{3-8} hydrocarbon or a bicyclic C_{6-12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point or more than one points of attachment to the rest of the molecule.

[0036] ***Cycloalkyl***: As used herein, the term "cycloalkyl" refers to an optionally substituted saturated ring monocyclic or polycyclic system of about 3 to about 10 ring carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0037] ***Dosage form*** or ***unit dosage form***: Those skilled in the art will appreciate that the term "dosage form" may be used to refer to a physically discrete unit of an active agent (e.g., a therapeutic or diagnostic agent) for administration to a subject. Typically, each such unit contains a predetermined quantity of active agent. In some embodiments, such quantity is a unit dosage amount (or a whole fraction thereof) appropriate for administration in accordance with a dosing regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population (i.e., with a therapeutic dosing regimen).

[0038] ***Dosing regimen*** or ***therapeutic regimen***: Those skilled in the art will appreciate that the terms "dosing regimen" and "therapeutic regimen" may be used to refer to a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which is separated in time from other doses. In some embodiments, individual doses are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount. In some embodiments, a dosing regimen is correlated with a desired or beneficial outcome when administered across a relevant population (i.e., is a therapeutic dosing regimen).

[0039] ***Effective Amount***: The term "effective amount" refers to the amount of a compound sufficient to effect beneficial or desired results (*e.g.*, a therapeutic, ameliorative, inhibitory, or preventative result). An effective amount can be administered in one or more administrations,

applications, or dosages and is not intended to be limited to a particular formulation or administration route.

[0040] ***Excipient:*** As used herein, the term "excipient" refers to a non-therapeutic agent that may be included in a pharmaceutical composition, for example, to provide or contribute to a desired consistency or stabilizing effect. Suitable pharmaceutical excipients include, for example, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like.

[0041] ***Halogen:*** The term "halogen" or "halo" means F, Cl, Br, or I.

[0042] ***Heteroaliphatic***: The term "heteroaliphatic" or "heteroaliphatic group", as used herein, denotes an optionally substituted hydrocarbon moiety having, in addition to carbon atoms, from one to five heteroatoms, that may be straight–chain (i.e., unbranched), branched, or cyclic ("heterocyclic") and may be completely saturated or may contain one or more units of unsaturation, but which is not aromatic. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. The term "nitrogen" also includes a substituted nitrogen. Unless otherwise specified, heteroaliphatic groups contain 1–10 carbon atoms wherein 1–3 carbon atoms are optionally and independently replaced with heteroatoms selected from oxygen, nitrogen, and sulfur. In some embodiments, heteroaliphatic groups contain 1–4 carbon atoms, wherein 1–2 carbon atoms are optionally and independently replaced with heteroatoms selected from oxygen, nitrogen, and sulfur. In yet other embodiments, heteroaliphatic groups contain 1–3 carbon atoms, wherein 1 carbon atom is optionally and independently replaced with a heteroatom selected from oxygen, nitrogen, and sulfur. Suitable heteroaliphatic groups include, but are not limited to, linear or branched, heteroalkyl, heteroalkenyl, and heteroalkynyl groups. For example, a 1- to 10 atom heteroaliphatic group includes the following exemplary groups: $-O-CH_3$, $-CH_2-O-CH_3$, $-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_3$, and the like.

[0043] ***Heteroaryl:*** The terms "heteroaryl" and "heteroar–", used alone or as part of a larger moiety, e.g., "heteroaralkyl", or "heteroaralkoxy", refer to monocyclic or bicyclic ring groups having 5 to 10 ring atoms (e.g., 5- to 6-membered monocyclic heteroaryl or 9- to 10-membered bicyclic heteroaryl); having 6, 10, or 14 π-electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. Heteroaryl groups include, without limitation,

thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, pteridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-a]pyridyl, imidazo[4,5-b]pyridyl, imidazo[4,5-c]pyridyl, pyrrolopyridyl, pyrrolopyrazinyl, thienopyrimidinyl, triazolopyridyl, and benzoisoxazolyl. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring (i.e., a bicyclic heteroaryl ring having 1 to 3 heteroatoms). Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzothiadiazolyl, benzoxazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, pyrido[2,3–b]–1,4–oxazin–3(4H)–one, 4H-thieno[3,2-b]pyrrole, and benzoisoxazolyl. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic", any of which terms include rings that are optionally substituted.

[0044] ***Heteroatom:*** The term "heteroatom" as used herein refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen.

[0045] ***Heterocycle:*** As used herein, the terms "heterocycle", "heterocyclyl", "heterocyclic radical", and "heterocyclic ring" are used interchangeably and refer to a stable 3- to 8-membered monocyclic, a 6- to 10-membered bicyclic, or a 10- to 16-membered polycyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, such as one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl), or NR^+ (as in N-substituted pyrrolidinyl). A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, azetidinyl, oxetanyl, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl,

piperidinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and thiamorpholinyl. A heterocyclyl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. A bicyclic heterocyclic ring also includes groups in which the heterocyclic ring is fused to one or more aryl rings. Exemplary bicyclic heterocyclic groups include indolinyl, isoindolinyl, benzodioxolyl, 1,3-dihydroisobenzofuranyl, 2,3-dihydrobenzofuranyl, and tetrahydroquinolinyl. A bicyclic heterocyclic ring can also be a spirocyclic ring system (e.g., 7- to 11-membered spirocyclic fused heterocyclic ring having, in addition to carbon atoms, one or more heteroatoms as defined above (e.g., one, two, three or four heteroatoms)). A bicyclic heterocyclic ring can also be a bridged ring system (e.g., 7- to 11-membered bridged heterocyclic ring having one, two, or three bridging atoms.

[0046] ***Modulator***: The term "modulator," as used herein, refers to a compound (e.g., a small molecule) that can alter the activity of another molecule (e.g., a protein). For example, in some embodiments, a modulator can cause an increase or decrease in the magnitude of a certain activity of a type of molecule as compared to the magnitude of the activity in the absence of the modulator. For example, a modulator can be an agonist or an antagonist of a particular target, as those terms are defined herein. For example, in some embodiments, a modulator is an agonist. In some embodiments, a modulator is an antagonist.

[0047] ***Oral:*** The phrases "oral administration" and "administered orally" as used herein have their art-understood meaning referring to administration by mouth of a compound or composition.

[0048] ***Parenteral:*** The phrases "parenteral administration" and "administered parenterally" as used herein have their art-understood meaning referring to modes of administration other than enteral and topical administration, usually by injection, and include, without limitation, intravenous, intramuscular, intra-arterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

[0049] ***Partially unsaturated:*** As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic (e.g., aryl or heteroaryl) moieties, as herein defined.

[0050] ***Patient*** or ***subject:*** As used herein, the term "patient" or "subject" refers to any organism to which a provided composition is or may be administered, e.g., for experimental, diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients or subjects include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and/or humans). In some embodiments, a patient is a human. In some embodiments, a patient or a subject is suffering from or susceptible to one or more disorders or conditions. In some embodiments, a patient or subject displays one or more symptoms of a disorder or condition. In some embodiments, a patient or subject has been diagnosed with one or more disorders or conditions. In some embodiments, a patient or a subject is receiving or has received certain therapy to diagnose and/or to treat a disease, disorder, or condition.

[0051] ***Pharmaceutical composition:*** As used herein, the term "pharmaceutical composition" refers to an active agent, formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, the active agent is present in unit dose amount appropriate for administration in a therapeutic or dosing regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

[0052] ***Pharmaceutically acceptable:*** As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

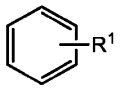
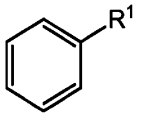
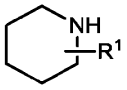
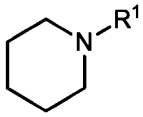
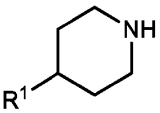
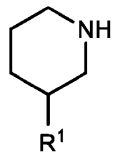
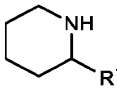
[0053] ***Pharmaceutically acceptable salt:*** The term "pharmaceutically acceptable salt", as used herein, refers to salts of such compounds that are appropriate for use in pharmaceutical contexts, i.e., salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower 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, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 66: 1-19 (1977). 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 used 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, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0054] Further, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al.*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al.*, *Journal of Pharmaceutical Sciences* **1977**, *66*(1), 1-19; P. Gould, *International J. of Pharmaceutics* **1986**, *33*, 201-217; Anderson *et al.*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference.

[0055] 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, loweralkyl sulfonate and aryl sulfonate.

[0056] ***Prevent*** or ***prevention:*** As used herein, the terms "prevent" or "prevention", when used in connection with the occurrence of a disease, disorder, and/or condition, refer to reducing the risk of developing the disease, disorder and/or condition and/or to delaying onset of one or more characteristics or symptoms of the disease, disorder or condition. Prevention may be considered complete when onset of a disease, disorder or condition has been delayed for a predefined period of time.

[0057] ***Substituted*** or ***optionally substituted:*** As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. "Substituted" applies to one or more hydrogens that are either explicit or implicit from the structure (e.g.,  refers to at least  ; and  refers to at least  ,  ,  , or ). Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes provided herein. Groups described as being "substituted" preferably have between 1 and 4 substituents, more preferably 1 or 2 substituents. Groups described as being "optionally substituted" may be unsubstituted or be "substituted" as described above.

[0058] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; –CH=CHPh, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; –CN; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5- to 6-membered heteroaryl ring), or a 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3- to 12-membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0059] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$, $-O(haloR^\bullet)$, –CN, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 3- to 6-membered saturated, partially unsaturated, or aryl ring having

0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0060] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O ("oxo"), =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0061] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, -(halo$R^\bullet$), -OH, $-OR^\bullet$, -(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0062] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3- to 12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0063] Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, $-R^\bullet$, -(halo$R^\bullet$), –OH, $-OR^\bullet$, -(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$,

or -NO_2, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0064] ***Small molecule:*** As used herein, the term "small molecule" means a low molecular weight organic and/or inorganic compound. In general, a "small molecule" is a molecule that is less than about 5 kilodaltons (kD) in size. In some embodiments, a small molecule is less than about 4 kD, 3 kD, about 2 kD, or about 1 kD. In some embodiments, the small molecule is less than about 800 daltons (D), about 600 D, about 500 D, about 400 D, about 300 D, about 200 D, or about 100 D. In some embodiments, a small molecule is less than about 2000 g/mol, less than about 1500 g/mol, less than about 1000 g/mol, less than about 800 g/mol, or less than about 500 g/mol. In some embodiments, a small molecule is not a polymer.

[0065] In some embodiments, a small molecule does not include a polymeric moiety. In some embodiments, a small molecule is not and/or does not comprise a protein or polypeptide (e.g., is not an oligopeptide or peptide). In some embodiments, a small molecule is not and/or does not comprise a polynucleotide (e.g., is not an oligonucleotide). In some embodiments, a small molecule is not and/or does not comprise a polysaccharide; for example, in some embodiments, a small molecule is not a glycoprotein, proteoglycan, glycolipid, *etc.*). In some embodiments, a small molecule is not a lipid.

[0066] In some embodiments, a small molecule is a modulating agent (e.g., is an inhibiting agent or an activating agent). In some embodiments, a small molecule is biologically active. In some embodiments, a small molecule is detectable (e.g., comprises at least one detectable moiety). In some embodiments, a small molecule is a therapeutic agent.

[0067] Those of ordinary skill in the art, reading the present disclosure, will appreciate that certain small molecule compounds described herein may be provided and/or utilized in any of a variety of forms such as, for example, crystal forms (e.g., polymorphs, solvates, etc), salt forms, protected forms, pro-drug forms, ester forms, isomeric forms (e.g., optical and/or structural isomers), isotopic forms, etc.

[0068] Those of ordinary skill in the art will appreciate that certain small molecule compounds have structures that can exist in one or more steroisomeric forms. In some embodiments, such a small molecule may be utilized in accordance with the present disclosure in the form of an

individual enantiomer, diastereomer or geometric isomer, or may be in the form of a mixture of stereoisomers; in some embodiments, such a small molecule may be utilized in accordance with the present disclosure in a racemic mixture form.

[0069] Those of skill in the art will appreciate that certain small molecule compounds have structures that can exist in one or more tautomeric forms. In some embodiments, such a small molecule may be utilized in accordance with the present disclosure in the form of an individual tautomer, or in a form that interconverts between tautomeric forms.

[0070] Those of skill in the art will appreciate that certain small molecule compounds have structures that permit isotopic substitution (e.g., ^{2}H or ^{3}H for H; ^{11}C, ^{13}C or ^{14}C for ^{12}C; ^{13}N or ^{15}N for ^{14}N; ^{17}O or ^{18}O for ^{16}O; ^{36}Cl for ^{35}Cl or ^{37}Cl; ^{18}F for ^{19}F; ^{131}I for ^{127}I; etc.). In some embodiments, such a small molecule may be utilized in accordance with the present disclosure in one or more isotopically modified forms, or mixtures thereof.

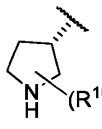
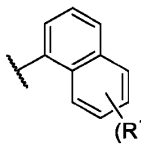
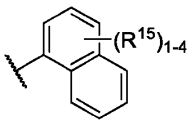
[0071] In some embodiments, reference to a particular small molecule compound may relate to a specific form of that compound. In some embodiments, a particular small molecule compound may be provided and/or utilized in a salt form (e.g., in an acid-addition or base-addition salt form, depending on the compound); in some such embodiments, the salt form may be a pharmaceutically acceptable salt form.

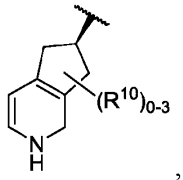
[0072] In some embodiments, where a small molecule compound is one that exists or is found in nature, that compound may be provided and/or utilized in accordance in the present disclosure in a form different from that in which it exists or is found in nature. Those of ordinary skill in the art will appreciate that, in some embodiments, a preparation of a particular small molecule compound that contains an absolute or relative amount of the compound, or of a particular form thereof, that is different from the absolute or relative (with respect to another component of the preparation including, for example, another form of the compound) amount of the compound or form that is present in a reference preparation of interest (e.g., in a primary sample from a source of interest such as a biological or environmental source) is distinct from the compound as it exists in the reference preparation or source. Thus, in some embodiments, for example, a preparation of a single stereoisomer of a small molecule compound may be considered to be a different form of the compound than a racemic mixture of the compound; a particular salt of a small molecule compound may be considered to be a different form from another salt form of the compound; a preparation that contains only a form of the compound that contains one conformational isomer

((Z) or (E)) of a double bond may be considered to be a different form of the compound from one that contains the other conformational isomer ((E) or (Z)) of the double bond; a preparation in which one or more atoms is a different isotope than is present in a reference preparation may be considered to be a different form; etc.

[0073] Those skilled in the art will further appreciate that, in small molecule structures, the symbol ~~~, as used herein, refers to a point of attachment between two atoms. Additionally or alternatively, the symbol ~~~ refers to a point of attachment ring in a spirocyclic manner.

[0074] ***Treat:*** As used herein, the terms "treat," "treatment," or "treating" refer to any method used to partially or completely alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition. In some embodiments, treatment may be administered to a subject who exhibits only early signs of the disease, disorder, and/or condition, for example, for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[0075] In some embodiments, a "floating" substituent drawn on a ring indicates that a substituent may exist at any position of the ring. For example, for a ring such as , a substituent may exist at any position and may replace a hydrogen atom of a CH moiety, a hydrogen atom of an NH moiety, and/or one or both hydrogen atoms of a CH_2 moiety. In some embodiments, a "floating" substituent drawn on one ring of a bicyclic moiety, indicates that a substituent may exist on any ring of the bicyclic moiety (e.g.,  is equivalent to ). A substituent may exist at any position of any ring of the bicyclic moiety, and may replace one or more hydrogen atoms attached to an atom in one or more of the rings of the

bicyclic moiety. For example, for a bicyclic moiety such as 

, a substituent may exist on either ring, and may replace a hydrogen atom of a CH moiety, a hydrogen atom of an NH moiety, and/or one or both hydrogen atoms of a CH_2 moiety.

TRPML and Autophagy

[0076] Autophagy is a mechanism of the cell that degrades cytoplasmic material and organelles. There are multiple types of autophagy: (1) macroautophagy (generally referred to as autophagy); (2) microautophagy; and (3) chaperone-mediated autophagy. *See* Eskelinen & Saftig, Biochimica et Biophysica Acta – Mol. Cell Res., 1793(4):664-673 (2009). In macroautophagy, the autophagosome engulfs waste materials in the cytoplasm and fuses to the lysosome, where materials are delivered for degradation. The lysosome is as a subcellular organelle containing more than 50 soluble acid hydrolases useful for digesting cellular components. Fusion of the lysosome to the autophagosome is activated, in part, by release of ions through ion channels in the membrane of the lysosome, including Ca^{2+}. *See* Cao, *et al.*, J. Bio. Chem., 292(20)8424-8435 (2017).

[0077] Transient Receptor Potential Mucolipin-1 (also known as TRPML1 or ML1) is a Ca^{2-} channel in the lysosome that regulates autophagy. *See* Wang, *et al.*, PNAS, E1373-E1381 (March 2, 2015). In particular, TRPML1 is an inwardly rectifying current channel that transports cations from the lumen of the lysosome to the cytosol. *See* Di Paolda, *et al.*, Cell Calcium 69:112-121 (2018). Release of Ca^{2+} from the lysosome via TRPML1 modulates transcription factor EB activity via ATG16L1 recruitment and GABARAP conjugation, which ultimately induces autophagy and lysosomal biogenesis. *See* Goodwin, *et al.*, Science Advances, Vol. 7, No 40 (2021).

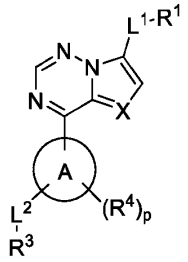
[0078] It has recently been discovered that upregulation of autophagy is beneficial to patients suffering from a number of diseases and disorders. For example, it has been reported that inducing autophagy promotes clearance of hepatotoxic alpha-1-anti-trypsin (ATZ) in the liver. *See* Pastore, *et al.*, EMBO Mol. Med. 5(3): 397-412 (Mar. 2013). Moreover, autophagy was recently found to be useful in the treatment of neurodegenerative disorders, cancer, and heart disease. *See*

Pierzynowska, *et al.*, Metab. Brain Dis., 33(4); 989-1008 (2018) (discussing neurodegenerative disorders); Nelson & Shacka, Curr. Pathobiol. Rep., 1(4): 239-245 (2013) (discussing cancer); Sciaretta, *et al.*, Annual Review of Physiology, 80:1-26 (2018) (discussing heart disease); Maiuri & Kroemer, Cell Death & Differentiation, 26: 680-689 (2019) (discussing therapeutic applications of autophagy, generally). It is, therefore, desirable to identify methods and modes of promoting autophagy. Given TRPML's role in autophagy, described herein are TRPML1 modulators useful for promoting autophagy and/or treating certain diseases, disorders, or conditions.

[0079] The present disclosure provides the insight that TRMPL may represent a particularly desirable target that, among other things, may permit modulation (e.g., enhancement) of autophagy in certain contexts.

TRPML Modulators

[0080] In some embodiments, the present disclosure provides and/or utilizes TRMPL modulators (e.g., TRPML1, TPRML2, and/or TPRML3) that are small molecule compounds having a chemical structure as indicated below in Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

X is N or CR^2;

R^1 is 5- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S, C_6-C_{12} aryl, or C_3-C_{12} cycloaliphatic, wherein R^1 is optionally substituted with one or more instances of R^{1a};

each R^{1a} is independently -CN, halogen, $-OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)R^a$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_3-C_7 cycloaliphatic;

L^1 is a bond, $N(R^a)$, O, or optionally substituted C_1-C_6 aliphatic;

R^2 is H, optionally substituted C_3-C_7 cycloaliphatic, optionally substituted phenyl, optionally substituted 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, optionally substituted C_1-C_6 aliphatic, or optionally substituted 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S;

Ring A is 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S;

L^2 is -C(O)-, -C(O)O-, -N(R^a)C(O)-, -C(O)N(R^a)-, -S(O)-, -$S(O)_2$-, optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, or optionally substituted 4- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S;

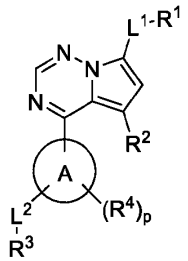
R^3 is optionally substituted C_1-C_6 aliphatic or optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S;

each R^4 is independently optionally substituted C_1-C_6 aliphatic;

each R^a is independently selected from H and optionally substituted C_1-C_6 aliphatic; and

p is 0, 1, 2, 3, or 4.

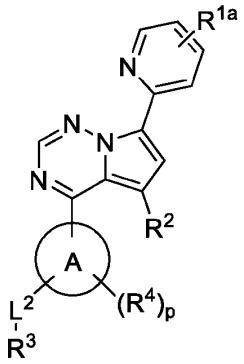
[0081] In some embodiments, the present disclosure provides a compound represented by Formula I-2:



I-2

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

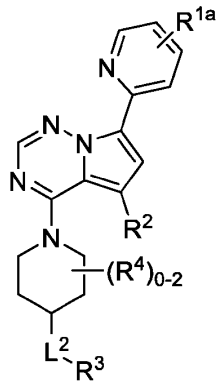
[0082] In some embodiments, the present disclosure provides a compound represented by Formula II-1:



II-1

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

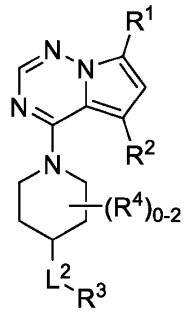
[0083] In some embodiments, the present disclosure provides a compound represented by Formula II-2:



II-2

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

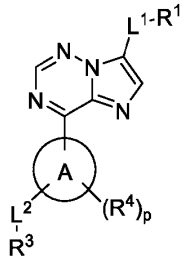
[0084] In some embodiments, the present disclosure provides a compound represented by Formula III-1:



III-1

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

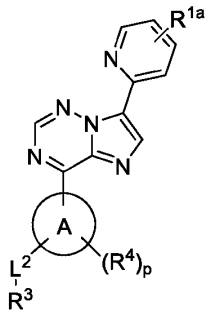
[0085] In some embodiments, the present disclosure provides a compound represented by Formula IV-1:



IV-1

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

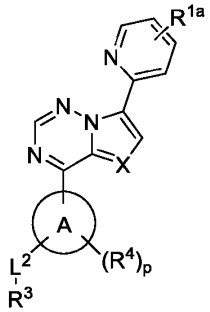
[0086] In some embodiments, the present disclosure provides a compound represented by Formula IV-2:



IV-2

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

[0087] In some embodiments, the present disclosure provides a compound represented by Formula V-1:



V-1

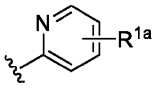
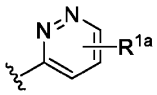
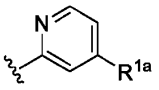
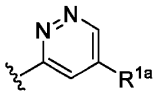
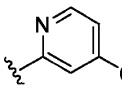
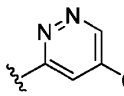
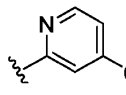
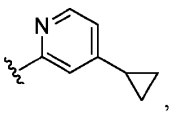
or a pharmaceutically acceptable salt thereof, wherein X, R^{1a}, R^3, R^4, Ring A, L^2, and p are as described in classes and subclasses herein, both singly and in combination.

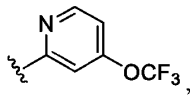
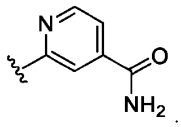
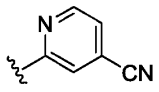
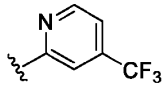
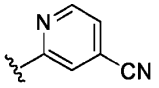
[0088] As described herein with respect to any provided Formula, X is N or CR^2. In some embodiments, X is N. In some embodiments, X is CR^2.

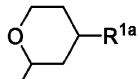
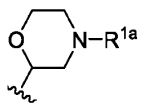
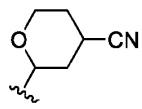
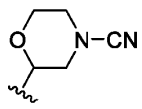
[0089] As described herein with respect to any provided Formula, L^1 is a bond, $N(R^a)$, O, or optionally substituted C_1-C_6 aliphatic. In some embodiments, L^1 is a bond. In some embodiments, L^1 is $-N(R^a)-$. In some embodiments, L^1 is -N(H)-. In some embodiments, L^1 is $-N(C_1$-C_6 aliphatic). In some embodiments, L^1 is $-N(CH_3)-$. In some embodiments, L^1 is -O-. In some embodiments, L^1 is optionally substituted C_1-C_6 aliphatic. In some embodiments, L^1 is optionally substituted C_1-C_6 alkylene. In some embodiments, L^1 is $-CH_2-$. In some embodiments, L^1 is a bond or optionally substituted C_1-C_6 aliphatic.

[0090] As described herein with respect to any provided Formula, R^1 is 5- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S, C_6-C_{12} aryl, or C_3-C_{12} cycloaliphatic, wherein R^1 is optionally substituted with one or more instances of R^{1a}.

[0091] In some embodiments, R^1 is 5- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, and is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is bicyclic 7- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S. In some embodiments, R^1 is monocyclic 5- to 6-membered

heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S, and is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is monocyclic 5- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S, and is substituted with one or more instances of R^{1a}. In some embodiments, R^1 is monocyclic 5- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S, and is substituted with one instance of R^{1a}. In some embodiments, R^1 is monocyclic 5- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S, and is substituted with -CN. In some embodiments, R^1 is monocyclic 5- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S, and is substituted with -CN, optionally substituted C_1-C_6 aliphatic, optionally substituted C_3-C_7 cycloaliphatic, $-OR^a$, or $-C(O)N(R^a)_2$. In some embodiments, R^1 is monocyclic 5- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S, and is substituted with -CN, -CF3, cyclopropyl, $-OCF_3$, or $-C(O)NH_2$. In some embodiments, R^1 is monocyclic 5- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S, and is substituted with one instance of R^{1a}, wherein R^{1a} is selected from -CN, optionally substituted C_1-C_6 aliphatic, optionally substituted C_3-C_7 cycloaliphatic, $-OR^a$, and $-C(O)N(R^a)_2$. In some embodiments, R^1 is monocyclic 5- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S, and is substituted with one instance of R^{1a}, wherein R^{1a} is selected from -CN, -CF3, cyclopropyl, $-OCF_3$, and $-C(O)NH_2$. In some embodiments, R^1 is pyridinyl or pyrazinyl optionally substituted with one or more instance of R^{1a}. In some embodiments, R^1 is pyridinyl or pyrazinyl and is substituted with one or more instances of R^{1a}. In some embodiments, R^1 is:  or . In some embodiments, R^1 is  or . In some embodiments, R^1 is , , , ,

, or . In some embodiments, R^1 is  or . In some embodiments, R^1 is .

[0092] In some embodiments, R^1 is 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S and is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is monocyclic 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and, S, and is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is monocyclic 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and, S, and is optionally substituted with one or more instances of -CN. In some embodiments, R^1 is monocyclic 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and, S, and is optionally substituted with one instance of -CN. In some embodiments, R^1 is monocyclic 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and, S, and is substituted with one or more instances of R^{1a}. In some embodiments, R^1 is monocyclic 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and, S, and is substituted one instance of R^{1a}. In some embodiments, R^1 is monocyclic 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and, S, and is substituted with one or more instances of -CN. In some embodiments, R^1 is monocyclic 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and, S, and is substituted one instance of -CN. In some embodiments, R^1 is azetidinyl, pyrrolidinyl, piperidinyl, pyrazinyl, tetrahydropyranyl, or morpholinyl, and is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is tetrahydropyranyl or morpholinyl, and is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is  or . In some embodiments, R^{1a} is  or .

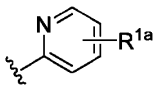
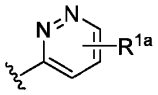
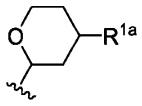
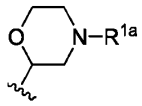
[0093] In some embodiments, R^1 is bicyclic 7- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S, and is optionally substituted with one or more instances of R^{1a}.

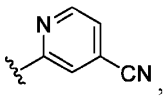
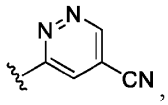
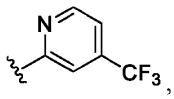
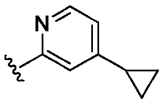
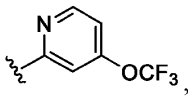
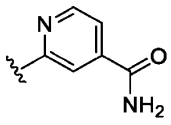
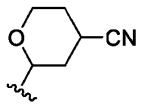
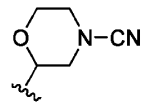
[0094] In some embodiments, R^1 is C_6-C_{12} aryl and is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is phenyl and is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is naphthyl and is optionally substituted with one or more instances of R^{1a}.

[0095] In some embodiments, R^1 is or C_3-C_{12} cycloaliphatic and is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is monocyclic C_3-C_7 cycloaliphatic and is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is bicyclic C_7-C_{12} cycloaliphatic and is optionally substituted with one or more instances of R^{1a}.

[0096] In some embodiments, R^1 is 5- to 1-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S or 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S, wherein R^1 is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S or 4- to 7-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S, wherein R^1 is optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S or 4- to 7-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S, wherein R^1 is optionally substituted with one instance of R^{1a}. In some embodiments, R^1 is 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S or 4- to 7-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S, wherein R^1 is substituted with one instance of R^{1a}.

[0097] In some embodiments, R^1 is pyridinyl, pyridazinyl, tetrahydropyranyl, or morpholinyl, optionally substituted with one or more instances of R^{1a}. In some embodiments, R^1 is pyridinyl, pyridazinyl, tetrahydropyranyl, or morpholinyl, optionally substituted with one instance of R^{1a}. In some embodiments, R^1 is pyridinyl, pyridazinyl, tetrahydropyranyl, or morpholinyl, substituted with one or more instances of R^{1a}. In some embodiments, R^1 is pyridinyl, pyridazinyl, tetrahydropyranyl, or morpholinyl, substituted with one instance of R^{1a}.

[0098] In some embodiments, R^1 is , ,  or .

[0099] In some embodiments, R^1 is , , , , , ,  or .

[0100] As described herein, each R^{1a} is independently -CN, halogen, $-OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)R^a$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_3-C_7 cycloaliphatic.

[0101] In some embodiments, R^{1a} is -CN.

[0102] In some embodiments, R^{1a} is halogen. In some embodiments, R^{1a} is fluorine, iodine, bromine, or chlorine.

[0103] In some embodiments, R^{1a} is $-OR^a$. In some embodiments, R^{1a} is OH. In some embodiments, R^{1a} is -O-C_1-C_6 aliphatic. In some embodiments, R^{1a} is $-OCH_3$. In some embodiments, R^{1a} is -O-(optionally substituted C_1-C_6 aliphatic). In some embodiments, R^{1a} is $-OCF_3$.

[0104] In some embodiments, R^{1a} is $-C(O)N(R^a)_2$. In some embodiments, R^{1a} is $-C(O)NH_2$. In some embodiments, R^{1a} is $-C(O)N(H)(CH_3)$. In some embodiments, R^{1a} is $-C(O)N(CH_3)_2$.

[0105] In some embodiments, R^{1a} is $-N(R^a)C(O)R^a$. In some embodiments, R^{1a} is $-N(H)C(O)CH_3$.

[0106] In some embodiments, R^{1a} is optionally substituted C_1-C_6 aliphatic. In some embodiments, R^{1a} is optionally substituted C_1-C_6 alkyl. In some embodiments, R^{1a} is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In some embodiments, R^{1a} is $-CF_3$.

[0107] In some embodiments, R^{1a} is optionally substituted C_3-C_7 cycloaliphatic. In some embodiments, R^{1a} is C_3-C_7 cycloaliphatic. In some embodiments, R^{1a} is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. In some embodiments, R^{1a} is cyclopropyl.

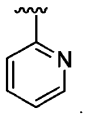
[0108] In some embodiments, each R^{1a} is independently -CN, -OR^a, -$C(O)N(R^a)_2$, optionally substituted C_1-C_6 aliphatic, or optionally substituted C_3-C_7 cycloaliphatic. In some embodiments, each R^{1a} is independently -CN, -OR^a, -$C(O)N(R^a)_2$, optionally substituted C_1-C_6 aliphatic, or C_3-C_7 cycloaliphatic. In some embodiments, each R^{1a} is independently -CN, -CF3, cyclopropyl, -OCF_3, or -$C(O)NH_2$.

[0109] As described herein, R^2 is H, optionally substituted C_3-C_7 cycloaliphatic, optionally substituted phenyl, optionally substituted 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, optionally substituted C_1-C_6 aliphatic, or optionally substituted 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

[0110] In some embodiments, R^2 is H.

[0111] In some embodiments, R^2 is optionally substituted C_3-C_7 cycloaliphatic. In some embodiments, R^2 is C_3-C_7 cycloaliphatic. In some embodiments, R^2 is optionally substituted C_3-C_7 cycloalkyl. In some embodiments, R^2 is C_3-C_7 cycloalkyl. In some embodiments, R^2 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. In some embodiments, R^2 is .

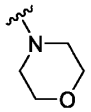
[0112] In some embodiments, R^2 is optionally substituted phenyl. In some embodiments, R^2 is phenyl.

[0113] In some embodiments, R^2 is optionally substituted 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S. In some embodiments, R^2 is 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S. In some embodiments, R^2 is pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyrimidinyl, or pyridazinyl. In some embodiments, R^2 is pyridinyl. In some embodiments, R^2 is 

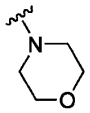
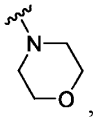
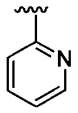
.

[0114] In some embodiments, R^2 is optionally substituted C_1-C_6 aliphatic. In some embodiments, R^2 is C_1-C_6 aliphatic. In some embodiments, R^2 is optionally substituted C_1-C_6 alkyl. In some embodiments, R^2 is C_1-C_6 alkyl. In some embodiments, R^2 is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In some embodiments, R^2 is -CH_2-CH_3 or -CH_3. In some embodiments,

R^2 is C_1-C_6 aliphatic optionally substituted with halogen. In some embodiments, R^2 is $-CF_3$. In some embodiments, R2 is $-CH_2-CH_3$, $-CH_3$, or $-CF_3$.

[0115] In some embodiments, R^2 is optionally substituted 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S. In some embodiments, R^2 is 4- to 7-membered heterocycle. In some embodiments, R^2 is optionally substituted morpholinyl. In some embodiments, R^2 is morpholinyl. In some embodiments, R^2 is: .

[0116] In some embodiments, R^2 is H, optionally substituted C_3-C_7 cycloaliphatic, optionally substituted 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, optionally substituted C_1-C_6 aliphatic, or optionally substituted 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S. In some embodiments, R^2 is H, C_3-C_7 cycloaliphatic, 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, optionally substituted C_1-C_6 aliphatic, or 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

[0117] In some embodiments, R^2 is: -H, $-CH_3$, $-CH_2-CH_3$, $-CF_3$, , or . In some embodiments, R^2 is: -H, $-CH_3$, $-CH_2-CH_3$, $-CF_3$, , , or .

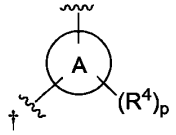
[0118] As described herein, Ring A is 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S. In some embodiments, Ring A is optionally substituted monocyclic 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S. In some embodiments, Ring A is optionally substituted piperidinyl or piperazinyl. In some embodiments, Ring A is 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, optionally substituted with $-(CH_2)_{0-4}R°$. In some embodiments, Ring A is 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, optionally substituted with R°, wherein R° is C_1-C_6 aliphatic. In some embodiments, Ring A is 4- to 6-

membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, optionally substituted with methyl, ethyl, propyl, butyl, pentyl, or hexyl. In some embodiments, Ring A is 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, optionally substituted with $-CH_3$. In some embodiments, Ring A is 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

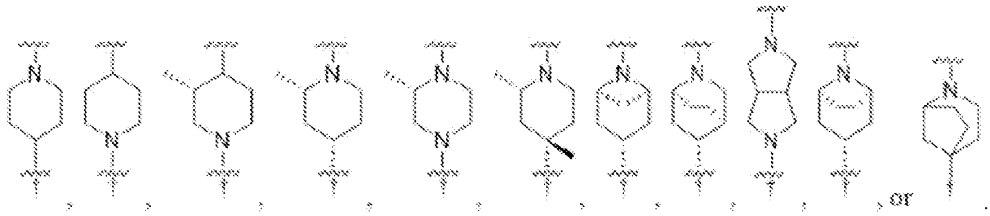
[0119] In some embodiments, Ring A is 7- to 12-membered bicyclic (e.g., bridged bicyclic) heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S. In some embodiments, Ring A is 7- to 8-membered bicyclic (e.g., bridged bicyclic) heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S.

[0120] In some embodiments, Ring A is 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S or 7- to 8-membered bicyclic (e.g., bridged bicyclic) heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S.

[0121] In some embodiments, a moiety:

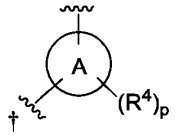


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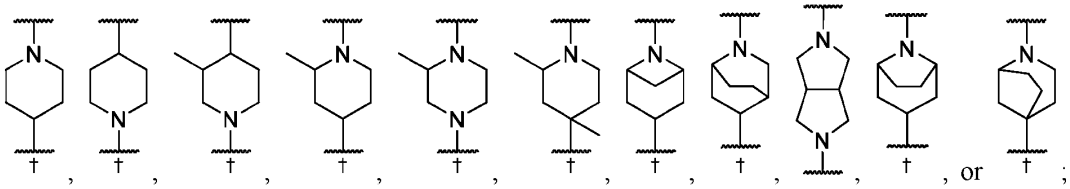


; where † represents a point of attachment to L^2.

[0122] In some embodiments, a moiety:

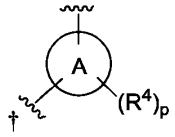


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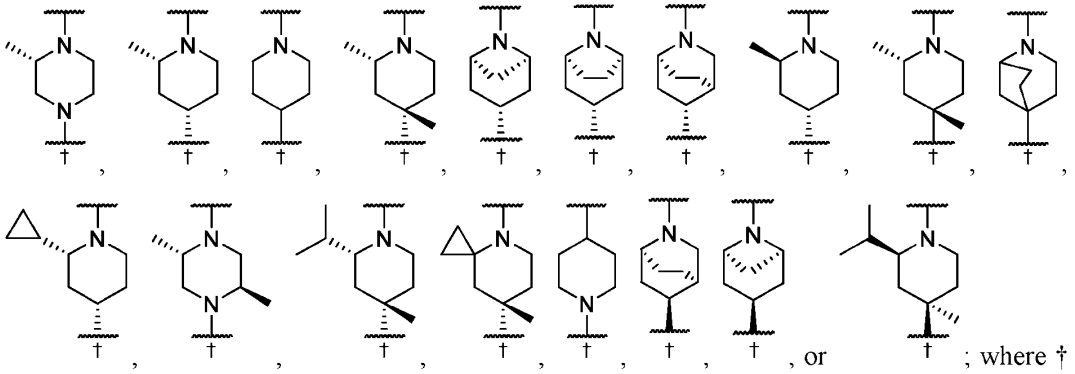


where † represents a point of attachment to L^2.

[0123] In some embodiments, a moiety:

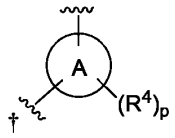


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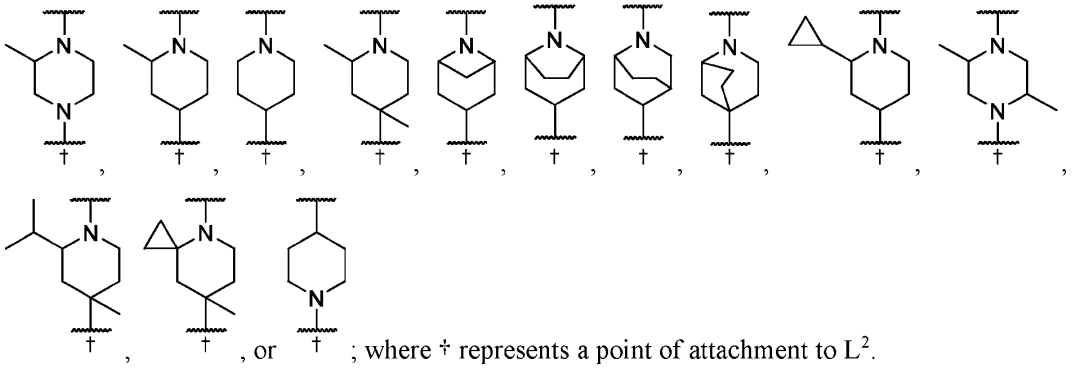


represents a point of attachment to L^2.

[0124] In some embodiments, a moiety:

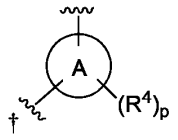


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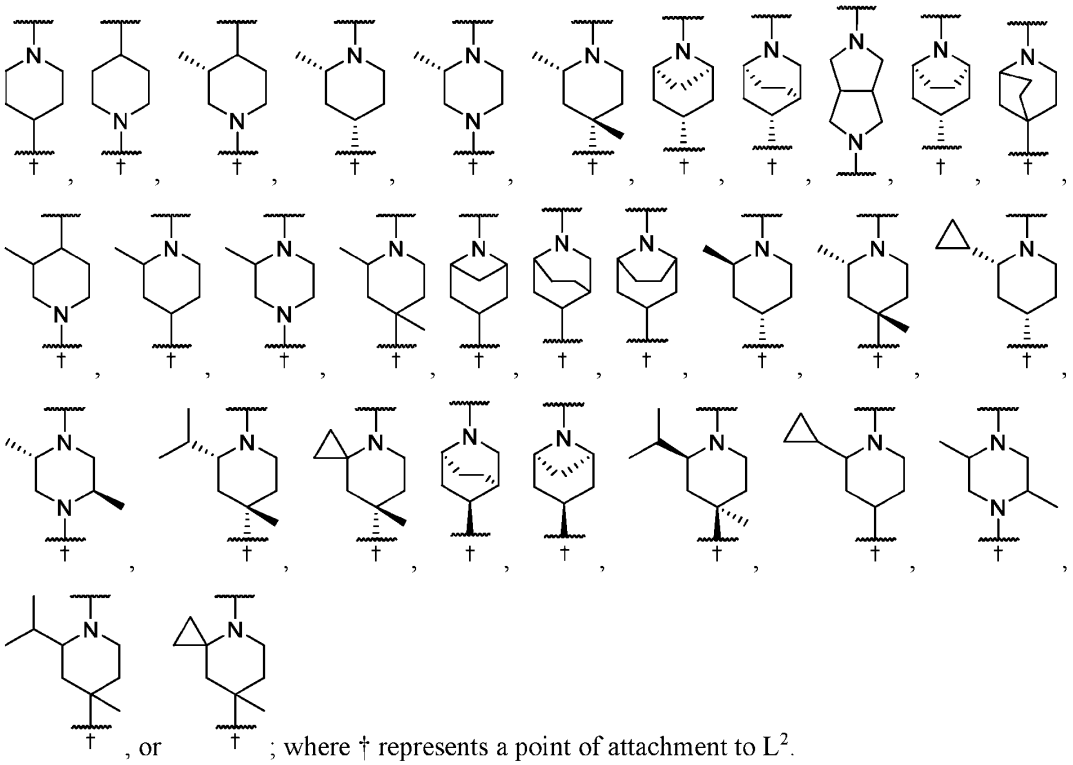


; where † represents a point of attachment to L^2.

[0125] In some embodiments, a moiety:

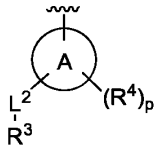


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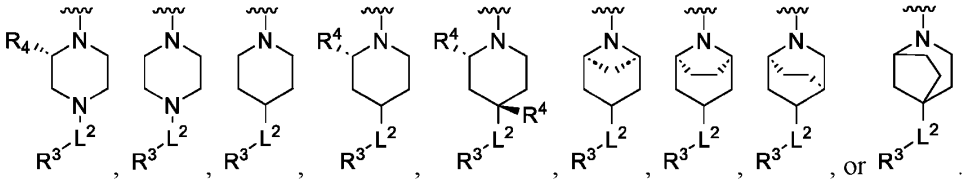


; where † represents a point of attachment to L^2.

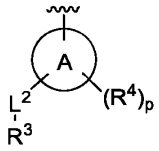
[0126] In some embodiments, a moiety:



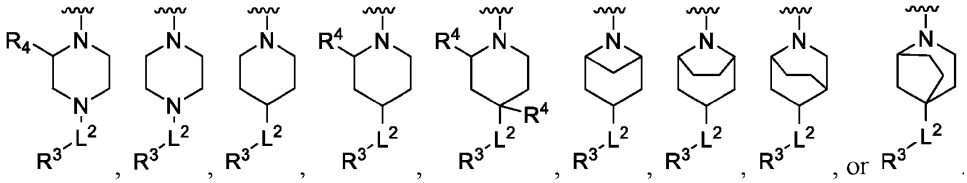
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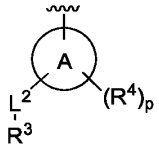
[0127] In some embodiments, a moiety:



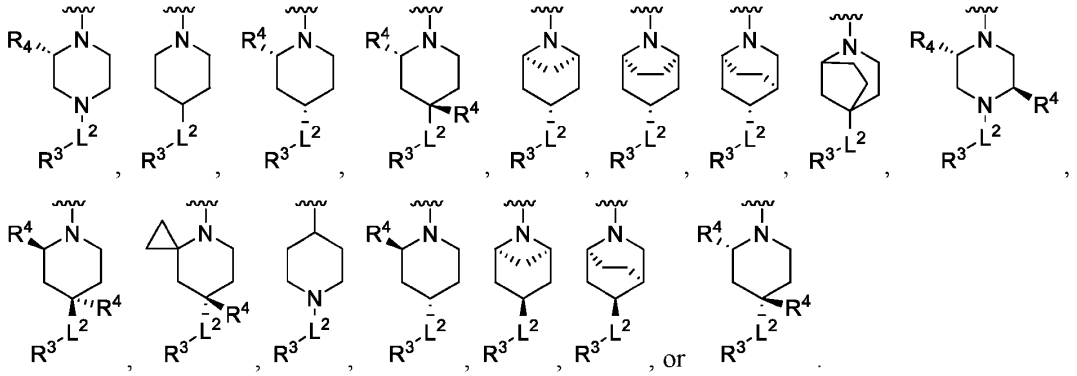
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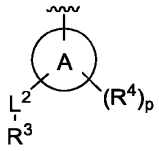
[0128] In some embodiments, a moiety:



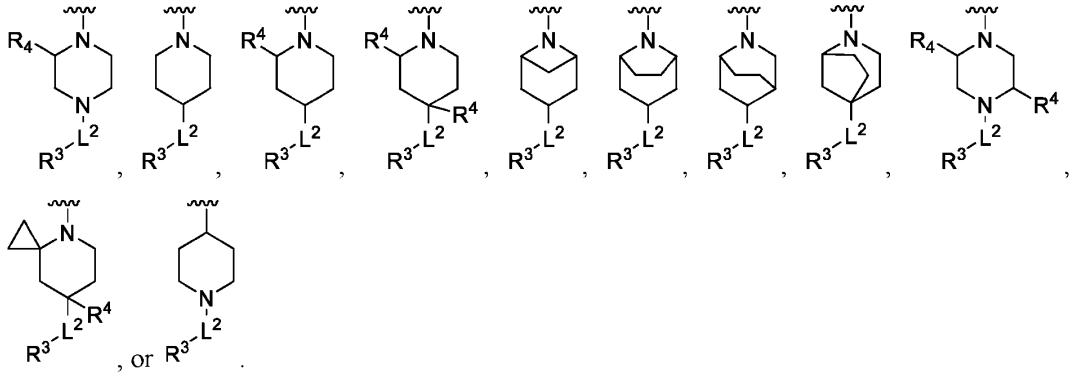
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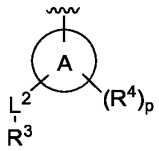
[0129] In some embodiments, a moiety:



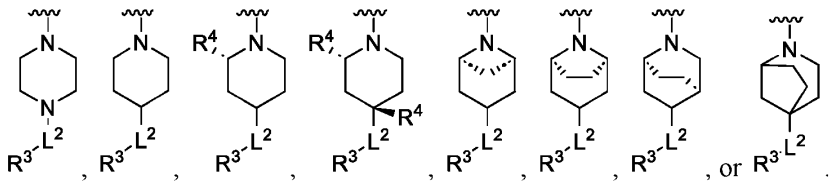
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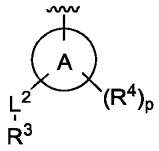
[0130] In some embodiments, a moiety:



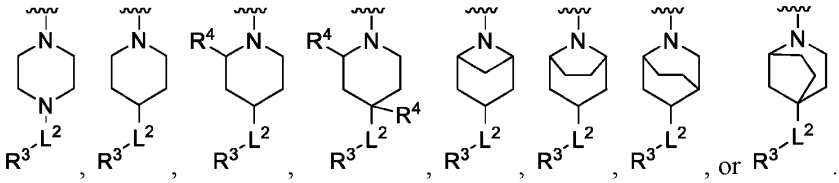
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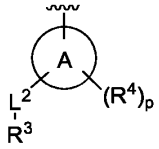
[0131] In some embodiments, a moiety:



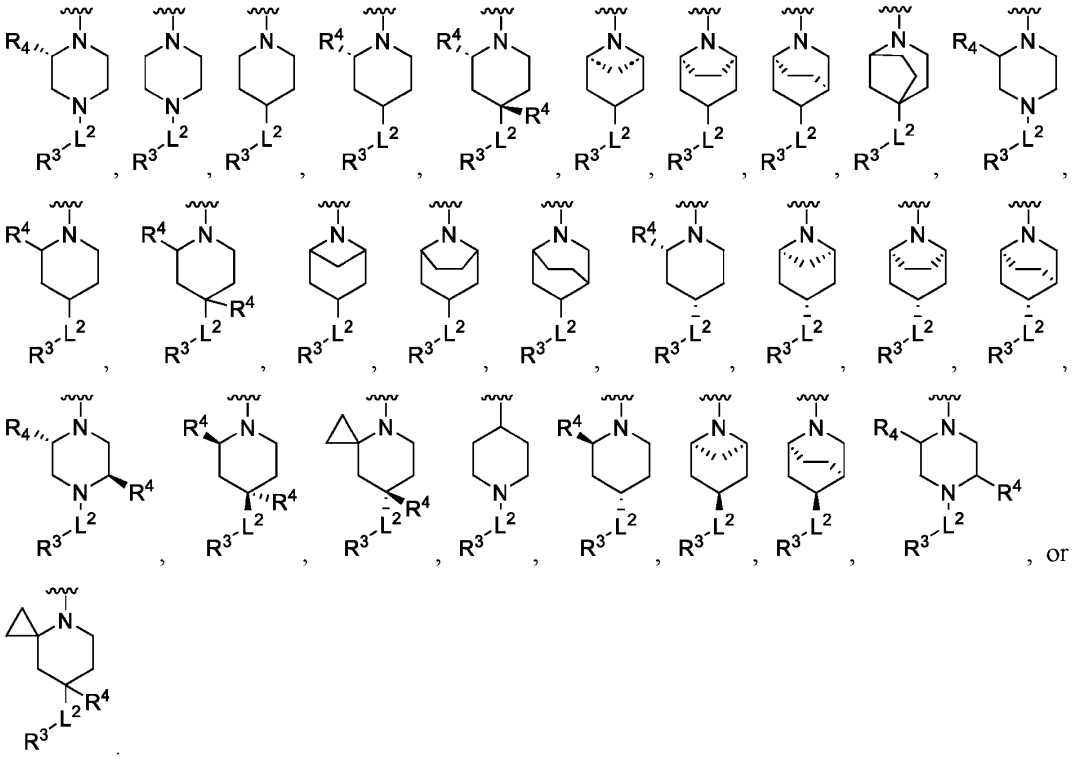
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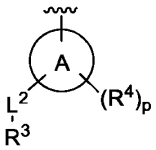
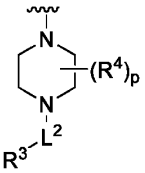
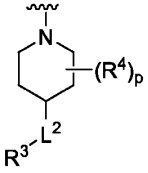
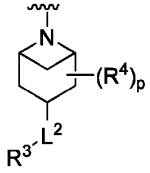
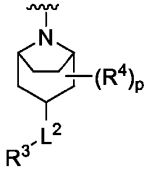
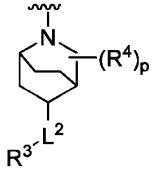
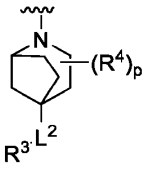
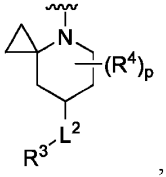
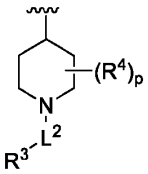


[0132] In some embodiments, a moiety:



is:



[0133] In some embodiments, a moiety  is selected from: , , , , , , , and .

[0134] As described herein, L^2 is -C(O)-, -C(O)O-, -N(R^a)C(O)-, -C(O)N(R^a)-, -S(O)-, -$S(O)_2$-, optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, or optionally substituted 4- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S.

[0135] In some embodiments, L^2 is -C(O)-.

[0136] In some embodiments, L^2 is -C(O)O-. In some embodiments, L^2 is -C(O)O-*, where * represents a point of attachment to R^3.

[0137] In some embodiments, L^2 is -N(R^a)C(O)-.

[0138] In some embodiments, L^2 is -C(O)N(R^a)-.

[0139] In some embodiments, L^2 is -S(O)-.

[0140] In some embodiments, L^2 is -$S(O)_2$-.

[0141] In some embodiments, L^2 is -C(O)-, -C(O)O- or -$S(O)_2$-.

[0142] In some embodiments, L^2 is optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

[0143] In some embodiments, L^2 is optionally substituted 4- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S.

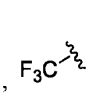
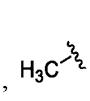
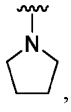
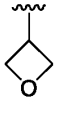
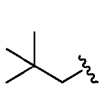
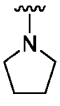
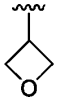
[0144] In some embodiments, L^2 is -C(O)-, -C(O)O-, -S(O)-, or -$S(O)_2$-.

[0145] As described herein, R^3 is optionally substituted C_1-C_6 aliphatic or optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and

S. In some embdoiments, R^3 is C_1-C_6 aliphatic or optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

[0146] In some embodiments, R^3 is optionally substituted C_1-C_6 aliphatic. In some embodiments, R^3 is C_1-C_6 aliphatic. In some embodiments, R^3 is C_1-C_6 aliphatic optionally substituted with halogen. In some embodiments, R^3 is optionally substituted C_1-C_6 alkyl. In some embodiments, R^3 is C_1-C_6 alkyl. In some embodiments, R^3 is methyl, ethyl, propyl, butyl, pentyl, or heptyl. In some embodiments, R^3 is $-CH_3$, $-CH(CH_3)_2$, or $-C(CH_3)_3$. In some embodiments, R^3 is , , , or . In some embodiments, R^3 is $-C(CH_3)_3$, $-CH(CH_3)_2$, or $-CH_2$-$C(CH_3)_3$.

[0147] In some embodiments, R^3 is optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S. In some embodiments, R^3 is 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, and is optionally substituted with $-(CH_2)_{0-4}R°$. In some embodiments, R^3 is 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, and is optionally substituted with R°, wherein R° is C_1-C_6 aliphatic. In some embodiments, R^3 is 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, and is optionally substituted with $-CH_3$. In some embodiments, R^3 is optionally substituted oxetane. In some embodiments, R^3 is oxetane, optionally substituted with $-CH_3$. In some embodiments, R^3 is oxetane, substituted with $-CH_3$. In some embodiments, R^3 is pyrrolidinyl. In some embodiments, R^3 is optionally substituted oxetane or pyrrolidinyl. In some embodiments, R^3 is oxetane or pyrrolidinyl, optionally substituted with $-CH_3$.

[0148] In some embodiments, R^3 is , , , , , , or . In some embodiments, R^3 is , , , , , or .

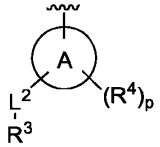
[0149] In some embodiments, L^2 is -C(O)-, -C(O)O- or $-S(O)_2$-, and R^3 is optionally substituted C_1-C_6 aliphatic or optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S. In some embodiments, L^2 is -C(O)-, -C(O)O- or $-S(O)_2$-, and R^3 is optionally substituted C_1-C_6 aliphatic. In some embodiments, L^2 is -C(O)-, -

C(O)O-, S(O), or -$S(O)_2$-, and R^3 is optionally substituted C_1-C_6 aliphatic or optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S. In some embodiments, L^2 is -C(O)-, -C(O)O-, S(O), or -$S(O)_2$-, and R^3 is C_1-C_6 aliphatic or optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

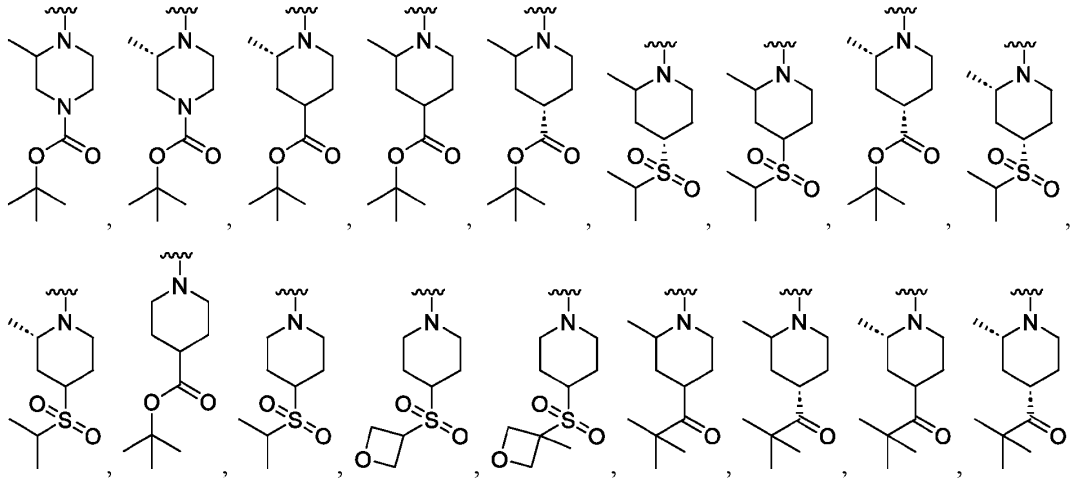
[0150] As described herein, each R^4 is independently optionally substituted C_1-C_6 aliphatic. In some embodiments, R^4 is optionally substituted C_1-C_6 alkyl. In some embodiments, R^4 is methyl, ethyl, propyl, butyl, pentyl, hexyl, or heptyl. In some embodiments, R^4 is -CH_3. In some embodiments, R^4 is cyclopropyl. In some embodiments, R^4 is methyl, isopropyl, or cyclopropyl.

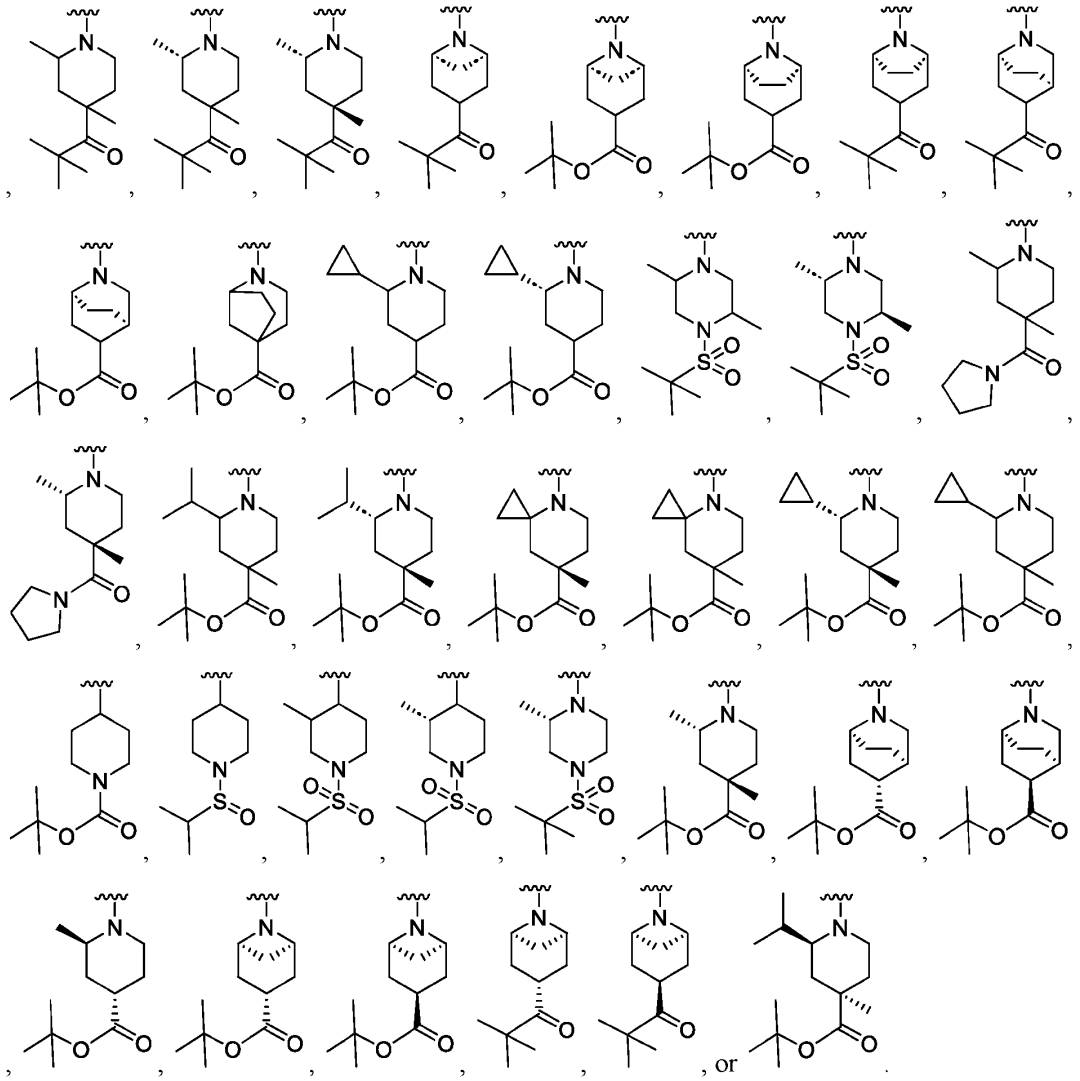
[0151] As described herein, p is 0, 1, 2, 3, or 4. In some embodiments, p is 0. In some embodiments, p is 1-4. In some embodiments, p is 0, 1, or 2. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4.

[0152] In some embodiments, a moiety:

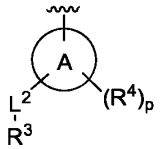


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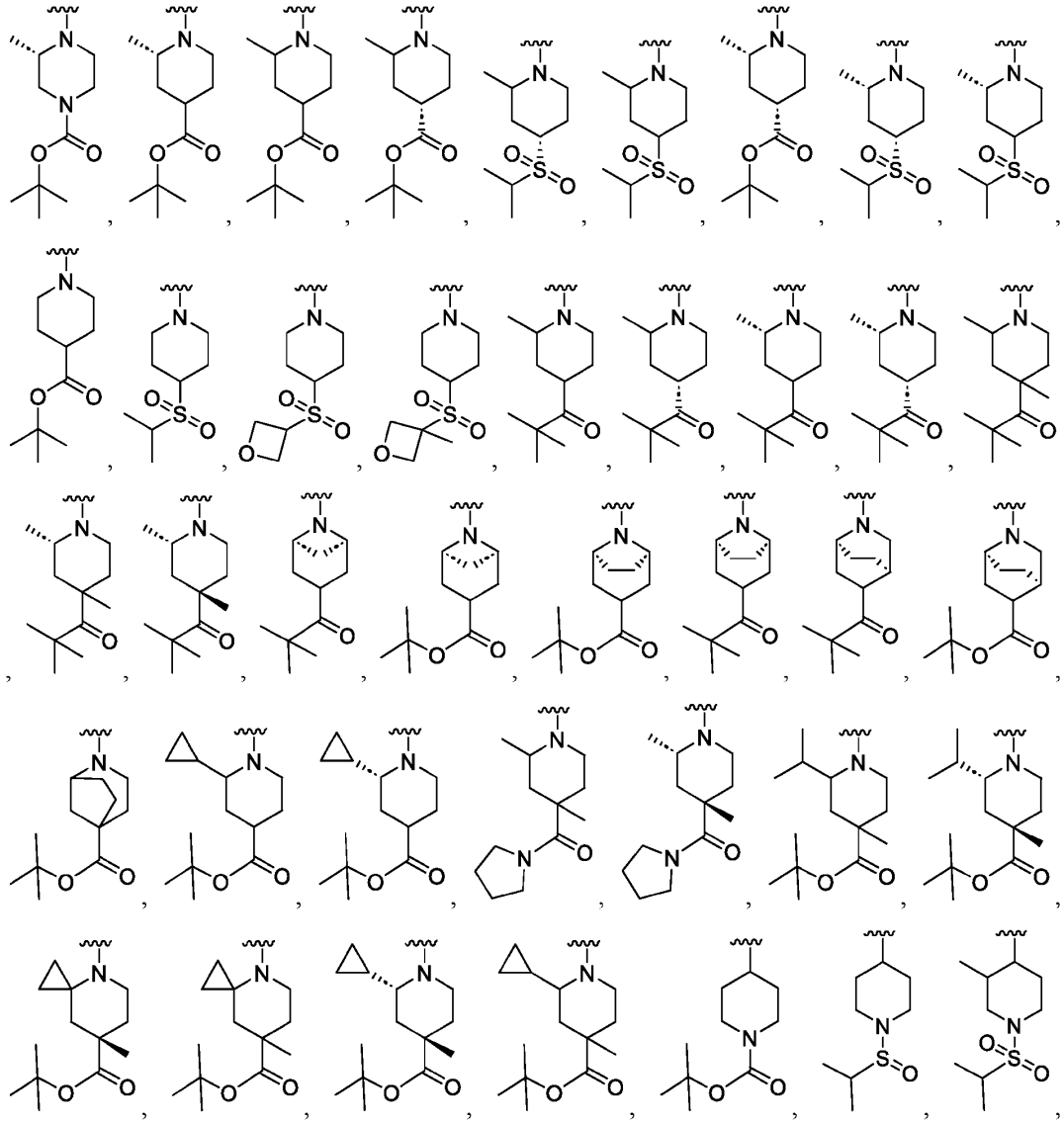


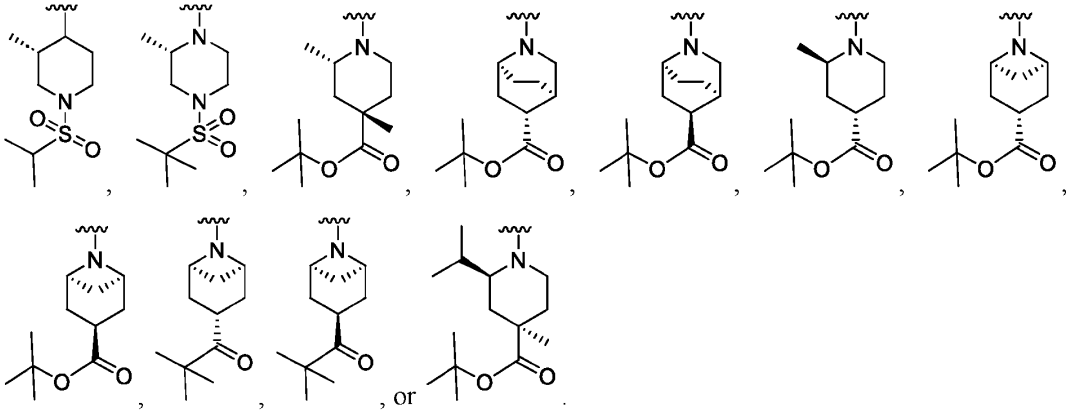


[0153] In some embodiments, a moiety:

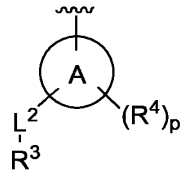


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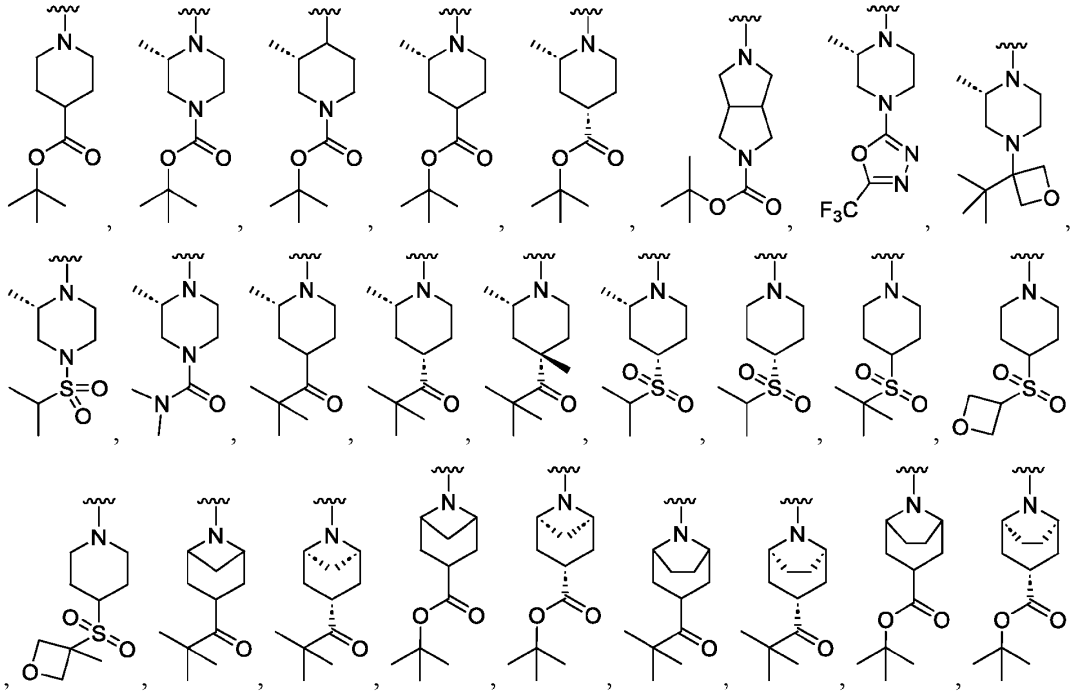


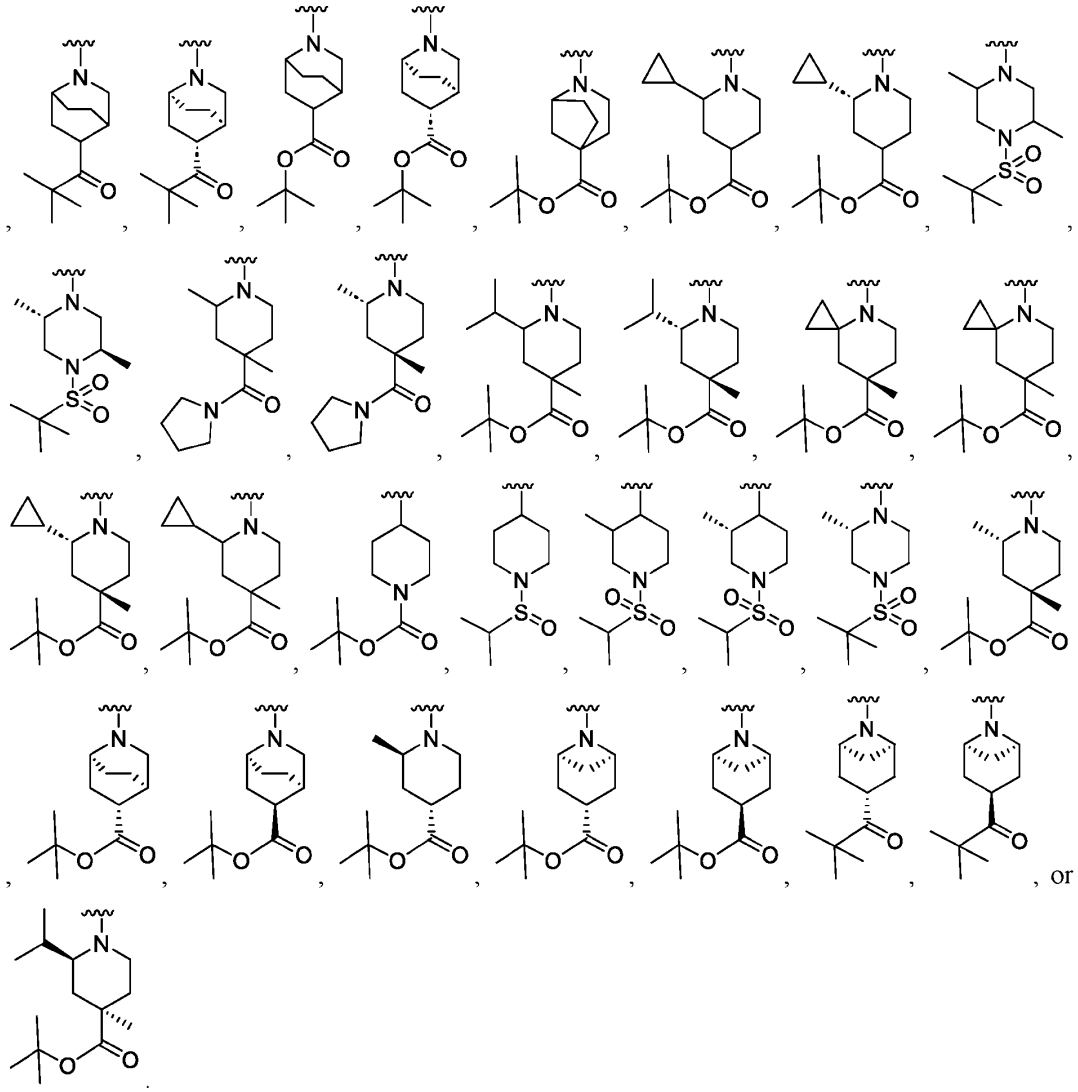


[0154] In some embodiments, a moiety:

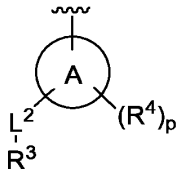


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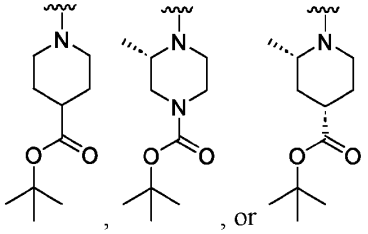




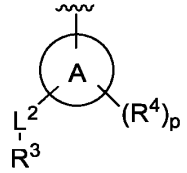
[0155] In some embodiments, a moiety:



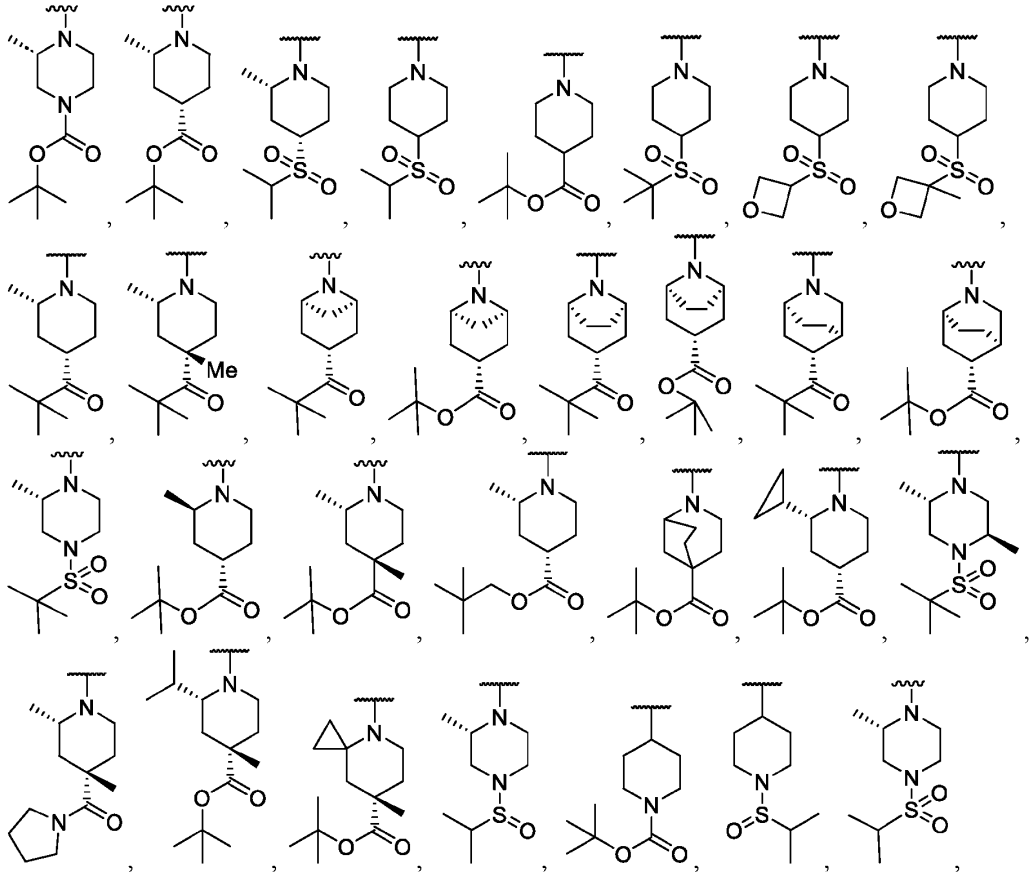
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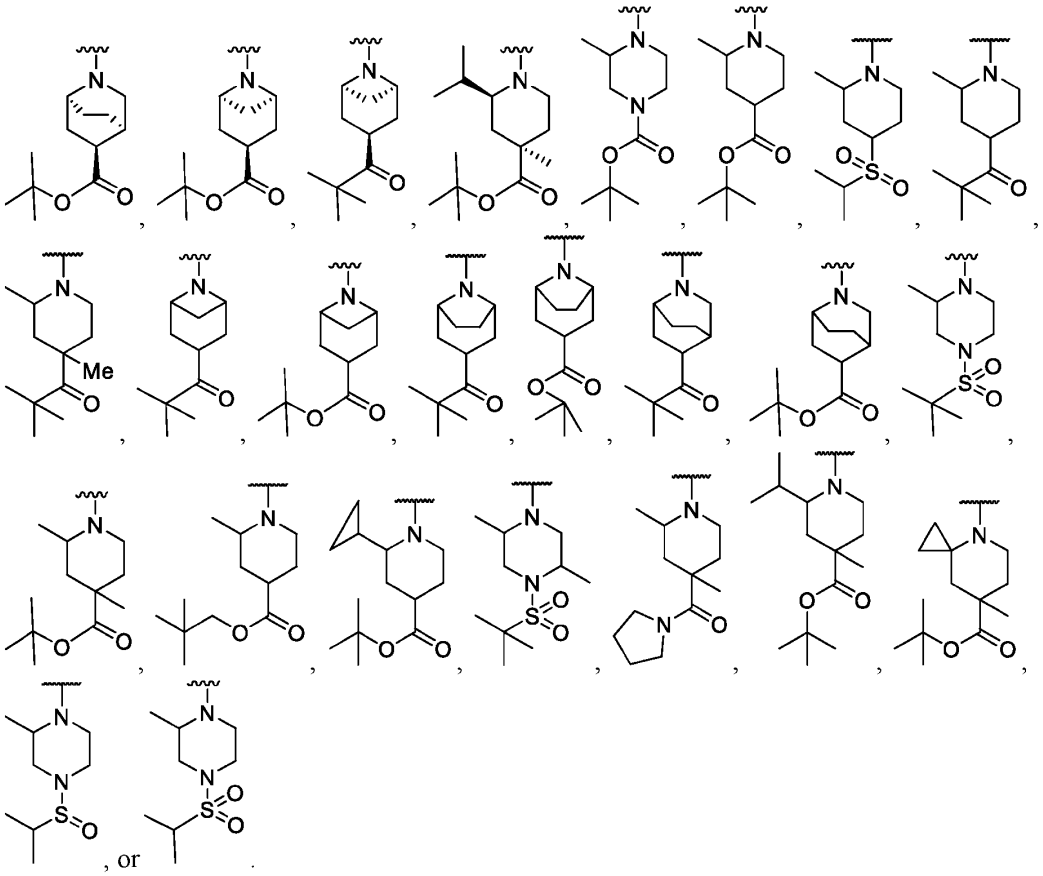


[0156] In some embodiments, a moiety:



is:





[0157] As described herein, each R^a is independently selected from H and optionally substituted C_1-C_6 aliphatic.

[0158] In some embodiments, R^a is H.

[0159] In some embodiments, R^a is optionally substituted C_1-C_6 aliphatic. In some embodiments, R^a is optionally substituted C_1-C_6 alkyl. In some embodiments, R^a is $-CH_3$. In some embodiments, R^a is $-CF_3$.

[0160] In some embodiments, a compound described herein is a compound represented by Formula I, wherein:

R^1 is 5- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, wherein R^1 is optionally substituted with one or more instances of R^{1a};

each R^{1a} is independently -CN or halogen;

L^1 is a bond;

R^2 is H, optionally substituted C_3-C_7 cycloaliphatic, optionally substituted C_1-C_6 aliphatic, or optionally substituted 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S;

Ring A is 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S;

L^2 is -C(O)-, -C(O)O-, -N(R^a)C(O)-, -C(O)N(R^a)-, -S(O)-, -S$(O)_2$-;

each R^4 is independently optionally substituted C_1-C_6 aliphatic;

each R^a is independently selected from H and optionally substituted C_1-C_6 aliphatic; and

p is 0, 1 or 2, and wherein X is N or CR^2 and R^3 is optionally substituted C_1-C_6 aliphatic or optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

[0161] In some embodiments, a compound described herein is a compound represented by Formula I, wherein:

X is N or CR^2;

R^1 is 5- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S or 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S, , wherein R^1 is optionally substituted with one or more instances of R^{1a};

each R^{1a} is independently -CN, -OR^a, -C(O)N(R^a)$_2$, optionally substituted C_1-C_6 aliphatic, or C_3-C_7 cycloaliphatic;

L^1 is a bond;

R^2 is C_3-C_7 cycloaliphatic, 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, optionally substituted C_1-C_6 aliphatic, or 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S;

Ring A is 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S;

L^2 is -C(O)-, -C(O)O-, -S(O)-, or -S$(O)_2$-;

R^3 is C_1-C_6 aliphatic or optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S;

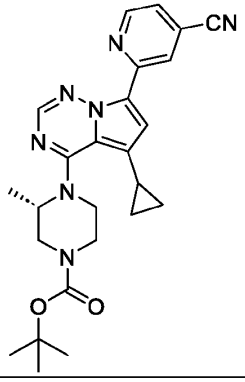
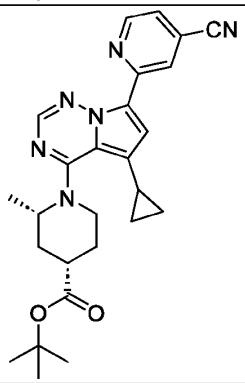
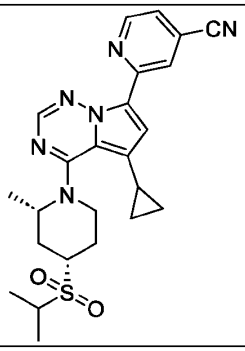
each R^4 is independently C_1-C_6 aliphatic;

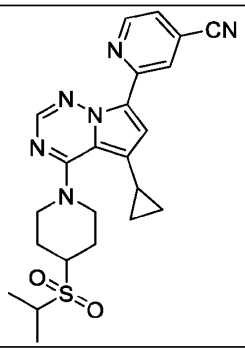
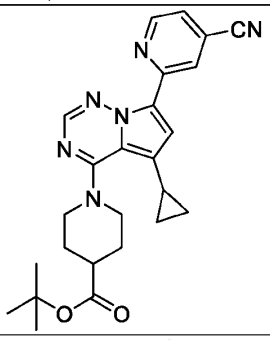
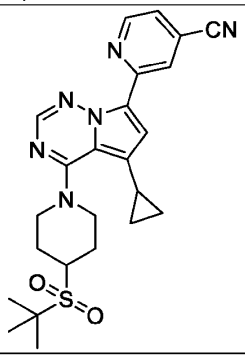
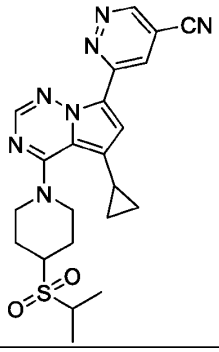
each R^a is independently selected from H and optionally substituted C_1-C_6 aliphatic; and

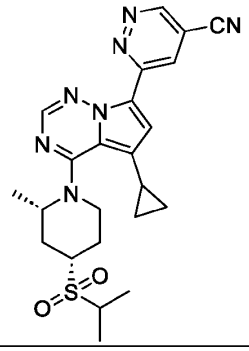
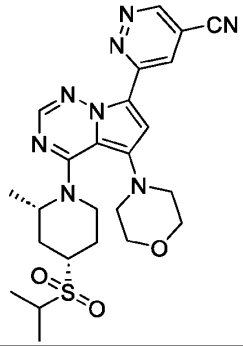
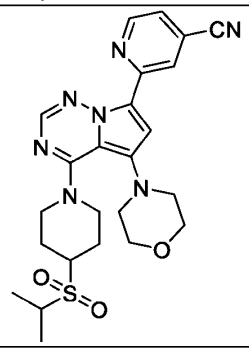
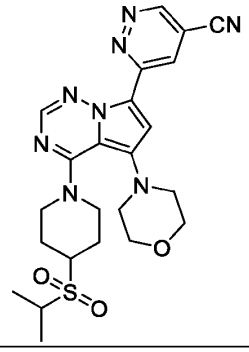
p is 0, 1, or 2.

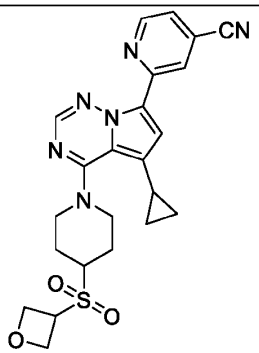
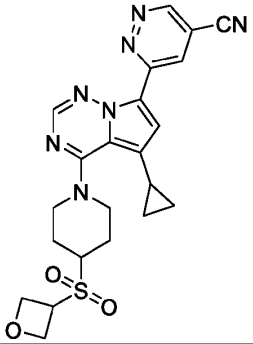
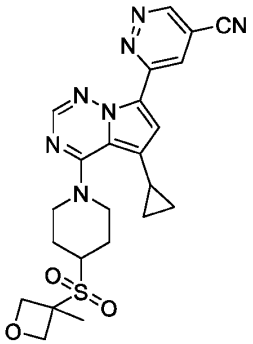
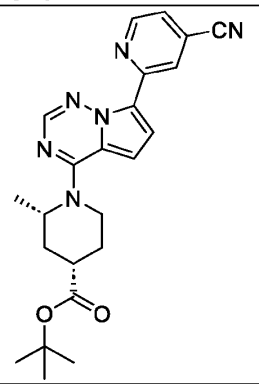
[0162] In some embodiments, a compound of a formula described herein (e.g., a Formula of any one of Formula I to V-1) is selected from Table 1:

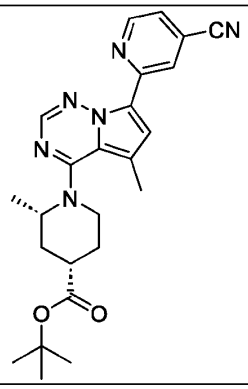
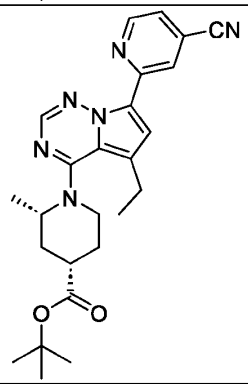
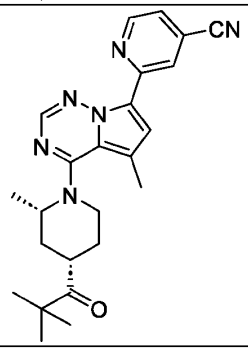
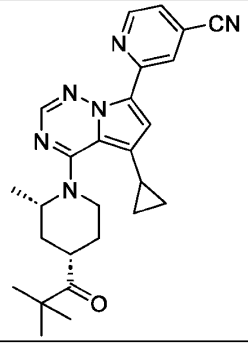
Table 1

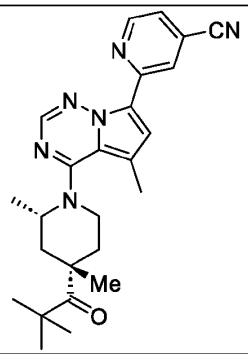
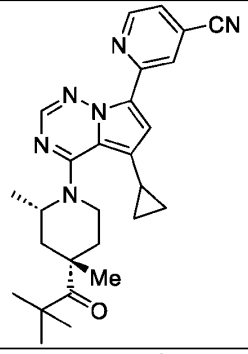
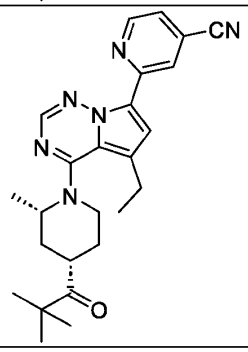
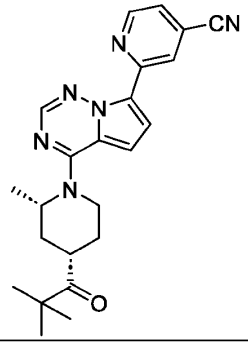
Compound No.	Structure
I-1	
I-2	
I-3	

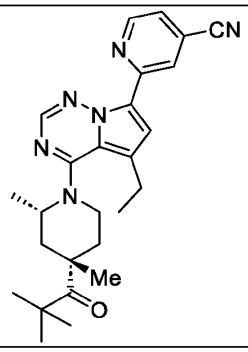
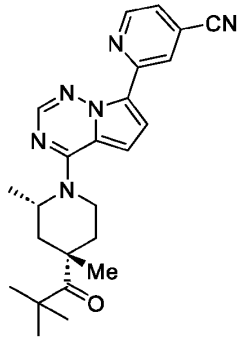
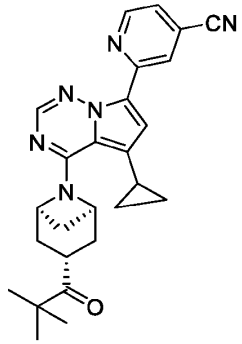
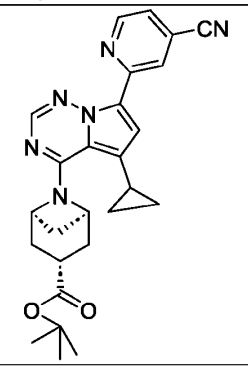
Compound No.	Structure
I-4	
I-5	
I-6	
I-7	

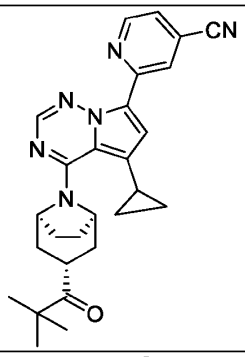
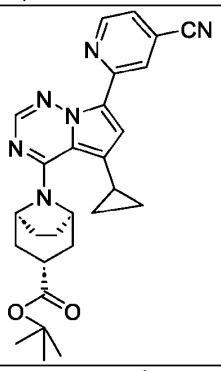
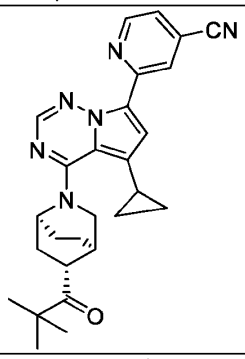
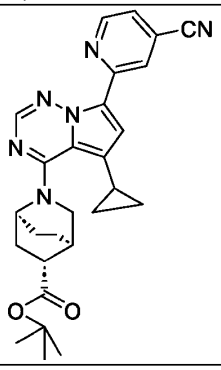
Compound No.	Structure
I-8	
I-9	
I-10	
I-11	

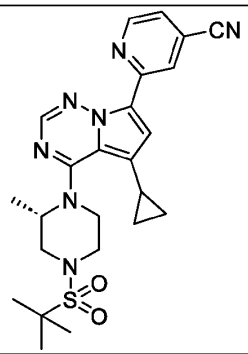
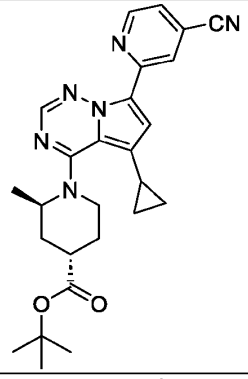
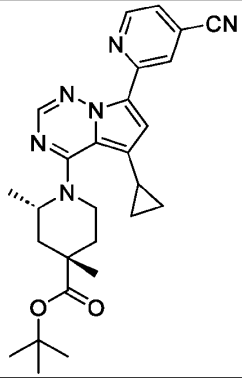
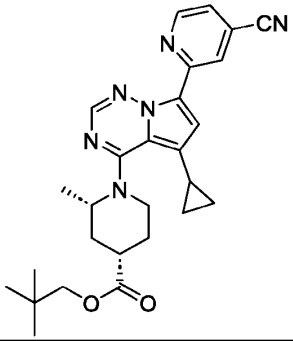
Compound No.	Structure
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I-13	
I-14	
I-15	

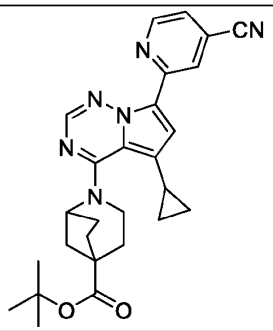
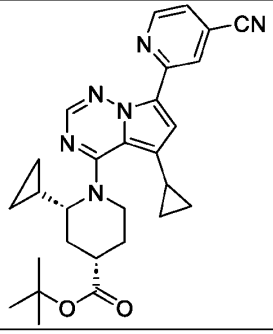
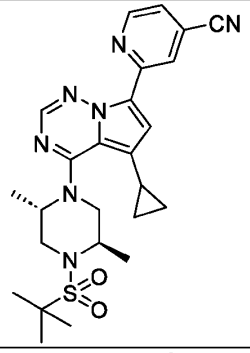
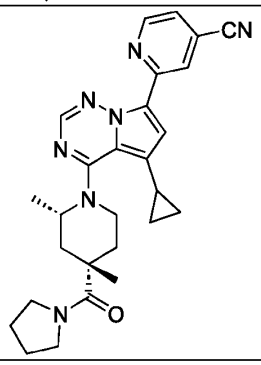
Compound No.	Structure
I-16	
I-17	
I-18	
I-19	

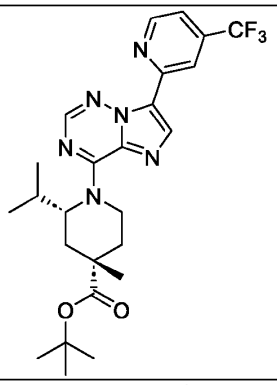
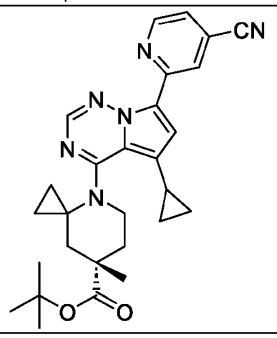
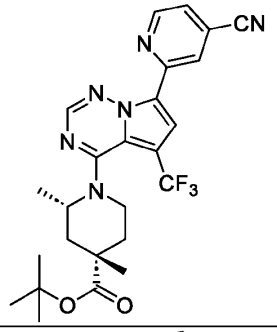
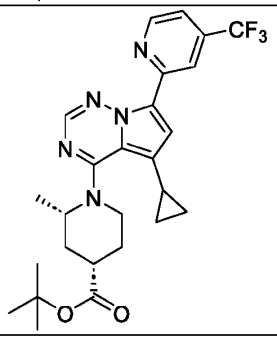
Compound No.	Structure
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I-21	
I-22	
I-23	

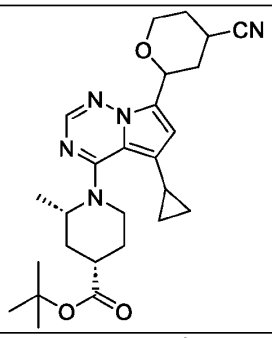
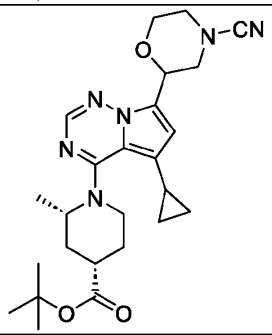
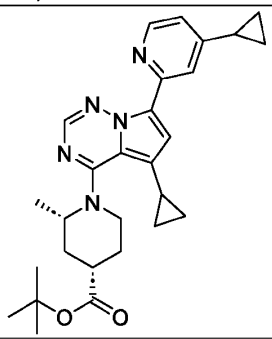
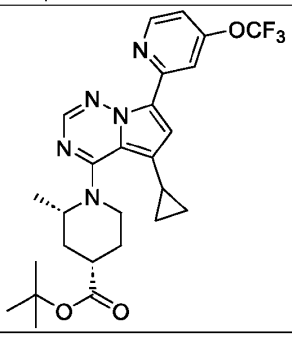
Compound No.	Structure
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I-25	
I-26	
I-27	

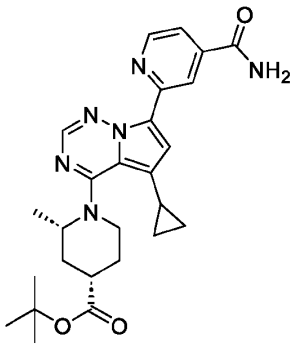
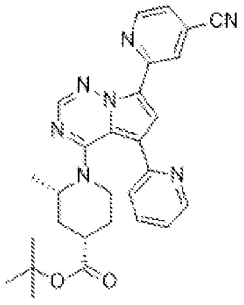
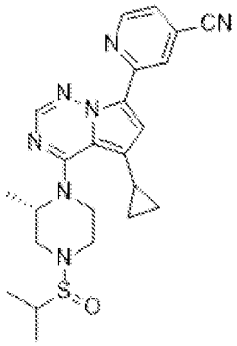
Compound No.	Structure
I-28	
I-29	
I-30	
I-31	

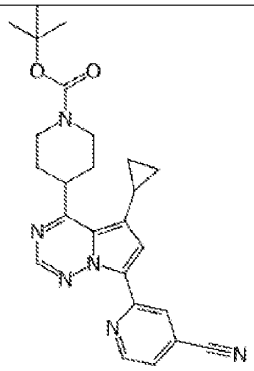
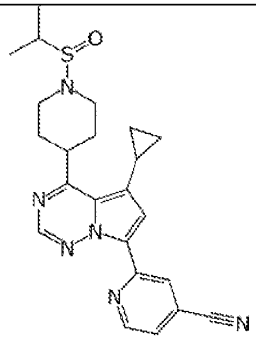
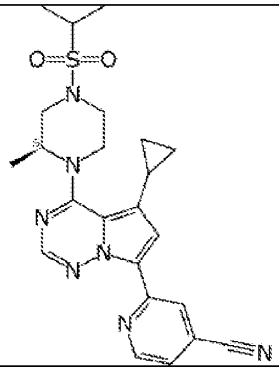
Compound No.	Structure
I-32	
I-33	
I-34	
I-35	

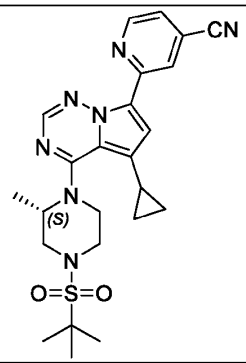
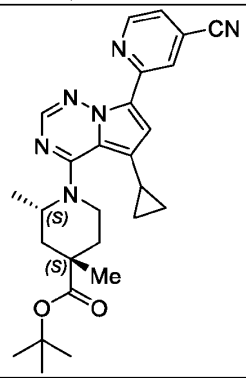
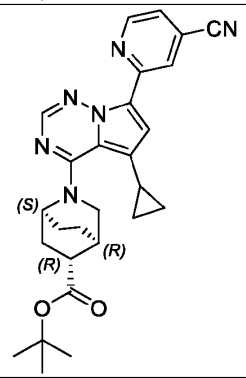
Compound No.	Structure
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I-37	
I-38	
I-39	

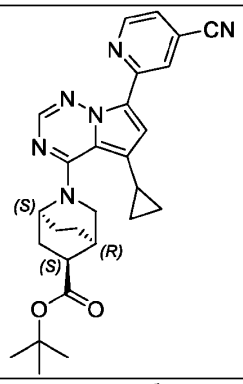
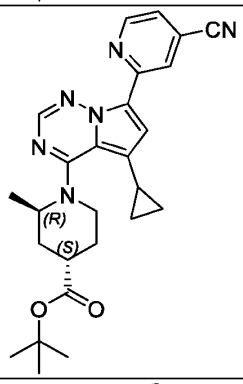
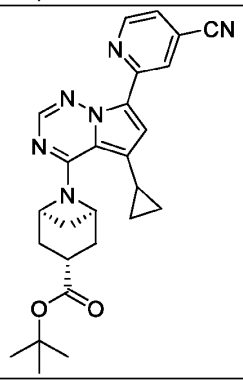
Compound No.	Structure
I-40	
I-41	
I-42	
I-43	

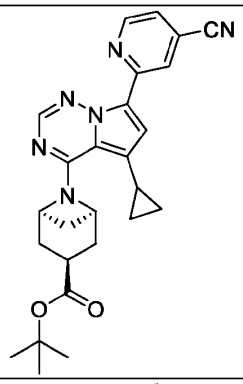
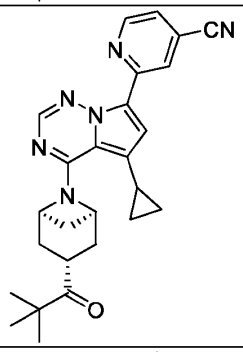
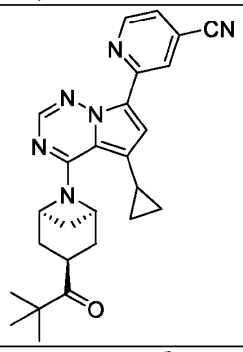
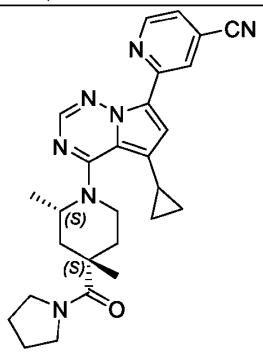
Compound No.	Structure
I-44	
I-45	
I-46	
I-47	

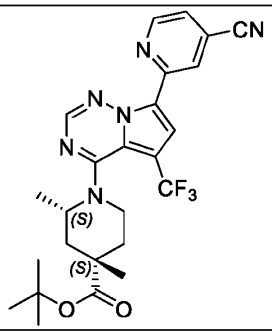
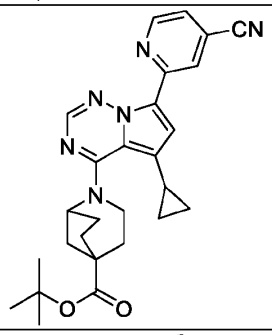
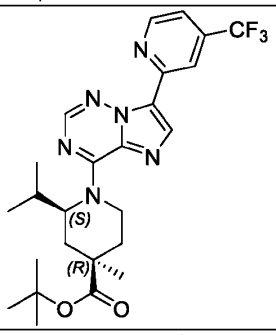
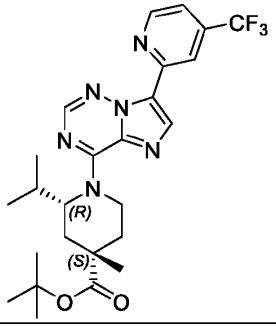
Compound No.	Structure
I-48	
I-49	
I-50	

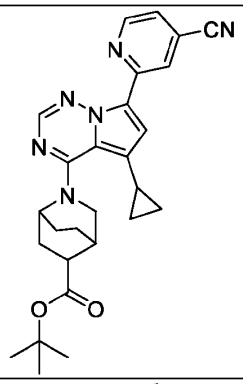
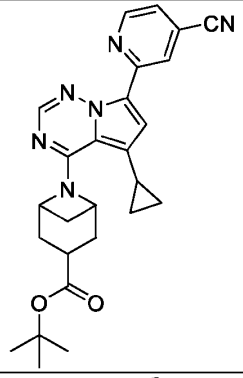
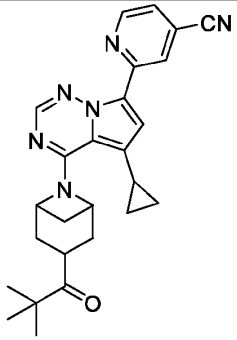
Compound No.	Structure
I-51	
I-52	
I-53	

Compound No.	Structure
I-54	
I-55	
I-56	

Compound No.	Structure
I-57	
I-58	
I-59	

Compound No.	Structure
I-60	
I-61	
I-62	
I-63	

Compound No.	Structure
I-64	
I-65	
I-66	
I-67	

Compound No.	Structure
I-68	
I-69	
I-70	

[0163] In some embodiments, provided compounds are provided and/or utilized in a salt form (e.g., a pharmaceutically acceptable salt form). Reference to a compound provided herein is understood to include reference to salts thereof, unless otherwise indicated.

Uses, Formulation, and Administration

Pharmaceutically Acceptable Compositions

[0164] According to another embodiment, the present disclosure provides a composition comprising a compound described herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. In certain embodiments, a composition described herein is formulated for administration to a patient in need of such composition. In some embodiments, a composition described herein is formulated for oral administration to a patient.

[0165] Compounds and compositions, according to method of the present disclosure, are administered using any amount and any route of administration effective for treating or lessening the severity of a disorder provided herein. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds described herein are preferably formulated in unit dosage form for ease of administration and uniformity of dosage.

[0166] Compositions of the present disclosure may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally, intraperitoneally, intracisternallyor via an implanted reservoir. In some embodiments, the compositions are administered orally, intraperitoneally or intravenously.

[0167] Sterile injectable forms of the compositions described herein may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic 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 and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0168] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans

and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0169] 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.

[0170] In order to prolong the effect of a compound of the present disclosure, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0171] In some embodiments, provided pharmaceutically acceptable compositions are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions described herein are administered without food. In other embodiments, pharmaceutically acceptable compositions described herein are administered with food. Pharmaceutically acceptable compositions described herein may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0172] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound 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/or 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.

[0173] 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 that 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 polethylene glycols and the like.

[0174] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, 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 that can be used include polymeric substances and waxes.

[0175] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (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, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0176] Alternatively, pharmaceutically acceptable compositions described herein may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0177] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0178] Pharmaceutically acceptable compositions described herein may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0179] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[0180] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds described herein include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0181] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[0182] Pharmaceutically acceptable compositions described herein may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0183] Dosage forms for topical or transdermal administration of a compound disclosed herein include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this disclosure. Additionally, the present disclosure contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption

enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Applications and Uses

[0184] The present application provides a variety of uses and applications for compounds and/or compositions as described herein, for example in light of their activities and/or characteristics as described herein. In some embodiments, such uses may include therapeutic and/or diagnostic uses. Alternatively, in some embodiments such uses may include research, production, and/or other technological uses.

[0185] Among other things, in some embodiments, the present disclosure provides technologies for modulating TRPML activity (e.g., TRPML1, TRPML2, TRPML3, or combinations thereof). In some embodiments, the present application relates to a method of modulating TRPML activty (e.g., TRPML1, TRPML2, TRPML3, or combinations thereof) in a subject comprising administering to the subject a provided compound, or a composition as described herein. In some embodiments, the present application relates to a method of modulating TRPML1 activity in a subject comprising administering to the subject a provided compound, or a composition as described herein. In some embodiments, the present application relates to a method of modulating TRPML2 activity in a subject comprising administering to the subject a provided compound, or a composition as described herein. In some embodiments, the present application relates to a method of modulating TRPML3 activity in a subject comprising administering to the subject a provided compound, or a composition as described herein. In some embodiments, the present application relates to a method of modulating TRPML1, TRPML2, and/or TRPML3 activity in a subject comprising administering to the subject a provided compound, or a composition as described herein.

Diseases, Disorders, and Conditions

[0186] The present disclosure demonstrates that compounds and/or compositions as described herein may be useful in medicine (e.g., in the treatment of one or more diseases, disorders, or conditions).

[0187] Among other things, as described herein, the present disclosure provides an insight that targeting (e.g., agonizing) TRPML (e.g., TRPML1, TRPML2, TRPML3, or combinations thereof) may be a particularly effective strategy for modulating (e.g., enhancing) autophagy, lysosomal biogenesis and/or lysosomal exocytosis.

[0188] In some embodiments, a disease, disorder or condition that may be treated as described herein may be or comprise a disease, disorder or condition associated with TRPML (e.g., TRPML1, TRPML2, TRPML3, or combinations thereof) deficiency. Furthermore, in some embodiments, the present disclosure identifies that TRMPL (e.g., TRPML1, TRPML2, TRPML3, or combinations thereof) deficiency is associated with particular diseases, disorders or conditions, some or all of which may be treated in accordance with the present disclosure.

[0189] In some embodiments, treatment provided herein involves administration of a TRMPL1 modulator as described herein in an amount effective to modulate TRMPL (e.g., TRPML1, TRPML2, TRPML3, or combinations thereof) activity in a lysosome and/or increase autophagy.

[0190] In some embodiments, a disease, disorder, or condition amenable to treatment as described herein is or comprises a liver disease, a neurodegenerative disorder, cancer, or a heart disease.

[0191] In some embodiments, a disease, disorder, or condition amenable to treatment as described herein is or comprises a lysosomal storage disease, such as Niemann-Pick C (NPC) disease, Gaucher disease, Fabry disease, Cholesterol Ester Storage disease, Batten disease and Pompe disease.

[0192] In some embodiments, a disease, disorder, or condition amenable to treatment as described herein is an age-related common neurodegenerative disease, such as Alzheimer's Disease, Parkinson's Disease, Amyotrophic lateral sclerosis and Huntington's Disease.

[0193] In some embodiments, a disease, disorder, or condition amenable to treatment as described herein is a type IV Mucolipidosis (ML4) neurodegenerative lysosomal storage disease caused by mutations in TRPML (e.g., TRPML1, TRPML2, TRPML3, or combinations thereof).

[0194] In some embodiments, a disease, disorder, or condition amenable to treatment as described herein is related to reactive oxygen species or oxidative stress.

[0195] In some embodiments, the present application relates to use of a compound and/or composition described herein for use in the manufacture of a medicament e.g., for modulation of TRPML (e.g., TRPML1, TRPML2, TRPML3, or combinations thereof) activity.

[0196] In some embodiments, the present application relates to use of a compound and/or composition described herein for use in the manufacture of a medicament for treating a disease, disorder or condition, e.g., through modulation of TRPML (e.g., TRPML1, TRPML2, TRPML3, or combinations thereof) activity; in some embodiments, the disease, disorder, or condition is a liver disease, a neurodegenerative disorder, cancer, or a heart disease.

[0197] In some embodiments, a disease, disorder, or condition is a muscular disease, a liver disease, a metabolic disease, an atherosclerotic disease, an inflammatory bowel disease, an atherosclerotic disease, a neurodegenerative disease, or an oncological disease. In some embodiments, a disease, disorder, or condition is a muscular disease. In some embodiments, a muscular disease is a muscular dystrophy. In some embodiments, a muscular dystrophy is Duchenne muscular dystrophy.

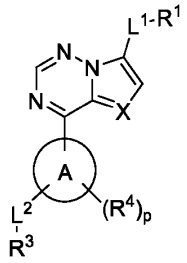
[0198] In some embodiments, a disease, disorder, or condition is an infectious disease. In some embodiments, an infectious disease is an infection of *Heliobacter pylori* or *Mycobacterium tuberculosis*.

[0199] In some embodiments, a disease, disorder, or condition is tuberculosis.

EXEMPLARY EMBODIMENTS

[0200] The following numbered embodiments, while non-limiting, are exemplary of certain aspects of the disclosure:

Embodiment 1. A compound represented by formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

X is N or CR^2;

R^1 is 5- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S, C_6-C_{12} aryl, or C_3-C_{12} cycloaliphatic, wherein R^1 is optionally substituted with one or more instances of R^{1a};

each R^{1a} is independently -CN, halogen, $-OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)R^a$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_3-C_7 cycloaliphatic;

L^1 is a bond, $N(R^a)$, O, or optionally substituted C_1-C_6 aliphatic;

R^2 is H, optionally substituted C_3-C_7 cycloaliphatic, optionally substituted phenyl, optionally substituted 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, optionally substituted C_1-C_6 aliphatic, or optionally substituted 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S;

Ring A is 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S;

L^2 is -C(O)-, -C(O)O-, $-N(R^a)C(O)$-, $-C(O)N(R^a)$-, -S(O)-, $-S(O)_2$-, optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, or optionally substituted 4- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S;

R^3 is optionally substituted C_1-C_6 aliphatic or optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S;

each R^4 is independently optionally substituted C_1-C_6 aliphatic;

each R^a is independently selected from H and optionally substituted C_1-C_6 aliphatic; and

p is 0, 1, 2, 3, or 4.

Embodiment 2. The compound of Embodiment 1, wherein L^1 is a bond.

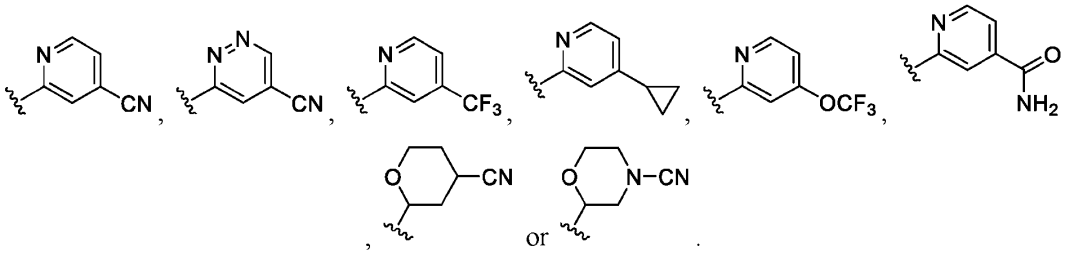
Embodiment 3. The compound of Embodiments 1 or 2, wherein R^1 is 5- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, and is optionally substituted with one or more instances of R^{1a}.

Embodiment 4. The compound of any one of Embodiments 1-3, wherein R^1 is monocyclic 5- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S, and is substituted with one or more instances of R^{1a}.

Embodiment 5. The compound of any one of Embodiments 1-4, wherein R^1 is pyridine, substituted with R^{1a}.

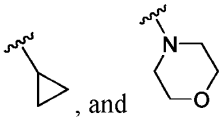
Embodiment 6. The compound of any one of Embodiments 1-5, wherein R^{1a} is -CN.

Embodiment 7. The compound of any one of Embodiments 1-6, wherein R^1 is:



Embodiment 8. The compound of any one of Embodiments 1-7, wherein R^2 is optionally substituted C_3-C_7 cycloaliphatic.

Embodiment 9. The compound of any one of Embodiments 1-8, wherein R^2 is selected from: -H, $-CH_3$, $-CH_2-CH_3$, $-CF_3$,



Embodiment 10. The compound of any one of Embodiments 1-9, wherein Ring A is monocyclic 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

Embodiment 11. The compound of any one of Embodiments 1-10, wherein Ring A is piperidine or piperazine.

Embodiment 12. The compound of any one of Embodiments 1-11, wherein Ring A is piperidine.

Embodiment 13. The compound of any one of Embodiments 1-9, wherein Ring A is bridged bicyclic 6- to 10-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

Embodiment 14. The compound of any one of Embodiments 1-13, wherein p is 0.

Embodiment 15. The compound of any one of Embodiments 1-13, wherein p is 1 or 2.

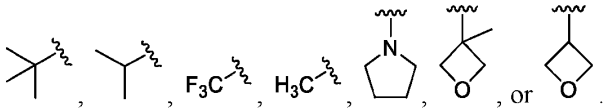
Embodiment 16. The compound of any one of Embodiments 1-13 or 15, wherein each R^4 is $-CH_3$.

Embodiment 17. The compound of any one of Embodiments 1-16, wherein L^2 is -C(O)-, -C(O)O-*, or $-S(O)_2-$, where * indicates a point of attachment to moiety R^3.

Embodiment 18. The compound of any one of Embodiments 1-17, wherein L^2 is -C(O)O-*, where * indicates a point of attachment to moiety R^3.

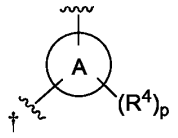
Embodiment 19. The compound of any one of Embodiments 1-18, wherein R^3 is optionally substituted C_1-C_6 aliphatic.

Embodiment 20. The compound of any one of Embodiments 1-19, wherein R^3 is:

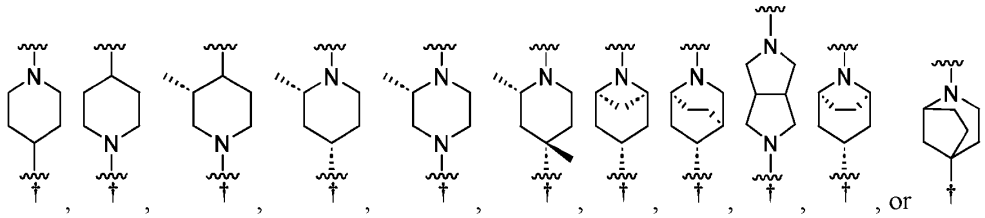


, or .

Embodiment 21. The compound of any one of Embodiments 1-20, wherein moiety:

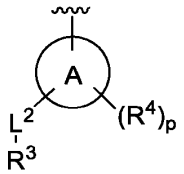


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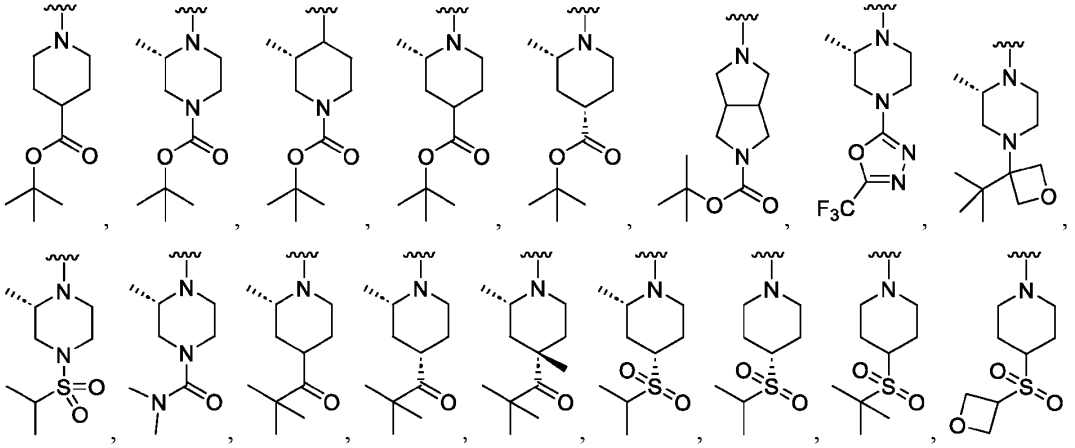


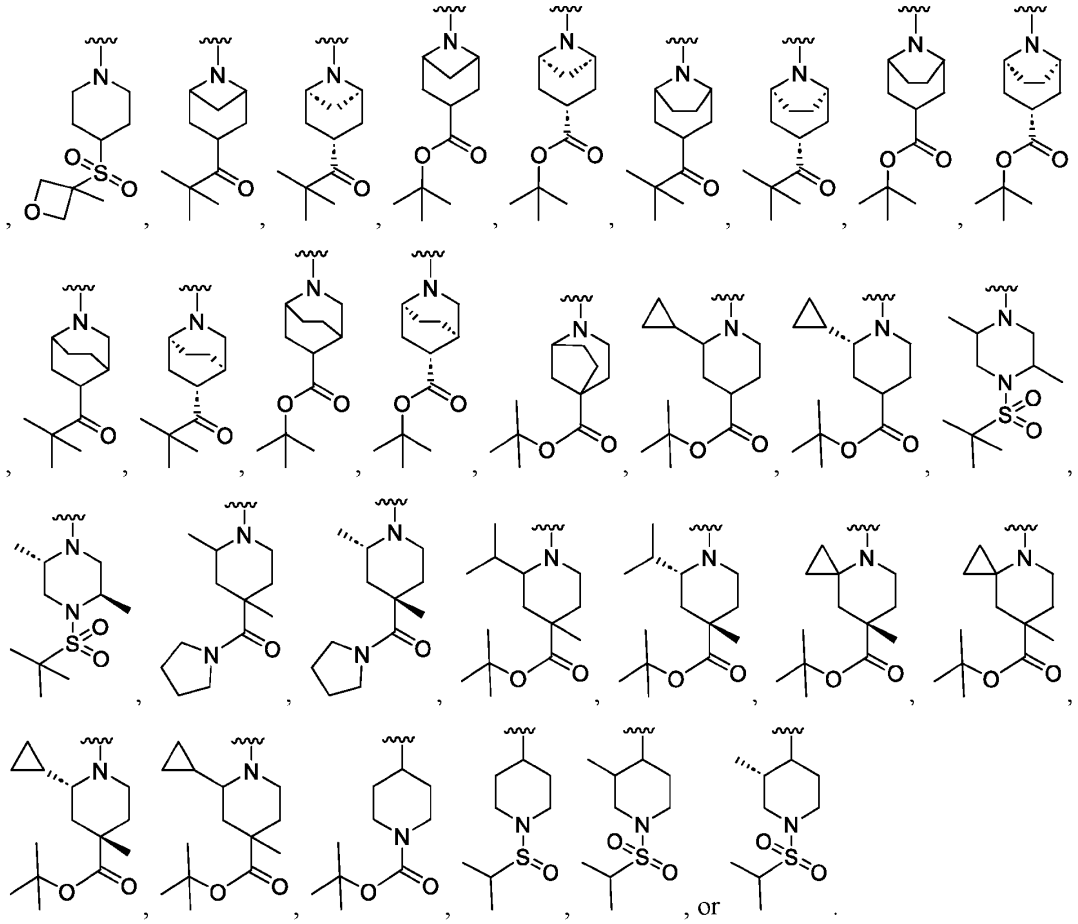
; where † represents a point of attachment to L^2.

Embodiment 22. The compound of any one of Embodiments 1-21, wherein moiety:

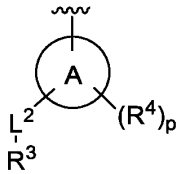


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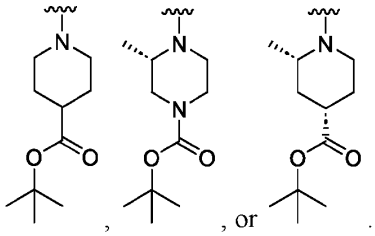




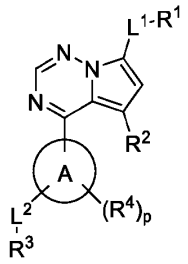
Embodiment 23. The compound of any one of Embodiments 1-12 or 14-22, wherein



is:



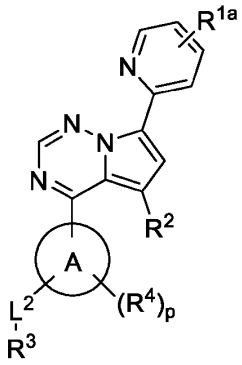
Embodiment 24. The compound of any one of Embodiments 1-23, wherein the compound is represented by formula I-2:



I-2

or a pharmaceutically acceptable salt thereof.

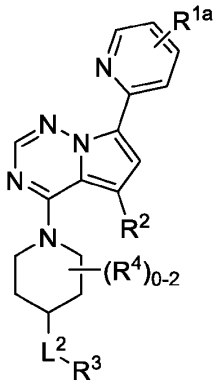
Embodiment 25. The compound of any one of Embodiments 1-24, wherein the compound is represented by formula II-1:



II-1

or a pharmaceutically acceptable salt thereof.

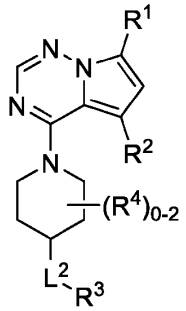
Embodiment 26. The compound of any one of Embodiments 1-12 or 14-25, wherein the compound is represented by formula II-2:



II-2

or a pharmaceutically acceptable salt thereof.

Embodiment 27. The compound of any one of Embodiments 1-12 or 14-26, wherein the compound is represented by formula III-1



III-1

or a pharmaceutically acceptable salt thereof.

Embodiment 28. The compound of any one of Embodiments 1-27, wherein the compound, or a pharmaceutically acceptable salt thereof, is selected from Table 1.

Embodiment 29. A pharmaceutical composition comprising the compound of any one of Embodiments 1-28, and a pharmaceutically acceptable carrier or excipient.

Embodiment 30. A method of modulating TRMPL in a subject comprising administering to the subject a compound of any one of Embodiments 1-28 or a pharmaceutical composition of Embodiment 29.

Embodiment 31. A method of treating a disease, disorder, or condition in a subject comprising administering to the subject a compound of any one of Embodiments 1-28, or a pharmaceutical composition of Embodiment 29.

Embodiment 32. The method of Embodiment 31, wherein the disease, disorder, or condition is a lysosomal storage disorder.

Embodiment 33. The method of Embodiment 32, wherein the lysosomal storage disorder is selected from Niemann-Pick C disease, Gaucher disease, Batten disease, cholesteryl ester storage disease, Fabry disease, and Pompe disease.

Embodiment 34. The method of Embodiment 31, wherein the disease, disorder, or condition is age-related common neurodegenerative disease.

Embodiment 35. The method of Embodiments 31 or 34, wherein the disease, disorder, or condition is selected from Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease.

Embodiment 36. The method of Embodiment 31 or 32, wherein the disease, disorder, or condition is a type IV Mucolipidosis (ML4) neurodegenerative lysosomal storage disease caused by mutations in a TRPML.

Embodiment 37. The method of Embodiment 31, wherein the disease, disorder, or condition is a muscular disease, a liver disease, a metabolic disease, an atherosclerotic disease, an inflammatory bowel disease, an atherosclerotic disease, a neurodegenerative disease, an oncological disease, or an infectious disease.

Embodiment 38. The method of Embodiment 37, wherein the disease, disorder, or condition is a muscular disease.

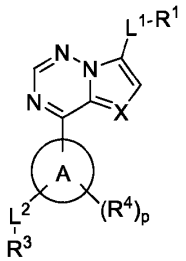
Embodiment 39. The method of Embodiment 38, wherein the muscular disease is a muscular dystrophy.

Embodiment 40. The method of Embodiment 39, wherein the muscular dystrophy is Duchenne muscular dystrophy.

Embodiment 41. The method of Embodiment 31, wherein the disease, disorder, or condition is an infectious disease.

Embodiment 42. The method of Embodiment 41, wherein the infectious disease is an infection of *Heliobacter pylori* or *Mycobacterium tuberculosis*.

Embodiment 43. A compound represented by formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

X is N or CR^2;

R^1 is 5- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S, C_6-C_{12} aryl, or C_3-C_{12} cycloaliphatic, wherein R^1 is optionally substituted with one or more instances of R^{1a};

each R^{1a} is independently -CN, halogen, $-OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)R^a$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_3-C_7 cycloaliphatic;

L^1 is a bond, $N(R^a)$, O, or optionally substituted C_1-C_6 aliphatic;

R^2 is H, optionally substituted C_3-C_7 cycloaliphatic, optionally substituted phenyl, optionally substituted 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, optionally substituted C_1-C_6 aliphatic, or optionally substituted 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S;

Ring A is 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S;

L^2 is -C(O)-, -C(O)O-, $-N(R^a)C(O)$-, $-C(O)N(R^a)$-, -S(O)-, $-S(O)_2$-, optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, or optionally substituted 4- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S;

R^3 is optionally substituted C_1-C_6 aliphatic or optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S;

each R^4 is independently optionally substituted C_1-C_6 aliphatic;

each R^a is independently selected from H and optionally substituted C_1-C_6 aliphatic; and

p is 0, 1, 2, 3, or 4.

Embodiment 44. The compound of Embodiment 43, wherein L^1 is a bond.

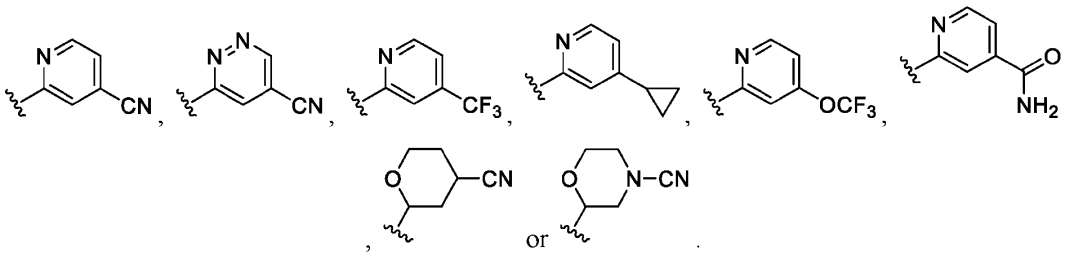
Embodiment 45. The compound of Embodiments 43 or 44, wherein R^1 is 5- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, and is optionally substituted with one or more instances of R^{1a}.

Embodiment 46. The compound of any one of Embodiments 43-45, wherein R^1 is monocyclic 5- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S, and is substituted with one or more instances of R^{1a}.

Embodiment 47. The compound of any one of Embodiments 43-46, wherein R^1 is pyridinyl, substituted with R^{1a}.

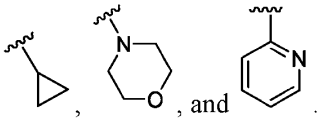
Embodiment 48. The compound of any one of Embodiments 43-47, wherein R^{1a} is -CN.

Embodiment 49. The compound of any one of Embodiments 43-48, wherein R^1 is:



Embodiment 50. The compound of any one of Embodiments 43-49, wherein R^2 is optionally substituted C_3-C_7 cycloaliphatic.

Embodiment 51. The compound of any one of Embodiments 43-50, wherein R^2 is selected from: -H, $-CH_3$, $-CH_2-CH_3$, $-CF_3$,



Embodiment 52. The compound of any one of Embodiments 43-51, wherein Ring A is monocyclic 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

Embodiment 53. The compound of any one of Embodiments 43-52, wherein Ring A is piperidinyl or piperazinyl.

Embodiment 54. The compound of any one of Embodiments 43-53, wherein Ring A is piperidinyl.

Embodiment 55. The compound of any one of Embodiments 43-51, wherein Ring A is bridged bicyclic 6- to 10-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

Embodiment 56. The compound of any one of Embodiments 43-55, wherein p is 0.

Embodiment 57. The compound of any one of Embodiments 43-55, wherein p is 1 or 2.

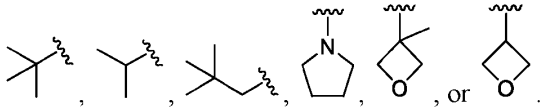
Embodiment 58. The compound of any one of Embodiments 43-55 or 57, wherein each R^4 is $-CH_3$.

Embodiment 59. The compound of any one of Embodiments 43-58, wherein L^2 is -C(O)-, -C(O)O-*, -S(O)-, or $-S(O)_2-$, where * indicates a point of attachment to moiety R^3.

Embodiment 60. The compound of any one of Embodiments 43-59, wherein L^2 is -C(O)O-*, where * indicates a point of attachment to moiety R^3.

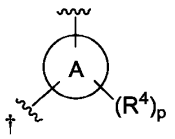
Embodiment 61. The compound of any one of Embodiments 43-60, wherein R^3 is optionally substituted C_1-C_6 aliphatic.

Embodiment 62. The compound of any one of Embodiments 43-61, wherein R^3 is:

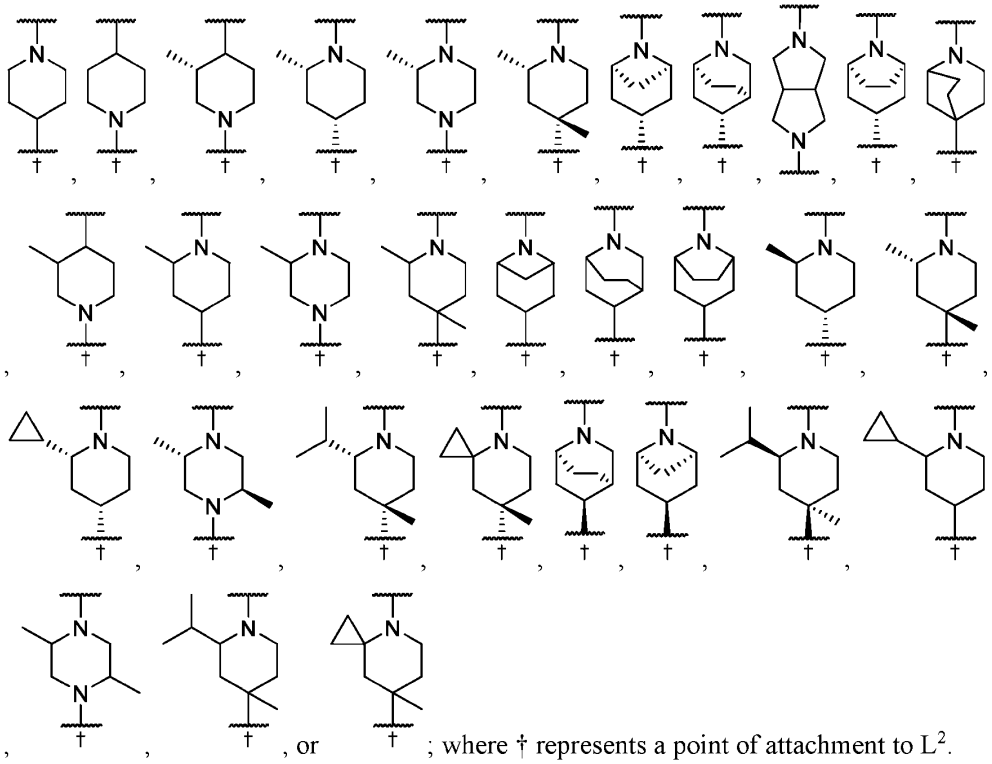


, or .

Embodiment 63. The compound of any one of Embodiments 43-62, wherein moiety:

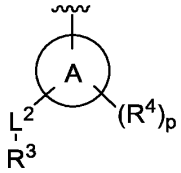


is:

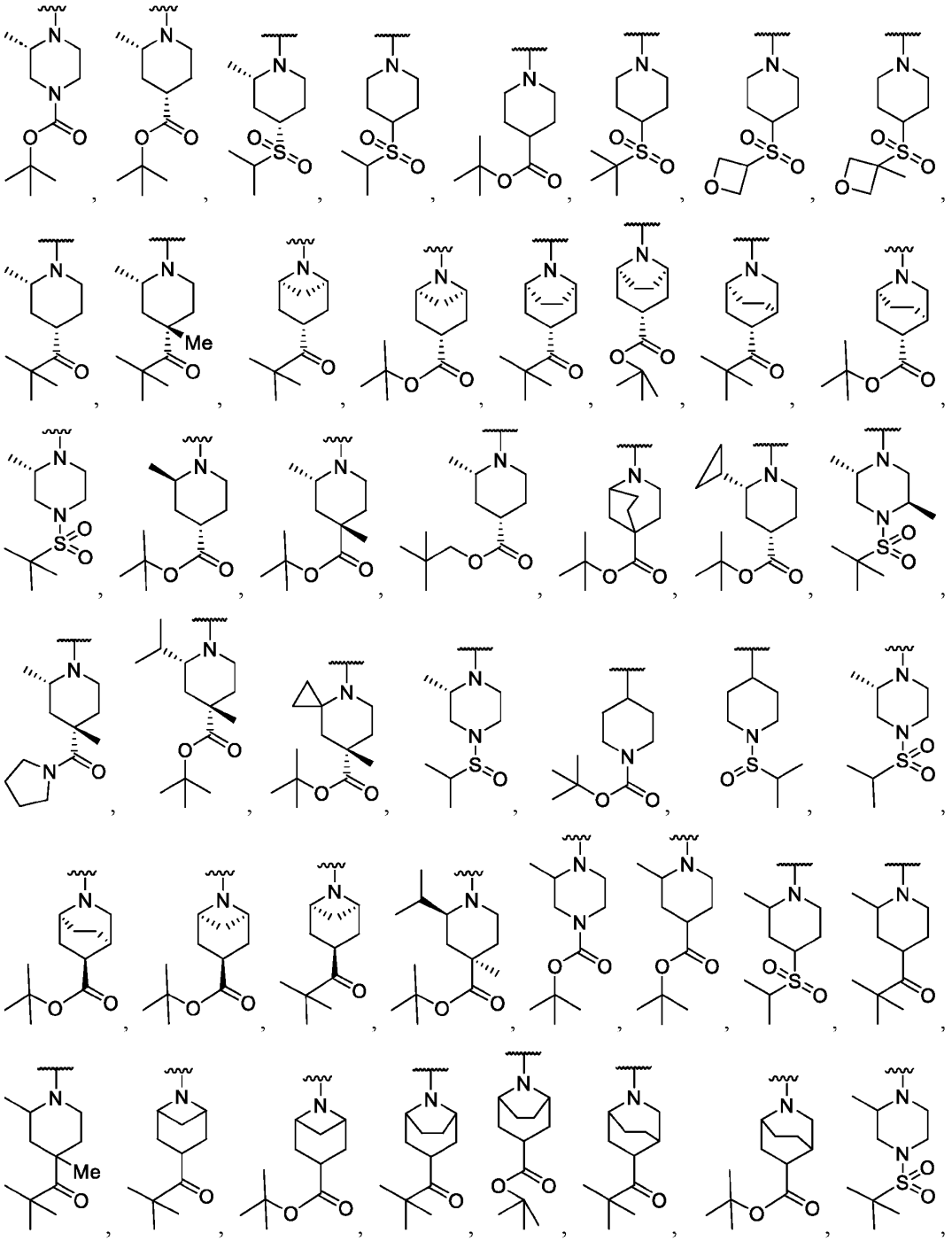


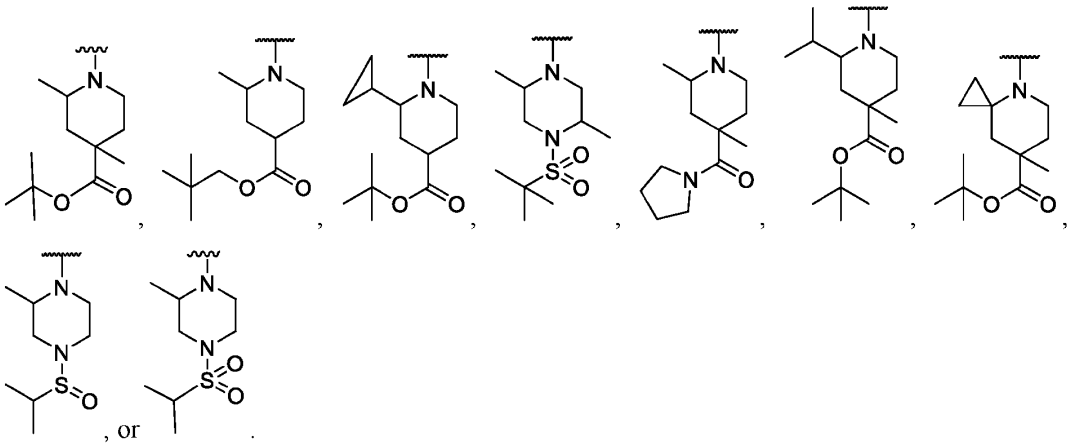
; where † represents a point of attachment to L^2.

Embodiment 64. The compound of any one of Embodiments 43-63, wherein moiety:

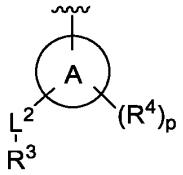


is:

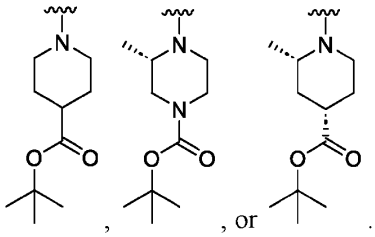




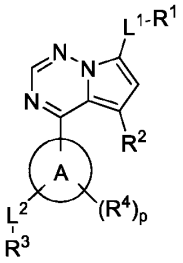
Embodiment 65. The compound of any one of Embodiments 43-54 or 56-64, wherein



is:



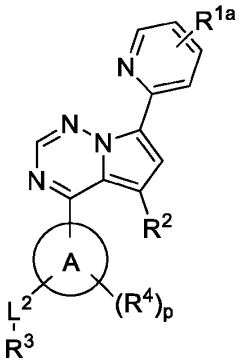
Embodiment 66. The compound of any one of Embodiments 43-65, wherein the compound is represented by formula I-2:



I-2

or a pharmaceutically acceptable salt thereof.

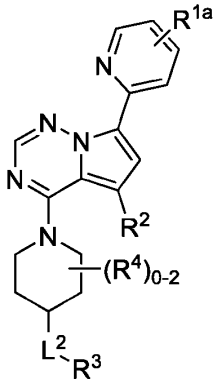
Embodiment 67. The compound of any one of Embodiments 43-66, wherein the compound is represented by formula II-1:



II-1

or a pharmaceutically acceptable salt thereof.

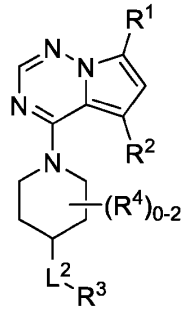
Embodiment 68. The compound of any one of Embodiments 43-54 or 56-67, wherein the compound is represented by formula II-2:



II-2

or a pharmaceutically acceptable salt thereof.

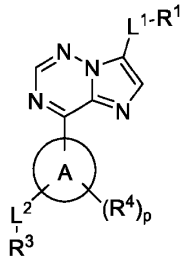
Embodiment 69. The compound of any one of Embodiments 43-54 or 56-68, wherein the compound is represented by formula III-1



III-1

or a pharmaceutically acceptable salt thereof.

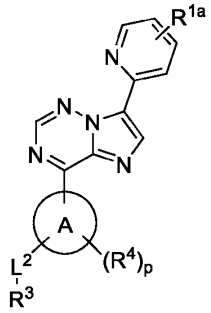
Embodiment 70. The compound of any one of Embodiments 43-65, wherein the compound is represented by formula IV-1



IV-1

or a pharmaceutically acceptable salt thereof.

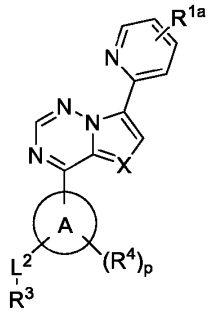
Embodiment 71. The compound of any one of Embodiments 43-65 or 70, wherein the compound is represented by formula IV-2



IV-2

or a pharmaceutically acceptable salt thereof.

Embodiment 72. The compound of any one of Embodiments 43-71, wherein the compound is represented by formula V-1



V-1

or a pharmaceutically acceptable salt thereof.

Embodiment 73. The compound of any one of Embodiments 43-72, wherein the compound, or a pharmaceutically acceptable salt thereof, is selected from Table 1.

Embodiment 74. A pharmaceutical composition comprising the compound of any one of Embodiments 43-73, and a pharmaceutically acceptable carrier or excipient.

Embodiment 75. A method of modulating TRMPL in a subject comprising administering to the subject a compound of any one of Embodiments 43-73 or a pharmaceutical composition of Embodiment 74.

Embodiment 76. A method of treating a disease, disorder, or condition in a subject comprising administering to the subject a compound of any one of Embodiments 43-73, or a pharmaceutical composition of Embodiment 74.

Embodiment 77. The method of Embodiment 76, wherein the disease, disorder, or condition is a lysosomal storage disorder.

Embodiment 78. The method of Embodiment 77, wherein the lysosomal storage disorder is selected from Niemann-Pick C disease, Gaucher disease, Batten disease, cholesteryl ester storage disease, Fabry disease, and Pompe disease.

Embodiment 79. The method of Embodiment 76, wherein the disease, disorder, or condition is age-related common neurodegenerative disease.

Embodiment 80. The method of Embodiments 76 or 79, wherein the disease, disorder, or condition is selected from Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease.

Embodiment 81. The method of Embodiment 76 or 77, wherein the disease, disorder, or condition is a type IV Mucolipidosis (ML4) neurodegenerative lysosomal storage disease caused by mutations in a TRPML.

Embodiment 82. The method of Embodiment 76, wherein the disease, disorder, or condition is a muscular disease, a liver disease, a metabolic disease, an atherosclerotic disease, an inflammatory bowel disease, an atherosclerotic disease, a neurodegenerative disease, an oncological disease, or an infectious disease.

Embodiment 83. The method of Embodiment 82, wherein the disease, disorder, or condition is a muscular disease.

Embodiment 84. The method of Embodiment 83, wherein the muscular disease is a muscular dystrophy.

Embodiment 85. The method of Embodiment 84, wherein the muscular dystrophy is Duchenne muscular dystrophy.

Embodiment 86. The method of Embodiment 76, wherein the disease, disorder, or condition is an infectious disease.

Embodiment 87. The method of Embodiment 86, wherein the infectious disease is an infection of *Heliobacter pylori* or *Mycobacterium tuberculosis*.

EXAMPLES

[0201] As described in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present disclosure, the following general methods and other methods known to one of ordinary skill in the art can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

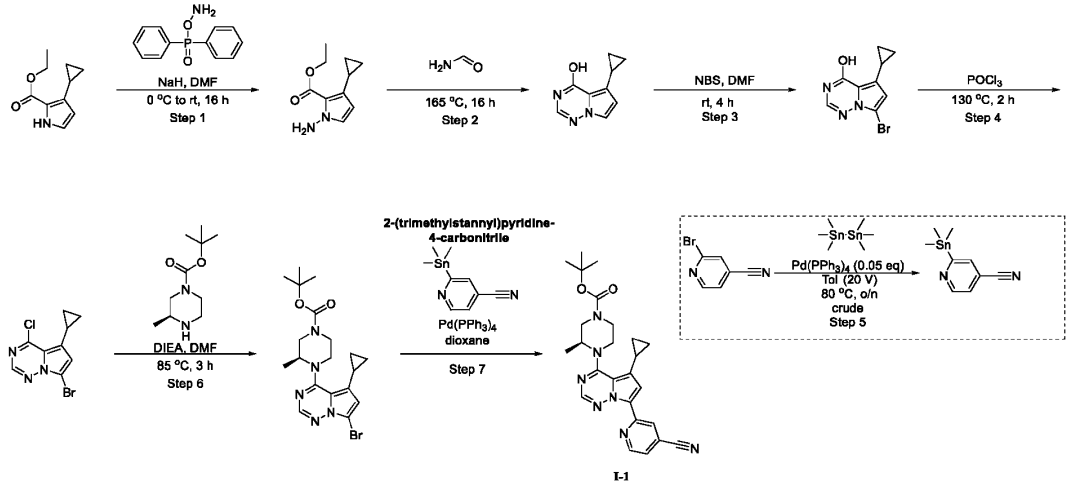
Table of Abbreviations

Abbreviation	Definition
DMF	N,N-Dimethyformamide
rt/RT	room temperature
h	hour(s)
NBS	N-bromosuccinimide
DIEA	N,N-Diisopropylethylamine
Tol	toluene
o/n / o.n.	overnight
eq/equiv	equivalent
TLC	thin layer chromatography
LCMS/LC-MS	liquid chromatography-mass spectrometry
sat.	saturated
aq.	aqueous
EA/EtOAC	ethyl acetate
vol/V	volume
HPLC	high performance liquid chromatography
FA	formic acid
CAN	acetonitrile
Min	minute(s)
DMSO	dimethyl sulfoxide
THF	tetrahydrofuran
Boc	tert-butyloxycarbonyl
DMAP	4-dimethylaminopyridine
PE	pentane
Ph	phenyl
LiHMDS	lithium hexamethyldisalizide
Ms	mesyl
TEA	triethylamine
m-CPBA	meta-chloroperoxylbenzoic acid
Y	yield
B_2Pin_2	4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane
Ac	Acetyl
$Pd(dppf)Cl_2$	[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloride
Bn	benzyl

Abbreviation	Definition
t-BuXPhos Pd G3	3rd Generation t-BuXPhos precatalyst
t-amyl	tert-amyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
PyBOP	benzotriazole-1-yloxytripyrrolidinophosphonium hexafluorophosphate
TFA	trifluoroacetic acid
LCAP	liquid chromatography area percent
DCM	dichloromethane

Example 1. Synthesis of Exemplary Compounds.

Example 1.1. Synthesis of tert-butyl (S)-4-(7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-3-methylpiperazine-1-carboxylate (I-1).



[0202] **Ethyl 1-amino-3-cyclopropyl-1H-pyrrole-2-carboxylate**. To a suspension of sodium hydride (0.50 g, 20.8 mmol, 1.5 eq) in DMF (25 mL) was added a solution of ethyl 3-cyclopropyl-1H-pyrrole-2-carboxylate (2.5 g, 13.9 mmol, 1 eq) in DMF (120 mL) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 30 minutes and then amino diphenylphosphinate (5.5 g, 23.7 mmol, 1.7 eq) was added portion wise. The reaction mixture was then allowed to stir at rt for 12 h. Progress of reaction was monitored by TLC. After completion, DMF was removed under reduced pressure and the residue was diluted with water (300 mL) and extracted with ethyl acetate (200 mL×3). Combined organic layer was washed with brine (250 mL) and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure afforded ethyl 1-amino-3-cyclopropyl-1H-pyrrole-2-carboxylate (2.9 g, crude). The product was used in the next step directly without further purification.

[0203] **5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-ol**. A solution of ethyl 1-amino-3-cyclopropyl-1H-pyrrole-2-carboxylate (2.9 g, 14.9 mmol, 1 eq) in formamide (29 mL) was allowed to stir at 165 °C for 16 h. Progress of reaction was monitored by TLC. After completion, the reaction mixture was cooled to RT and diluted with cold water (100 mL) while stirring. The formed precipitate was filtered and dried under vacuum to afford 5-cyclopropylpyrrolo[2,1-

f][1,2,4]triazin-4-ol (1.97 g, crude). The product was used in the next step directly without further purification.

[0204] 7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-ol. A mixture of 5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-ol (1.8 g, 10.3 mmol, 1.0 equiv) and NBS (1.7 g, 9.8 mmol, 0.95 equiv) in DMF (40 vol, 72mL) was stirred at room temperature for 4.0 hours. LCMS showed reaction was completed. The reaction was quenched with addition of sat. aq. sodium sulfite (50 mL). Water was then added to the mixture (40 ml) and the mixture was extracted with EA (40 mL x 2). The combined organic layers were washed with water (100 mL x 3), brine (100 mL x 1), and then dried over Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to afford 7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-ol (2.5 g, crude) as a white solid. The product was used in the next step directly without further purification.

[0205] 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazine. A mixture of methyl 7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-ol (1.5 g, 5.9 mmol, 1.0 equiv) in phosphoryl oxychloride (15 mL, 10 vol) was allowed to stir at 130 °C for 2.0 hours. LCMS showed the reaction was finished. After completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (30 mL x 1) and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to give 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazine (1.4 g, crude) as a yellow solid. The product was used in the next step directly without further purification.

[0206] Tert-butyl (S)-4-(7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-3-methylpiperazine-1-carboxylate. A mixture of 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazine (1.4 g, 5.1 mmol, 1.0 equiv), tert-butyl (S)-3-methylpiperazine-1-carboxylate (1.1 g, 5.6 mmol, 1.1 equiv) and DIEA (1.33 g, 10.3 mmol, 2.0 equiv) in DMF (14 ml, 10 vol) was allowed to stir at 85 °C for 3h. Progress of reaction was monitored by TLC. LCMS showed reaction was finished. After completion, reaction mixture was diluted with cold water (20 mL) and extracted with ethyl acetate (20 mL x 2). Combined organic layer was washed with brine (50 mL x 1) and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to obtain the crude product which was purified by reversed phase chromatography to afford tert-butyl (S)-4-(7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-3-methylpiperazine-1-carboxylate (700 mg, crude) as a yellow solid. The product was used in the next step directly without further purification.

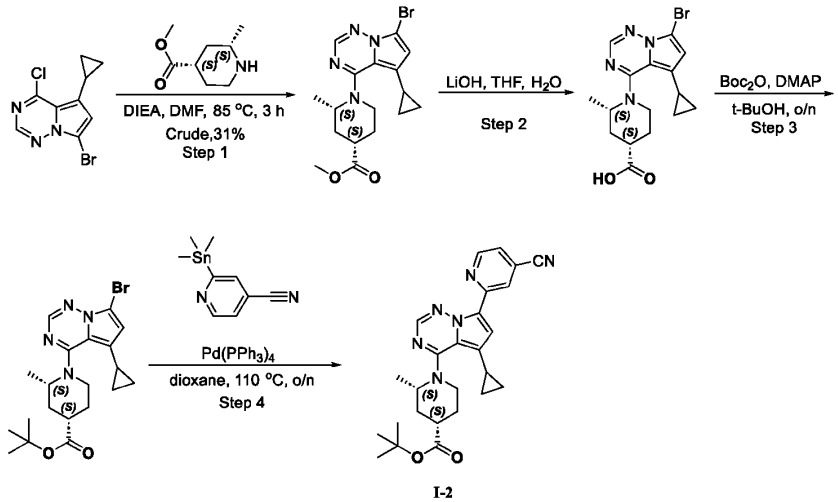
[0207] 2-(trimethylstannyl)pyridine-4-carbonitrile. Into a 40 mL vial was placed a solution of 2-bromopyridine-4-carbonitrile (1.0 g, 5.464 mmol, 1.0 equiv) in toluene (20.0 mL) and hexamethyldistannane (3.6 g, 10.928 mmol, 2.0 equiv) was added at room temperature. The mixture was bubbled with N_2 for 1 min then $Pd(PPh_3)_4$ (0.32 g, 0.273 mmol, 0.05 equiv) was added at room temperature. The mixture was bubbled with N_2 again for 1 min. The resulting mixture was stirred overnight at 80 °C. The mixture was allowed to cool to room temperature and then was concentrated under reduced pressure. This resulted in 2-(trimethylstannyl)pyridine-4-carbonitrile (1.7 g, crude) as a brown yellow solid.

[0208] Tert-butyl (S)-4-(7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-3-methylpiperazine-1-carboxylate (I-1). A mixture of tert-butyl (S)-4-(7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-3-methylpiperazine-1-carboxylate (200 mg, 0.458 mmol, 1.0 equiv), 2-(trimethylstannyl)pyridine-4-carbonitrile (244.68 mg, 0.9 mmol, 2 equiv) in dioxane (4 ml, 20 vol) was allowed to stir at rt. The mixture was degassed by a cycle of nitrogen and vacuum 3 times. Tetrakis(triphenylphosphine)palladium(0) (53 mg, 0.046 mmol, 0.1 equiv) was added into the flask at rt. The mixture was degassed by a cycle of nitrogen and vacuum 3 times. The resulting mixture was heated to 110 °C. The mixture was stirred at 110 °C for 24 h. LCMS showed the reaction was completed. The mixture was cooled to rt. The mixture was filtered. To the filtrate was added water (20 ml) and it was extracted with EA (20 mL x 2). The combined organic layers were washed with water (50 mL x 3), brine (50 mL x 1), and dried over with Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to afford tert-butyl (S)-4-(7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-3-methylpiperazine-1-carboxylate . The product was purified by Flash-Prep-HPLC with the following conditions. Column: Xselect CSH F-Phenyl OBD Column 30*150mm 5μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 65% B over 12 min; Wave Length: 254nm/220nm; RT1 (min): 9.27, Detector, UV 210 nm to afford tert-butyl (S)-4-(7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-3-methylpiperazine-1-carboxylate (I-1) (84.6 mg, 15.1%) as light yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.91 – 8.84 (m, 2H), 8.21 (s, 1H), 7.76 (dd, J = 4.9, 1.6 Hz, 1H), 7.60 (ddd, J = 18.6, 11.0, 7.0 Hz, 1H), 7.15 (s, 1H), 4.69 (s, 1H), 4.02 (s, 1H), 3.94 (d, J = 13.5 Hz, 1H), 3.83 (d, J = 13.4 Hz, 1H), 3.48 (t, J = 11.5 Hz, 1H), 3.02 (s, 1H), 2.16 – 2.06 (m, 1H), 1.44 (s, 9H), 1.20 (d, J = 6.6 Hz, 3H), 1.14 – 1.01 (m, 1H), 0.88 (p, J = 5.0, 4.4 Hz, 1H), 0.83 – 0.76 (m, 1H). LC-MS: $[M+H]^+$ = 460.55.

[0209] The following compound was prepared in a manner analogous to the procedures described in Example 1.1 above for tert-butyl (S)-4-(7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-3-methylpiperazine-1-carboxylate (I-1):

[0210] **Tert-butyl 1-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]piperidine-4-carboxylate (I-5)** (60.3 mg, 28.1%) as a white solid. Tert-butyl piperidine-4-carboxylate was used in place of tert-butyl (S)-3-methylpiperazine-1-carboxylate in Step 6. ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*): δ 8.91 – 8.83 (m, 2H), 8.19 (s, 1H), 7.76 (dd, J = 5.0, 1.5 Hz, 1H), 7.13 (s, 1H), 4.19 (d, J = 13.1 Hz, 2H), 3.22 (t, J = 12.0 Hz, 2H), 2.62 – 2.54 (m, 1H), 2.14 – 2.04 (m, 1H), 2.02 – 1.91 (m, 2H), 1.76 – 1.61 (m, 2H), 1.42 (s, 9H), 1.13 – 1.04 (m, 2H), 0.90 – 0.80 (m, 2H). LC-MS: (ES, *m/z*): $[M+H]^-$ = 445.

Example 1.2. Synthesis of tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-methylpiperidine-4-carboxylate (I-2).



I-2

[0211] **7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazine**. Prepared in a manner analogous to the procedure described above in steps 1-4 of Example 1.1.

[0212] **Methyl (2*S*,4*S*)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate**. Into a 40 mL vial was placed a solution of 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazine (1.1 g, 4.036 mmol, 1.0 equiv), methyl (2*S*,4*S*)-2-methylpiperidine-4-carboxylate (0.70 g, 4.440 mmol, 1.1 equiv) and DIEA (2.09 g, 16.144 mmol, 4.0 equiv) in DMF (20 mL) at room temperature under nitrogen atmosphere. The reaction was

heated to 85 °C and stirred for 3 h. LCMS showed the reaction was finished. The reaction was cooled to RT. To the reaction was added water (100 mL) and the reaction was extracted with EA (2 x 20 mL). The combined organic layers were washed with water (2 x 15 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to afford crude product methyl (2*S*,4*S*)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate (1.8 g, 113.4%) as brown oil. The crude product was used into next step directly without further purification.

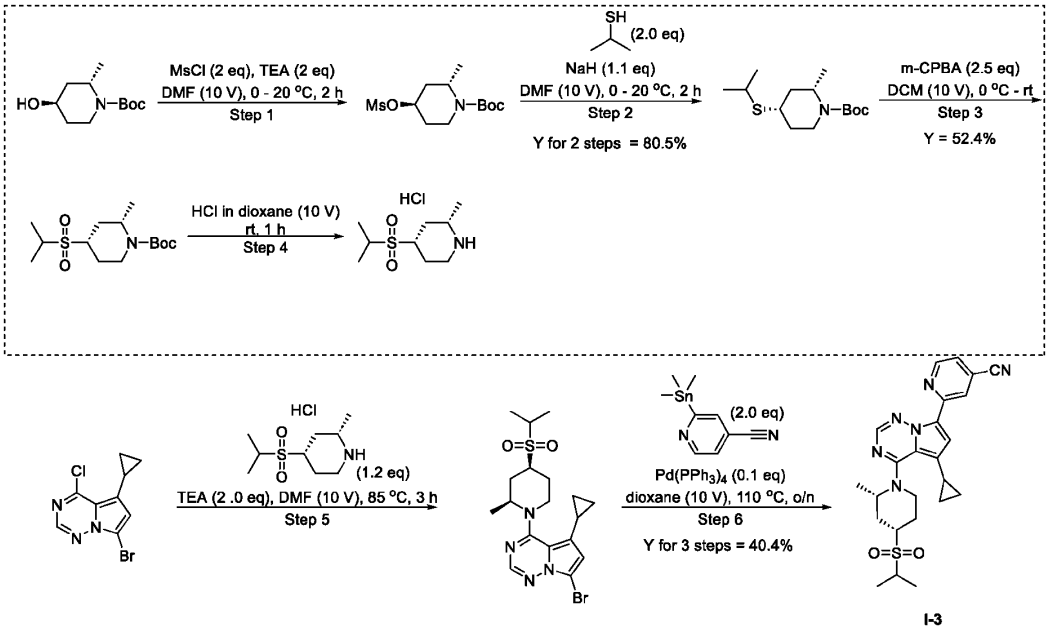
[0213] (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperi-dine-4-carboxylic acid. Into a 100 mL 3-necked round-bottom flask was placed a solution of methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate (1.8 g, 4.577 mmol, 1.0 equiv) in THF (18 mL) and H_2O (18 mL) at room temperature under nitrogen atmosphere. Then, LiOH (0.33 g, 13.731 mmol, 3.0 equiv) was added to the mixture. The reaction was stirred for 2 h at room temperature. LCMS showed the reaction was finished. To the reaction was added water (50 mL) and the reaction was extracted with EA (2 x 20 mL). The water phase was acidified to pH 1 with aqueous HCl (1 mol/L). The mixture was extracted with EA (2 x 20 mL). The combined organic layers were washed with water (15 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to afford crude product (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperi-dine-4-carboxylic acid (1.5 g, 86.4%). The crude product was used into next step directly without further purification.

[0214] Tert-butyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 40 mL vial was placed a solution of (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylic acid (750.0 mg, 1.978 mmol, 1.0 equiv), Boc_2O (647.4 mg, 2.967 mmol, 1.5 equiv) and DMAP (724.8 mg, 5.934 mmol, 3.0 equiv) in t-BuOH (15 mL) at room temperature under nitrogen atmosphere. The reaction was stirred for 12 h at room temperature. LCMS showed the reaction was finished. To the reaction was added water (60 mL) and the reaction was extracted with EA (2 x 20 mL). The combined organic layers were washed with water (15 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to afford crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford tert-butyl

(2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (690 mg, 80.1%) as an off-white foam.

[0215] Tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-methylpiperidine-4-carboxylate (I-2). Prepared in a manner analogous to the procedure described above in step 7 of Example 1.1 except that tert-butyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate was used in place of tert-butyl (S)-4-(7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-3-methylpiperazine-1-carboxylate; (78.9 mg, 36.9%) as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d_6, *ppm*): δ 8.91 – 8.84 (m, 2H), 8.28 (s, 1H), 7.76 (dd, J = 4.9, 1.5 Hz, 1H), 7.14 (s, 1H), 4.17 – 4.10 (m, 1H), 3.75 (d, J = 8.8 Hz, 1H), 3.48 – 3.40 (m, 1H), 2.60 (t, J = 6.6 Hz, 1H), 2.23 (hept, J = 5.0 Hz, 1H), 2.12 – 2.04 (m, 1H), 1.83 (p, J = 7.7, 6.4 Hz, 3H), 1.44 (s, 9H), 1.25 (d, J = 6.4 Hz, 3H), 1.11 – 1.04 (m, 2H), 0.98 – 0.91 (m, 1H), 0.76 – 0.67 (m, 1H). LC-MS: (ES, *m/z*): $[M+H]^+$ = 459.

Example 1.3. Synthesis of 2-{5-cyclopropyl-4-[(2S,4S)-2-methyl-4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-3).



[0216] **Tert-butyl (2S,4R)-4-(methanesulfonyloxy)-2-methylpiperidine-1-carboxylate**. Into 250 mL 3-necked round bottom flask was placed a solution of tert-butyl (2S,4R)-4-hydroxy-

2-methylpiperidine-1-carboxylate (9.0 g, 41.803 mmol, 1.0 equiv) in DMF (90 mL). The solution was treated with TEA (8.46 g, 83.606 mmol, 2.0 equiv) at room temperature under nitrogen atmosphere followed by the addition of MsCl (9.58 g, 83.606 mmol, 2.0 equiv) in portions at 0°C. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (12 g) was used in the next step directly without further purification.

[0217] Tert-butyl (2S,4S)-4-(isopropylsulfanyl)-2-methylpiperidine-1-carboxylate. In a separate flask, 2-propanethiol (6.23 g, 81.806 mmol, 2.0 equiv) in DMF was cooled to 0°C. To the mixture was added NaH (1.08 g, 44.993 mmol, 1.1 equiv), and the mixture was stirred at room temperature for 2 h. Then, tert-butyl (2S,4R)-4-(methanesulfonyloxy)-2-methylpiperidine-1-carboxylate (12.0 g, 40.903 mmol, 1.0 equiv) was dissolved in DMF and added slowly to the thiolate solution. Upon completion of addition, the mixture was stirred until the reaction was complete. Water and ethyl acetate were added to the mixture, and the organic phase was dried over sodium sulfate and concentrated yielding a residue. The residue was purified by flash column chromatography to afford tert-butyl (2S,4S)-4-(isopropylsulfanyl)-2-methylpiperidine-1-carboxylate (9 g, 80.5%).

[0218] Tert-butyl (2S,4S)-2-methyl-4-(propane-2-sulfonyl)piperidine-1-carboxylate. To a stirred mixture of tert-butyl (2S,4S)-4-(isopropylsulfanyl)-2-methylpiperidine-1-carboxylate (9.4 g, 34.377 mmol, 1 equiv) in DCM (94 mL) was added m-CPBA (14.83 g, 85.943 mmol, 2.5 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The reaction was quenched with aqueous Na_2SO_3 solution at 0°C. The resulting mixture was extracted with DCM. The combined organic layers were washed with aqueous Na_2SO_3 solution (until m-CPBA is washed clean), washed with aqueous $NaHCO_3$ solution, and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA to afford tert-butyl (2S,4S)-2-methyl-4-(propane-2-sulfonyl)piperidine-1-carboxylate (5.5 g, 52.4%) as a light yellow oil.

[0219] (2S,4S)-4-(isopropylsulfonyl)-2-methylpiperidine hydrochloride. Into a 40 mL vial were added tert-butyl (2S,4S)-2-methyl-4-(propane-2-sulfonyl)piperidine-1-carboxyl ate (2.0 g,

6.548 mmol, 1.0 equiv) and HCl (gas) in 1,4-dioxane (20 mL) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum. The crude product (1.3 g) was used in the next step directly without further purification.

[0220] **7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazine**. Prepared in a manner analogous to the procedure described above in steps 1-4 of Example 1.1.

[0221] **(2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4] triazin-4-yl}-2-methyl-4-(propane-2-sulfonyl)piperidine**. Into a 40 mL vial was added a solution of 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazine (600.0 mg, 2.202 mmol, 1.0 equiv), (2S,4S)-4-(isopropylsulfonyl)-2-methylpiperidine hydrochloride (540.0 mg, 2.642 mmol, 1.2 equiv) and TEA (0.60 mL, 4.317 mmol, 2.0 equiv) in DMF (6 mL) at room temperature. The resulting mixture was stirred for 3 h at 85°C. The mixture was allowed to cool down to room temperature. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture (600 mg) was used in the next step directly without further purification.

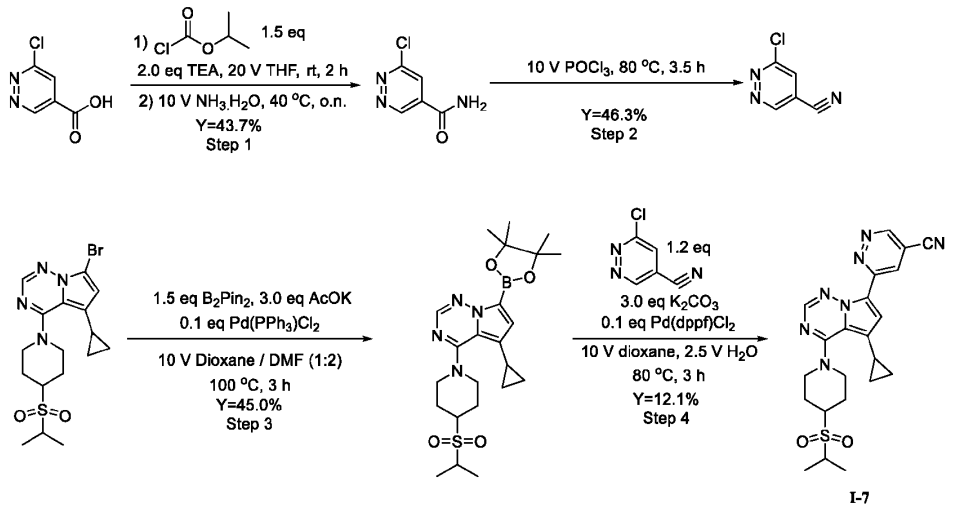
[0222] **2-{5-cyclopropyl-4-[(2S,4S)-2-methyl-4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-3).** Prepared in a manner analogous to the procedure described above in step 7 of Example 1.1 except that (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4] triazin-4-yl}-2-methyl-4-(propane-2-sulfonyl)piperidine was used in place of tert-butyl (S)-4-(7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-3-methylpiperazine-1-carboxylate; (87.3 mg, 40.4%) as a yellow solid. ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 8.87 – 8.82 (m, 2H), 8.34 (s, 1H), 7.74 (dd, J = 5.2, 1.2 Hz, 1H), 7.14 (s, 1H), 4.02 (dt, J = 12.9, 4.2 Hz, 1H), 3.80 (ddt, J = 11.7, 9.3, 5.7 Hz, 1H), 3.61 (tt, J = 11.2, 4.1 Hz, 1H), 3.47 – 3.37 (m, 1H), 3.28 – 3.14 (m, 1H), 2.30 (td, J = 8.3, 4.1 Hz, 1H), 2.17 (d, J = 12.9 Hz, 1H), 2.09 (dd, J = 10.9, 4.6 Hz, 1H), 1.80 (qd, J = 15.2, 13.6, 10.0 Hz, 2H), 1.36 (d, J = 6.0 Hz, 3H), 1.27 (dd, J = 6.8, 2.7 Hz, 6H), 1.13 – 1.02 (m, 2H), 0.96 (dt, J = 8.5, 3.9 Hz, 1H), 0.69 – 0.59 (m, 1H). LC-MS: (ES, *m/z*): $[M+H]^+$ = 465.

[0223] The following compounds were prepared in a manner analogous to the procedures described in Example 1.3 above for 2-{5-cyclopropyl-4-[(2S,4S)-2-methyl-4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-3):

[0224] **2-{5-cyclopropyl-4-[4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-**carbonitrile **(I-4)** (30 mg, 9.4%) as a white solid. Commercially-available tert-butyl (S)-3-methylpiperazine-1-carboxylate is used in place of (2S,4S)-4-(isopropylsulfonyl)-2-methylpiperidine hydrochloride in step 5. ^{1}H-NMR: (300 MHz, DMSO-d_6, *ppm*) δ 8.92 – 8.83 (m, 2H), 8.21 (s, 1H), 7.76 (dd, J = 4.9, 1.6 Hz, 1H), 7.14 (s, 1H), 4.42 (d, J = 13.0 Hz, 2H), 3.65 (t, J = 5.7 Hz, 1H), 3.42 (p, J = 6.8 Hz, 1H), 3.24 (q, J = 13.1, 12.4 Hz, 2H), 2.20 – 1.99 (m, 3H), 1.86 – 1.69 (m, 2H), 1.27 (d, J = 6.8 Hz, 6H), 1.17 – 1.05 (m, 2H), 0.86 (td, J = 6.5, 6.1, 4.1 Hz, 2H). LC-MS: (ES, *m/z*): $[M+H]^+$ = 451.

[0225] 2-{5-cyclopropyl-4-[4-(2-methylpropane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-6) (57.3 mg, 27.2%) as a white solid. Commercially-available tert-butyl 4-bromopiperidine-1-carboxylate is used in place of tert-butyl (2S,4R)-4-(methanesulfonyloxy)-2-methylpiperidine-1-carboxylate and 2-methyl-2-propanethiol is used in place of propanethiol in step 2. ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 9.00 (s, 1H), 8.78 (d, 1H), 8.11 (s, 1H), 7.38 (d, 1H), 7.17 (s, 1H), 4.49 (m, 2H), 3.45 (m, 1H), 3.23 (m, 2H), 3.08 (m, 3H), 2.30-2.10 (m, 5H), 1.54 (s, 9H), 1.12 (m, 2H), 0.90 (m, 2H). LC-MS: (ES, *m/z*): $[M+H]^+$ = 465.

Example 1.4. Synthesis of 6-{5-cyclopropyl-4-[4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl} pyridazine -4-carbonitrile (I-7).



[0226] **6-chloropyridazine-4-carboxamide**. Into a 1 L 3-necked round bottom flask was placed a solution of 6-chloropyridazine-4-carboxylic acid (25.0 g, 157.689 mmol, 1.0 equiv), TEA (31.91 g, 315.378 mmol, 2.0 equiv) and isopropyl carbonochloridate (32.31 g, 236.534 mmol, 1.5 equiv) in THF (500 mL) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature. To the above solution was added ammonia solution (25% in H_2O, 250 mL). The resulting mixture was stirred for overnight at 40 °C. The resulting mixture was quenched by the addition of water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by trituration with DCM (25 mL). The precipitated solids were collected by filtration and washed with DCM (3 x 25 mL) to afford 6-chloropyridazine-4-carboxamide (11.2 g, 43.7%) as a brown solid.

[0227] **6-chloropyridazine-4-carbonitrile**. Into a 500 mL 3-necked round bottom flask was placed a solution of 6-chloropyridazine-4-carboxamide (11.2 g, 71.084 mmol, 1.0 equiv) in phosphoroyl trichloride (112 mL) and the reaction was stirred for 3.5 h at 80 °C. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 5% to 100% gradient in 24 min; detector, UV 254 nm. This resulted in 6-chloropyridazine-4-carbonitrile (4.8 g, 46.3%) as a brown solid.

[0228] **1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-4-(propane-2-sulfonyl)piperidine**. Prepared in a manner analogous to the procedure described above in step 5 of Example 1.3 except that 4-(isopropylsulfonyl)piperidine hydrochloride was used in place of (2S,4S)-4-(isopropylsulfonyl)-2-methylpiperidine hydrochloride. 4-(isopropylsulfonyl)piperidine hydrochloride was prepared in a manner analogous to the procedure described above in steps 2-4 of Example 1.3 except that tert-butyl 4-bromopiperidine-1-carboxylate was used as a starting material in place of tert-butyl (2S,4R)-4-(methanesulfonyloxy)-2-methylpiperidine-1-carboxylate.

[0229] 1-[5-cyclopropyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-4-(propane-2-sulfonyl)piperidine. Into a 40 mL vial was placed a solution of 1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-4-(propane-2-sulfonyl)piperidine

(300.0 mg, 0.702 mmol, 1.0 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (267.4 mg, 1.053 mmol, 1.5 equiv), $Pd(PPh_3)Cl_2$ (51.4 mg, 0.070 mmol, 0.1 equiv) and AcOK (206.7 mg, 2.106 mmol, 3.0 equiv) in DMF (1 mL) and dioxane (2 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 100 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure and purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 1-[5-cyclopropyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-4-(propane-2-sulfonyl)piperidine (0.15 g, 45.0%) as a yellow solid.

[0230] 6-{5-cyclopropyl-4-[4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl} pyridazine -4-carbonitrile. Into a 20 mL vial was placed a solution of 1-[5-cyclopropyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrrolo[2,1-f][1,2,4]triazin-4-yl]-4-(propane-2-sulfonyl)piperidine (200.0 mg, 0.422 mmol, 1.0 equiv), 6-chloropyridazine-4-carbonitrile (70.6 mg, 0.506 mmol, 1.2 equiv), K_2CO_3 (174.8 mg, 1.266 mmol, 3.0 equiv) and $Pd(dppf)Cl_2$ (23.3 mg, 0.042 mmol, 0.1 equiv) in dioxane (2 mL) and H_2O (0.5 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 80 °C. The mixture was allowed to cool down to room temperature and concentrated under reduced pressure. The crude product was purified by reverse phase flash column chromatography with the following conditions (Column: Xbridge Prep phenyl OBD Colum, 30*150 nm, 5 μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 45% B over 15 min; Wave Length: 254nm/220nm; RT1(min): 11.5. This resulted in 6-{5-cyclopropyl-4-[4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl} pyridazine -4-carbonitrile (23.2 mg, 12.1%) as a yellow solid. ^{1}H-NMR: (300 MHz, DMSO-d_6, *ppm*) δ 9.53 (d, J = 1.9 Hz, 1H), 9.08 (d, J = 2.0 Hz, 1H), 8.21 (s, 1H), 7.33 (s, 1H), 4.44 (d, J = 13.1 Hz, 2H), 3.74 – 3.61 (m, 1H), 3.48 – 3.25 (m, 3H), 2.21 – 2.03 (m, 3H), 1.86 – 1.73 (m, 2H), 1.27 (d, J = 6.7 Hz, 6H), 1.13 (dd, J = 7.9, 2.2 Hz, 2H), 0.96 – 0.85 (m, 2H). LC-MS: (ES, *m/z*): $[M+H]^+$ = 452.

[0231] The following compounds were prepared in a manner analogous to the procedures described in Example 1.4 above for 6-{5-cyclopropyl-4-[4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl} pyridazine -4-carbonitrile (I-7):

[0232] 6-{5-cyclopropyl-4-[(2S,4S)-2-methyl-4-(propane-2-sulfonyl)piperidin-1-yl]-4aH,5H-pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridazine-4-carbonitrile (I-8) (44 mg, 22.9%) as a

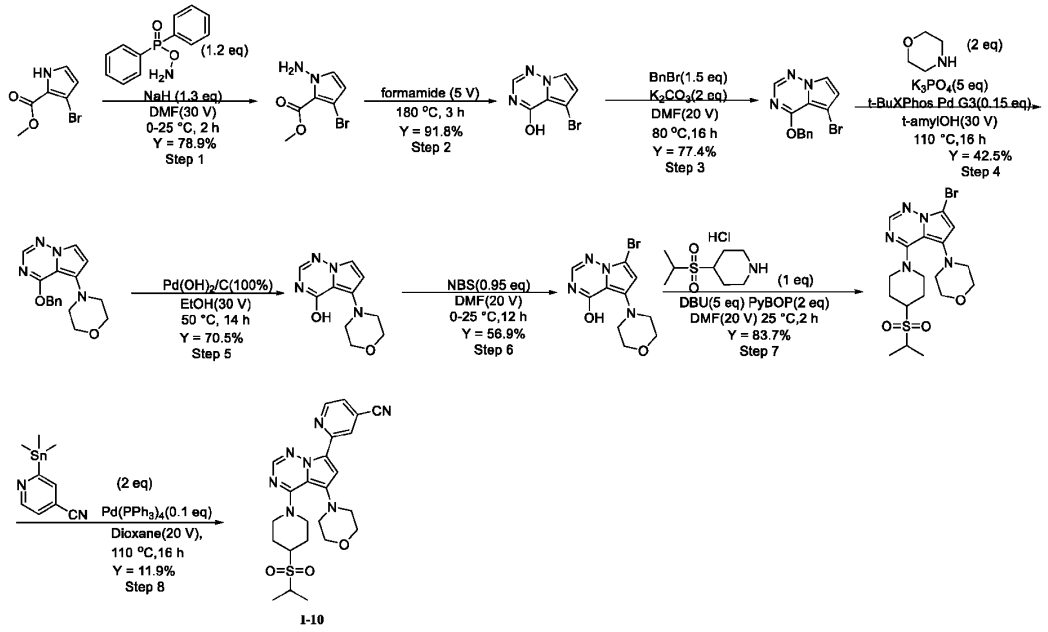
light yellow solid. (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methyl-4-(propane-2-sulfonyl)piperidine is used in place of 1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-4-(propane-2-sulfonyl)piperidine in step 3. ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 9.53 (s, 1H), 9.08 (s, 1H), 8.35 (s, 1H), 7.36 (s, 1H), 4.06 (d, J = 13.0 Hz, 1H), 3.77-3.91 (m, 1H), 3.68-3.56 (m, 1H), 3.34-3.24 (m, 1H), 2.37-2.27 (m, 1H), 2.24 – 2.04 (m, 2H), 1.85 (d, J = 16.1 Hz, 2H), 1.38 (d, J = 5.9 Hz, 3H), 1.33 – 1.20 (m, 6H), 1.16 – 0.96 (m, 3H), 0.78-0.63 (m, 1H). LC-MS: (ES, *m/z*): $[M+H]^+$ = 466.

[0233] (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methyl-4-(propane-2-sulfonyl)piperidine is prepared in a manner analogous to the procedure described above in steps 1-5 of Example 1.3.

[0234] **6-{5-cyclopropyl-4-[4-(oxetane-3-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridazine-4-carbonitrile (I-13)** (15 mg, 10.3%) as a yellow solid. 1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4]triazin-4-yl}-4-(oxetane-3-sulfonyl)piperidine is used as the starting material in step 3 in place of 1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-4-(propane-2-sulfonyl)piperidine. ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 9.52 (s, 1H), 9.08 (s, 1H), 8.20 (s, 1H), 7.33 (s, 1H), 4.90 (q, 1H), 4.76 (d, 2H), 4.44 (d, 2H), 4.45 (d, 2H), 3.52 (t, 1H), 3.32 (t, 2H), 2.06-2.11 (m, 3H), 1.72-1.76 (m, 2H), 1.30 (d, 2H), 1.12 (s, 2H). LC-MS: (ES, *m/z*): $[M+H]^+$ = 466.

[0235] 1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4]triazin-4-yl}-4-(oxetane-3-sulfonyl)piperidine was prepared in a manner analogous to the procedure described below in steps 1-4 of Example 1.7.

Example 1.5. Synthesis of 2-[5-(morpholin-4-yl)-4-[4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f] [1,2,4]triazin-7-yl]pyridine-4-carbonitrile (I-10).



[0236] **Methyl 1-amino-3-bromopyrrole-2-carboxylate**. Into a 1 L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl 3-bromo-1H-pyrrole-2-carboxylate (25.0 g, 122.535 mmol, 1.0 equiv) in DMF (250 mL) at 20°C. To the above mixture was added NaH (3.82 g, 159.296 mmol, 1.3 equiv, 60% wt) at 0 °C. The mixture was stirred for 0.5 h at 0 °C under nitrogen atmosphere. To the above mixture was added amino diphenylphosphinate (34.29 g, 147.042 mmol, 1.2 equiv) in DMF (500 mL) at 0 °C over 10 min. The final reaction mixture was stirred for 2 h at 25 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to 0 °C. The reaction was quenched with water/ice (750 mL) at 0 °C. The resulting mixture was diluted with ethyl acetate (750 mL). The aqueous layer was extracted with EtOAc (2 x 750 mL). The combined organic layers were washed with brine (5 x 750 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1 : 1) to afford methyl 1-amino-3-bromopyrrole-2-carboxylate (22.3 g, 78.9%) as an off-white solid.

[0237] **5-bromopyrrolo[2,1-f] [1,2,4]triazin-4-ol**. Into a 250 mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl

1-amino-3-bromopyrrole-2-carboxylate (22.3 g, 96.718 mmol, 1.0 equiv, 95%wt) in formamide (111.5 mL) at 20 °C. The final reaction mixture was stirred for 3 h at 180 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to 20 °C. The precipitated solids were collected by filtration and washed with water (3 x 50 mL) to give a 5-bromopyrrolo[2,1-f] [1,2,4]triazin-4-ol (20 g, 91.8%) as a brown solid.

[0238] 4-(benzyloxy)-5- bromopyrrolo[2,1-f][1,2,4]triazine. Into a 500 mL 3-necked round bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 5-bromopyrrolo[2,1-f][1,2,4]triazin-4-ol (10.0 g, 45.322 mmol, 1.0 equiv, 97%wt) in DMF (200 mL) at 20 °C. To the above mixture was added K_2CO_3 (12.53 g, 90.644 mmol, 2.0 equiv) in portions at 20 °C. The resulting mixture was stirred for additional 5 min at 20 °C. To the above mixture was added BnBr (11.63 g, 67.983 mmol, 1.5 equiv) dropwise at 20 °C. The final reaction mixture was stirred for 16 h at 80 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to 20 °C. The reaction was quenched with water/ice (300 mL) at 0 °C. The resulting mixture was diluted with ethyl acetate (30 mL). The aqueous layer was extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with brine (5 x 200 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: Column, Ultimate XB-C18 Column, 50*250 mm, 10μm; mobile phase, MeCN in Water (0.1% FA), 20% to 100% gradient over 20 min; detector, UV 210/254 nm to afford 4-(benzyloxy)-5-bromopyrrolo[2,1-f][1,2,4]triazine (11 g, 77.4%) as a brown solid.

[0239] 4-[4-(benzyloxy)pyrrolo[2,1-f][1,2,4]triazin-5-yl] morpholine. Into a 1 L 3-necked round bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 4-(benzyloxy)-5-bromopyrrolo[2,1-f][1,2,4]triazine (12.0 g, 38.271 mmol, 1.0 equiv, 97%wt) in t-AmOH (360 mL) at 20 °C. To the above mixture was added K_3PO_4 (40.62 g, 191.355 mmol, 5.0 equiv) in portions at 20 °C. The resulting mixture was stirred for additional 5 min at 20 °C. To the above mixture was added morpholine (6.67 g, 76.542 mmol, 2.0 equiv) dropwise at 20 °C. To the above mixture was added 3rd Generation t-BuXPhos precatalyst (4.57 g, 5.741 mmol, 0.15 equiv) in one portion at 20 °C. The final reaction mixture was stirred for 16 h at 110 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected

by LCMS. The mixture was allowed to cool down to 20 °C. The resulting mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: Column, Ultimate XB-C18 Column, 50*250 mm, 10μm; mobile phase, MeCN in Water (0.1% FA), 20% to 100% gradient over 20 min; detector, UV 210/254 nm to afford4-[4-(benzyloxy)pyrrolo[2,1-f][1,2,4]triazin-5-yl] morpholine (5.2 g, 42.5%) as an off-white solid.

[0240] **5-(morpholin-4-yl)pyrrolo[2,1-f][1,2,4] triazin-4-ol**. Into a 250 mL 3-necked round bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 4-[4-(benzyloxy)pyrrolo[2,1-f][1,2,4]triazin-5-yl]morpholine (2.2 g, 6.876 mmol, 1.0 equiv, 97%) in EtOH (66 mL) at 20 °C. To the above mixture was added $Pd(OH)_2/C$ (2.2 g) in one portion at 20 °C. The mixture was hydrogenated at 50 °C for 14 h under hydrogen atmosphere using a hydrogen balloon. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to 20 °C. The resulting mixture was filtered through a Celite pad, the filtrate was concentrated under reduced pressure to afford 5-(morpholin-4-yl)pyrrolo[2,1-f][1,2,4] triazin-4-ol (1.1 g, 70.5%) as an off-white solid.

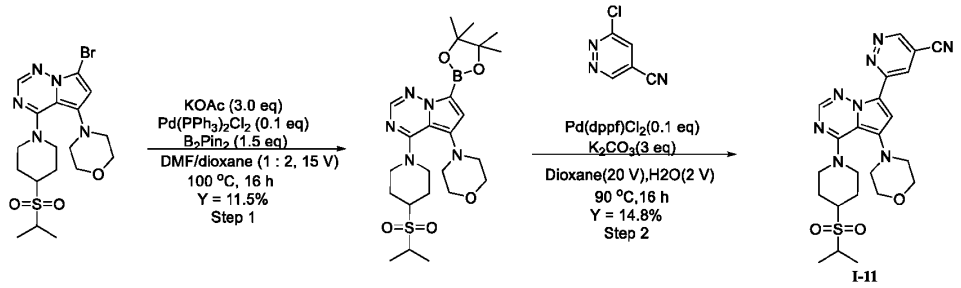
[0241] **7-bromo-5-(morpholin-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-ol**. Into a 40 mL vial purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 5-(morpholin-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-ol (1.5 g, 6.607 mmol, 1.0 equiv) in DMF (15 mL) at 0 °C. To the above mixture was added a solution of NBS (1.12 g, 6.277 mmol, 0.95 equiv) in DMF (15 mL) dropwise over 30 min at 0 °C. The final reaction mixture was stirred for 12 h at 25 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to 20 °C. The residue was purified by reversed-phase flash chromatography with the following conditions: Column, Ultimate XB-C18 Column, 50*250 mm, 10μm; mobile phase, MeCN in Water (0.1% FA), 30% to 60% gradient over 30 min; detector, UV 210/254 nm to afford 7-bromo-5-(morpholin-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-ol (1.16 g, 56.9%) as a brown solid.

[0242] **4-(propane-2-sulfonyl)piperidine hydrochloride** was prepared in a manner analogous to the procedure described above in steps 2-4 of Example 1.3 except that tert-butyl 4-bromopiperidine-1-carboxylate was used as a starting material in place of tert-butyl (2S,4R)-4-(methanesulfonyloxy)-2-methylpiperidine-1-carboxylate.

[0243] **4-(7-bromo-4-[4-(propane-2-sulfonyl)piperidin-1-yl] pyrrolo[2,1-f][1,2,4]triazin-5-ylmorpholine**. Into a 40 mL vial purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 7-bromo-5-(morpholin-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-ol (280.0 mg, 0.908 mmol, 1.0 equiv) in DMF (5.6 mL) at 20 °C. To the above mixture was added 4-(propane-2-sulfonyl)piperidine (173.7 mg, 0.908 mmol, 1.0 equiv) in one portion at 20 °C. To the above mixture was added DBU (691.2 mg, 4.540 mmol, 5.0 equiv) in one portion at 20 °C. To the above mixture was added PyBOP (945.0 mg, 1.816 mmol, 2.0 equiv) in one portion at 20 °C. The final reaction mixture was stirred for 2 h at 25 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The residue was purified by reversed-phase flash chromatography with the following conditions: Column, Ultimate XB-C18 Column, 50*250 mm, 10μm; mobile phase, MeCN in Water (0.1% FA), 25% to 55% gradient over 30 min; detector, UV 210/254 nm to afford 4-(7-bromo-4-[4-(propane-2-sulfonyl)piperidin-1-yl] pyrrolo[2,1-f][1,2,4]triazin-5-ylmorpholine (370 mg, 83.7%) as an off-white solid.

[0244] 2-[5-(morpholin-4-yl)-4-[4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f] [1,2,4]triazin-7-yl]pyridine-4-carbonitrile (I-10). Prepared in a manner analogous to the procedure described above in step 7 of Example 1.1 except that 4-(7-bromo-4-[4-(propane-2-sulfonyl)piperidin-1-yl] pyrrolo[2,1-f][1,2,4]triazin-5-ylmorpholine was used in place of tert-butyl (S)-4-(7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-3-methylpiperazine-1-carboxylate; (22.4 mg, 11.9%) as a yellow solid. ^{1}H-NMR: (300 MHz, DMSO-d_6, *ppm*) δ 8.94 (d, J = 5.1 Hz, 1H), 8.11 (d, J = 7.1 Hz, 2H), 7.93 (s, 1H), 7.80 (d, J = 5.1 Hz, 1H), 4.75 (d, J = 13.1 Hz, 2H), 3.67 (d, J = 13.1 Hz, 5H), 3.42 (s, 1H), 3.21(s, 2H), 3.03 (s, 4H), 2.08 (d, J = 12.6 Hz, 2H), 1.74 (d, J = 12.0 Hz, 2H), 1.27 (d, J = 6.7 Hz, 6H). LC-MS: (ES, *m/z*): $[M+H]^+$ = 496.

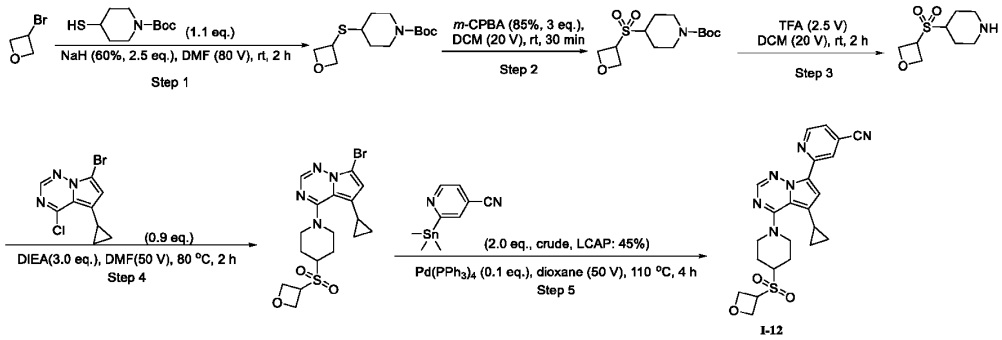
Example 1.6. Synthesis of 6-[5-(morpholin-4-yl)-4-[4-(propane-2-sulfonyl)piperidin-1-yl] pyrrolo[2,1-f][1,2,4]triazin-7-yl]pyridazine-4-carbonitrile (I-11).



[0245] 4-(4-[4-(propane-2-sulfonyl)piperidin-1-yl]-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,1-f][1,2,4]triazin-5-ylmorpholine (I-11). Prepared in a manner analogous to the procedure described above in steps 3-4 of Example 1.4 except that 4-(7-bromo-4-[4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-5-ylmorpholine was used as a starting material in step 3 in place of 1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-4-(propane-2-sulfonyl)piperidine; (22.4 mg, 11.9%) as a yellow solid. ^{1}H-NMR: (300 MHz, DMSO-d_6, *ppm*) δ 8.94 (d, J = 5.1 Hz, 1H), 8.11 (d, J = 7.1 Hz, 2H), 7.93 (s, 1H), 7.80 (d, J = 5.1 Hz, 1H), 4.75 (d, J = 13.1 Hz, 2H), 3.67 (d, J = 13.1 Hz, 5H), 3.42 (s, 1H), 3.21(s, 2H), 3.03 (s, 4H), 2.08 (d, J = 12.6 Hz, 2H), 1.74 (d, J = 12.0 Hz, 2H), 1.27 (d, J = 6.7 Hz, 6H). LC-MS: (ES, *m/z*): $[M+H]^+$ = 496.

[0246] 4. (7-bromo-4-[4-(propane-2-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-5-ylmorpholine was prepared in a manner analogous to the procedure described above in steps 1-7 of Example 1.5.

Example 1.7. Synthesis of 2-{5-cyclopropyl-4-[4-(oxetane-3-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-12).



[0247] **Tert-butyl 4-(oxetan-3-ylsulfanyl)piperidine-1-carboxylate**. To a solution of N,N-dimethylformamide (80 mL) under nitrogen atmosphere was added NaH (0.73 g, 18.253 mmol, 2.5 equiv, 60%) in portions at 0 °C. Then, tert-butyl 4-sulfanylpiperidine-1-carboxylate (1.75 g, 8.031 mmol, 1.1 equiv) and 3-bromooxetane (1.0 g, 7.301 mmol, 1.0 equiv) were added at room temperature under N_2 atmosphere. The resulting mixture was stirred for additional 2 hours at room temperature. The reaction was quenched by the addition of aqueous NH_4Cl (300 mL) at 0 °C. The resulting mixture was washed with EA (3 x 50 mL). The combined organic layers were washed with brine (3 x 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was

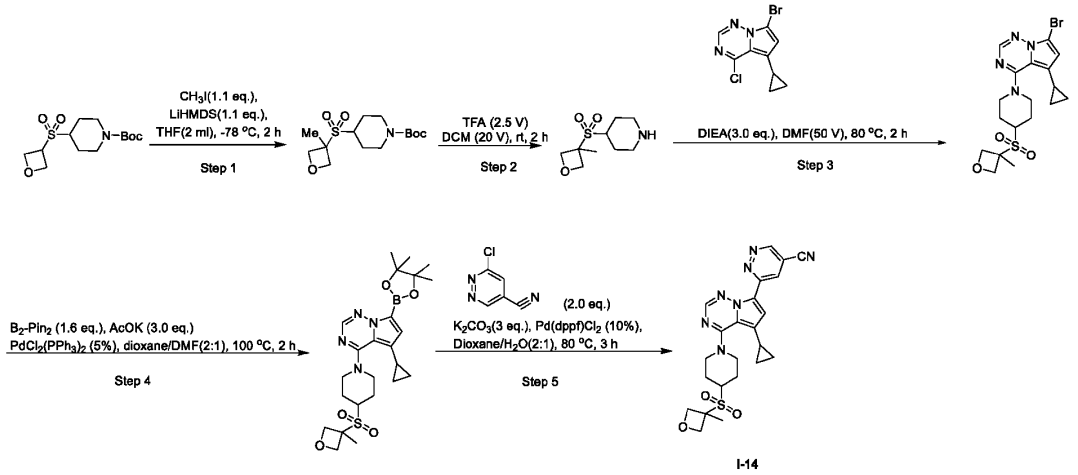
concentrated under reduced pressure. This resulted in crude of tert-butyl 4-(oxetan-3-ylsulfanyl)piperidine-1-carboxylate (1.3 g, 13.7%) as a yellow oil.

[0248] **Tert-butyl 4-(oxetane-3-sulfonyl)piperidine-1-carboxylate**. Prepared in a manner analogous to the procedure described above in step 3 of Example 1.3 except that tert-butyl 4-(oxetan-3-ylsulfanyl)piperidine-1-carboxylate was used in place of tert-butyl (2S,4S)-4-(isopropylsulfanyl)-2-methylpiperidine-1-carboxylate.

[0249] **4-(oxetane-3-sulfonyl)piperidine**. Into a 40 mL vial was added tert-butyl 4-(oxetane-3-sulfonyl)piperidine-1-carboxylate (300.0 mg, 0.982 mmol, 1.0 equiv) in dichloromethane (6 mL) at room temperature. To the above mixture was added 2,2,2-trifluoroacetic acid (0.75 mL) dropwise at room temperature. The resulting mixture was stirred for additional 2 hours at room temperature. The resulting mixture was concentrated under vacuum. The crude product 4-(oxetane-3-sulfonyl)piperidine (400 mg) was used in the next step directly without further purification.

[0250] **2-{5-cyclopropyl-4-[4-(oxetane-3-sulfonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-12)**. Prepared in a manner analogous to the procedure described above in steps 6-7 of Example 1.1 except that 4-(oxetane-3-sulfonyl)piperidine was used as a starting material in step 6 in place of tert-butyl (S)-3-methylpiperazine-1-carboxylate; (40 mg, 22.0%) as a white solid. ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 9.00 (s, 1H), 8.78 (d, 1H), 8.09 (s, 1H), 7.38 (d, 1H), 7.16 (s, 1H), 5.09 (m, 2H), 4.89 (m, 2H), 4.56 (m, 3H), 3.08 (m, 3H), 2.2 – 1.90 (m, 6H), 1.1 (m, 2H), 0.89 (m, 2H). LC-MS: (ES, *m/z*): $[M+H]^+$ = 465.

Example 1.8. Synthesis of 6-{5-cyclopropyl-4-[4-(3-methyloxetan-3-ylsulfonyl)piperidin-1-yl]pyrrolo [2,1-f][1,2,4]triazin-7-yl}pyridazine-4-carbonitrile (I-14).



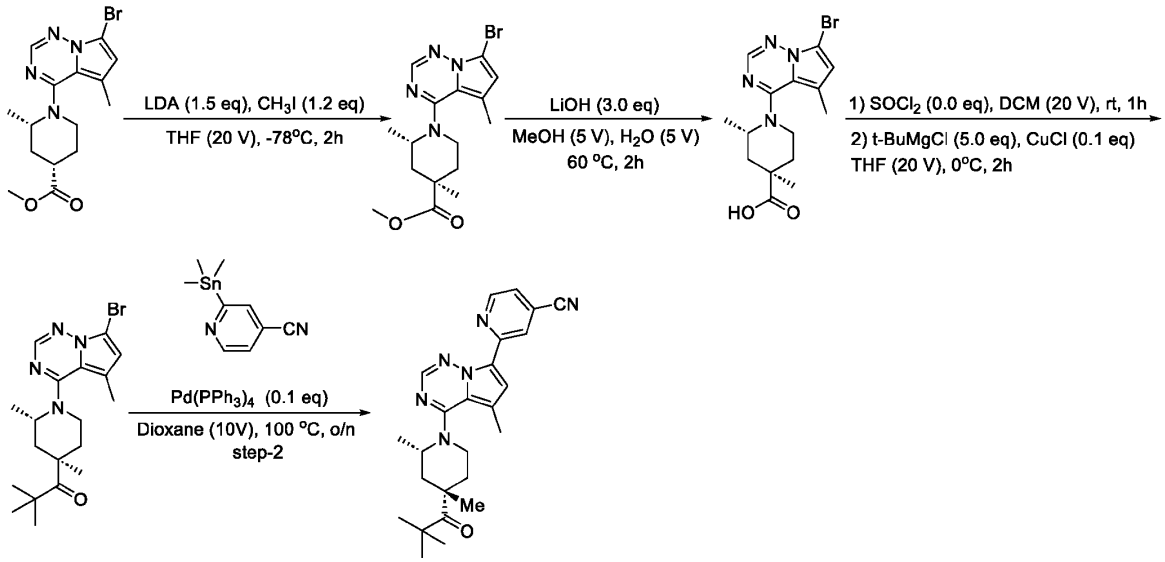
[0251] Tert-butyl 4-(3-methyloxetan-3-ylsulfonyl)piperidine-1-carboxylate. Into a 8 mL vial was added a solution of tert-butyl 4-(oxetane-3-sulfonyl)piperidine-1-carboxylate (700.0 mg, 2.292 mmol, 1.0 equiv) in THF (2 mL) at room temperature. To a stirred mixture was added LiHMDS (421.9 mg, 2.521 mmol, 1.1 equiv) dropwise at −78 °C under N_2 atmosphere. The resulting mixture was stirred at −78°C for 20 min under N_2 atmosphere. To the above mixture was added iodomethane (357.9 mg, 2.521 mmol, 1.1 equiv) dropwise over 10 min at −78 °C. The resulting mixture was stirred at −78 °C for an additional 2 h as the reaction temperature naturally rose to room temperature. The resulting mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC to afford tert-butyl 4-(3-methyloxetan-3-ylsulfonyl)piperidine-1-carboxylate (220 mg, 30.1%) as a white solid.

[0252] 1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-4-(3-methyloxetan-3-ylsulfonyl)piperidine. Prepared in a manner analogous to the procedure described above in steps 3-4 of Example 1.7 except that tert-butyl 4-(3-methyloxetan-3-ylsulfonyl)piperidine-1-carboxylate was used as a starting material in step 3 in place of tert-butyl 4-(oxetane-3-sulfonyl)piperidine-1-carboxylate.

[0253] 6-{5-cyclopropyl-4-[4-(3-methyloxetan-3-ylsulfonyl)piperidin-1-yl]pyrrolo [2,1-f][1,2,4]triazin-7-yl}pyridazine-4-carbonitrile (I-14). Prepared in a manner analogous to the procedure described above in steps 3-4 of Example 1.4 except that 1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-4-(3-methyloxetan-3-ylsulfonyl)piperidine was

used as a starting material in step 3 in place of 1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-4-(propane-2-sulfonyl)piperidine; (8 mg, 15.2%) as a yellow solid. ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 9.63 (s, 1H), 9.62 (s, 1H), 8.31 (s, 1H), 7.43 (s, 1H), 5.02 (d, 2H), 4.59 (d, 2H), 4.52 (d, 2H), 3.98 (t, 1H), 3.34 (t, 2H), 2.17 (s, 1H), 2.05 (d, 2H), 1.93(s, 5H) ,1.22 (d, 2H), 1.20 (s, 2H). LC-MS: (ES, *m/z*): $[M+H]^+$ = 480.

Example 1.9. Synthesis of 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-20)



I-20

Methyl (2S,4R)-1-(7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-2,4-dimethylpiperidine-4-carboxylate. Into a 50 mL 3-necked round bottom flask was placed a solution of methyl (2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (1.0 g, 2.723 mmol, 1.0 equiv) in THF (20 mL). Then, LDA (2.04 mL, 4.084 mmol, 1.5 equiv) was added at -78 °C for 15 min under nitrogen atmosphere followed by the addition of iodomethane (0.46 g, 3.268 mmol, 1.2 equiv) dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 2 h under nitrogen atmosphere. The reaction was quenched by the addition of water (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced

pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in methyl (2S,4R)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (700 mg, 67.4% yield) as a yellow solid.

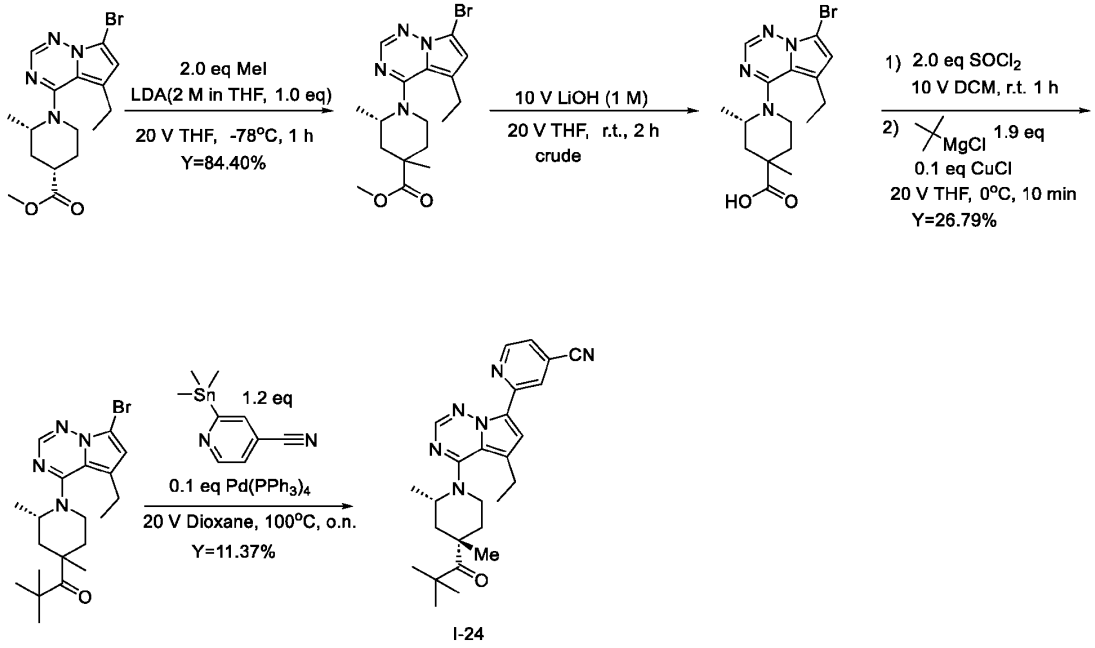
[0255] (2S,4R)-1-(7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-2,4-dimethylpiperidine-4-carboxylic acid. Into a 20 mL vial was placed a solution of methyl (2S,4R)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (700.0 mg, 1.836 mmol, 1.0 equiv) and LiOH (131.9 mg, 5.508 mmol, 3.0 equiv) in MeOH (3.5 mL) and water (3.5 mL). Then, the solution was stirred at 60 °C for 2 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The mixture was acidified to pH 3 with 2 mol/L aqueous HCl. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% TFA), 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in (2S,4R)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid (650 mg, 71.1% yield) as a yellow solid.

[0256] 1-((2S,4R)-1-(7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-2,4-dimethylpiperidin-4-yl)-2,2-dimethylpropan-1-one. Into a 20 mL vial was placed a solution of thionyl chloride (421.1 mg, 3.540 mmol, 2.0 equiv) and (2S,4R)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid (650.0 mg, 1.770 mmol, 1.0 equiv) in DCM (8.4 mL). The solution was stirred at room temperature for 1 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in THF (8.4 mL) were added CuCl (17.5 mg, 0.177 mmol, 0.1 equiv) and tert-butyl(chloro) magnesium (1.03 g, 8.850 mmol, 5.0 equiv). The resulting mixture was stirred at 0 °C for 2 h under nitrogen atmosphere. The reaction was quenched by the addition of water (10 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash

chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 10% to 85% gradient in 20 min; detector, UV 254 nm. This resulted in 1-[(2S,4R)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidin-4-yl]-2,2-dimethylpropan-1-one (160 mg, 22.2% yield) as a yellow solid.

[0257] 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-20). Into a 20 mL vial was placed a solution of 2-(trimethylstannyl)pyridine-4-carbonitrile (126.0 mg, 0.471 mmol, 1.2 equiv) and 1-[(2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperi-din-4-yl]-2,2-dimethylpropan-1-one (160.0 mg, 0.393 mmol, 1.0 equiv) and tetrakis(triphenylphosphine) palladium(0) (45.0 mg, 0.039 mmol, 0.1 equiv) in 1,4-dioxane (3 mL). The solution was stirred at 100 °C overnight under nitrogen atmosphere then cooled to room temperature. The resulting mixture was concentrated under reduced pressure. The crude product (36 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column 30*150 mm, 5 m; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 45% B in 7 min; Wave Length: 254 nm/220 nm. This resulted in 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (5.5 mg, 3.25% yield) as a white solid. LC-MS: (ES, *m/z*): 431.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6, *ppm*): δ 8.89 (s, 1H), 8.87-8.86 (m, 1H), 8.21 (s, 1H), 7.79-7.69 (m, 1H), 7.37 (s, 1H), 4.29-4.27 (m, 1H), 3.61-3.45 (m, 2H), 2.47 (s, 3H), 2.31-2.22 (m, 2H), 1.88-1.84 (m, 1H), 1.50-1.45 (m, 1H), 1.30 (s, 3H), 1.26 (s, 9H), 1.15 (d, J = 6.3 Hz, 4H).

Example 1.10. Synthesis of 2-{4-[(2S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl]-5-ethylpyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-24)



[0258] Methyl (2S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate. Into a 40 mL vial were added a solution of methyl (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (400.0 mg, 1.049 mmol, 1.0 equiv) in THF (8 mL) at room temperature under nitrogen atmosphere. To the above mixture was added LDA (2 M in THF) (2.1 mL, 1.049 mmol, 1.0 equiv) at -78 °C under nitrogen atmosphere. The reaction mixture was stirred at -78 °C for 30 min. Then a solution of iodomethane (297.8 mg, 2.098 mmol, 2.0 equiv) in 1 mL THF was added dropwise and the mixture was stirred for another 30 mins. The reaction was quenched by the addition of water (4 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford methyl (2S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (350 mg, 84.4% yield) as yellow oil.

[0259] (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid. Into a 100 mL round-bottom flask was added a solution of methyl

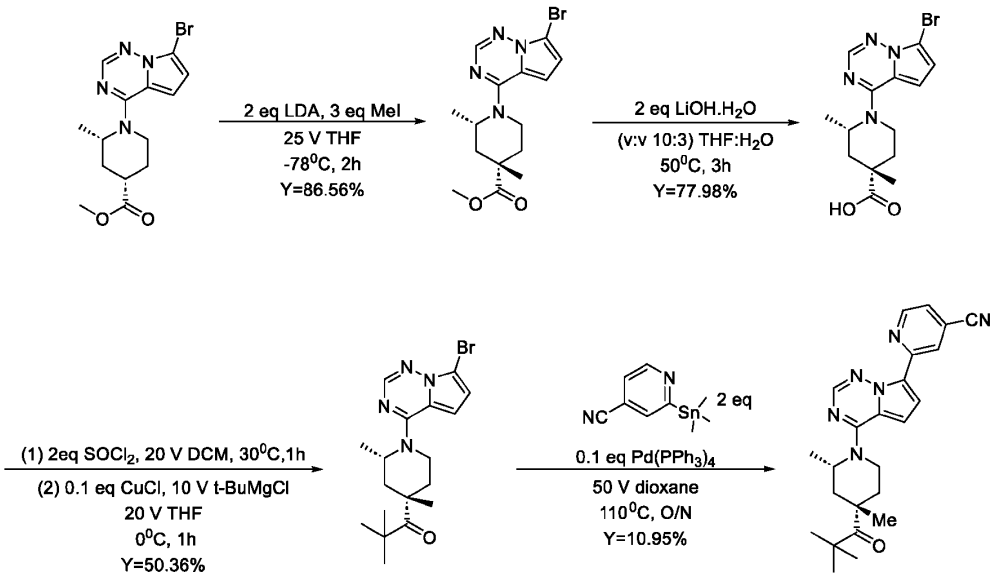
(2S,4S)-1-{7-bromo-5-ethylpyrrolo [2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (350.0 mg, 0.885 mmol, 1.0 equiv) and LiOH (1 M in H_2O, 3.5 mL) in THF (7 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The mixture was acidified to pH 4 with 1 mol/L aqueous HCl. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethyl-piperidine-4-carboxylic acid (320 mg, crude) as a yellow solid.

[0260] 1-[(2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidin-4-yl]-2,2-dimethylpropan-1-one. Into a 40 mL vial were added a solution of (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid (320.0 mg, 0.839 mmol, 1.0 equiv) and $SOCl_2$ (199.7 mg, 1.678 mmol, 2.0 equiv) in DCM (3.2 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure. The residue was added THF (6.4 mL) at room temperature under nitrogen atmosphere. Then, CuCl (8.4 mg, 0.084 mmol, 0.1 equiv) and tert-butyl(chloro)magnesium (1.7 mL, 7.760 mmol, 1.9 equiv) were added at 0 °C and stirred for 10 min. The reaction was quenched by the addition of water (5 mL) at 0 °C. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 1-[(2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidin-4-yl]-2,2-dimethylpropan-1-one (103 mg, 26.8% yield) as a yellow oil.

[0261] 2-{4-[(2S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl]-5-ethylpyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-24). Into an 8 mL vial were added a solution of 1-[(2S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidin-4-yl]-2,2-dimethylpropan-1-one (100.0 mg, 0.237 mmol, 1.0 equiv), 2-(trimethylstannyl)pyridine-4-carbonitrile (76.0 mg, 0.284 mmol, 1.2 equiv) and $Pd(PPh_3)_4$ (27.4 mg, 0.024 mmol, 0.1 equiv) in dioxane (2 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 100 °C overnight. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: Column:

Xbridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3+0.05%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 68% B to 98% B in 10 min; Wave Length: 254 nm/220 nm; RT1(min): 9.18. This resulted in 2-{4-[(2S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl]-5-ethylpyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (12.0 mg, 11.4% yield) as a white solid. LC-MS: (ES, *m/z*): 445.25 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6, *ppm*): δ 8.94 – 8.86 (m, 2H), 8.26 (s, 1H), 7.76 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.46 (s, 1H), 4.22 (s, 1H), 3.48 (dt, *J* = 10.4, 4.8 Hz, 2H), 2.87 (q, *J* = 7.4 Hz, 2H), 2.22 (dt, *J* = 14.5, 7.4 Hz, 2H), 1.88 (dd, *J* = 14.0, 3.9 Hz, 1H), 1.50 (ddd, *J* = 13.1, 8.2, 4.2 Hz, 1H), 1.29 (d, *J* = 21.5 Hz, 15H), 1.15 (d, *J* = 6.3 Hz, 3H).

Example 1.11 Synthesis of 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-25)



[0262] Methyl (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate. Into a 50 mL 3-necked round bottom flask was placed a solution of methyl (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (500.0 mg, 1.41 mmol, 1.0 equiv) and LDA (1.4 mL, 2.83 mmol, 2.0 equiv, 2 M) in THF (12.5 mL). The solution was stirred at -78 °C for 1 h under nitrogen atmosphere. To the above mixture was added iodomethane (602.0 mg, 4.24 mmol, 3.0 equiv) dropwise over 5 min at -78 °C. The resulting mixture was stirred at -78 °C for additional 1 h. The reaction was quenched with

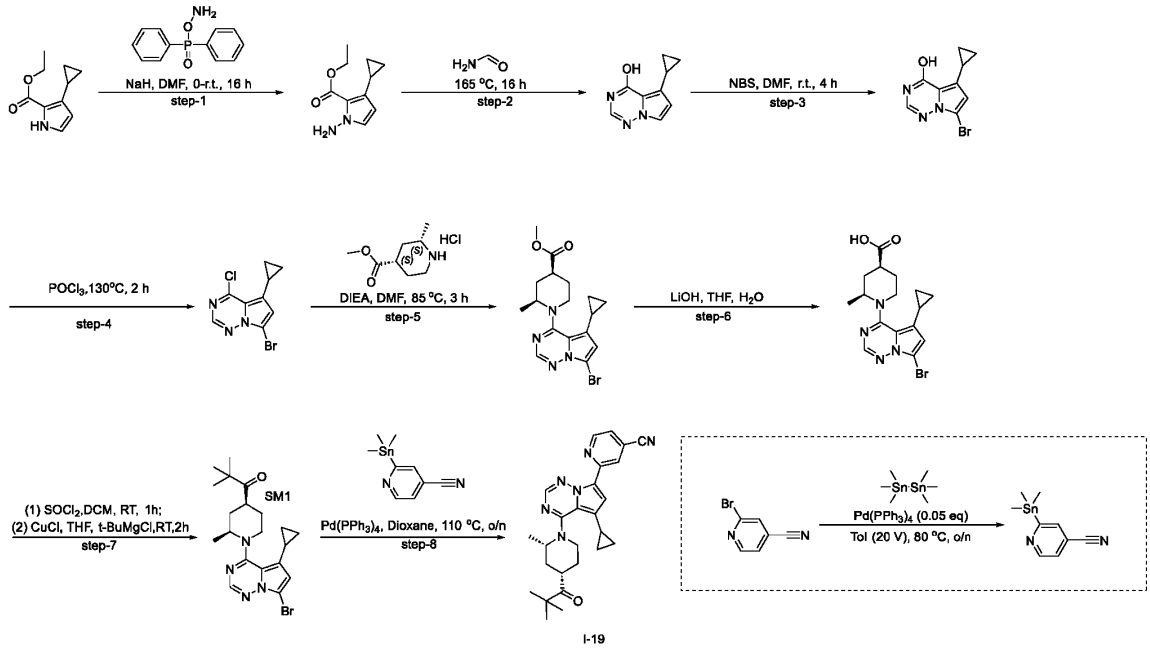
aqueous NH_4Cl at -78 °C, then slowly warmed to room temperature. The aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 10% to 70% gradient in 15 min; detector, UV 254 nm to afford methyl (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (450 mg, 86.6% yield) as light brown oil.

[0263] (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperi-dine-4-carboxylic acid. Into a 20 mL vial was placed a solution of methyl (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (400.0 mg, 1.08 mmol, 1.0 equiv) and $LiOH.H_2O$ (91.0 mg, 2.17 mmol, 2.0 equiv) in THF (4 mL) and H_2O (1.2 mL). The solution was stirred at 50 °C for 3 h under nitrogen atmosphere. The mixture was acidified to pH 5 with aqueous HCl. The resulting mixture was concentrated under reduced pressure. The resulting mixture was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (5:1) to afford (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperi-dine-4-carboxylic acid (300 mg, 78.0%) as light yellow oil.

[0264] 1-[(2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidin-4-yl]-2,2-dimethylpropan-1-one. Into a 20 mL vial was placed a solution of (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid (250.0 mg, 0.72 mmol, 1.0 equiv) and thionyl chloride (168.0 mg, 1.44 mmol, 2.0 equiv) in DCM (5 mL). The solution was stirred at 30 °C for 1 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in THF (5 mL) and CuCl (7.0 mg, 0.07 mmol, 0.1 equiv) was added in portions at 0 °C under nitrogen atmosphere. Then, to the above mixture was added tert-butyl(chloro)magnesium (2.5 mL, 1M in THF) dropwise over 10 min at 0 °C. The resulting mixture was stirred at 0 °C for additional 1 h. The reaction was quenched with aqueous NH_4Cl at 0 °C. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 1-[(2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidin-4-yl]-2,2-dimethylpropan-1-one (140 mg, 50.4% yield) as an off-white solid.

[0265] 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-25). Into a 20 mL vial was placed a solution of 2-(trimethylstannyl)pyridine-4-carbonitrile (135.0 mg, 0.50 mmol, 2.0 equiv), 1-[(2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidin-4-yl]-2,2-dime-thylpropan-1-one (100.0 mg, 0.25 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (29.0 mg, 0.02 mmol, 0.1 equiv) in dioxane (5 mL). The solution was stirred at 110 °C overnight under nitrogen atmosphere then cooled to room temperature. The resulting mixture was filtered, the filter cake was washed with MeOH (2 x 5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 10% to 90% gradient in 10 min; detector, UV 254 nm to afford 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (11.6 mg, 11.0% yield) as a white solid. (ES, *m/z*): 417.30 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6, *ppm*): δ 8.99 (s, 1H), 8.88 (dd, *J* = 4.9, 1.0 Hz, 1H), 8.14 (s, 1H), 7.75 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.47 (d, *J* = 4.9 Hz, 1H), 7.11 (d, *J* = 5.0 Hz, 1H), 4.85 – 4.76 (m, 1H), 4.54 – 4.50 (m, 1H), 3.52 – 3.42 (m, 1H), 2.37 – 2.23 (m, 2H), 1.88 – 1.83(m, 1H), 1.75 – 1.66 (m, 1H), 1.25 – 1.25 (m, 12H), 1.20 (s, 3H).

Example 1.12 Synthesis of 2-{5-cyclopropyl-4-[(2*S*,4*S*)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-19)



[0266] Ethyl 1-amino-3-cyclopropylpyrrole-2-carboxylate. Into a 1 L 3-necked round bottom flask was placed a suspension of NaH (8.37 g, 209.24 mmol, 1.5 equiv, 60%wt) in DMF (500 mL). The solution was cooled to 0°C. Then, ethyl 3-cyclopropyl-1H-pyrrole-2-carboxylate (25.0 g, 139.49 mmol, 1.0 equiv) was added at 0°C and stirred for 30 min. After that, amino diphenylphosphinate (55.3 g, 237.14 mmol, 1.7 equiv) was added in 3 portions at 0°C. The reaction was warmed to room temperature and stirred for 16 h. LCMS showed the reaction was finished. The reaction was poured into 2 L H_2O. The solution was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with water (5 x 200 mL), brine (200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to obtained crude product ethyl 1-amino-3-cyclopropylpyrrole-2-carboxylate (30.0 g, crude) as a brown oil.

[0267] 5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-ol. Into a 1 L 3-necked round bottom flask was placed a solution of ethyl 1-amino-3-cyclopropylpyrrole-2-carboxylate (30.0 g, 154.45 mmol, 1.0 equiv) in formamide (300 mL). The mixture was allowed to stir at 165°C for 16 h. Progress of reaction is monitored by LCMS. After completion, reaction mixture was cooled to

room temperature. The reaction mixture was diluted with cold water (1 L) under stirring. The formed precipitate was filtered and dried under vacuum to afford 5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-ol (24.0 g, crude). The product was used in the next step directly without further purification.

[0268] 7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-ol. Into a 2 L 3-necked round bottom flask was placed a solution of 5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-ol (24.0 g, 136.99 mmol, 1.0 equiv) in DMF (900 mL). The solution was cooled to 0°C and NBS (23.16 g, 130.14 mmol, 0.95 equiv) was added to the mixture. The reaction was stirred for 4 h at room temperature. LCMS showed the reaction was finished. The reaction was quenched by the addition of aqueous sodium sulfite (1.1 L), The mixture was added water (1.1 L) and extracted with EA (3 x 300 mL). The combined organic layers were washed with water (5 x 300 mL), brine (500 mL), dried over with Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford 7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-ol (30 g, 90% purity) as an off-white solid. The product was used in the next step directly without further purification.

[0269] 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazine. Into a 1 L 3-necked round bottom flask was placed a solution of methyl 7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-ol (30.0 g, 118.07 mmol, 1.0 equiv) in phosphorus oxychloride (300 mL). The mixture was allowed to stir at 130°C for 2 hours. LCMS showed reaction was finished. The reaction was diluted with cold water (2 L) and extracted with ethyl acetate (2 x 300 mL). The combined organic layers were washed with brine (300 mL) and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to give as a yellow solid. The crude product was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazine (20 g, 62% yield) as a yellow solid.

[0270] Methyl (2*S*,4*S*)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 40 mL vail was placed a solution of 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazine (1.2 g, 4.40 mmol, 1.0 equiv), methyl (2*S*,4*S*)-2-methylpiperidine-4-carboxylate hydrochloride (0.94 g, 4.84 mmol, 1.1 equiv) and DIEA (2.28 g, 17.61 mmol, 4.0 equiv) in DMF (20 mL) at room temperature under nitrogen atmosphere. The reaction was heated to 85°C and stirred for 3 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The reaction was added water (100 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with water (2 x 15 mL), brine

(20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product methyl (2*S*,4*S*)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate (1.6 g, 90.7% yield) as brown oil. The crude product was used into next step directly without further purification.

[0271] *(2S,4S)*-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperi-dine-4-carboxylic acid. Into a 100 mL 3-necked round-bottom flask was placed a solution of methyl *(2S,4S)*-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate (1.8 g, 4.068 mmol, 1.0 equiv) in THF (16 mL) and H_2O (16 mL) at room temperature under nitrogen atmosphere. Then, LiOH (0.29 g, 12.20 mmol, 3.0 equiv) was added to the mixture. The reaction was stirred for 2 h at room temperature. LCMS showed the reaction was finished. The reaction was added water (50 mL) and extracted with EA (2 x 20 mL). The water phase was acidified to pH 1 with aqueous HCl (1 mol/L). The mixture was extracted with EA (2 x 20 mL). The combined organic layers were washed with water (15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product *(2S,4S)*-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperi-dine-4-carboxylic acid (1.4 g, crude). The crude product was used into next step directly without further purification.

[0272] 1-[(2*S*,4*S*)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one. Into a 50 ml 3-necked round-bottom flask was placed (2*S*,4*S*)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylic acid (1.4 g, 3.69 mmol, 1.0 equiv) in DCM (28 mL) at room temperature under nitrogen atmosphere. Then, thionyl chloride (0.54 mL, 7.45 mmol, 2.02 equiv) was added. The reaction was stirred for 1 h. LCMS showed the reaction was finished. The solution was concentrated under vacuum to afford crude product. The residue was used to next step. The residue was dissolved with THF (28 mL). Then, CuCl (0.04 g, 0.369 mmol, 0.1 equiv) was added and stirred for 10 min. After that, tert-butyl(chloro)magnesium (10.8 mL, 18.46 mmol, 5.0 equiv) was added and stirred 2 h. LCMS showed the reaction was finished. The mixture was poured into water (50 mL), extracted with EA (2 x 20 mL). The combined organic layers were washed with water (15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA (2 :1) to afford 1-[(2*S*,4*S*)-1-{7-bromo-5-

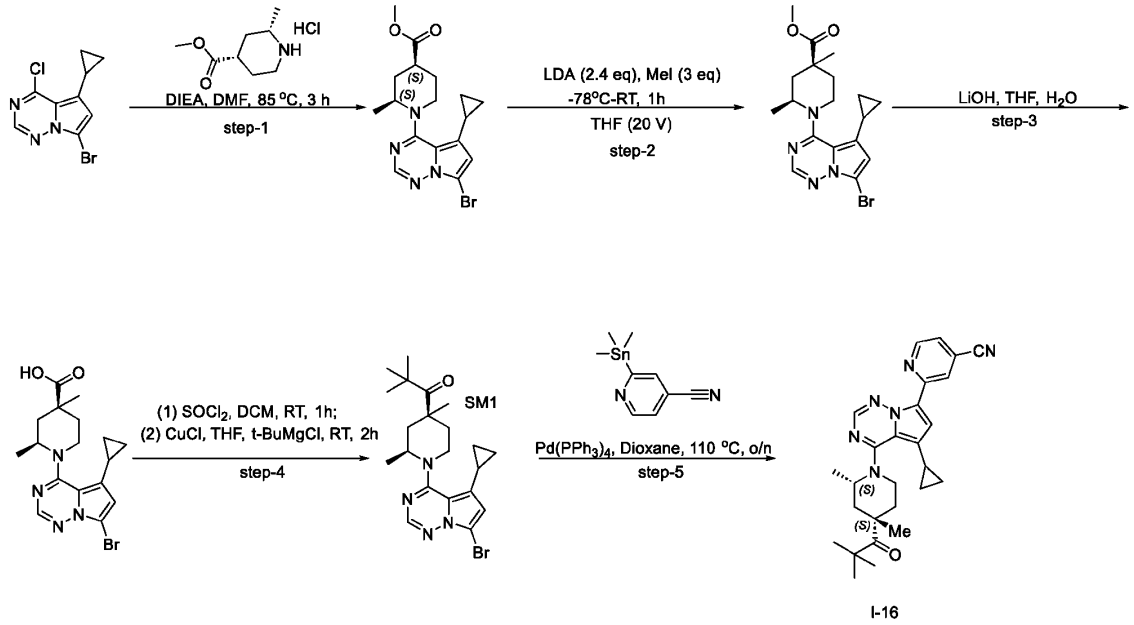
cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one (1.2 g, 77.5% yield) as an off-white solid.

[0273] 2-(trimethylstannyl) pyridine-4-carbonitrile. Into a 50 mL 3-necked flask was placed a solution of 2-bromopyridine-4-carbonitrile (1.0 g, 5.46 mmol, 1.0 equiv) in toluene (20 mL) under nitrogen. Then, hexamethyldistannane (3.58 g, 10.93 mmol, 2.0 equiv) was added at room temperature. The mixture was replaced with nitrogen for 3 times. After that, $Pd(PPh_3)_4$ (0.32 g, 0.277 mmol, 0.05 equiv) was added at room temperature. The mixture was replaced with nitrogen for 3 times. The resulting mixture was stirred overnight at 80°C under nitrogen. The mixture was allowed to cool to room temperature. The mixture was concentrated under reduced pressure. This resulted in 2-(trimethylstannyl) pyridine-4-carbonitrile (2.8 g, crude) as a brown yellow solid. The crude product was used into next step directly without further purification.

[0274] 2-{5-cyclopropyl-4-[(2*S*,4*S*)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile. Into a 20 mL vail was placed 1-[(2*S*,4*S*)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one (120.0 mg, 0.286 mmol, 1.0 equiv), 2-(trimethylstannyl)isonicotinonitrile (154 mg, 0.572 mmol, 2.0 equiv) and $Pd(PPh_3)_4$ (33.1 mg, 0.029 mmol, 0.1 equiv) in dioxane (5 mL). The reaction was heated to 110°C and stirred for 12 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The reaction was added water (25 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product. The crude product was purified by Flash-Prep-HPLC with the following condition (Column: XBridge Prep Shield RP18 OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water (0.05%TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 50% B to 80% B in 15 min; Wave Length: 254 nm/220 nm; RT1(min): 13.9) to obtain the pure product 2-{5-cyclopropyl-4-[(2*S*,4*S*)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (20.4 mg, 16.1% yield) as an orange solid. LC-MS-PH-CSM-SMC-2024-01-V0037: (ES, *m/z*): 443 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6, *ppm*): δ 8.93 – 8.85 (m, 2H), 8.38 (s, 1H), 7.77 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.17 (s, 1H), 3.96 (dt, *J* = 12.7, 4.0 Hz, 1H), 3.75 (ddd, *J* = 11.6, 5.9, 3.5 Hz, 1H), 3.28 (td, *J* = 10.3, 4.1 Hz, 1H), 3.19 – 3.06 (m, 1H), 2.39 – 2.31 (m, 1H), 1.83 –

1.54 (m, 4H), 1.28 (d, J = 5.9 Hz, 3H), 1.13 (s, 9H), 1.11 – 1.04 (m, 2H), 1.04 – 0.96 (m, 1H), 0.66 – 0.59 (m, 1H).

Example 1.13 Synthesis of 2-{5-cyclopropyl-4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl] pyrrolo[2,1-f] [1,2,4] triazin-7-yl} pyridine-4-carbonitrile (I-16)



[0275] Methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 40 mL vail was placed a solution of 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazine (1.4 g, 5.14 mmol, 1.0 equiv), methyl (2S,4S)-2-methylpiperidine-4-carboxylate hydrochloride (1.09 g, 5.63 mmol, 1.1 equiv) and DIEA (2.66 g, 20.55 mmol, 4.0 equiv) in DMF (27 mL) at room temperature under nitrogen atmosphere. The reaction was heated to 85°C and stirred for 3 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The reaction was added water (100 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with water (5 x 15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product as a brown oil. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate (2 g, 99.0% yield) as a yellow solid.

[0276] Methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate. Into a 50 mL 3-necked round-bottom flask was placed a solution of methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate (1.0 g, 2.54 mmol, 1.0 equiv) in THF (20 mL) at room temperature under nitrogen atmosphere. The reaction was cooled to -78°C. Then, LDA (0.65 g, 6.10 mmol, 2.4 equiv) was added and stirred for 30 min. After that, iodomethane (1.08 g, 7.63 mmol, 3.0 equiv) was added. The reaction was warmed to rt stirred for 1 h at room temperature. LCMS showed the reaction was finished. The reaction was poured into water (50 mL) and extracted with EA (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (600 mg, 57.9% yield) as a yellow solid.

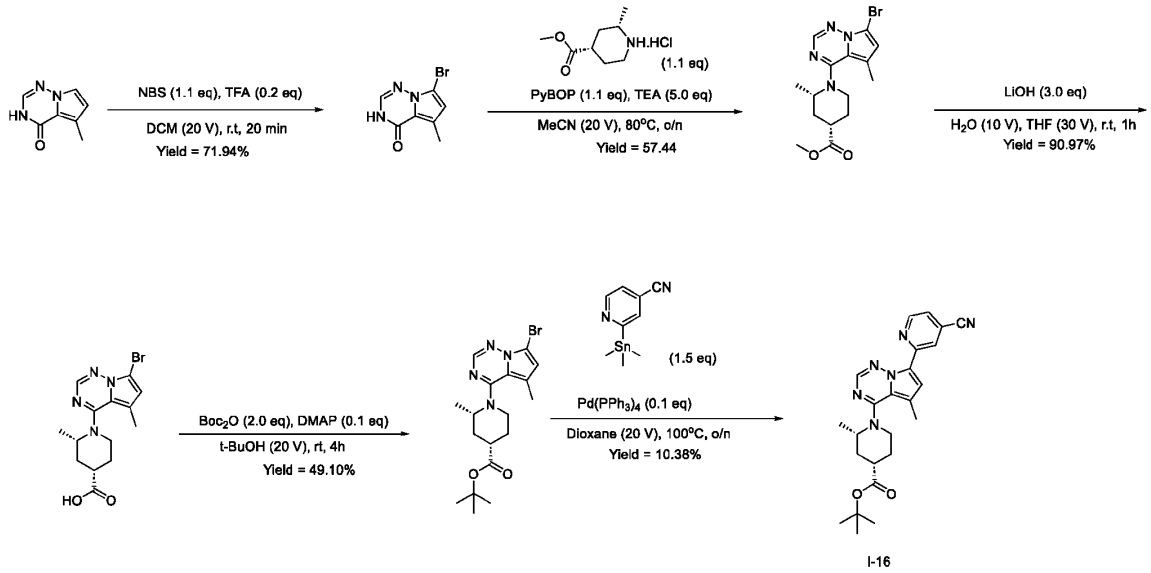
[0277] (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid. Into a 40 mL vail was placed methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (600.0 mg, 1.47 mmol, 1.0 equiv) in THF (6 mL) and H_2O (6 mL) at room temperature under nitrogen atmosphere. Then, LiOH (105.8 mg, 4.42 mmol, 3.0 equiv) was added. The reaction was heated to 60°C and stirred for 12 h. LCMS showed the reaction was finished. The reaction was diluted with water (20 mL). The solution was acidified to pH 1 with 1 N HCl (aq.). The mixture was extracted with EA (2 x 20 mL). The combined organic layers were washed with water (4 x 15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid (500 mg, crude). The crude product was used into next step directly without further purification.

[0278] 1-[(2*S*,4*S*)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidin-4-yl]-2,2-dimethylpropan-1-one. Into a 50 mL 3-necked round-bottom flask was placed a solution of (2*S*,4*S*)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid (500.0 mg, 1.27 mmol, 1.0 equiv) in DCM (22 mL) at room temperature under nitrogen atmosphere. Then, thionyl chloride (0.18 mL, 2.48 mmol, 1.95 equiv) was added. The reaction was stirred for 1 h. LCMS showed the reaction was finished. The

solution was concentrated under vacuum to afford crude product. The residue was used to next step. The residue was dissolved with THF (22 mL). Then, CuCl (12.6 mg, 0.127 mmol, 0.1 equiv) was added and stirred for 10 min. After that, tert-butyl(chloro)magnesium (742.9 mg, 6.36 mmol, 5.0 equiv) was added and stirred 2 h. LCMS showed the reaction was finished. The mixture was poured into water (50 mL), extracted with EA (2 x 20 mL). The combined organic layers were washed with water (15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA (2 :1) to afford 1-[(2*S*,4*S*)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidin-4-yl]-2,2-dimethylpropan-1-one (120 mg, 21.8% yield) as a yellow oil.

[0279] 2-{5-cyclopropyl-4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl] pyrrolo[2,1-f] [1,2,4] triazin-7-yl} pyridine-4-carbonitrile. Into a 40 mL vail was placed a solution of 1-[(2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidin-4-yl]-2,2-dimethylpropan-1-one (120.0 mg, 0.277 mmol, 1.0 equiv), 2-(trimethylstannyl)isonicotinonitrile (148 mg, 0.554 mmol, 2.0 equiv) and $Pd(PPh_3)_4$ (32.0 mg, 0.028 mmol, 0.1 equiv) in 1,4-dioxane (10 mL). The reaction was heated to 110°C and stirred for 12 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The reaction was added water (25 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product. The crude product was purified by Flash-Prep-HPLC with the following condition (Column: Xselect CSH Prep C18 OBD Colum, 19*250 nm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 65% B to 95% B in 12 min; Wave Length: 254 nm/220 nm; RT1(min): 12) to obtain the pure product 2-{5-cyclopropyl-4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2,4-dimethylpiperidin-1-yl] pyrrolo[2,1-f] [1,2,4] triazin-7-yl} pyridine-4-carbonitrile (18.1 mg, 14.3% yield) as a yellow solid. LC-MS: (ES, *m/z*): 457 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6, *ppm*): δ 8.92 – 8.84 (m, 2H), 8.21 (s, 1H), 7.75 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.13 (s, 1H), 4.46 (td, *J* = 6.8, 4.3 Hz, 1H), 3.77 (dt, *J* = 13.6, 4.7 Hz, 1H), 3.64 (ddd, *J* = 13.4, 9.9, 3.1 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.28 – 2.20 (m, 1H), 2.14 (td, *J* = 8.3, 4.3 Hz, 1H), 1.87 (dd, *J* = 14.1, 4.3 Hz, 1H), 1.47 (ddd, *J* = 13.7, 9.6, 3.8 Hz, 1H), 1.30 (s, 3H), 1.26 (s, 9H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.11 – 1.00 (m, 2H), 0.97 – 0.87 (m, 1H), 0.72 (ddt, *J* = 7.2, 5.2, 2.5 Hz, 1H).

Example 1.14. Synthesis of tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)-5-methylpyrrolo[2,1-f][1,2,4] triazin-4-yl]-2-methylpiperidine-4-carboxylate (I-16)



I-16

7-bromo-5-methyl-3H-pyrrolo[2,1-f][1,2,4]triazin-4-one. Into a 250 mL 3-necked round bottom flask was placed a solution of 5-methyl-3H-pyrrolo[2,1-f][1,2,4]triazin-4-one (5.0 g, 33.52 mmol, 1.0 equiv) and NBS (6.56 g, 36.88 mmol, 1.1 equiv), TFA (0.76 g, 6.71 mmol, 0.2 equiv) in DCM (100 mL). The solution was stirred at room temperature for 20 min under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with MeOH (50 mL). The precipitated solids were collected by filtration and washed with MeOH (3 x 10 mL). This resulted in 7-bromo-5-methyl-3H-pyrrolo[2,1-f][1,2,4]triazin-4-one (5.5 g, 71.9% yield) as a white solid.

[0281] Methyl (2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 250 mL 3-necked round bottom flask was placed a solution of 7-bromo-5-methyl-3H-pyrrolo[2,1-f][1,2,4]triazin-4-one (4.0 g, 17.54 mmol, 1.0 equiv) and methyl (2S,4S)-2-methylpiperidine-4-carboxylate hydrochloride (3.74 g, 19.29 mmol, 1.1 equiv), PyBOP (10.04 g, 19.29 mmol, 1.1 equiv), TEA (8.87 g, 87.70 mmol, 5.0 equiv) in MeCN (100 mL). The solution was stirred at 80°C overnight under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% TFA), 10% to 100 % gradient in 30 min; detector, UV 254 nm. This resulted

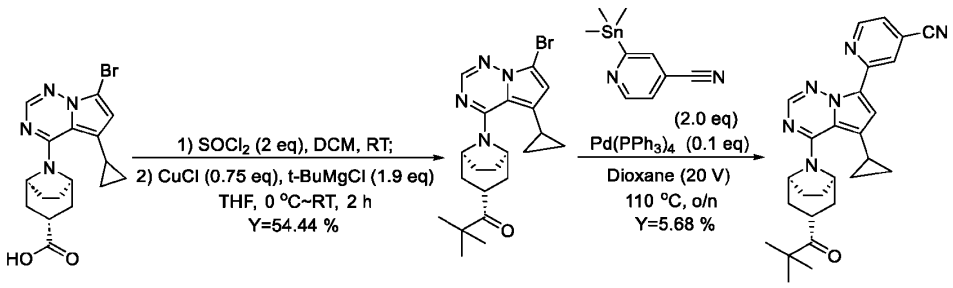
in methyl (2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (3.7 g, 57.4% yield) as a yellow oil.

[0282] (2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylic acid. Into a 100 mL 3-necked round bottom flask was placed a solution of methyl (2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (3.2 g, 8.71 mmol, 1.0 equiv) and lithium hydroxide (630.0 mg, 26.14 mmol, 3.0 equiv) in THF (96 mL) and water (32 mL). This solution was stirred at room temperature for 1 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The mixture was acidified to pH 2 with aqueous citric acid. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% TFA), 10% to 50% gradient in 20 min; detector, UV 254 nm. This resulted in (2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylic acid (2.8 g, 91.0% yield) as a brown yellow solid.

[0283] 1-[(2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one. Into a 40 mL vial was placed a solution of (2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carbonyl chloride (500.0 mg, 1.35 mmol, 1.0 equiv) and di-tert-butyl dicarbonate (619.3 mg, 2.84 mmol, 2.0 equiv), DMAP (17.3 mg, 0.14 mmol, 0.1 equiv) in t-BuOH (10 mL). This solution was stirred at room temperature for 4 h under nitrogen atmosphere. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% TFA), 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 1-[(2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one (260 mg, 49.10% yield) as a yellow oil.

[0284] Tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)-5-methylpyrrolo[2,1-f][1,2,4] triazin-4-yl]-2-methylpiperidine-4-carboxylate. Into a 20 mL vial was placed a solution of tert-butyl (2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (170.0 mg, 0.415 mmol, 1.0 equiv) and 2-(trimethyl-stannyl)pyridine-4-carbonitrile (145.0 mg, 0.620 mmol, 1.5 equiv), tetrakis(triphenylphosphine)palladium(0) (48.0 mg, 0.042 mmol, 0.1 equiv) in 1,4-dioxane (5 mL). This solution was stirred at 100°C overnight under nitrogen atmosphere. The reaction was quenched by the addition of water (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (54 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column 30*150 mm, 5m; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 44% B in 7 min; Wave Length: 254 nm/220 nm. This resulted in tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)-5-methylpyrrolo[2,1-f][1,2,4] triazin-4-yl]-2-methylpiperidine-4-carboxylate (19 mg, 10.4% yield) as a white solid. LC-MS: (ES, *m/z*): 433 $[M+H]^+$; ^{1}H-NMR: (300 MHz, DMSO-d_6, *ppm*) δ 8.96 – 8.83 (m, 2H), 8.29 (s, 1H), 7.75 (dd, J = 4.9, 1.6 Hz, 1H), 7.40 (s, 1H), 3.97-3.91 (m, 1H), 3.63-3.55 (m, 1H), 3.30-3.22 (m, 1H), 2.61-2.52 (m, 1H), 2.13-2.02 (m, 1H), 1.93-1.75 (m, 3H), 1.44 (s, 8H), 1.23 (d, J = 6.3 Hz, 4H).

Example 1.15 Synthesis of 2-(5-cyclopropyl-4-((1R,3s,5S)-3-pivaloyl-8-azabicyclo [3.2.1]octan-8-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)isonicotinonitrile (I-28)



I-28

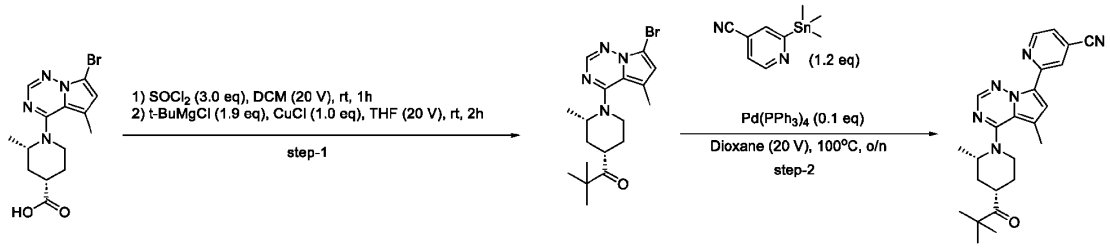
[0285] 1-((1R,3s,5S)-8-(7-bromo-5-cyclopropylpyrrolo [2,1-f] [1,2,4] triazin-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)-2,2-dimethylpropan-1-one. Into a 20 mL vial purged and maintained with an inert atmosphere of nitrogen, was placed a solution of (1R,3S,5S)-8-(7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)-8-azabicyclo[3.2.1]octane-3- carboxylic acid

(500.0 mg, 1.279 mmol, 1.0 equiv) in DCM (5 mL) at 20 °C. To the above mixture was added $SOCl_2$ (304.0 mg, 2.558 mmol, 2.0 equiv) at 20 °C. The mixture was stirred for 2 h at 20 °C under nitrogen atmosphere. The reaction was monitored by LCMS (quenched by MeOH). The reaction was concentrated under reduced pressure and dissolved in THF (5 mL) at 20 °C. To the above mixture was added CuCl (95.0 mg, 0.959 mmol, 0.75 equiv) at 20 °C, and t-BuMgCl (2.4 mL, 2.430 mmol, 1.9 equiv, 1.7 M) was slowly dropwise in the reaction at 20 °C. The final reaction mixture was stirred for 2 h at 20 °C under nitrogen atmosphere. Desired product could be detected by LCMS. The mixture was allowed to cool down to 0 °C. The reaction was quenched with water/ice (10 mL) at 0 °C. The mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: Column, Ultimate XB-C18 Column, 50*250 mm, 10 μm; mobile phase, MeCN in Water (0.1% NH_4HCO_3), 70% to 100% gradient in 40 min; detector, UV 210/254 nm. This resulted in 1-((1R,3s,5S)-8-(7-bromo-5-cyclopropylpyrrolo [2,1-f] [1,2,4] triazin-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)-2,2-dimethylpropan-1-one (300 mg, 54.4% yield) as a yellow solid.

[0286] 2-(5-cyclopropyl-4-((1R,3s,5S)-3-pivaloyl-8-azabicyclo [3.2.1]octan-8-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)isonicotinonitrile. Into a 40 mL vial purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 1-((1R,3s,5S)-8-(7-bromo-5-cyclopropylpyrrolo [2,1-f] [1,2,4] triazin-4-yl)-8-azabicyclo[3.2.1] octan-3-yl)-2,2-dimethylpropan-1-one (300.0 mg, 0.696 mmol, 1.0 equiv) in 1,4-dioxane (6 mL) at 20 °C. To the above mixture was added 2-(trimethylstannyl)isonicotinonitrile (371.7 mg, 1.39 mmol, 2.0 equiv) at 20 °C. To the above mixture was added $Pd(PPh_3)_4$ (80.9 mg, 0.070 mmol, 0.1 equiv) at 20 °C. The final reaction mixture was stirred for 16 h at 110 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to 30 °C. The resulting mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: Column, Ultimate XB-C18 Column, 50*250 mm, 10 μm; mobile phase, MeCN in Water (0.05% TFA), 60% to 90% gradient in 40 min; detector, UV 210/254 nm. This resulted in 2-(5-cyclopropyl-4-((1R,3s,5S)-3-pivaloyl-8-azabicyclo [3.2.1]octan-8-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)isonicotinonitrile (18 mg, 5.7% yield) as a yellow solid. LCMS :(ES,

m/z):455.25 $[M+H]^+$. ^{1}H-NMR: (300 MHz, THF-d_8, *ppm*) δ 8.95 (dd, *J* = 1.5, 1.0 Hz, 1H), 8.64 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.93 (s, 1H), 7.36 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.13 (s, 1H), 4.88 (t, *J* = 3.8 Hz, 2H), 3.47 (s, 2H), 2.16 (tt, *J* = 8.2, 5.2 Hz, 1H), 2.01–1.85 (m, 4H), 1.86–1.71 (m, 2H), 1.68–1.50 (m, 2H), 1.05 (s, 9H), 1.01– 0.93 (m, 2H), 0.82– 0.71 (m, 2H).

Example 1.16. Synthesis of 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-16)

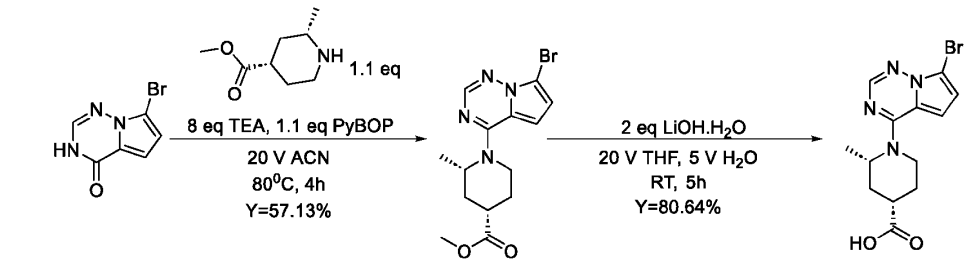


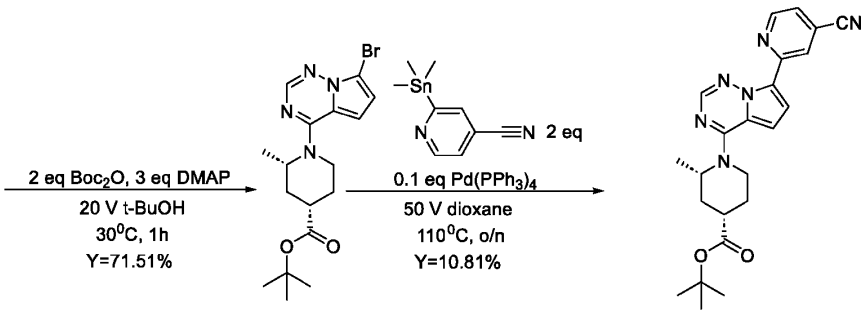
1-[(2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one. Into a 20 mL vial was placed a solution of (2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylic acid (500.0 mg, 1.42 mmol, 1.0 equiv) and thionyl chloride (336.8 mg, 2.83 mmol, 2.0 equiv) in DCM (10mL). This solution was stirred at room temperature for 1h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in THF (10 mL) was added CuCl (140.1 mg, 1.42 mmol, 1.0 equiv), tert-butyl(chloro)magnesium (314.3 mg, 2.69 mmol, 1.9 equiv). The resulting mixture was stirred at room temperature for 2h under nitrogen atmosphere. The reaction was quenched by the addition of water (10 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in 1-[(2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one (262 mg, 44.7% yield) as a yellow oil.

[0288] 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile. Into a 20 mL vial was placed a solution of 1-[(2S,4S)-1-{7-bromo-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-

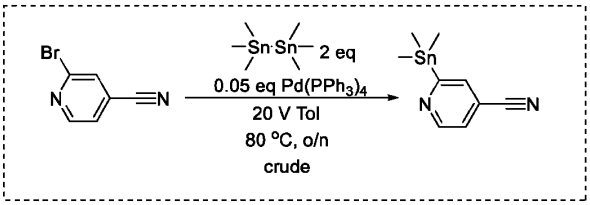
methylpiperidin-4-yl]-2,2-dimethylpropan-1-one (220.0 mg, 0.559 mmol, 1.0 equiv) and 2-(trimethyl-stannyl)pyridine-4-carbonitrile (179.2 mg, 0.671 mmol, 1.2 equiv), tetrakis(triphenylphosphine)palladium(0) (64.6 mg, 0.056 mmol, 0.1 equiv) in 1,4-dioxane (40 mL). The solution was stirred at 100°C overnight under nitrogen atmosphere. The reaction was quenched by the addition of water (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (54 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column 30*150 mm, 5um Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 54% B in 7 min; Wave Length: 254 nm/220 nm. This resulted in 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (16.7 mg, 7.2% yield) as a white solid. LC-MS (ES, *m/z*): 417.15 $[M+H]^+$; ^{1}H-NMR (300 MHz, DMSO-d_6, *ppm*) δ 8.96 – 8.82 (m, 2H), 8.37 (s, 1H), 7.81 – 7.71 (m, 1H), 7.43 (s, 1H), 3.72 – 3.62 (m, 2H), 3.31 – 3.21 (m, 1H), 3.1 – 3.0 (m, 1H), 2.52 (s, 3H), 1.85 – 1.54 (m, 3H), 1.23 (d, J = 5.9 Hz, 3H), 1.13 (s, 9H).

Example 1.17. Synthesis of tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-methylpiperidine-4-carboxylate (I-15)





I-15



Methyl (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 250 mL 3-necked round bottom flask was placed a solution of methyl (2S,4S)-2-methylpiperidine-4-carboxylate (2.83 g, 17.98 mmol, 1.1 equiv), 7-bromo-3H-pyrrolo[2,1-f][1,2,4]triazin-4-one (3.5 g, 16.35 mmol, 1.0 equiv), PyBOP (9.36 g, 17.98 mmol, 1.1 equiv) and Et_3N (13.24 g, 130.82 mmol, 8.0 equiv) in ACN (70 mL). The solution was stirred at 80°C for 4 h under nitrogen atmosphere. The resulting mixture was diluted with water (300 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted

with PE / EA (5:1) to afford methyl (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (3.3 g, 57.1%) as a light brown solid.

[0290] (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperi-dine-4-carboxylic acid. Into a 100 mL 3-necked round bottom flask was placed a solution of methyl (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (3.3 g, 9.34 mmol, 1.0 equiv) and $LiOH.H_2O$ (0.78 g, 18.68 mmol, 2.0 equiv) in THF (66 mL) and H_2O (16.5 mL) and stirred at room temperature for 5 h under nitrogen atmosphere. The mixture was acidified to pH 5 with conc. aqueous HCl. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (5:1) to afford (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperi-dine-4-carboxylic acid (2.5 g, 80.6%) as a light brown solid.

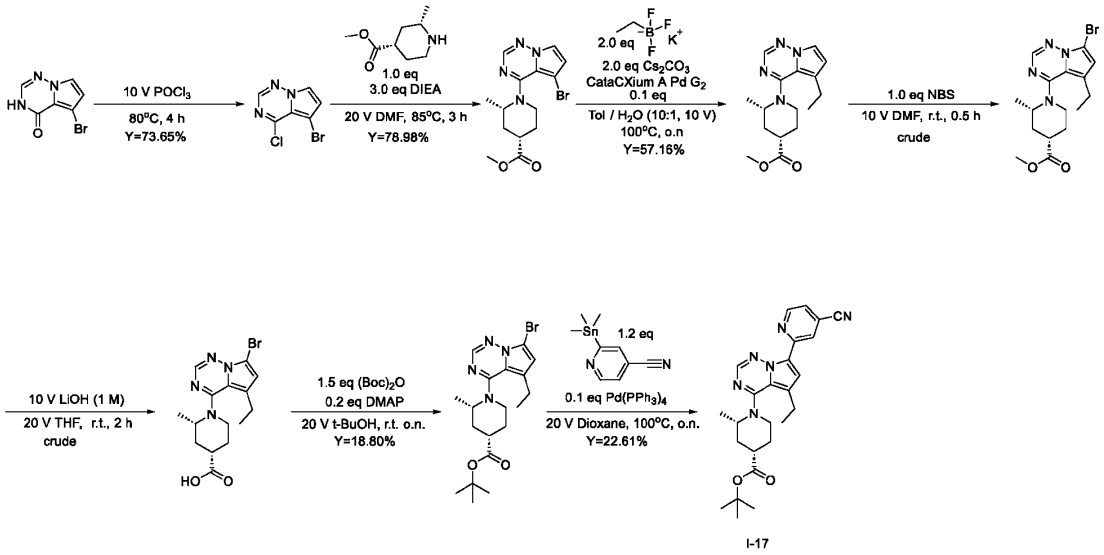
[0291] (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 20 mL vial was placed a solution of (2S,4S)-1-{7-bromopyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylic acid (300.0 mg, 0.88 mmol, 1.0 equiv), di-tert-butyl dicarbonate (386.0 mg, 1.76 mmol, 2.0 equiv) and DMAP (324.0 mg, 2.65 mmol, 3.0 equiv) in tert-Butanol (6 mL). The solution was stirred at 30°C for 1 h under nitrogen atmosphere. The resulting mixture was diluted with water (40 mL). The resulting mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford tert-butyl (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (250 mg, 71.5% yield) as a light brown oil.

[0292] 2-(trimethylstannyl)pyridine-4-carbonitrile. Into a 40 mL vial was placed a solution of 2-bromopyridine-4-carbonitrile (1.0 g, 5.46 mmol, 1.0 equiv), hexamethyldistannane (3.58 g, 10.92 mmol, 2.0 equiv) and $Pd(PPh_3)_4$ (0.32 g, 0.27 mmol, 0.05 equiv) in toluene (20 mL). The solution was stirred at 80°C overnight under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. This resulted in 2-(trimethylstannyl)pyridine-4-carbonitrile (1.5 g, crude) as a brown yellow solid.

[0293] Tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-methylpiperidine-4-carboxylate. Into a 20 mL vial was placed a solution of tert-butyl (2S,4S)-1-{7-bromopyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate (200.0 mg, 0.50

mmol, 1.0 equiv), 2-(trimethylstannyl)pyridine-4-carbonitrile (270.0 mg, 1.01 mmol, 2.0 equiv) and $Pd(PPh_3)_4$ (58.0 mg, 0.05 mmol, 0.1 equiv) in dioxane (10 mL). The solution was stirred at 110°C overnight under nitrogen atmosphere. The resulting mixture was filtered, and the filter cake was washed with MeOH (2 x 20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-methylpiperidine-4-carboxylate (24.5 mg, 10.8%) as a white solid. LC-MS: (ES, *m/z*): 419.15 $[M+H]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*): δ 8.98 (s, 1H), 8.88 (dd, *J* = 4.9, 1.0 Hz, 1H), 8.14 (s, 1H), 7.75 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.46 (d, *J* = 4.8 Hz, 1H), 7.08 (d, *J* = 5.0 Hz, 1H), 4.91 – 4.87 (m, 1H), 4.57 – 4.49 (m, 1H), 3.52 – 3.40 (m, 1H), 2.61 – 2.57 (m, 1H), 2.17 – 1.88 (m, 4H), 1.44 (s, 9H), 1.32 (d, *J* = 6.6 Hz, 3H).

Example 1.18. Synthesis of tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-methylpiperidine-4-carboxylate (I-17)



[0294] 5-bromo-4-chloropyrrolo[2,1-f][1,2,4]triazine. Into a 250 mL 3-necked round-bottom flask was added a solution of 5-bromo-3H-pyrrolo[2,1-f][1,2,4]triazin-4-one (5.0 g, 23.36 mmol, 1.0 equiv) in phosphorus oxychloride (50 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80°C for 4 h. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The

residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 5-bromo-4-chloropyrrolo[2,1-f][1,2,4]triazine (4.0 g, 73.7% yield) as a yellow solid.

[0295] Methyl (2S,4S)-1-{5-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 250 mL 3-necked round-bottom flask was added a solution of 5-bromo-4-chloropyrrolo[2,1-f][1,2,4] triazine (4.0 g, 17.21 mmol, 1.0 equiv), methyl (2S,4S)-2-methylpiperidine-4-carboxylate (2.7 g, 17.21 mmol, 1.0 equiv), DIEA (6.67 g, 51.62 mmol, 3.0 equiv) in DMF (80 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 85°C for 3 h. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford methyl (2S,4S)-1-{5-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (4.8 g, 79.0% yield) as a yellow solid.

[0296] Methyl (2S,4S)-1-{5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 100 mL 3-necked round-bottom flask was added methyl (2S,4S)-1-{5-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (4.7 g, 13.31 mmol, 1.0 equiv), potassium ethyltrifluoroborate (3.62 g, 26.61 mmol, 2.0 equiv), Cs_2CO_3 (8.67 g, 26.61 mmol, 2.0 equiv) in toluene (50 mL) and H_2O (5 mL). Then, CataCXium A Pd G2 (0.89 g, 1.33 mmol, 0.1 equiv) was added at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 100°C overnight. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford methyl (2S,4S)-1-{5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (2.3 g, 57.2% yield) as a yellow oil.

[0297] Methyl (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 100 mL round-bottom flask was added a solution of methyl (2S,4S)-1-{5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (2.3 g, 7.61 mmol, 1.0 equiv) in DMF (23 mL) at room temperature. To the above mixture was added NBS (1.35 g, 7.61 mmol, 1.0 equiv) in portions over 5 min at room temperature and stirred for 30 min. The reaction was poured into water (30 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under

reduced pressure. This resulted in methyl (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (2.0 g, crude) as a yellow oil.

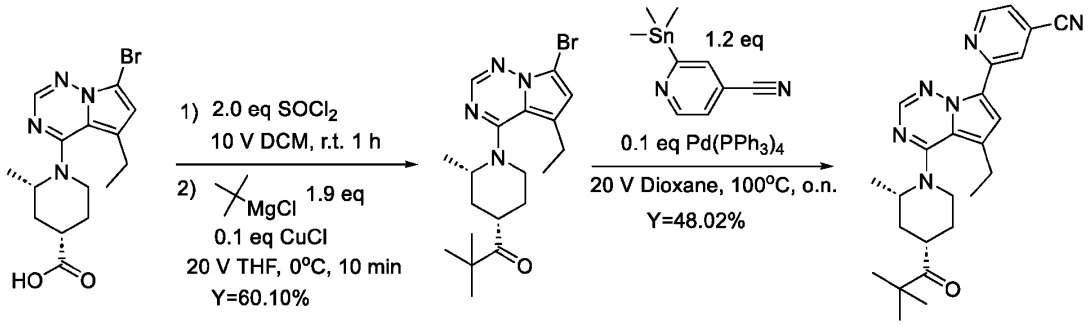
[0298] (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methyl piperidine-4-carboxylic acid. Into a 100 mL round-bottom flask was added a solution of methyl (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (2.0 g, 5.25 mmol, 1.0 equiv) and LiOH (1 M in H_2O, 20mL) in THF (40 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The mixture was acidified to pH 4 with aqueous HCl (1 mol/L). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methyl piperidine-4-carboxylic acid (2.1 g, crude) as a yellow solid.

[0299] Tert-butyl (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 20 mL vial was added a solution of (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylic acid (0.6 g, 1.63 mmol, 1.0 equiv), $(Boc)_2O$ (0.53 g, 2.45 mmol, 1.5 equiv) and DMAP (0.04 g, 0.327 mmol, 0.2 equiv) in tert-Butanol (12 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature overnight. The resulting mixture was concentrated under reduced pressure and purified by Prep-TLC (PE / EA 5:1) to afford tert-butyl (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (130 mg, 18.8% yield) as a yellow oil.

[0300] Tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-methylpiperidine-4-carboxylate. Into a 20 mL vial was added a solution of tert-butyl (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (130.0 mg, 0.307 mmol, 1.0 equiv), 2-(trimethylstannyl)pyridine-4-carbonitrile (98.4 mg, 0.368 mmol, 1.2 equiv) and $Pd(PPh_3)_4$ (35.5 mg, 0.031 mmol, 0.1 equiv) in dioxane (2.6 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 100°C overnight. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: Column: Xbridge Prep OBD C18 Column, 30*150 mm, 5μm Mobile Phase A: Water (10 mmol/L NH_4HCO_3+0.05%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60

mL/min; Gradient: 66% B to 96% B in 10 min; Wave Length: 254 nm/220 nm; RT1(min): 8.8. This resulted in tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-methylpiperidine-4-carboxylate (31.0 mg, 22.6% yield) as a yellow solid. LC-MS: (ES, *m/z*): 447.25 $[M+H]^+$; ^{1}H-NMR: (300 MHz, DMSO-d_6, *ppm*) δ 8.96 – 8.86 (m, 2H), 8.36 (s, 1H), 7.78 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.51 (s, 1H), 3.86 – 3.84 (m, 1H), 3.33 – 3.55 (m, 1H) 3.21 – 3.10 (m, 1H), 2.98 – 2.84 (m, 2H), 2.56 – 2.54 (m, 1H), 2.07 (d, *J* = 13.8 Hz, 1H), 1.88 – 1.62 (m, 3H), 1.44 (s, 9H), 1.32 (t, *J* = 7.5 Hz, 3H), 1.22 (d, *J* = 6.3 Hz, 3H).

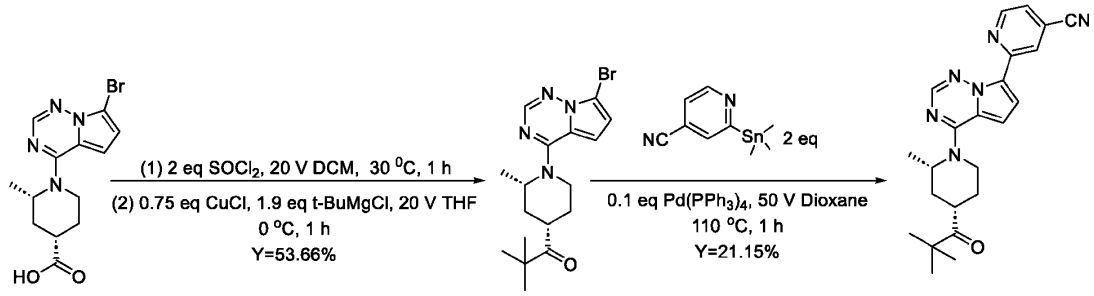
Example 1.19. Synthesis of 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]-5-ethylpyrrolo[2,1-f][1,2,4]triazin-7-yl} pyridine-4-carbonitrile (I-22)



[0301] 1-[(2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one. Into a 100 mL 3-necked round-bottom flask were added (2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylic acid (1.5 g, 4.08 mmol, 1.0 equiv) and $SOCl_2$ (0.97 g, 8.17 mmol, 2.0 equiv) in DCM (15 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure. The residue was added THF (30 mL) at room temperature under nitrogen atmosphere. Then, CuCl (4 mg, 0.408 mmol, 0.1 equiv) and tert-butyl(chloro)magnesium (7.5 mL, 7.76 mmol, 1.9 equiv) were added at 0°C and stirred for 10 min. The reaction was quenched by the addition of water (50 mL) at 0°C. The resulting mixture was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 1-[(2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one (1 g, 60.1% yield) as a yellow solid.

[0302] 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]-5-ethylpyrrolo[2,1-f][1,2,4]triazin-7-yl} pyridine-4-carbonitrile. Into a 20 mL vial were added 1-[(2S,4S)-1-{7-bromo-5-ethylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one (200.0 mg, 0.491 mmol, 1.0 equiv), 2-(trimethylstannyl) pyridine-4-carbonitrile (157.3 mg, 0.589 mmol, 1.2 equiv) and $Pd(PPh_3)_4$ (56.7 mg, 0.049 mmol, 0.1 equiv) in dioxane (4 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 100°C overnight. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: Column: XSelect CSH Prep C18 OBD Column, 30*150 mm, 5 μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 62% B to 90% B in 12 min; Wave Length: 254 nm/220 nm; RT1(min): 9.18. This resulted in 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]-5-ethylpyrrolo[2,1-f][1,2,4]triazin-7-yl} pyridine-4-carbonitrile (101.5 mg, 48.0% yield) as a yellow solid. LC-MS: (ES, *m/z*): 431.30 $[M+H]^+$; ^{1}H-NMR: (300 MHz, DMSO-d_6, *ppm*) δ 8.97 – 8.87 (m, 2H), 8.43 (s, 1H), 7.79 (dd, J = 4.9, 1.5 Hz, 1H), 7.52 (s, 1H), 3.70 – 3.62 (m, 2H), 3.34 – 3.33 (m, 1H), 3.03 – 2.92 (m, 3H), 1.78 –1.59 (m, 4H), 1.33 (t, J = 7.5 Hz, 3H), 1.22 (d, J = 5.9 Hz, 3H), 1.14 (s, 9H).

Example 1.20. Synthesis of 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-23)

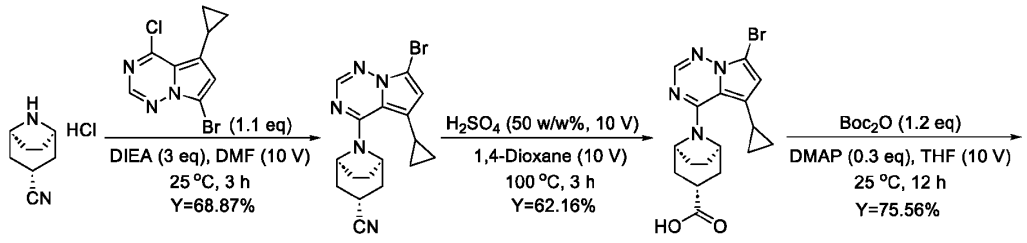


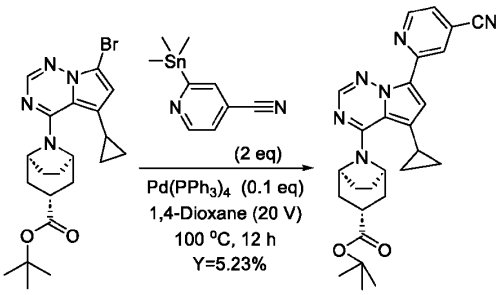
[0303] 1-[(2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one. A solution of (2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylic acid (500 mg, 1.47 mmol, 1 equiv) and Thionyl chloride (350 mg, 2.94 mmol, 2 equiv) in DCM (10 mL) was stirred at room temperature for 1 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was Re-

dissolved in THF (10 mL) and were added CuCl (109 mg, 1.10 mmol, 0.75 equiv) in portions at 0 °C under nitrogen atmosphere. Then, to the above mixture was added tert-butyl(chloro)magnesium (327 mg, 2.80 mmol, 1.9 equiv, 1M) dropwise over 10 min at 0 °C. The resulting mixture was stirred at 0 °C for additional 1 h. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The aqueous layer was extracted with EtOAc (3 x 50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 1-[(2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one (300 mg, 53.66%) as an off-white solid.

[0304] 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile. A solution of 1-[(2S,4S)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidin-4-yl]-2,2-dimethylpropan-1-one (120 mg, 0.31 mmol, 1 equiv), 2-(trimethylstannyl)pyridine-4-carbonitrile (168 mg, 0.63 mmol, 2 equiv) and $Pd(PPh_3)_4$ (36 mg, 0.03 mmol, 0.1 equiv) in Dioxane (6 mL) was stirred at 110 °C overnight under nitrogen atmosphere. The mixture was cooled down to room temperature. The resulting mixture was filtered, the filter cake was washed with MeOH (2 x 10 mL). The filtrate was concentrated under reduced pressure. The resulting mixture was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 10% to 80% gradient in 20 min; detector, UV 254 nm. This resulted in 2-{4-[(2S,4S)-4-(2,2-dimethylpropanoyl)-2-methylpiperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (27.4 mg, 21.15%) as a white solid. LC-MS: (ES, *m/z*): 403.15 $[M+H]^+$. ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*): δ 9.00 (s, 1H), 8.88 (d, J = 5.0 Hz, 1H), 8.14 (s, 1H), 7.75 (d, J = 5.0, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.07 (d, J = 5.0 Hz, 1H), 4.74 – 4.54 (m, 2H), 3.46 – 3.36 (m, 1H), 3.26 – 3.14 (m, 1H), 2.08 – 1.95 (m, 1H), 1.90 – 1.81 (m, 1H), 1.71– 1.61 (m, 2H), 1.37 (d, J = 6.2 Hz, 3H), 1.07 (s, 9H).

Example 1.21 Synthesis of tert-butyl (1R,3S,5S)-8-[7-(4-cyanopyridin -2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-8-azabicyclo[3.2.1]octane-3-carboxylate (I-29)





[0305] (1R,3S,5S)-8-{7-bromo-5- cyclopropylpyrrolo[2,1-f][1,2,4] triazin-4-yl} -8-azabicyclo[3.2.1]octane-3-carbonitrile. Into a 50 mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of (1R,3S,5S)-8-azabicyclo[3.2.1]octane-3-carbonitrile hydrochloride (1.0 g, 5.792 mmol, 1.0 equiv) in DMF (10 mL) at 25 °C. To the above mixture was added DIEA (2.25 g, 17.409 mmol, 3.0 equiv). To the above mixture was added 7-bromo-4-chloro-5- cyclopropylpyrrolo[2,1-f] [1,2,4] triazine (1.74 g, 6.385 mmol, 1.1 equiv) at 25 °C. The final reaction mixture was stirred for 3 h at 25 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in H_2O (0.05% TFA), 40% to 70% gradient in 30 min; detector, UV 210 nm. This resulted in (1R,3S,5S)-8-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4] triazin-4-yl} -8-azabicyclo[3.2.1]octane-3-carbonitrile (1.5 g, 68.9% yield) as a light yellow solid.

[0306] (1R,3S,5S)-8-{7-bromo-5- cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-8-azabicyclo[3.2.1]octane-3-carboxylic acid. Into a 50 mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of (1R,3S,5S)-8-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-8- azabicyclo[3.2.1]octane-3-carbonitrile

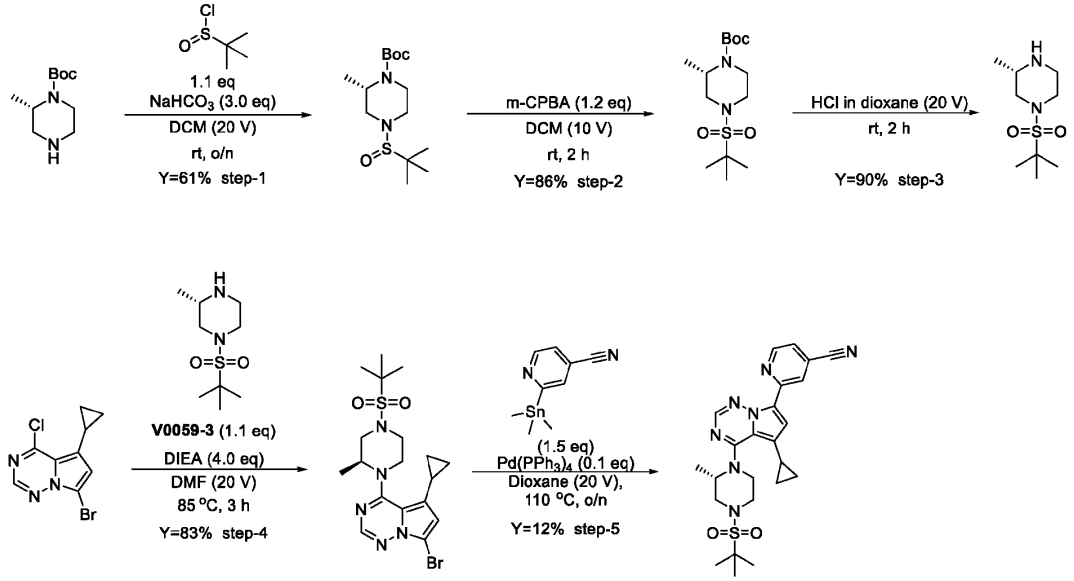
(1.5 g, 4.029 mmol, 1.0 equiv) in 1,4-dioxane (15 mL) at 25 °C. To the above mixture was added H_2SO_4 (15 mL, 50 w/w%). The final reaction mixture was stirred for 3 h at 100 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The reaction was quenched with water/ice (50 mL) at 0 °C. The mixture was adjusted to pH 8 with 2 mol/L aqueous NaOH. The mixture was washed with EtOAc (100 mL). The water layers were collected; the mixture was adjusting to pH 5 with 1 mol/L aqueous HCl. The mixture was extracted with EtOAc (2 x 50 mL), then organic layers washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford (1R,3S,5S)-8-{7-bromo-5- cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-8-azabicyclo[3.2.1]octane-3-carboxylic acid (1.0 g, 62.2% yield) as a light yellow solid.

[0307] Tert-butyl (1R,3S,5S)-8-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-8-azabicyclo[3.2.1] octane-3-carboxylate. Into a 10 mL 2-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of (1R,3S,5S)-8-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-8- azabicyclo[3.2.1]octane-3-carboxylic acid (0.3 g, 0.767 mmol, 1.0 equiv) in THF (2 mL) at 25 °C. To the above mixture was added DMAP (0.03 g, 0.230 mmol, 0.3 equiv). To the above mixture was added a solution of Boc_2O (0.20 g, 0.920 mmol, 1.2 equiv) in THF (1 mL) at 25 °C. The final reaction mixture was stirred for 12 h at 25 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The reaction was quenched with 10% aqueous citric acid (5 mL) at 25 °C. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in tert-butyl (1R,3S,5S)-8-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}- 8-azabicyclo[3.2.1] octane-3-carboxylate (0.27 g, 75.6% yield) as a light yellow solid.

[0308] Tert-butyl (1R,3S,5S)-8-[7-(4-cyanopyridin -2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-8-azabicyclo[3.2.1]octane-3-carboxylate. Into a 20 mL vial purged and maintained with an inert atmosphere of nitrogen, was placed a solution of tert-butyl (1R,3S,5S)-8-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-8-azabicyclo[3.2.1]octane -3-carboxylate (0.27 g, 0.604 mmol, 1.0 equiv) in 1,4-dioxane (5.4 mL) at 25 °C. To the above mixture was added 2-(trimethylstannyl) pyridine-4-carbonitrile (0.32 g, 1.208 mmol, 2.0 equiv) at 25 °C. The solution was degassed (bubbling nitrogen). To the above mixture was added $Pd(PPh_3)_4$

(0.07 g, 0.060 mmol, 0.1 equiv) at 25 °C. The final reaction mixture was stirred for 12 h at 100 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to 25 °C. The resulting mixture was filtered; the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: Column, Ultimate XB-C18 Column, 50*250 mm, 10 μm; mobile phase, MeCN in Water (0.05% TFA), 60% to 90% gradient in 30 min; detector, UV 210/254 nm to afford tert-butyl (1R,3S,5S)-8-[7-(4-cyanopyridin -2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-8-azabicyclo[3.2.1]octane-3-carboxylate (0.0139 g, 5.2% yield) as a white solid. LCMS: (ES, *m/z*): 471.20 $[M+H]^+$; ^{1}H-NMR: (300 MHz, DMSO-d_6, *ppm*) δ 8.91 – 8.81 (m, 2H), 8.14 (s, 1H), 7.74 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.13 (s, 1H), 4.90 (s, 2H), 2.83 (tt, *J* = 11.7, 6.1 Hz, 1H), 2.14 – 1.74 (m, 9H), 1.39 (s, 9H), 1.08 (dt, *J* = 8.5, 3.0 Hz, 2H), 0.92 – 0.81 (m, 2H).

Example 1.22. Synthesis of 2-{5-cyclopropyl-4-[(2S)-2-methyl-4-(2-methylpropane-2-sulfonyl)piperazin-1-yl] pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-54)



[0309] Tert-butyl (2S)-2-methyl-4-(2-methylpropane-2-sulfinyl)piperazine-1-carboxylate. Into 250 mL 3-necked round bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of tert-butyl (2S)-2-methylpiperazine-1-carboxylate (3.0 g, 15.0 mmol, 1.0 equiv) in DCM (60 mL). The mixture was cooled down to 0°C, then, 2-methylpropane-2-sulfinyl chloride (2.32 g, 16.5 mmol, 1.1 equiv) and $NaHCO_3$ (3.77 g, 44.9

mmol, 3.0 equiv) were added at 0°C to the mixture. After the addition, the mixture was warm up to room temperature and then stirred overnight. The mixture was quenched with 1 mol/L aqueous HCl, extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in tert-butyl (2S)-2-methyl-4-(2-methylpropane-2-sulfinyl)piperazine-1-carboxylate (2.8 g, 61% yield) as a yellow solid.

[0310] Tert-butyl (2S)-2-methyl-4-(2-methylpropane-2-sulfonyl)piperazine-1-carboxylate. Into 100 mL 3-necked round bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of tert-butyl (2S)-2-methyl-4-(2-methylpropane-2-sulfinyl)piperazine-1-carboxylate (3.3 g, 10.8 mmol, 1.0 equiv) in DCM (33 mL). The mixture was cooled down to 0°C, then, 3-chloroperoxy-benzoic acid (2.24 g, 13.0 mmol, 1.2 equiv) was added at 0°C to the mixture. After the addition, the mixture was warm up to room temperature and stirred for 2 h. The mixture was quenched with sodium bicarbonate aqueous solution, extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1). This resulted in tert-butyl (2S)-2-methyl-4-(2-methylpropane-2-sulfonyl)piperazine-1-carboxylate (3.0 g, 86% yield) as a white solid.

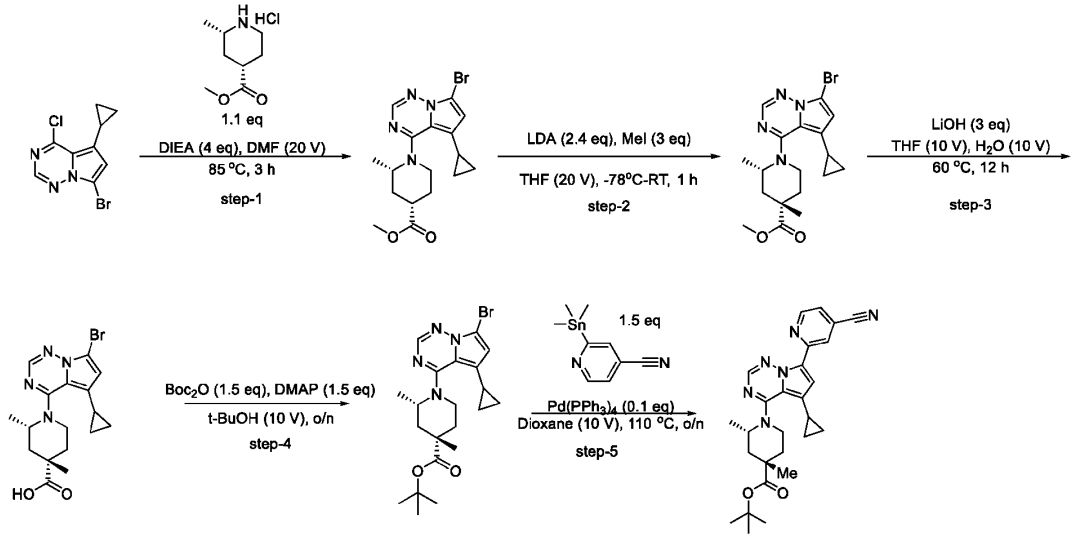
[0311] (3S)-3-methyl-1-(2-methylpropane-2-sulfonyl)piperazine. Into a 40 mL vial purged and maintained with an inert atmosphere of nitrogen was placed a solution of tert-butyl (2S)-2-methyl-4-(2-methylpropane-2-sulfonyl)piperazine-1-carboxylate (1.6 g, 4.99 mmol, 1.0 equiv) in hydrogen chloride (4.0 M in 1,4-dioxane) (32 mL). The resulting mixture was stirred for 2 h at room temperature and concentrated under reduced pressure. This resulted in (3S)-3-methyl-1-(2-methylpropane-2-sulfonyl)piperazine (1.0 g, 90% yield) as a yellow oil.

[0312] (2S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methyl-4-(2-methylpropane-2-sulfonyl) piperazine. Into a 40 mL vial purged and maintained with an inert atmosphere of nitrogen was placed a solution of 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazine (650.0 mg, 2.39 mmol, 1.0 equiv) in DMF (13 mL). (3S)-3-methyl-1-(2-methylpropane-2-sulfonyl)piperazine (578.1 mg, 2.62 mmol, 1.1 equiv) and DIEA (1.23 g, 9.54 mmol, 4.0 equiv) were added to the mixture. The resulting mixture was stirred for 3 h at 85°C. The reaction was cooled to room temperature. The reaction mixture was purified by reverse phase flash

with the following conditions (A: 0.1% NH_4HCO_3 in water, B: ACN; 50% B-100% B, 40 min). This resulted in (2S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methyl-4-(2-methylpropane-2-sulfonyl) piperazine (900 mg, 83% yield) as a yellow solid.

[0313] 2-{5-cyclopropyl-4-[(2S)-2-methyl-4-(2-methylpropane-2-sulfonyl)piperazin-1-yl] pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile. Into a 40 mL vial purged and maintained with an inert atmosphere of nitrogen was placed a solution of (2S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methyl-4-(2-methylpropane-2-sulfonyl) piperazine (900.0 mg, 1.97 mmol, 1.0 equiv) in 1,4-dioxane (18 mL). Then, 2-(trimethylstannyl) pyridine-4-carbonitrile (789.5 mg, 2.96 mmol, 1.5 equiv) was added to the mixture. The mixture was bubbled with N_2 for 5 min, $Pd(PPh_3)_4$ (227.9 mg, 0.197 mmol, 0.1 equiv) was added and then bubbled with N_2 for 5 min. The resulting mixture was stirred overnight at 110°C. The reaction was cooled to room temperature. The reaction mixture was purified by reverse phase flash with the following conditions: Column: YMC-Actus Triart C18 ExRS30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3+0.05%NH_3 H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 51% B to 81% B in 10 min; Wave Length: 254 nm/220 nm; RT1(min): 9.18. This resulted in 2-{5-cyclopropyl-4-[(2S)-2-methyl-4-(2-methylpropane-2-sulfonyl)piperazin-1-yl] pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (117.4 mg, 12% yield) as a yellow solid. LC-MS: (ES, *m/z*): 480.20 $[M+H]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 8.90 – 8.85 (m, 2H), 8.22 (s, 1H), 7.76 (dd, J = 4.9, 1.6 Hz, 1H), 7.15 (s, 1H), 4.71 (d, J = 7.2 Hz, 1H), 3.99 (d, J = 13.4 Hz, 1H), 3.75 (d, J = 12.4 Hz, 1H), 3.63 – 3.42 (m, 3H), 3.34 – 3.26 (m, 1H), 2.13 (dq, J = 8.2, 4.5, 3.1 Hz, 1H), 1.40 – 1.22 (m, 12H), 1.18 – 1.01 (m, 2H), 0.88 (p, J = 4.8, 4.3 Hz, 1H), 0.80 (dt, J = 11.1, 5.3 Hz, 1H).

Example 1.23. Synthesis of tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,4-dimethylpiperidine-4-carboxylate (I-55)



[0314] Methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 40 mL vail was placed a solution of 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazine (1.1 g, 4.04 mmol, 1.0 equiv), methyl (2S,4S)-2-methylpiperidine-4-carboxylate hydrochloride (0.86 g, 4.44 mmol, 1.1 equiv) and DIEA (2.09 g, 16.1 mmol, 4.0 equiv) in DMF (20 mL) at room temperature under nitrogen atmosphere. The reaction was heated to 85°C and stirred for 3 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The reaction was added water (100 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with water (5 x 15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product as a brown oil. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (1.5 g, 94.5% yield) as a yellow solid.

[0315] Methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate. Into a 50 mL 3-necked round-bottom flask was placed a solution of methyl (2S,4S)-1-{7-bromo-5-cyclo-propylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (1.5 g, 3.81 mmol, 1.0 equiv) in THF (30 mL) at room temperature under nitrogen atmosphere. The reaction was cooled to -78°C. Then, LDA (4.58 mL, 9.15 mmol, 2.4 equiv) was added and stirred for 30 min. After that, iodomethane (1.62 g, 11.4 mmol, 3.0 equiv) was added. The reaction was warmed to rt stirred for 1 h at room temperature. LCMS showed the

reaction was finished. The reaction was poured into water (50 mL) and extracted with EA (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to afford crude product. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (1.5 g, 96.6% yield) as a yellow solid.

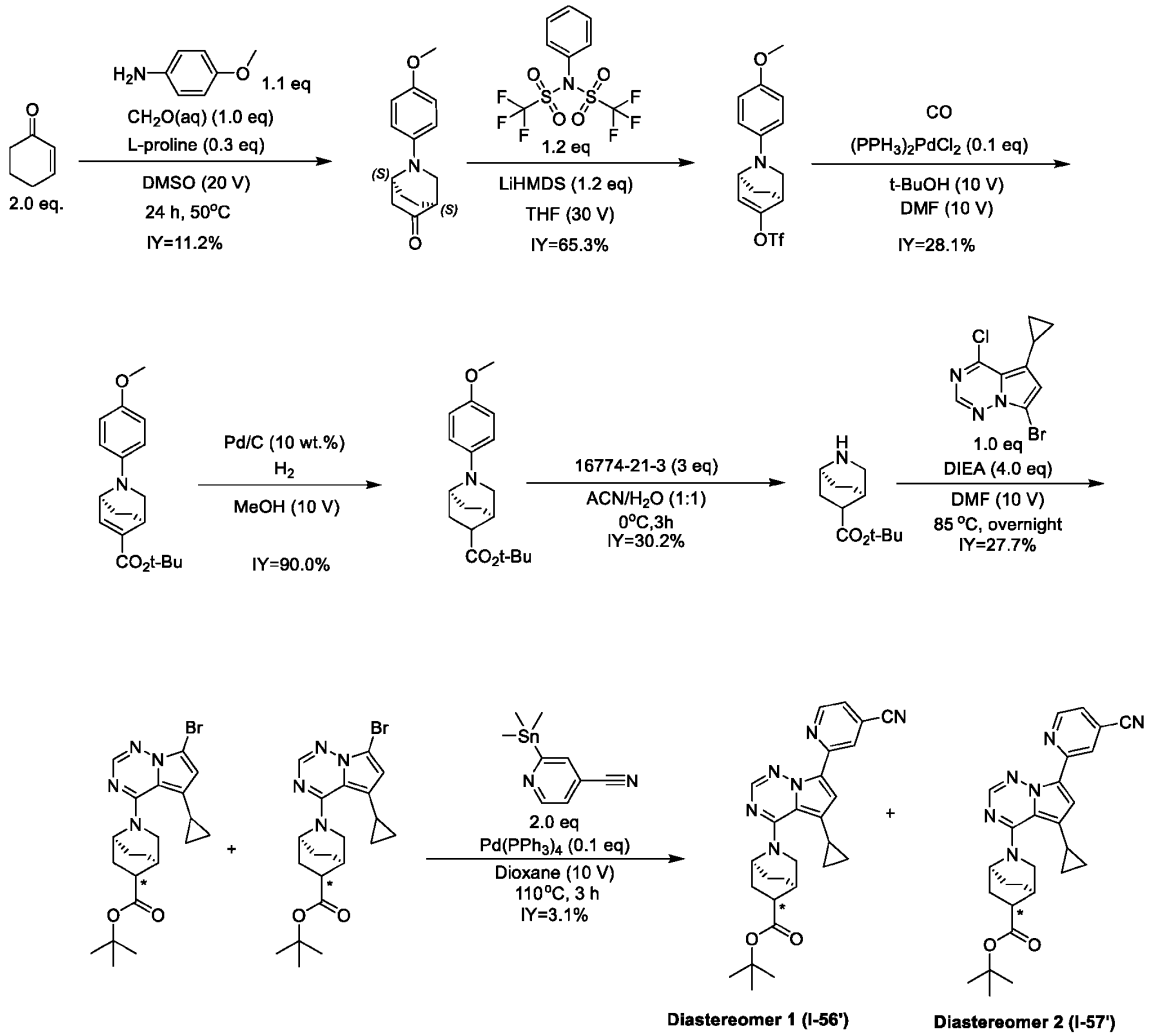
[0316] (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid. Into a 40 mL vail was placed a solution of methyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (1.5 g, 3.68 mmol, 1.0 equiv) in THF (15 mL) and H_2O (15 mL) at room temperature under nitrogen atmosphere. Then, LiOH (0.26 g, 11.0 mmol, 3.0 equiv) was added. The reaction was heated to 60°C and stirred for 12 h. LCMS showed the reaction was finished. The reaction was diluted with water (20 mL). The solution was acidified to pH 1 with 1 mol/L aqueous HCl. The mixture was extracted with EA (2 x 20 mL). The combined organic layers were washed with water (4 x 15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid (1 g, 69.0% yield). The crude product was used into next step directly without further purification.

[0317] (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate. Into a 20 mL vail was placed a solution of (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid (500.0 mg, 1.27 mmol, 1.0 equiv), di-tert-butyl dicarbonate (416.0 mg, 1.91 mmol, 1.5 equiv) and DMAP (233.0 mg, 1.91 mmol, 1.5 equiv) in 2-methylpropan-2-ol (5 mL) at room temperature under nitrogen atmosphere. The reaction was heated to 70°C and stirred overnight. LCMS showed the reaction was finished. The mixture was cooled down to room temperature. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 70% to 95% gradient in 30 min; detector, UV 254 nm. This resulted in tert-butyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (380 mg, 66.5% yield) as a yellow solid.

[0318] Tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,4-dimethylpiperidine-4-carboxylate. Into a 20 mL vail was placed a solution of tert-butyl (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (380.0 mg, 0.846 mmol, 1.0 equiv) and 2-(trimethylstannyl)pyridine-4-carbonitrile (339.0 mg, 1.27 mmol, 1.5 equiv) in 1,4-dioxane (3.8 mL). Then, $Pd(PPh_3)_4$ (97.7 mg, 0.085 mmol, 0.1 equiv) was added at room temperature. The mixture was replaced with N_2 for 1 min. The reaction was heated to 110°C and stirred for 12 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The reaction was added water (25 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product. The crude product was purified with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 70% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in tert-butyl (2S,4S)-1-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,4-dimethylpiperidine-4-carboxylate (115.7 mg, 29.0% yield) as a yellow solid. LC-MS (ES, *m/z*): 473.30 $[M+H]^+$; ^{1}H-NMR-PH-CSM-SMC-2024-01-V0061: (400 MHz, DMSO-d_6, *ppm*) δ 8.90 – 8.79 (m, 2H), 8.14 (s, 1H), 7.72 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.09 (s, 1H), 4.74 (td, *J* = 8.1, 4.3 Hz, 1H), 3.96 (dt, *J* = 13.9, 3.7 Hz, 1H), 3.52 – 3.38 (m, 1H), 2.15 (dd, *J* = 13.5, 2.4 Hz, 2H), 2.06 (tt, *J* = 8.2, 5.1 Hz, 1H), 1.78 (dd, *J* = 13.9, 5.3 Hz, 1H), 1.45 (s, 9H), 1.50 – 1.35 (m, 1H), 1.13 (t, *J* = 3.5 Hz, 6H), 1.09 – 1.03 (m, 2H), 0.91 – 0.85 (m, 1H), 0.77 (ddt, *J* = 9.5, 6.6, 3.6 Hz, 1H).

Example 1.24. Synthesis of tert-butyl (1S,4R,5R)-2-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-azabicyclo[2.2.2]octane-5-carboxylate and tert-butyl (1S,4R,5S)-2-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-azabicyclo[2.2.2]octane-5-carboxylate

*** = stereochemistry unknown**



[0319] **(1S,4S)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-one**. Into a 2 L 3-necked round bottom flask was placed a solution of P-anisidine (33.0 g, 268 mmol, 1.1 equiv), cyclohexenone (46.8 g, 487 mmol, 2.0 equiv), L-proline (8.41 g, 73 mmol, 0.3 equiv) and formaldehyde solution (7.31 g, 243 mmol, 1.0 equiv) in in DMSO (960 mL) at room temperature for 5 min under nitrogen atmosphere. The final reaction mixture was irradiated with microwave radiation at 50°C for 24 h. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (400 mL) at room temperature. The aqueous layer was extracted with EtOAc (3 x 400 mL). The resulting mixture was washed with brine (3 x 400 mL). The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1).

The crude product (12 g) was purified by Prep-SFC to afford (1S,4S)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-one (6.3 g, 11.2% yield) as a light yellow solid.

[0320] (1S,4S)-2-(4-methoxyphenyl)-2-azabicyclo [2.2.2]oct-5-en-5-yl trifluoromethanesulfonate. In a 250-mL round bottom flask was placed a solution of (1S,4S)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2] octan-5-one (4.0 g, 17.3 mmol, 1.0 equiv) in THF (80 mL), then, LiHMDS (20.7 mL, 20.7 mmol, 1.2 equiv) was added dropwise at -78°C under N_2 atmosphere. The reaction mixture was stirred at -78°C for 1 h. Then a solution of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethane)sulfonylmethanesulfonamide (7.41 g, 20.8 mmol, 1.2 equiv) in THF (40 mL) was added dropwise and the mixture was stirred for another 30 min. The resulting mixture was stirred at room temperature overnight under nitrogen atmosphere. The reaction was quenched with water (40 mL), and then the mixture was extracted with ether/EtOAc (3 x 40 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford (1S,4S)-2-(4-methoxyphenyl)-2-azabicyclo [2.2.2]oct-5-en-5-yl trifluoromethanesulfonate (4.1 g, 65.3% yield) as a light yellow solid.

[0321] Tert-butyl (1S,4R)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]oct-5-ene-5-carboxylate. Into a pressure tank was placed a solution of (1S,4S)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]oct-5-en-5-yl trifluoromethanesulfonate (4.1 g, 11.3 mmol, 1.0 equiv) in DMF (41 mL) and tert-Butanol (41 mL), then, dichlorobis(triphenylphosphine)palladium(II) (0.79 g, 1.13 mmol, 0.1 equiv) was added, then, CO was introduced in. The mixture was hydrogenated at room temperature under 5 bar of carbon monoxide pressure overnight, filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (column, C18 silica gel; mobile phase, MeCN in Water (0.1% TFA), 30% to 70% gradient in 30 min; detector, UV 210 nm) to afford tert-butyl (1S,4R)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]oct-5-ene-5-carboxylate (1 g, 28.1% yield) as a light brown solid.

[0322] Tert-butyl (1S,4R)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octane-5-carboxylate. Into a 250 mL round-bottom flask was placed a solution of tert-butyl (1S,4R)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]oct-5-ene-5-carboxylate (1.0 g, 3.17 mmol, 1.0 equiv) in MeOH (10 mL), then, Pd/C (10%, 100 mg) was added under nitrogen atmosphere. Then, hydrogen gas was introduced in at room temperature for 3 h under hydrogen atmosphere using a hydrogen

balloon, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% TFA), 30% to 70% gradient in 30 min; detector, UV 210 nm. This resulted in tert-butyl (1S,4R)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octane-5-carboxylate (1 g, 90.0% yield) as a light brown oil.

[0323] Tert-butyl (1S,4R)-2-azabicyclo [2.2.2]octane-5-carboxylate. Into a 100 mL 3-necked round bottom flask was placed a stirred solution of tert-butyl (1S,4R)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octane-5-carboxylate (800.0 mg, 2.52 mmol, 1.0 equiv) in MeCN (40 mL), then, ammonium cerium(IV) nitrate (4.14 g, 7.56 mmol, 3 equiv) in H_2O (40 mL) was added dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 3 h under nitrogen atmosphere. Adjusted the pH value of the mixture to 10 with aqueous NaOH (2 mol/L). The aqueous layer was extracted with CH_2Cl_2 (5 x 100 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (5:1) to afford tert-butyl (1S,4R)-2-azabicyclo [2.2.2]octane-5-carboxylate (161 mg, 30.2% yield) as a dark red oil.

[0324] Tert-butyl (1S,4R,5*)-2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo[2.2.2] octane-5-carboxylate. Into a 20 mL vial was added a solution of tert-butyl (1S,4R)-2-azabicyclo[2.2.2]octane-5-carboxylate (116.0 mg, 0.549 mmol, 1.0 equiv), DIEA (284.0 mg, 2.20 mmol, 4.0 equiv) and 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4] triazine (150.0 mg, 0.549 mmol, 1.0 equiv) in DMF (1.16 mL). The solution was stirred at 85°C overnight under nitrogen atmosphere. The reaction was quenched by the addition of water (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 5:1) to afford tert-butyl (1S,4R,5*)-2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo[2.2.2] octane-5-carboxylate (68 mg each for peak 1 and peak 2) as a yellow solid.

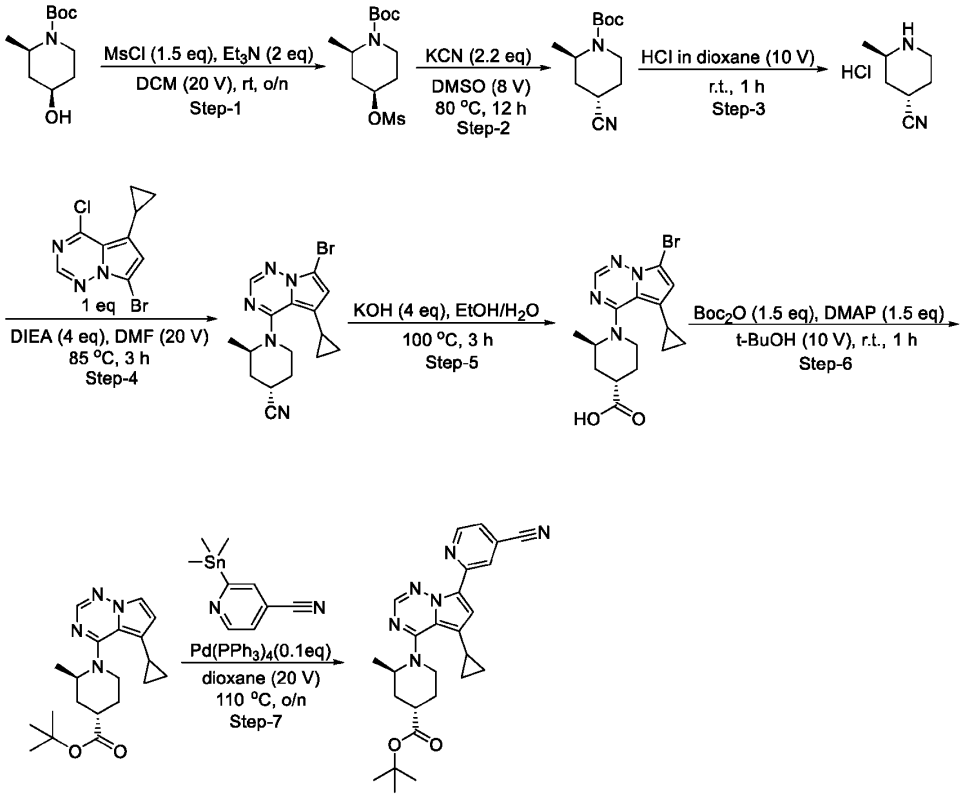
[0325] Tert-butyl (1S,4R,5*)-2-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-azabicyclo[2.2.2]octane-5-carboxylate (Diastereomer 1 (I-56')). Into a 8 mL vial was placed a solution of tert-butyl (1S,4R,5*)-2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo[2.2.2]octane-5-carboxylate (peak 1, 68.0 mg, 0.152 mmol, 1.0 equiv), 2-(trimethylstannyl)pyridine-4-carbonitrile (81.1 mg, 0.304 mmol, 2.0 equiv) and

tetrakis(triphenylphosphine) palladium(0) (17.6 mg, 0.015 mmol, 0.1 equiv) in dioxane (680 uL) was stirred at 110 °C for 3 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 5:1) to afford crude product. The crude product was purified by reverse phase flash with the following conditions (A: 0.05% TFA in water; B: ACN; 132-1T TFA-A-XS-2.416-2.657) to afford tert-butyl (1S,4R,5*)-2-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-azabicyclo[2.2.2]octane-5-carboxylate (**Diastereomer 1 (I-56')**, 2.2 mg, 3.1% yield, 98.5% purity) as a light yellow solid. LC-MS: (ES, *m/z*) 471.20 $[M+H]^+$; ^{1}H-NMR: (300 MHz, Methanol-d_4, *ppm*) δ 8.92 (t, *J* = 1.2 Hz, 1H), 8.78 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.97 (s, 1H), 7.57 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.23 (s, 1H), 4.74 (s, 1H), 4.09 (d, *J* = 12.1 Hz, 1H), 3.96 – 3.84 (m, 1H), 2.85 – 2.71 (m, 1H), 2.53 (ddt, *J* = 13.9, 5.8, 3.1 Hz, 1H), 2.41 (d, *J* = 2.9 Hz, 1H), 2.24 – 2.11 (m, 1H), 2.11 – 1.92 (m, 2H), 1.89 – 1.80 (m, 3H), 1.37 (s, 9H), 1.11 (ddd, *J* = 10.6, 5.2, 2.4 Hz, 2H), 0.94 – 0.81 (m, 2H).

[0326] Tert-butyl (1S,4R,5*)-2-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-azabicyclo[2.2.2]octane-5-carboxylate (Diastereomer 2 (I-57')). Into a 8 mL vial was placed a solution of tert-butyl (1S,4R,5*)-2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo[2.2.2]octane-5-carboxylate (peak 2, 68.0 mg, 0.152 mmol, 1.0 equiv), 2-(trimethylstannyl)pyridine-4-carbonitrile (81.1 mg, 0.304 mmol, 2.0 equiv) and tetrakis(triphenylphosphine) palladium(0) (17.6 mg, 0.015 mmol, 0.1 equiv) in dioxane (680 uL) was stirred at 110 °C for 3 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 5:1) to afford crude product. The crude product was purified by reverse phase flash with the following conditions (A: 0.05% TFA in water; B: ACN; 132-1T TFA-A-XS-2.416-2.657) to afford tert-butyl (1S,4R,5*)-2-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-azabicyclo[2.2.2]octane-5-carboxylate (**Diastereomer 2 (I-57')**, 2.2 mg, 3.1% yield, 98.5%

purity) as a light yellow solid. LC-MS: (ES, *m/z*) 471.25 $[M+H]^+$; ^{1}H-NMR: (300 MHz, Methanol-d_4, *ppm*) δ 8.91 – 8.86 (m, 1H), 8.81 (dd, *J* = 5.0, 1.0 Hz, 1H), 8.13 (s, 1H), 7.61 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.29 (d, *J* = 0.8 Hz, 1H), 7.14 (t, *J* = 3.9 Hz, 1H), 3.81 – 3.65 (m, 2H), 3.04 (d, *J* = 20.3 Hz, 1H), 2.42 – 2.15 (m, 3H), 2.01 – 1.86 (m, 1H), 1.81 – 1.62 (m, 3H), 1.48 (s, 9H), 1.22 – 1.09 (m, 2H), 0.95 – 0.78 (m, 2H).

Example 1.25. Synthesis of (2R,4S)-1-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-methylpiperidine-4-carboxylate (I-58)



[0327] Tert-butyl (2R,4R)-4-(methanesulfonyloxy)-2-methylpiperidine-1-carboxylate. Into a 100 mL 3-necked round-bottom flask was placed a solution of tert-butyl (2R,4R)-4-hydroxy-2-methylpiperidine-1-carboxylate (3.0 g, 13.934 mmol, 1.0 equiv) and triethylamine (2.82 g, 27.868 mmol, 2.0 equiv) in DCM (60 mL). Then, methanesulfonyl chloride (2.39 g, 20.901 mmol, 1.5 equiv) was added to the mixture at room temperature. The reaction was stirred overnight at room temperature. The reaction was added water (25 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude

product. The crude product was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford tert-butyl (2R,4R)-4-(methanesulfonyloxy)-2-methylpiperidine-1-carboxylate (3.5 g, 85.6% yield) as a white solid.

[0328] Tert-butyl (2R,4S)-4-cyano-2-methylpiperidine-1-carboxylate. Into a 40 mL vail was placed a solution tert-butyl (2R,4R)-4-(methanesulfonyloxy)-2-methylpiperidine-1-carboxylate (3.0 g, 10.226 mmol, 1.0 equiv) in DMSO (24 mL). Then, KCN (1.46 g, 22.497 mmol, 2.2 equiv) was added at room temperature. The reaction was heated to 80°C and stirred for 4 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The reaction was added aqueous $NaHCO_3$ (25 mL) and extracted with EA (3 x 10 m). The combined organic layers were washed with brine (10 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product. The crude product was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford tert-butyl (2R,4S)-4-cyano-2-methylpiperidine-1-carboxylate (320 mg, 14.0% yield) as a white solid.

[0329] (2R,4S)-2-methylpiperidine-4-carbonitrile. Into a 20 mL vail was placed a solution of tert-butyl (2R,4S)-4-cyano-2-methylpiperidine-1-carboxylate (320.0 mg, 1.427 mmol, 1.0 equiv) in hydrogen chloride (4.0 M in 1,4-dioxane) (3 mL, 12.000 mmol, 8.4 equiv). The reaction was stirred for 1 h at room temperature. LCMS showed the reaction was finished. The resulting mixture was concentrated under reduced pressure. This resulted in (2R,4S)-2-methylpiperidine-4-carbonitrile (crude) as a white solid. The crude product was used into next step directly without further purification.

[0330] (2R,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperi-dine-4-carbonitrile. Into a 40 mL vail was placed 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazine (395.0 mg, 1.449 mmol, 1.0 equiv), (2R,4S)-2-methylpiperidine-4-carbonitrile hydrochloride (180.0 mg, 1.449 mmol, 1.0 equiv) and DIEA (749.3 mg, 5.796 mmol, 4.0 equiv) in DMF (8 mL) at room temperature under nitrogen atmosphere. The reaction was heated to 85°C and stirred for 3 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The reaction was added water (100 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with water (5 x 15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product as a brown oil. The residue

was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford (2R,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperi-dine-4-carbonitrile (300 mg, 57.5% yield) as a yellow solid.

[0331] (2R,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylic acid. Into an 8 mL vail was placed (2R,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carbonitrile (300.0 mg, 0.833 mmol, 1.0 equiv) in EtOH (1.5 mL) and H_2O (1.5 mL) at room temperature under nitrogen atmosphere. Then, KOH (186.9 mg, 3.332 mmol, 4.0 equiv) was added to the mixture. The reaction was heated to 100°C and stirred for 3 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The reaction was diluted with water (20 mL). The solution was acidified to pH 1 with 1 mol/L aqueous HCl. The mixture was extracted with EA (2 x 20 m). The combined organic layers were washed with water (4 x 15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product of (2R,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylic acid (250 mg). The crude product was used into next step directly without further purification.

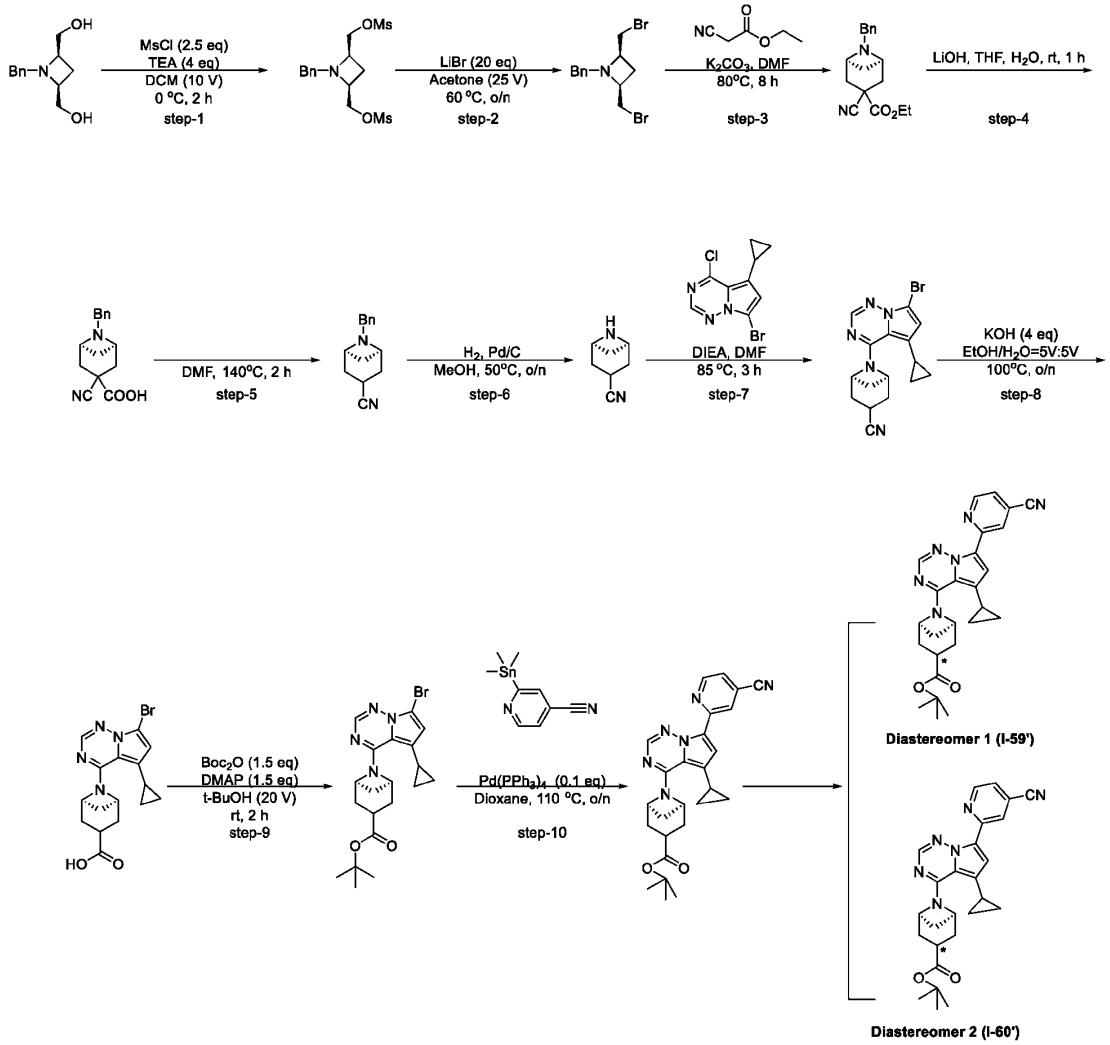
[0332] (2R,4S)-1-{5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into an 8 mL vail was placed a solution of (2R,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylic acid (250.0 mg, 0.659 mmol, 1.0 equiv), di-tert-butyl dicarbonate (215.8 mg, 0.989 mmol, 1.5 equiv) and DMAP (120.8 mg, 0.989 mmol, 1.5 equiv) in 2-methylpropan-2-ol (2.5 mL) at room temperature under nitrogen atmosphere. The reaction was stirred for 1 h at room temperature. LCMS showed the reaction was finished. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 70% to 95% gradient in 30 min; detector, UV 254 nm. This resulted in tert-butyl (2R,4S)-1-{5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (220 mg, 93.6% yield) as a yellow solid.

[0333] (2R,4S)-1-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-methylpiperidine-4-carboxylate. Into a 20 mL vail was placed a solution of tert-butyl (2R,4S)-1-{5-cyclopropylpyrrolo[2,1-f][1,2,4]tri-azin-4-yl}-2-methylpiperidine-4-carboxylate (270.0 mg, 0.620 mmol, 1.0 equiv) and 2-(trimethylstannyl) pyridine-4-carbonitrile (248.3 mg,

0.930 mmol, 1.5 equiv) in 1,4-dioxane (5.4 mL). Then, $Pd(PPh_3)_4$ (71.7 mg, 0.062 mmol, 0.1 equiv) was added at room temperature. The mixture was replaced with N_2 for 1 min. The reaction was heated to 110°C and stirred for 12 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The reaction was purified with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 70% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in tert-butyl (2R,4S)-1-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-methylpiperidine-4-carboxylate (80.4 mg, 28.3% yield) as a white solid. LC-MS: (ES, *m/z*) 459.30 $[M+H]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 8.90 – 8.80 (m, 2H), 8.16 (s, 1H), 7.74 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.11 (s, 1H), 4.86 (dd, *J* = 7.1, 3.7 Hz, 1H), 4.12 – 4.01 (m, 1H), 3.41 (td, *J* = 13.4, 2.7 Hz, 1H), 2.80 (dtd, *J* = 12.0, 8.4, 3.8 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.94 (dd, *J* = 13.4, 3.3 Hz, 1H), 1.82 (dd, *J* = 8.8, 3.7 Hz, 2H), 1.63 – 1.50 (m, 1H), 1.41 (s, 9H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.08 (dq, *J* = 5.5, 3.0 Hz, 2H), 0.93 – 0.76 (m, 2H).

Example 1.26. Synthesis of tert-butyl (1R,3R,5S)-6-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-azabicyclo[3.1.1]heptane-3-carboxylate and (1R,3S,5S)-6-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-azabicyclo[3.1.1]heptane-3-carboxylate

*** = stereochemistry unknown**



[0334] **((2S,4R)-1-benzylazetidine-2,4-diyl)bis(methylene)dimethanesulfonate**. Into a 500 mL 3-necked round bottom flask purged and maintained with N_2 was placed a solution of ((2S,4R)-1-benzylazetidine-2,4-diyl)dimethanol (25.0 g, 0.121 mol, 1.0 equiv) and TEA (48.8 g, 0.484 mol, 4.0 equiv) in DCM (250 mL). The mixture was cooled to 0°C and MsCl (34.4 g, 0.302 mol, 2.5 equiv) was added dropwise. The mixture was stirred for 2 h at this temperature and quenched with aqueous $NaHCO_3$ (200 mL). The separated water layer was extracted with DCM (2 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated. This resulted in 35 g (crude) ((2S,4R)-1-benzylazetidine-2,4-diyl)bis(methylene)dimethanesulfonate as a yellow oil.

[0335] **(2S,4R)-1-benzyl-2,4-bis(bromomethyl)azetidine**. Into a 1 L 3-necked round bottom flask purged and maintained with N_2 was placed a solution of ((2S,4R)-1-benzylazetidine-2,4-diyl)bis(methylene)dimethanesulfonate (25.0 g, 0.069 mol, 1.0 equiv) in acetone (625 mL). Then, LiBr (118.5 g, 1.38 mol, 20.0 equiv) was added and the mixture was warmed to 60°C. After stirring overnight, the mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by column chromatography eluted with EA : PE=0-5%. This resulted in 15 g (66% yield) (2S,4R)-1-benzyl-2,4-bis(bromomethyl)azetidine as a yellow solid.

[0336] **Ethyl 6-benzyl-3-cyano-6-azabicyclo[3.1.1]heptane-3-carboxylate**. Into a 1 L 3-necked round bottom flask purged and maintained with N_2 was placed a solution of (2S,4R)-1-benzyl-2,4-bis(bromomethyl)azetidine (17.0 g, 0.051 mol, 1.0 equiv) and ethyl 2-cyanoacetate (5.8 g, 0.051 mol, 1.0 equiv) in DMF (255 mL). Then, K_2CO_3 (21.2 g, 0.154 mol, 3.0 equiv) was added. The mixture was warmed to 80°C and stirred for 8 h. After cooling to room temperature, the mixture was filtered and the filtrate was diluted with EA (1 L) and washed with H_2O (3 x 300 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by column chromatography eluted with EA : PE =0-30%. This resulted in 3.9 g (27% yield) ethyl 6-benzyl-3-cyano-6-azabicyclo[3.1.1]heptane-3-carboxylate as an off-white solid.

[0337] **6-benzyl-3-cyano-6-azabicyclo[3.1.1]heptane-3-carboxylic acid**. Into a 250 mL 3-necked round bottom flask purged and maintained with N_2 was placed a solution of ethyl 6-benzyl-3-cyano-6-azabicyclo[3.1.1]heptane-3-carboxylate (4.0 g, 0.014 mol, 1.0 equiv) in THF (40 mL). Then, a solution of LiOH (0.51 g, 0.021 mol, 1.5 equiv) in H_2O (20 mL) was added dropwise and the mixture was stirred for 1 h. Concentrated to remove THF. The water layer was adjusted pH=3 with citric acid and extracted with EA (3 x 50 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated. This resulted in 2.7 g (75% yield) 6-benzyl-3-cyano-6-azabicyclo[3.1.1]heptane-3-carboxylic acid as a yellow oil.

[0338] **6-benzyl-6-azabicyclo[3.1.1]heptane-3-carbonitrile**. Into a 100 mL 3-necked round bottom flask purged and maintained with N_2 was placed a solution of 6-benzyl-3-cyano-6-azabicyclo[3.1.1]heptane-3-carboxylic acid (2.1 g, 8.2 mmol, 1.0 equiv) in DMF (21 mL). The mixture was warmed to 140°C and stirred for 2 h. After cooling to room temperature, the mixture was concentrated. This resulted in 2 g (crude) 6-benzyl-6-azabicyclo[3.1.1]heptane-3-carbonitrile as a yellow solid.

[0339] 6-azabicyclo[3.1.1]heptane-3-carbonitrile. Into a 100 mL round bottom flask was placed a solution of 6-benzyl-6-azabicyclo[3.1.1]heptane-3-carbonitrile (2 g, crude) in MeOH (40 mL). Then, Pd/C (0.4 g) was added and the system was purged with H_2 for 3 times. Then the mixture was warmed to 50 °C and stirred overnight under H_2 atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated. This resulted in 1.5 g (crude) 6-azabicyclo[3.1.1]heptane-3-carbonitrile as an oil.

[0340] 6-(7-bromo-5-cyclopropylpyrrolo[1,2-f][1,2,4]triazin-4-yl)-6-aza-bicyclo[3.1.1]heptane-3-carbonitrile. Into a 100 mL 3-necked round bottom flask was placed a suspension of 6-azabicyclo[3.1.1]heptane-3-carbonitrile (1.3 g, 10.6 mmol, 1.0 equiv), 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazine (3.2 g, 11.7 mmol, 1.1 equiv) and DIEA (4.13 g, 31.9 mmol, 3.0 equiv) in DMF (13 mL), the reaction was stirred for 3 h at 85°C. LCMS showed the reaction was finished. The reaction was poured into 50 mL water. The solution was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography, eluted with PE:EA=1:1 to afford 6-(7-bromo-5-cyclopropylpyrrolo[1,2-f][1,2,4]triazin-4-yl)-6-aza-bicyclo[3.1.1]heptane-3-carbonitrile (2.3 g, 60% yield) as a yellow solid.

[0341] 6-(7-bromo-5-cyclopropylpyrrolo[1,2-f][1,2,4]triazin-4-yl)-6-aza-bicyclo[3.1.1]heptane-3-carboxylic acid. Into a 50 mL 3-necked round bottom flask was placed a suspension of 6-(7-bromo-5-cyclopropylpyrrolo[1,2-f][1,2,4]triazin-4-yl)-6-aza-bicyclo[3.1.1]heptane-3-carbonitrile (2.3 g, 3.07 mmol, 1.0 equiv) and KOH (0.7 g, 12.3 mmol, 4.0 equiv) in EtOH (11.5 mL) /H_2O (11.5 mL), the reaction was stirred for 16 h at 100°C. LCMS showed the reaction was finished. After cooling to room temperature. The reaction was poured into 30 mL water, adjusted pH=1 by HCl, the solution was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 6-(7-bromo-5-cyclopropylpyrrolo[1,2-f][1,2,4]triazin-4-yl)-6-aza-bicyclo[3.1.1]heptane-3-carboxylic acid (1.7 g, 70% yield) as a yellow solid.

[0342] Tert-butyl 6-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-6-azabicyclo[3.1.1]heptane-3-carboxylate. Into an 8 mL vial was placed a suspension of 6-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-6-azabicyclo[3.1.1]heptane-3-carboxylic

acid (200.0 mg, 0.530 mmol, 1.0 equiv) in tert-Butanol (4 mL), then, DMAP (0.10 g, 0.795 mmol, 1.5 equiv) and di-tert-butyl dicarbonate (174.0 mg, 0.795 mmol, 1.5 equiv) were added, the reaction was stirred for 2 h at 25°C. LCMS showed the reaction was finished. The reaction was purified by reverse phase flash with the following conditions (Column: Regular C18, 20*40um, 330 g, Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 100 mL/min; Gradient: 60% B to 100% B in 20 min; Wave Length: 254 nm/210 nm; RT(min):15) to afford tert-butyl 6-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-6-azabicyclo[3.1.1]heptane-3-carboxylate (180 mg, 78% yield) as a yellow oil.

[0343] Tert-butyl 6-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-azabicyclo[3.1.1] heptane-3-carboxylate. Into an 8 mL vial was placed a suspension of tert-butyl 6-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-6-azabicyclo[3.1.1]heptane-3-carboxylate (180.0 mg, 0.415 mmol, 1.0 equiv) and 2-(trimethylstannyl)pyridine-4-carbonitrile (166.0 mg, 0.622 mmol, 1.5 equiv) in 1,4-dioxane (1.8 mL), the mixture was purged with N_2 for 2 min, then, $Pd(PPh_3)_4$ (48.0 mg, 0.042 mmol, 0.1 equiv) was added, the mixture was purged with N_2 for 2 min, the reaction was stirred for 16 h at 110°C. LCMS showed the reaction was finished. After cooling to room temperature. The reaction was purified by reverse phase flash with the following conditions (Column: Regular C18, 20*40 um, 330 g, Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 100 mL/min; Gradient: 75% B to 100% B in 30 min; Wave Length: 254/210 nm; RT (min): 23) to afford tert-butyl 6-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-azabicyclo[3.1.1] heptane-3-carboxylate (40.0 mg, 21% yield, 99.1% purity) as a yellow solid.

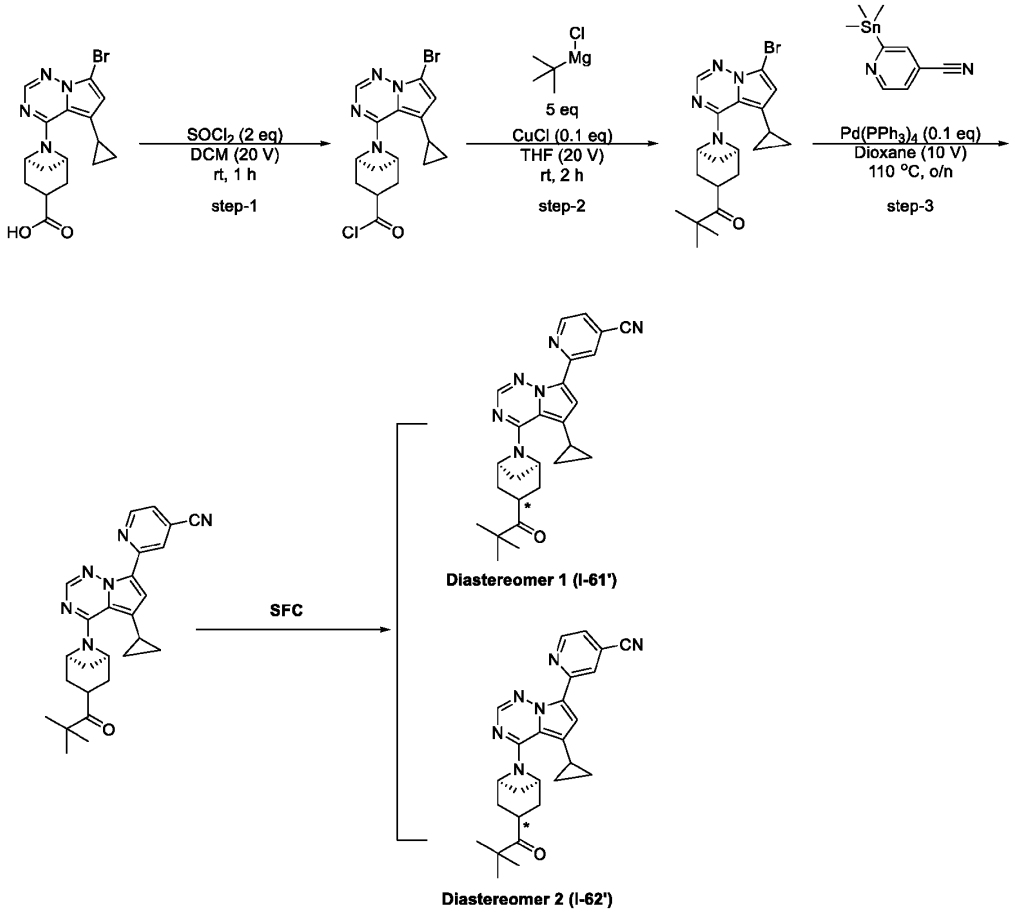
[0344] Tert-butyl (1R,3*,5S)-6-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-azabicyclo [3.1.1]heptane-3-carboxylate (Diastereomer 1 (I-59')). Tert-butyl 6-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-azabicyclo [3.1.1] heptane-3-carboxylate (40.0 mg) was purified by Prep-Chiral-HPLC with following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm; RT1 (min): 8.706; Sample Solvent: EtOH--HPLC; Injection Volume: 2 mL; Number Of Runs: 2) and lyophilization to afford tert-butyl (1R,3*,5S)-6-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-azabicyclo [3.1.1]heptane-3-carboxylate (**Diastereomer 1 (I-59')**, 18.9 mg, 47% yield) as an off-white solid. LC-MS: (ES,

m/z) 457.25 $[M+H]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 8.93 (s, 1H), 8.86 (d, *J* = 4.9 Hz, 1H), 8.06 (s, 1H), 7.74 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.16 (s, 1H), 5.02 (s, 1H), 4.12 (dd, *J* = 10.4, 3.8 Hz, 1H), 3.44 (d, *J* = 10.5 Hz, 1H), 2.87 (s, 1H), 2.72 – 2.65 (m, 1H), 2.16 (t, *J* = 11.4 Hz, 1H), 2.08 (hept, *J* = 5.1 Hz, 1H), 2.01 (dt, *J* = 12.7, 4.3 Hz, 1H), 1.72 – 1.60 (m, 2H), 1.43 (s, 9H), 1.08 – 0.92 (m, 3H), 0.71 (dd, *J* = 9.4, 5.3 Hz, 1H).

[0345] Tert-butyl (1R,3*,5S)-6-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-azabicyclo [3.1.1]heptane-3-carboxylate (Diastereomer 2 (I-60')). Tert-butyl 6-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-azabicyclo [3.1.1] heptane-3-carboxylate (40.0 mg, 0.088 mmol, 1.0 equiv) purified by Prep-Chiral-HPLC with following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm; RT2 (min): 13.677; Sample Solvent: EtOH--HPLC; Injection Volume: 2 mL; Number Of Runs: 2) and lyophilization to afford tert-butyl (1R,3*,5S)-6-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-azabicyclo[3.1.1]heptane-3-carboxylate (**Diastereomer 2 (I-60')**, 17.2 mg, 43% yield, 99.5% purity) as an off-white solid. LC-MS: (ES, *m/z*) 457.25 $[M+H]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 8.93 (d, *J* = 1.4 Hz, 1H), 8.86 (d, *J* = 5.0 Hz, 1H), 8.06 (s, 1H), 7.74 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.16 (s, 1H), 5.02 (s, 1H), 4.12 (dd, *J* = 10.5, 3.8 Hz, 1H), 3.44 (d, *J* = 10.5 Hz, 1H), 2.87 (d, *J* = 3.4 Hz, 1H), 2.69 (dd, *J* = 9.0, 5.0 Hz, 1H), 2.16 (t, *J* = 11.4 Hz, 1H), 2.08 (hept, *J* = 5.1 Hz, 1H), 2.01 (dt, *J* = 12.7, 4.3 Hz, 1H), 1.73 – 1.60 (m, 2H), 1.43 (s, 9H), 1.10 – 0.92 (m, 3H), 0.70 (p, *J* = 5.9, 5.3 Hz, 1H).

Example 1.27. Synthesis of 2-{5-cyclopropyl-4-[(1R,3R,5S)-3-(2,2-dimethylpropanoyl)-6-azabicyclo[3.1.1]heptan-6-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile and 2-{5-cyclopropyl-4-[(1R,3S,5S)-3-(2,2-dimethylpropanoyl)-6-azabicyclo[3.1.1]heptan-6-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile

*** = stereochemistry unknown**



[0346] 6-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-6-azabicyclo[3.1.1] heptane-3-carbonyl chloride. Into a 40 mL vial was placed a solution of 6-(7-bromo-5-cyclopropylpyrrolo[1,2-f][1,2,4]triazin-4-yl)-6-aza-bicyclo[3.1.1]heptane-3-carboxylic acid (400.0 mg, 1.06 mmol, 1.0 equiv) in DCM (8 mL), then, thionyl chloride (252.0 mg, 2.12 mmol, 2.0 equiv) was added, the mixture was stirred for 1 h at room temperature. LCMS showed the reaction was finished. The resulting mixture was concentrated under reduced pressure to afford 6-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-6-azabicyclo[3.1.1] heptane-3-carbonyl chloride (410.0 mg, crude) as a yellow solid.

[0347] 1-(6-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-6-azabicyclo[3.1.1]heptan-3-yl)-2,2-dimethylpropan-1-one. Into a 50 mL 3-necked round-bottom flask was placed a solution of 6-{7-bromo-5-cyclopropyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-6-azabicyclo[3.1.1]heptane-3-carbonyl chloride (410.0 mg, 1.04 mmol, 1.0 equiv) in THF (8.2 mL).

Then, CuCl (10.3 mg, 0.104 mmol, 0.1 equiv) was added and stirred for 10 min, after that, tert-butyl(chloro)magnesium (5.2 mL, 5.18 mmol, 5.0 equiv) was added and stirred 2 h. LCMS showed the reaction was finished. The mixture was poured into water (20 mL), extracted with EA (20 mL x 2). The combined organic layers were washed with water (15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to afford crude product 1-(6-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-6-azabicyclo[3.1.1]heptan-3-yl)-2,2-dimethylpropan-1-one (300.0 mg, 69.0% yield) as a yellow oil.

[0348] 2-{5-cyclopropyl-4-[3-(2,2-dimethylpropanoyl)-6-azabicyclo[3.1.1]heptan-6-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile. Into an 8 mL vial was placed a suspension of 1-(6-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-6-azabicyclo[3.1.1]heptan-3-yl)-2,2-dimethylpropan-1-one (300.0 mg, 0.719 mmol, 1.0 equiv) and 2-(trimethylstannyl)pyridine-4-carbonitrile (288.0 mg, 1.08 mmol, 1.5 equiv) in 1,4-dioxane (3 mL), the mixture was purged with N_2 for 2 min, $Pd(PPh_3)_4$ (83.1 mg, 0.072 mmol, 0.1 equiv) was added, the mixture was purged with N_2 for 2 min, the reaction was stirred for 16 h at 110 °C. LCMS showed the reaction was finished. The mixture was cooled down to room temperature. The reaction was purified by reverse phase flash with the following conditions (Column: Regular C18, 20*40 um, 330 g, Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 100 mL/min; Gradient: 75% B to 100% B in 30 min; Wave Length: 254 nm/210 nm; RT(min):23) to afford 2-{5-cyclopropyl-4-[3-(2,2-dimethylpropanoyl)-6-azabicyclo[3.1.1]heptan-6-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (40 mg, 12.6% yield) as a yellow solid.

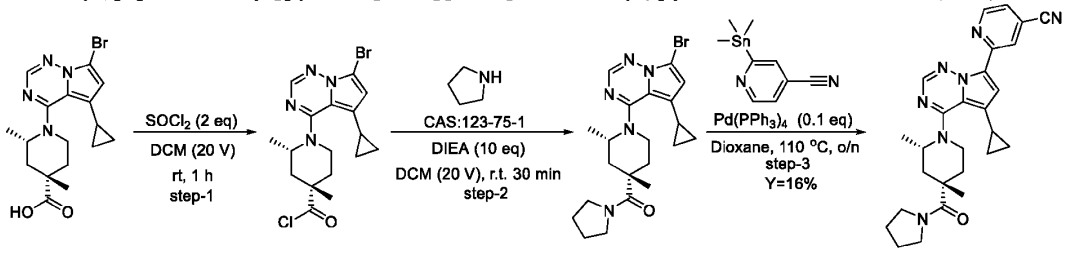
[0349] 2-{5-cyclopropyl-4-[(1R,3*,5S)-3-(2,2-dimethylpropanoyl)-6-azabicyclo[3.1.1]heptan-6-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (Diastereomer 1 (I-61')). 2-{5-cyclopropyl-4-[3-(2,2-dimethylpropanoyl)-6-azabicyclo[3.1.1]heptan-6-yl]pyrrolo[2,1-f][1,2,4] triazin-7-yl}pyridine-4-carbonitrile (40.0 mg, 0.091 mmol, 1.0 equiv) purified by Prep-Chiral-HPLC with following conditions (Column: CHIRAL ART Cellulose-SZ, 2.0*25 cm, 5 um; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 6) and lyophilization to afford 2-{5-cyclopropyl-4-[(1R,3*,5S)-3-(2,2-dimethylpropanoyl)-6-azabicyclo[3.1.1]heptan-6-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile

(**Diastereomer 1 (I-61')**, 16.3 mg, 40.8% yield, 99.6% purity) as an off-white solid. LC-MS: (ES, *m/z*): 441.25 $[M+H]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 8.92 (t, *J* = 1.2 Hz, 1H), 8.86 (dd, *J* = 5.0, 1.0 Hz, 1H), 8.05 (s, 1H), 7.73 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.16 (s, 1H), 4.95 (s, 1H), 4.10 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.54 (d, *J* = 9.9 Hz, 1H), 3.32 – 3.29 (m, 1H), 2.64 (s, 1H), 2.17 (t, *J* = 10.7 Hz, 1H), 2.07 (td, *J* = 8.4, 4.4 Hz, 1H), 1.88 (d, *J* = 9.9 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.68 (d, *J* = 10.0 Hz, 1H), 1.11 (s, 9H), 1.07 – 0.96 (m, 2H), 0.93 (dt, *J* = 9.8, 4.8 Hz, 1H), 0.69 (h, *J* = 5.1 Hz, 1H).

[0350] 2-{5-cyclopropyl-4-[(1R,3*,5S)-3-(2,2-dimethylpropanoyl)-6-azabicyclo[3.1.1]heptan-6-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (Diastereomer 2 (I-62')). 2-{5-cyclopropyl-4-[3-(2,2-dimethylpropanoyl)-6-azabicyclo[3.1.1]heptan-6-yl]pyrrolo[2,1-f][1,2,4] triazin-7-yl}pyridine-4-carbonitrile (40.0 mg, 0.091 mmol, 1.0 equiv) purified by Prep-Chiral-HPLC with following conditions (Column: CHIRAL ART Cellulose-SZ, 2.0*25 cm, 5 um; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 6) and lyophilization to afford 2-{5-cyclopropyl-4-[(1R,3*,5S)-3-(2,2-dimethylpropanoyl)-6-azabicyclo[3.1.1]heptan-6-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile

(**Diastereomer 2 (I-62')**, 17.4 mg, 43.5% yield, 99.7% purity) as an off-white solid. LC-MS: (ES, *m/z*): 441.25 $[M+H]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 8.92 (d, *J* = 1.4 Hz, 1H), 8.86 (dd, *J* = 5.0, 1.0 Hz, 1H), 8.05 (s, 1H), 7.73 (dd, *J* = 5.0, 1.6 Hz, 1H), 7.16 (s, 1H), 4.95 (s, 1H), 4.10 (dd, *J* = 10.1, 3.5 Hz, 1H), 3.53 (d, *J* = 10.3 Hz, 1H), 3.32 – 3.29 (m, 1H), 2.64 (s, 1H), 2.17 (t, *J* = 10.7 Hz, 1H), 2.07 (d, *J* = 8.1 Hz, 1H), 1.88 (d, *J* = 10.0 Hz, 1H), 1.80 (d, *J* = 7.3 Hz, 1H), 1.68 (d, *J* = 10.0 Hz, 1H), 1.11 (s, 9H), 1.07 – 0.96 (m, 2H), 0.92 (q, *J* = 4.8 Hz, 1H), 0.74 – 0.65 (m, 1H).

Example 1.28. Synthesis of 2-{5-cyclopropyl-4-[(2S,4S)-2,4-dimethyl-4-(pyrrolidine-1-carbonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile (I-63)



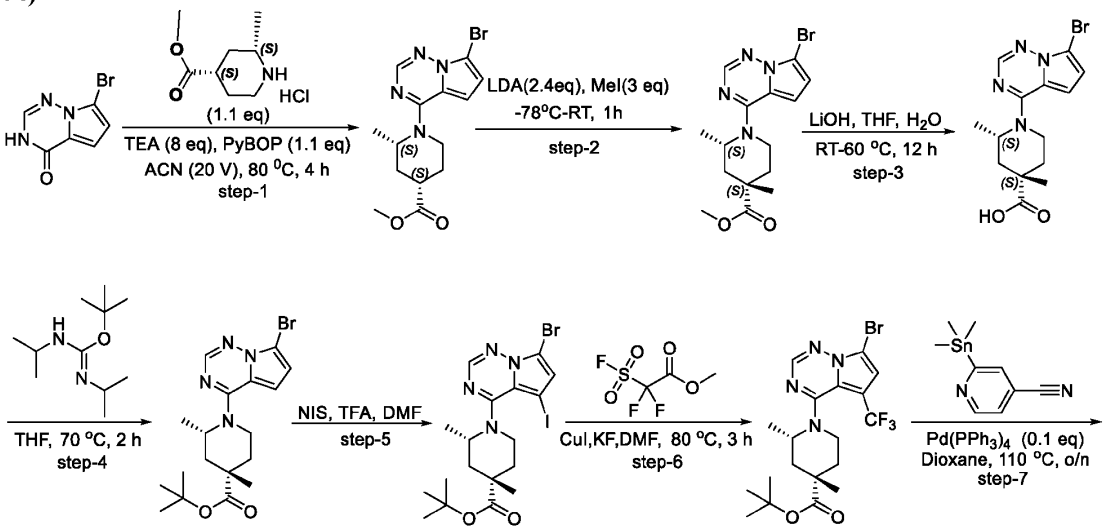
[0351] (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carbonyl chloride. Into an 8 mL vail was placed a solution of (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid (100.0 mg, 0.254 mmol, 1.0 equiv) and thionyl chloride (60.5 mg, 0.508 mmol, 2.0 equiv) in DCM (2.0 mL). The solution was stirred at room temperature for 1 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. This resulted in (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carbonyl chloride (110 mg, crude) as a white solid.

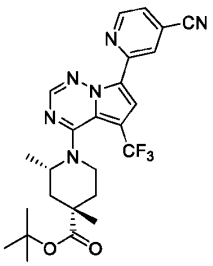
[0352] (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo [2,1-f][1,2,4]triazin-4-yl}-2,4-dimethyl-4-(pyrrolidine-1-carbonyl)piperidine. Into an 8 mL vail was placed a solution of pyrrolidine (34.5 mg, 0.486 mmol, 2.0 equiv) in DCM (2.0 mL). Then, DIEA (313.9 mg, 2.430 mmol, 10.0 equiv) was added at room temperature for 5 min under nitrogen atmosphere, this was followed by the addition of (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carbonyl chloride (100.0 mg, 0.243 mmol, 1.0 equiv) dropwise at room temperature. The resulting mixture was stirred at room temperature for 30 min. The resulting mixture was extracted with CH_2Cl_2 (3 x 2 mL). dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo [2,1-f][1,2,4]triazin-4-yl}-2,4-dimethyl-4-(pyrrolidine-1-carbonyl)piperidine (60 mg, crude) as a white solid.

[0353] 2-{5-cyclopropyl-4-[(2S,4S)-2,4-dimethyl-4-(pyrrolidine-1-carbonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-carbonitrile. Into an 8 ml vail was placed a solution of (2S,4S)-1-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4] triazin-4-yl}-2,4-dimethyl-4-(pyrrolidine-1-carbonyl)piperidine (100.0 mg, 0.224 mmol, 1.0 equiv) and 2-(trimethylstannyl)pyridine-4-carbonitrile (179.4 mg, 0.672 mmol, 3.0 equiv) in 1,4-dioxane (1.0 mL). Then, $Pd(PPh_3)_4$ (25.9 mg, 0.022 mmol, 0.1 equiv) was added at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 110 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. Column: Xselect CSH C18 OBD Column 30*150 mm 5 μ mn; Mobile Phase A: Water (10 mmol/L NH_4HCO+0.05%NH_3 H_2O), Mobile Phase B: ACN; Flow rate: 60mL/min; Gradient: 49% B to 79% B in 10 min; Wave Length: 254nm/220nm; RT1(min): 8.02. This resulted in 2-{5-cyclopropyl-4-[(2S,4S)-2,4-dimethyl-4-(pyrrolidine-1-carbonyl)piperidin-1-yl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyridine-4-

carbonitrile (17.1 mg, 16% yield) as a yellow solid. LC-MS: (ES, *m/z*) 470.30 $[M+H]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 8.89 (dt, *J* = 1.6, 0.7 Hz, 1H), 8.86 (dd, *J* = 4.9, 1.0 Hz, 1H), 8.15 (s, 1H), 7.74 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.11 (s, 1H), 4.76 – 4.66 (m, 1H), 3.95 (d, *J* = 13.8 Hz, 1H), 3.68 (t, *J* = 12.6 Hz, 2H), 3.61-3.50 (m, 1H), 3.41-3.31 (m, 3H), 2.46 – 2.28 (m, 2H), 2.12 – 2.02 (m, 1H), 1.98 – 1.60 (m, 4H), 1.41 – 1.26 (m, 1H), 1.18 (s, 3H), 1.10 (dd, *J* = 19.1, 7.1 Hz, 3H), 1.08-1.01 (m, 2H), 0.94 – 0.84 (m, 1H), 0.80 – 0.75 (m, 1H).

Example 1.29. Synthesis of tert-butyl (2*S*,4*S*)-1-[7-(4-cyanopyridin-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,4-dimethylpiperidine-4-carboxylate (I-64)





[0354] Methyl (2*S*,4*S*)-1-{7-bromopyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate. Into a 100 mL 3-necked round bottom flask was placed a solution of 7-bromo-3H-pyrrolo[2,1-f] [1,2,4] triazin-4-one (2.0 g, 9.345 mmol, 1.0 equiv), methyl (2*S*,4*S*)-2-methylpiperidine-4-carboxylate hydrochloride (1.99 g, 10.280 mmol, 1.1 equiv) and

benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (5.35 g, 10.280 mmol, 1.1 equiv) in MeCN (40 mL) at room temperature under nitrogen atmosphere. Then, Et_3N (7.57 g, 74.760 mmol, 8.0 equiv) was added. The reaction was heated to 80°C and stirred for 4 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The reaction was added water (100 mL) and extracted with EA (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford the residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford methyl (2*S*,4*S*)-1-{7-bromopyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2-methylpiperidine-4-carboxylate (1.9 g, 57.6% yield) as a brown solid.

[0355] Methyl (2*S*,4*S*)-1-{7-bromopyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate. Into a 100 mL 3-necked round bottom flask was placed a solution of methyl (2*S*,4*S*)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-methylpiperidine-4-carboxylate (1.9 g, 5.379 mmol, 1.0 equiv) in THF (60 mL) at room temperature under nitrogen atmosphere. The reaction was cooled to -78°C. Then, LDA (2.0M in THF) (1.38 g, 12.910 mmol, 2.4 equiv) was added and stirred for 30 min at -78°C. After that, CH_3I (2.29 g, 16.134 mmol, 3.0 equiv) was added to the mixture. The reaction was warmed to 25°C and stirred for 1 h. LCMS showed the reaction was finished. The reaction was quenched with water (100 mL) and extracted with EA (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford the crude product methyl (2*S*,4*S*)-1-{7-bromopyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (1.2 g, 60.7% yield) as a brown solid. The crude product was used in next step without further purification.

[0356] (2*S*,4*S*)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid. Into a 50 mL 3-necked round-bottom flask was placed a solution of methyl (2*S*,4*S*)-1-{7-bromopyrrolo [2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (1.2 g, 3.268 mmol, 1.0 equiv) in THF (12 mL) and water (12 mL) at room temperature under nitrogen atmosphere. Then, LiOH (234.8 mg, 9.803 mmol, 3.0 equiv) was added to the mixture. The reaction was heated to 60°C and stirred for 12 h. LCMS showed the reaction was finished. The reaction was added water (30 mL) and extracted with EA (2 x 10 mL). The water phase was acidified to pH = 1 with aqueous HCl (1 mol/L). The mixture was extracted with EA (2 x 20 mL).

The combined organic layers were washed with water (15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product (2*S*,4*S*)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid (1.4 g, crude). The crude product was used into next step directly without further purification.

[0357] Tert-butyl (2*S*,4*S*)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate. Into a 50 mL 3-necked round-bottom flask was placed a solution of (2*S*,4*S*)-1-{7-bromopyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylic acid (1.4 g, 3.964 mmol, 1.0 equiv) in THF (28 mL) at room temperature under nitrogen atmosphere. Then, (*E*)-(tert-butoxy)-*N*',*N*-bis(propan-2-yl)methanimid-amide (4.76 g, 23.784 mmol, 6.0 equiv) was added to the mixture. The reaction was heated to 70°C and stirred for 2 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature and filtrated. The filtrate was added with water (60 mL), extracted with EA (3 x 20 mL). The combined organic layers were washed with water (15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA (10 :1) to afford tert-butyl (2*S*,4*S*)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (1.4 g, 86.3% yield) as an off-white solid.

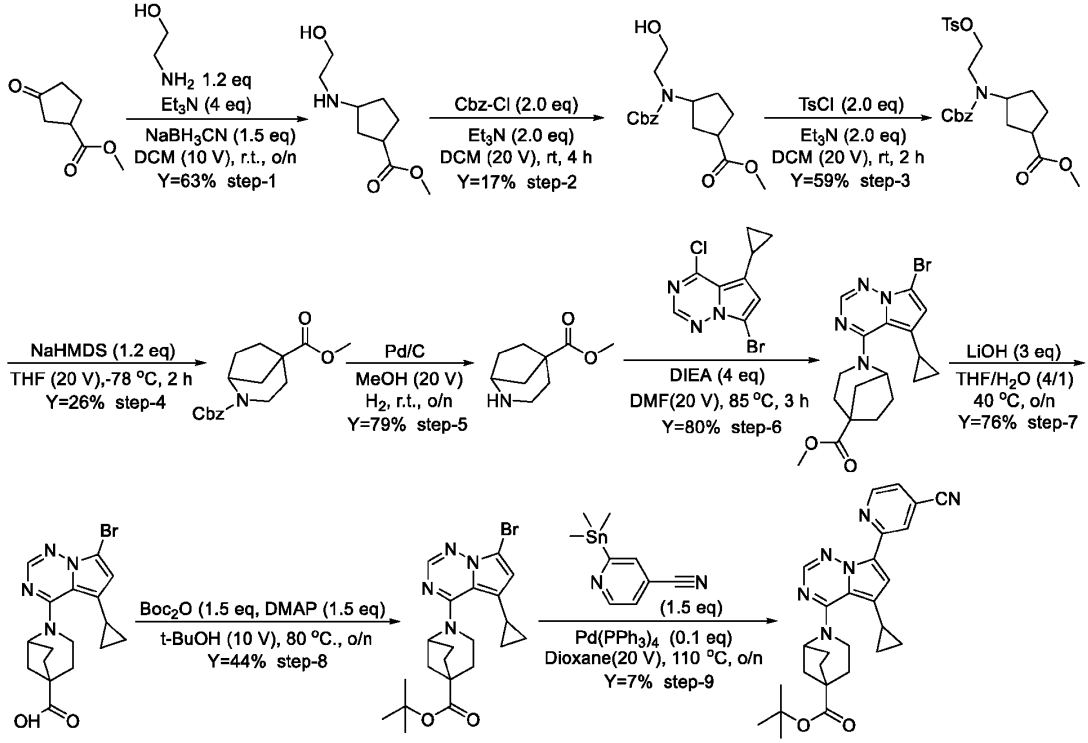
[0358] Tert-butyl (2*S*,4*S*)-1-{7-bromo-5-iodopyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate. Into a 50 mL 3-necked round-bottom flask was placed a solution of tert-butyl (2*S*,4*S*)-1-{7-bromopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (740.0 mg, 1.808 mmol, 1.0 equiv), trifluoroacetic acid (20.6 mg, 0.181 mmol, 0.1 equiv) and 1-iodopyrrolidine-2,5-dione (427.1 mg, 1.898 mmol, 1.05 equiv) in DMF (14.8 mL). The solution was stirred at room temperature for 12 h. LCMS showed reaction was completed. The reaction was quenched with addition of aqueous $NaHCO_3$ (20 mL), the mixture was added water (40 mL) and extracted with EA (2 x 40 mL). The combined organic layers were washed with water (3 x 100 mL), brine (100 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to afford tert-butyl (2*S*,4*S*)-1-{7-bromo-5-iodopyrrolo[2,1-f] [1,2,4] triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (950 mg, crude) as a yellow oil. The product was used in the next step directly without further purification.

[0359] Tert-butyl (2*S*,4*S*)-1-[7-bromo-5-(trifluoromethyl) pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,4-dimethylpiperidine-4-carboxylate. Into a 25 mL 3-necked round-bottom flask was placed a solution of tert-butyl (2*S*,4*S*)-1-{7-bromo-5-iodopyrrolo[2,1-f][1,2,4]triazin-4-yl}-2,4-dimethylpiperidine-4-carboxylate (300.0 mg, 0.561 mmol, 1.0 equiv), methyl 2,2-difluoro-2-(fluorosulfonyl) acetate (538.4 mg, 2.805 mmol, 5.0 equiv) in DMF (6 mL). The solution was allowed to stir at room temperature. The mixture was degassed by a cycle of nitrogen and vacuum for 3 times. Then, CuI (106.7 mg, 0.561 mmol, 1.0 equiv) and KF (97.7 mg, 1.683 mmol, 3.0 equiv) were added into the flask at room temperature. The mixture was degassed by a cycle of nitrogen and vacuum for 3 times. The resulting mixture was heated to 80°C. The mixture was stirred at 80°C for 3 h. LCMS showed the reaction was completed. The mixture was cooled to room temperature. The mixture was filtered. The filtrate was added water (20 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with water (3 x 50 mL), brine (50 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford tert-butyl (2*S*,4*S*)-1-[7-bromo-5-(trifluoromethyl) pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,4-dimethylpiperidine-4-carboxylate (400 mg, crude) as a yellow oil. The product was used in the next step directly without further purification.

[0360] Tert-butyl (2*S*,4*S*)-1-[7-(4-cyanopyridin-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,4-dimethylpiperidine-4-carboxylate. Into a 20 mL vial was placed a solution of tert-butyl (2*S*,4*S*)-1-[7-bromo-5-(trifluoromethyl) pyrrolo[2,1-f] [1,2,4]triazin-4-yl]-2,4-dimethylpiperidine-4-carboxylate (400.0 mg, 0.838 mmol, 1.0 equiv), 2-(trimethyl-stannyl)pyridine-4-carbonitrile (671.0 mg, 2.514 mmol, 3.0 equiv) in 1,4-dioxane (8 mL). The solution was allowed to stir at room temperature. The mixture was degassed by a cycle of nitrogen and vacuum for 3 times. Then, $Pd(PPh_3)_4$ (96.8 mg, 0.084 mmol, 0.1 equiv) was added into the flask at room temperature. The mixture was degassed by a cycle of nitrogen and vacuum for 3 times. The resulting mixture was heated to 110 °C. The mixture was stirred at 110 °C for 24 h. LCMS showed the reaction was completed. The mixture was cooled to room temperature. The mixture was filtered. The filtrate was added water (20 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with water (3 x 50 mL), brine (50 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford tert-butyl (2*S*,4*S*)-1-[7-(4-cyanopyridin-2-yl)-5-(trifluoromethyl) pyrrolo[2,1-f] [1,2,4]triazin-4-yl]-2,4-dimethylpiperidine-4-carboxylate. The product was purified by Flash-

Prep-HPLC with the following conditions Column: XBridge Shield RP18 OBD Column30*150 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 67% B to 97% B in 12 min; Wave Length: 254nm/220nm; RT1(min): 9.67, Detector, UV 210 nm to tert-butyl (2*S*,4*S*)-1-[7-(4-cyanopyridin-2-yl)-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,4-dimethylpiperidine-4-carboxylate (71.9 mg, 99.2%) as a white solid. LC-MS: (ES, m/z) 501.25, $[M+1]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 8.93 (dd, J = 5.0, 1.0 Hz, 1H), 8.87 (t, J = 1.2 Hz, 1H), 8.41 (s, 1H), 7.86 (dd, J = 5.0, 1.5 Hz, 1H), 7.80 (s, 1H), 4.75 (bs, 1H), 3.75 (d, J = 13.7 Hz, 1H), 3.54 (t, J = 12.4 Hz, 1H), 2.23 – 2.01 (m, 2H), 1.77 (dd, J = 13.8, 5.3 Hz, 1H), 1.45 (s, 9H), 1.33 (td, J = 12.8, 4.2 Hz, 1H), 1.24 – 1.01 (m, 6H).

Example 1.30. Synthesis of Tert-butyl 2-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-azabicyclo [3.2.1]octane-5-carboxylate (I-65)



[0361] Methyl 3-[(2-hydroxyethyl)amino]cyclopentane-1-carboxylate. Into 500 mL 3-neck round bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of methyl 3-oxocyclopentane-1-carboxylate (14.5 g, 102.002 mmol, 1.0 equiv) in DCM (145 mL). Then, ethanolamine (7.5 g, 153.003 mmol, 1.2 equiv), Et$_3$N (41.3 g, 408.008 mmol, 4.0 equiv) and sodium cyanoboranuide (9.6 g, 153.003 mmol, 1.5 equiv) were added to the mixture.

The mixture was stirred overnight at room temperature. The mixture was extracted with EtOAc (150 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in methyl 3-[(2-hydroxyethyl)amino]cyclopentane-1-carboxylate (12.0 g, 63% yield) as an orange oil.

[0362] Methyl 3-{[(benzyloxy)carbonyl](2-hydroxyethyl)amino}cyclopentane-1-carboxylate. Into 500 mL 3-neck round bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of methyl 3-[(2-hydroxyethyl)amino]cyclopentane-1-carboxylate (12.0 g, 64.089 mmol, 1.0 equiv) in DCM (240 mL). Then, benzyl chloroformate (21.9 g, 128.178 mmol, 2.0 equiv) and Et_3N (12.9 g, 128.178 mmol, 2.0 equiv) were added to the mixture. The mixture was stirred for 4 h at room temperature. The mixture was concentrated. The reaction mixture was purified by reverse phase flash with the following conditions (A: 0.1% NH_4HCO_3 in water, B: ACN; 25% B-70% B, 30 min). This resulted in methyl 3-{[(benzyloxy)carbonyl](2-hydroxyethyl)amino}cyclopentane-1-carboxylate (3.6 g, 17% yield) as an orange oil.

[0363] Methyl 3-{[(benzyloxy)carbonyl]({2-[(4-methylbenzenesulfonyl)oxy]ethyl})amino}cyclopentane-1-carboxylate. Into 250 mL 3-neck round bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of methyl 3-{[(benzyloxy)carbonyl](2-hydroxyethyl)amino}cyclopentane-1-carboxylate (3.6 g, 11.202 mmol, 1.0 equiv) in DCM (72 mL). Then, 4-Methylbenzenesulfonyl chloride (4.3 g, 22.404 mmol, 2.0 equiv) and Et_3N (2.3 g, 22.404 mmol, 2.0 equiv) were added to the mixture. The mixture was stirred for 2 h at room temperature. The reaction was quenched with H_2O (5 mL). The resulting mixture was concentrated under reduced pressure. The reaction mixture was purified by reverse phase flash with the following conditions (A: 0.1% NH_4HCO_3 in water, B: ACN; 50% B-100% B, 40 min). This resulted in methyl 3-{[(benzyloxy)carbonyl]({2-[(4-methylbenzenesulfonyl)oxy]ethyl})amino}cyclopentane-1-carboxylate (3.15 g, 59% yield) as a yellow oil.

[0364] 2-benzyl 5-methyl 2-azabicyclo[3.2.1] octane-2,5-dicarboxylate. Into 100 mL 3-neck round bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of methyl 3-{[(benzyloxy)carbonyl]({2-[(4-methylbenzenesulfonyl)oxy]ethyl})amino} cyclopentane -1-carboxylate (3.15 g, 6.624 mmol, 1.0 equiv) in THF (60 mL). Then, NaHMDS (3.97 mL, 21.649 mmol, 1.2 equiv) was added slowly to the mixture at -78°C. The mixture was

stirred for 2 h at -78°C. After the mixture completed, the mixture was warmed up to room temperature. The reaction was quenched with H_2O (3 mL). The reaction mixture was purified by reverse phase flash with the following conditions (A: 0.1% NH_4HCO_3 in water, B: ACN; 25% B-50% B, 30 min). This resulted in 2-benzyl 5-methyl 2-azabicyclo[3.2.1] octane-2,5-dicarboxylate (525 mg, 26% yield) as a yellow oil.

[0365] Methyl 2-azabicyclo[3.2.1] octane-5-carboxylate. Into a 40 mL vial purged and maintained with an inert atmosphere of H_2 was placed a solution of 2-benzyl 5-methyl 2-azabicyclo[3.2.1]octane-2,5-dicarboxylate (525.0 mg, 1.731 mmol, 1.0 equiv) in methanol (10.5 mL). Then, Pd/C (525.0 mg, 100%wt) was added to the mixture. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was filtered and concentrated under reduced pressure. The resulting mixture was concentrated under reduced pressure. This resulted in methyl 2-azabicyclo[3.2.1] octane-5-carboxylate (230 mg, 79% yield) as a colorless oil.

[0366] Methyl 2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo[3.2.1]octane-5-carboxylate. Into a 40 mL vial purged and maintained with an inert atmosphere of nitrogen was placed a solution of 7-bromo-4-chloro-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazine (336.7 mg, 1.235 mmol, 1.0 equiv) in DMF (6.8 mL). Then, methyl 2-azabicyclo[3.2.1]octane-5-carboxylate (230.0 mg, 1.359 mmol, 1.1 equiv), DIEA (638.8 mg, 4.942 mmol, 4.0 equiv) were added to the mixture, the mixture was stirred for 3 h at 85 °C. The reaction was cooled to room temperature. The reaction mixture was purified by reverse phase flash with the following conditions (A: 0.1% NH_4HCO_3 in water, B:ACN; 40% B-90% B, 30 min). This resulted in methyl 2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo[3.2.1]octane-5-carboxylate (400 mg, 80% yield) as an brick red oil.

[0367] 2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo[3.2.1]octane-5-carboxylic acid. Into a 40 mL vail was placed a solution of methyl 2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo[3.2.1]octane-5-carboxylate (400.0 mg, 0.987 mmol, 1.0 equiv) in THF (8 mL) and H_2O (2 mL) at room temperature under nitrogen atmosphere. Then, LiOH (70.9 mg, 2.961 mmol, 3.0 equiv) was added to the mixture. The reaction was heated to 40 °C and stirred overnight. LCMS showed the reaction was finished. The reaction was diluted with water (10 mL). The solution was acidified to pH 1 with 1 mol/L aqueous HCl. The mixture was extracted with EA (2 x 10 mL). The combined organic layers were washed with water (4 x 15 mL), brine (10 mL), dried over with anhydrous Na_2SO_4.

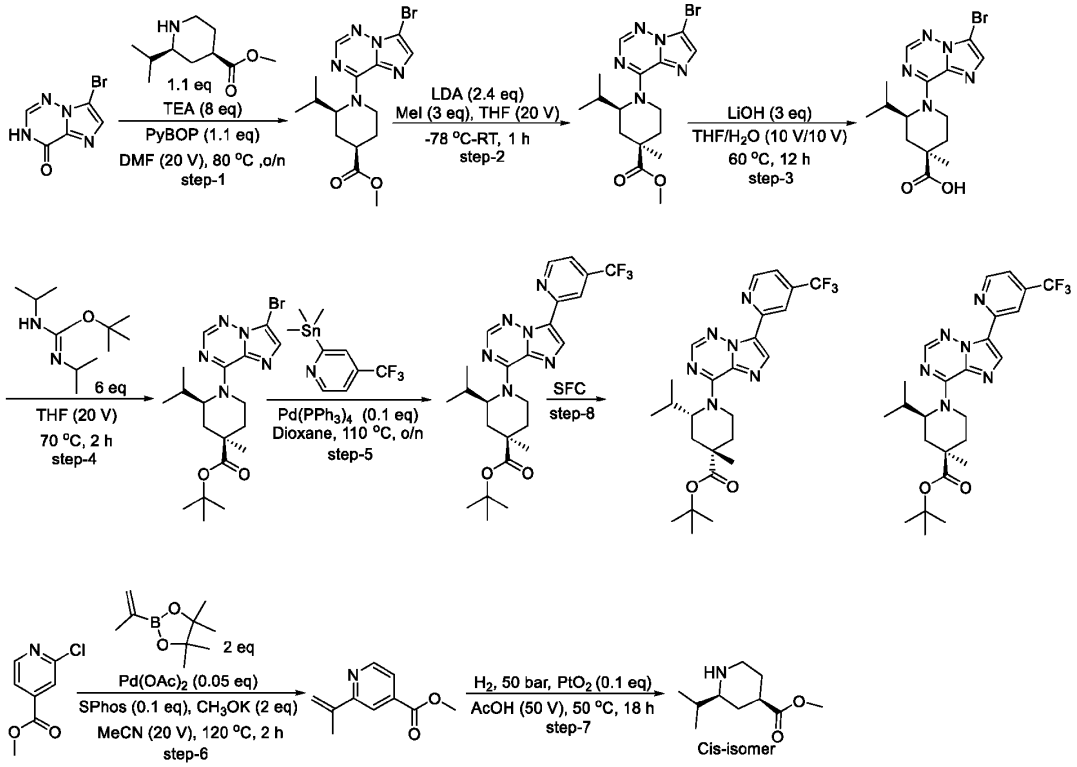
After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product (2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo[3.2.1]octane-5-carboxylic acid (295 mg, 76% yield). The crude product was used into next step directly without further purification.

[0368] Tert-butyl 2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo [3.2.1]octane-5-carboxylate. Into a 20 mL vial purged and maintained with an inert atmosphere of nitrogen was placed a solution of 2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo[3.2.1]octane-5-carboxylic acid (295.0 mg, 0.754 mmol, 1.0 equiv) in tert-Butanol (2.95 mL). Then, di-tert-butyl dicarbonate (246.8 mg, 1.131 mmol, 1.5 equiv), DMAP (138.2 mg, 1.131 mmol, 1.5 equiv) were added to the mixture, the mixture was stirred overnight at 80 °C. The reaction was cooled to room temperature. The reaction mixture was purified by reverse phase flash with the following conditions (A: 0.1% NH_4HCO_3 in water, B: ACN; 50% B-100% B, 40 min). This resulted in tert-butyl 2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo [3.2.1]octane-5-carboxylate (150 mg, 44% yield) as a white solid.

[0369] Tert-butyl 2-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-azabicyclo [3.2.1]octane-5-carboxylate. Into a 20 mL vial purged and maintained with an inert atmosphere of nitrogen was placed a solution of tert-butyl 2-{7-bromo-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl}-2-azabicyclo[3.2.1]octane-5-carboxyl-ate (150.0 mg, 0.335 mmol, 1.0 equiv) in 1,4-dioxane (3 mL). Then, 2-(trimethylstannyl)pyridine-4-carbonitrile (134.2 mg, 0.503 mmol, 1.5 equiv) was added to the mixture. The mixture was bubbled with N_2 for 5 min, $Pd(PPh_3)_4$ (38.75 mg, 0.034 mmol, 0.1 equiv) was added and then bubbled with N_2 for 5 min. The resulting mixture was stirred overnight at 110 °C. The reaction was cooled to room temperature. The reaction mixture was purified by reverse phase flash with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 65%B to 90%B in10.5 min; Wave Length: 254/220 nm; RT1(min): 9.87. This resulted in tert-butyl 2-[7-(4-cyanopyridin-2-yl)-5-cyclopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-azabicyclo [3.2.1]octane-5-carboxylate (10.7 mg, 7% yield) as an off-white solid. LC-MS: (ES, *m/z*) 472.25 $[M+H]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 8.91 – 8.83 (m, 2H), 8.16 (s, 1H), 7.74 (d, J = 5.0 Hz, 1H), 7.11 (s, 1H), 4.97 – 4.87 (m, 1H), 3.99 (d, J = 13.4 Hz, 1H), 3.46 (q, J = 12.6, 10.6 Hz, 1H), 2.21

– 2.09 (m, 1H), 2.05 – 1.88 (m, 3H), 1.90 – 1.68 (m, 5H), 1.42 (s, 9H), 1.09 (q, J = 6.9, 6.4 Hz, 2H), 1.02 – 0.89 (m, 1H), 0.77 – 0.64 (m, 1H).

Example 1.31. Synthesis of tert-butyl (2R,4S)-2-isopropyl-4-methyl-1-{7-[4-(trifluoromethyl) pyridin-2-yl]imidazo[2,1-f][1,2,4]triazin-4-yl}piperidine-4-carboxylate (I-67) and tert-butyl (2S,4R)-2-isopropyl-4-methyl-1-{7-[4-(trifluoromethyl)pyridin-2-yl]imidazo[2,1-f][1,2,4]triazin-4-yl}piperidine-4-carboxylate (I-66)



[0370] Methyl (2S,4R)-1-{7-bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropylpiperidine-4-carboxylate. Into a 40 mL vail was placed a solution of methyl (2S,4R)-2-isopropylpiperidine-4-carboxylate (862.5 mg, 4.655 mmol, 1.1 equiv), 7-bromo-3H-imidazo[2,1-f][1,2,4]triazin-4-one (910.0 mg, 4.232 mmol, 1.0 equiv), benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (2.42 g, 4.655 mmol, 1.1 equiv) and Et_3N (3.42 g, 33.856 mmol, 8.0 equiv) in DMF (18.2 mL). The solution was stirred overnight at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted

with PE/EA (5:1) to afford methyl (2S,4R)-1-{7-bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropylpiperidine-4-carboxylate (1.1 g, 68.0% yield) as an off-white solid.

[0371] Methyl (2S,4R)-1-{7-bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropyl-4-methylpiperidine-4-carboxylate. Into a 40 mL vial was placed a solution of methyl (2S,4R)-1-{7-bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropylpiperidine-4-carboxylate (1.1 g, 2.878 mmol, 1.0 equiv) in THF (22 mL) at room temperature under nitrogen atmosphere. The reaction was cooled to -78°C. Then, LDA (3.45 mL, 6.907 mmol, 2.4 equiv) was added to the mixture and stirred for 30 min. After that, iodomethane (1.23 g, 8.634 mmol, 3.0 equiv) was added to the mixture. The reaction was warmed to room temperature and stirred for 1 h at room temperature. LCMS showed the reaction was finished. The reaction was poured into water (50 mL) and extracted with EA (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford methyl (2S,4R)-1-{7-bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropyl-4-methylpiperidine-4-carboxylate (300 mg, 26.3% yield) as a yellow solid.

[0372] (2S,4R)-1-{7-bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropyl-4-methylpiperidine-4-carboxylic acid. Into a 20 mL vail was placed a solution of methyl (2S,4R)-1-{7-bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropyl-4-methylpiperidine-4-carboxylate (300.0 mg, 0.757 mmol, 1.0 equiv) in THF (3 mL) and H_2O (3 mL) at room temperature under nitrogen atmosphere. Then, LiOH (50.0 mg, 2.271 mmol, 3.0 equiv) was added to the mixture. The reaction was heated to 60°C and stirred for 12 h. LCMS showed the reaction was finished. The reaction was diluted with water (20 mL). The solution was acidified to pH = 1 with 1 mol/L aqueous HCl. The mixture was extracted with EA (2 x 20 mL). The combined organic layers were washed with water (4 x 15 mL), brine (20 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product (2S,4R)-1-{7-bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropyl-4-methylpiperidine-4-carboxylic acid (250 mg, 86.4% yield). The crude product was used into next step directly without further purification.

[0373] Tert-butyl (2S,4R)-1-{7-bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropyl-4-methylpiperidine-4-carboxylate. Into a 20 mL vail was placed a solution of (2S,4R)-1-{7-

bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropyl-4-methylpiperidine-4-carboxylic acid (250.0 mg, 0.654 mmol, 1.0 equiv) and (Z)-N,N'-diisopropyl-tert-butoxymethanimidamide (786.1 mg, 3.924 mmol, 6.0 equiv) in THF (5 mL) at room temperature under nitrogen atmosphere. The reaction was heated to 70°C and stirred for 2 h. LCMS showed the reaction was finished. The mixture was allowed to cool room temperature. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 70% to 95% gradient in 30 min; detector, UV 254 nm. This resulted in tert-butyl (2S,4R)-1-{7-bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropyl-4-methylpiperidine-4-carboxylate (230 mg, 80.2% yield) as an off-white solid.

[0374] Methyl 2-(prop-1-en-2-yl)pyridine-4-carboxylate. Into a 1 L 3-necked round bottom flask was placed a solution of methyl 2-chloropyridine-4-carboxylate (10.0 g, 58.282 mmol, 1.0 equiv), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (19.59 g, 116.564 mmol, 2.0 equiv) and potassium methanolate (8.17 g, 116.564 mmol, 2.0 equiv) in MeCN (200 mL). The mixture was replaced with nitrogen for 3 times. After that, S-Phos (2.39 g, 5.828 mmol, 0.1 equiv) and $Pd(OAc)_2$ (0.65 g, 2.914 mmol, 0.05 equiv) were added to the mixture. The mixture was replaced with nitrogen for 3 times. The reaction was stirred for 2 h at 120°C. LCMS showed the reaction was finished. The mixture was allowed to cool to room temperature. The reaction was added water 200 mL and extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over with anhydrous Na_2SO_4. After filtration, the filtrate was concentrated was concentrated under vacuum to afford crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA (5 :1) to afford methyl 2-(prop-1-en-2-yl)pyridine-4-carboxylate (5 g, 48.4% yield) as an yellow oil.

[0375] Methyl (2S,4R)-2-isopropylpiperidine-4-carboxylate. Into a 500 mL 3-necked round bottom flask was placed a solution of methyl 2-(prop-1-en-2-yl)pyridine-4-carboxylate (5.0 g, 28.216 mmol, 1.0 equiv) in HOAc (250 mL) was added platinum (IV) oxide (0.64 g, 2.822 mmol, 0.1 equiv). The mixture was then hydrogenated in a parr apparatus at 50 bar and 50°C for 18 h. It was then filtered through Celite and concentrated in vacuo. Then, aqueous NaOH (50 mL, 1 mol/L) was added to the mixture, and the mixture was extracted with CH_2Cl_2/MeOH (9:1, 3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by flash column chromatography (0-10%, 1M methanolic ammonia in

CH_2Cl_2) to give methyl (2S,4R)-2-isopropylpiperidine-4-carboxylate (2 g, 38.3% yield) as a colorless oil.

[0376] Tert-butyl (2R,4S)-2-isopropyl-4-methyl-1-{7-[4-(trifluoromethyl)pyridin-2-yl]imidazo [2,1-f][1,2,4]triazin-4-yl}piperidine-4-carboxylate. Into an 8 mL vail was placed a solution of tert-butyl (2S,4R)-1-{7-bromoimidazo[2,1-f][1,2,4]triazin-4-yl}-2-isopropyl-4-methylpiperidine-4-carboxylate (20.0 mg, 0.046 mmol, 1.0 equiv) and 4-(trifluoromethyl)-2-(trimethylstannyl)pyridine (21.2 mg, 0.069 mmol, 1.5 equiv) in 1,4-dioxane (0.4 mL). Then, $Pd(PPh_3)_4$ (5.3 mg, 0.005 mmol, 0.1 equiv) was added to the mixture at room temperature. The mixture was replaced with nitrogen for 1 min. The reaction was heated to 110°C and stirred for 12 h. LCMS showed the reaction was finished. The reaction was cooled to room temperature. The mixture was purified with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 70% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in tert-butyl (2R,4S)-2-isopropyl-4-methyl-1-{7-[4-(trifluoromethyl)pyridin-2-yl]imidazo [2,1-f][1,2,4]triazin-4-yl}piperidine-4-carboxylate (1.4 mg, 6.1% yield, racemic) as a white solid.

[0377] Tert-butyl (2R,4S)-2-isopropyl-4-methyl-1-{7-[4-(trifluoromethyl) pyridin-2-yl]imidazo[2,1-f][1,2,4]triazin-4-yl}piperidine-4-carboxylate (I-67).

[0378] The racemic intermediate was purified by SFC with the following conditions:Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: HEX (0.1%DEA), Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 2; Wave Length: 220/254 nm; RT1(min): 5.8654; Sample Solvent: EtOH; Injection Volume: 1.0 mL; Number Of Runs: 7. This resulted in tert-butyl (2R,4S)-2-isopropyl-4-methyl-1-{7-[4-(trifluoromethyl) pyridin-2-yl]imidazo[2,1-f][1,2,4]triazin-4-yl}piperidine-4-carboxylate (**I-67**, 11.4 mg, 32.6% yield) as a white solid. LC-MS: (ES, *m/z*) 505.35 $[M+H]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 9.01 – 8.85 (m, 2H), 8.41 – 8.29 (m, 2H), 7.80 – 7.72 (m, 1H), 6.26 – 6.09 (m, 1H), 5.07 – 4.95 (m, 1H), 2.98 (t, J = 13.1 Hz, 1H), 2.24 (t, J = 11.9 Hz, 1H), 1.99 (bs, 1H), 1.65 (dd, J = 14.5, 6.1 Hz, 1H), 1.60 – 1.29 (m, 11H), 1.16 – 1.04 (m, 6H), 0.75 (dd, J = 13.9, 6.4 Hz, 3H).

[0379] Tert-butyl (2S,4R)-2-isopropyl-4-methyl-1-{7-[4-(trifluoromethyl) pyridin-2-yl]imidazo[2,1-f][1,2,4]triazin-4-yl}piperidine-4-carboxylate (I-66). The racemic intermediate was purified by SFC with the following conditions:Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: HEX (0.1%DEA), Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min;

Gradient: isocratic 2; Wave Length: 220/254 nm; RT2(min): 7.999; Sample Solvent: EtOH; Injection Volume: 1.0 mL; Number Of Runs: 7. This resulted in tert-butyl (2S,4R)-2-isopropyl-4-methyl-1-{7-[4-(trifluoromethyl)pyridin-2-yl]imidazo[2,1-f][1,2,4]triazin-4-yl}piperidine-4-carboxylate (**I-66**, 14.5 mg, 41.4% yield) as a white solid. LC-MS: (ES, *m/z*) 505.35 $[M+H]^+$; ^{1}H-NMR: (400 MHz, DMSO-d_6, *ppm*) δ 8.96 (d, *J* = 5.0 Hz, 1H), 8.90 (s, 1H), 8.41 – 8.30 (m, 2H), 7.77 (dd, *J* = 5.0, 1.7 Hz, 1H), 6.17 (dd, *J* = 33.8, 11.4 Hz, 1H), 4.99 (dd, *J* = 19.5, 13.0 Hz, 1H), 2.97 (t, *J* = 13.2 Hz, 1H), 2.23 (t, *J* = 12.0 Hz, 1H), 1.99 (dd, *J* = 11.6, 5.6 Hz, 1H), 1.65 (dd, *J* = 14.4, 5.9 Hz, 1H), 1.45 (s, 11H), 1.08 (t, *J* = 4.2 Hz, 6H), 0.75 (dd, *J* = 13.7, 6.5 Hz, 3H).

Example 2. Biological Evaluation

TFEB nuclear translocation assay

[0380] For the TFEB nuclear translocation assay, HeLa WT or HeLa TRPML1 KO cells were plated at 3000 cells/well into black-walled, 384-well Cell carrier Ultra tissue culture treated plates in complete media and incubated overnight. The next day, cells are treated for 2 hrs with compounds and incubated at 37 °C. Cells were then fixed for 20 minutes at room temperature in 4% final PFA and washed with 1X PBS. PBS is aspirated from the wells and the cells are blocked with 30 µL blocking buffer (1:1 PBS/Odyssey block buffer containing 0.1% triton x-100 and 1% goat serum). After 30-60 minutes of block, blocking buffer is aspirated and 7.5 µL of primary anti-TFEB (rabbit) antibody is added for a final dilution of 1:400 antibody in 15 µL blocking buffer. Plates are spun at 40 x g for 15 seconds and incubated overnight at 4 °C. The following day, plates are washed again into PBS, 90 µL with three washes, all PBS is aspirated from the wells and the cells are incubated for 1 hr in 1:1000 goat-anti rabbit Alexa 488 secondary antibody, also containing 10 µg/mL Hoechst 33342. After the 1 hr RT incubation, plates are washed three times in PBS, sealed with foil and imaged with an automated epifluorescence microscopy (PerkinElmer Operetta CLS). Nine different fields were imaged per well using ×20 magnification for DAPI and FITC filter sets. Images were quantified using PerkinElmer Harmony software, briefly: apply flatfield correction (basic/ advanced) for input images. Use the Find Nuclei building block with channel set at Hoechst to find the nuclei. Use the Find cytoplasm building block with channel set to Alexa 488 to find the cytoplasm. Use select cell region with Channel set at Alexa 488 and region of interest as Nuclei and define outer border at 0 µm and inner at 45 µm to cover complete nuclei. Use select cell region with Channel set at Alexa 488 and region of interest as ring region and define outer border at -5 µm and inner at 0 µm to define a ring around the nucleus.

Use the find calculate intensity parameter to calculate intensity of the nuclear region and the ring region. Define results as Number of nuclei and ratio of A/B where A is Intensity of Nuclei and B is intensity of the ring region.

[0381] Table 2-1 shows the activity of selected compounds of this invention in TFEB assays. Compounds having an activity designated as "++++" provided an EC_{50} of ≤ 0.10 μM; compounds having an activity designated as "+++" provided an EC_{50} of 0.11-0.50 μM; compounds having an activity designated as "++" provided an EC_{50} of 0.51-1.00 μM; and compounds having an activity designated as "+" provided an EC_{50} of ≥ 1.01 μM. Compounds having an activity designated as "****" provided an Amax-Amin of ≤ 0.10; compounds having an activity designated as "***" provided an Amax-Amin of 0.11-0.50; compounds having an activity designated as "**" provided an Amax-Amin of 0.51-1.00; and compounds having an activity designated as "*" provided an Amax-Amin of ≥ 1.01.

Table 2-1

Compound No.	**TFEB WT EC_{50} (μM)**	**TFEB WT Amax - Amin**	**TFEB TRPML1 KO EC_{50} (μM)**	**TFEB TRPML1 KO Amax - Amin**
I-1	++++	**	++	***
I-2	++++	**	+++	***
I-3	+++	**	+	***
I-4	++	**	+	****
I-5	+++	*	+	***
I-6	++	**	+	***
I-7	+	**	+	***
I-8	+	**	+	****
I-10	+	****	+	****
I-11	+	***	+	***
I-12	+	**	+	***
I-13	+	***	+	****
I-14	+	***	+	***
I-15	++	**	+	****
I-16	++++	***	+	***
I-17	++++	**	+	***
I-18	++++	**	+	***
I-19	+++	**	+	***
I-20	++++	**	+	****
I-21	++++	**	+	****

Compound No.	TFEB WT EC_{50} (μM)	TFEB WT Amax - Amin	TFEB TRPML1 KO EC_{50} (μM)	TFEB TRPML1 KO Amax - Amin
I-22	+++	**	+	****
I-23	+	****	+	****
I-24	++++	*	+	****
I-25	+	****	+	****
I-28	+	**	+	**
I-29	+	***	+	****
I-50	+	**	+	***
I-51	+	**	+	****
I-52	+	****	+	****
I-53	+++	**	+	***
I-54	+++	*	+	****
I-55	+++	**	+	****
Diastereomer 1 (I-56')	+	**	+	****
Diastereomer 2 (I-57')	+	****	+	****
I-58	+	*	+	****
Diastereomer 1 (I-59')	++	**	+	***
Diastereomer 2 (I-60')	++	**	+	****
Diastereomer 1 (I-61')	+	*	+	****
Diastereomer 2 (I-62')	+++	*	+	****
I-63	+++	*	+	****
I-64	+++	*	+	****
I-65	++	***	+	****
I-66	+	*	+	****
I-67	++	**	+	****

EPhys assay

[0382] Recordings were run at room temperature (22-25 °C) using HEK293 cells expressing hTRPML1. Cells were cultured at 37 °C and expression of the receptor was induced with 1 μg/ml Tetracycline overnight and the next day cells were plated onto glass coverslips. The extracellular solution contained (in mM) modified Tyrode's solution (in mM, pH7.4): 153 NaCl, 5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 20 HEPES and 10 Glucose. The 'Low pH Tyrode' solution contained (in mM, pH4.6): 150 Na-Gluconate, 5 KCl, 2 CaCl2, 1 MgCl2, 10 glucose, 10 HEPES and 10 MES. All bath solutions were applied via a perfusion system, and the solution switching was achieved "completely exchanged" in the recording chamber within a few seconds (~ 5 seconds). The pipette

solution contained (in mM, pH7.2): 122 Cs-methano-sulphonate, 4 NaCl, 10 EGTA, 2 Na_2-ATP, 2 MgCl2 and 20 HEPES. The voltage protocol is described as follows: Holding potential at 0 mV. The voltage protocol was approximately 1 s in duration and was repeated every 4 s. Cells were repolarized first from 0 mV to -100 mV for 40 ms, followed by a "ramp up" voltage from -100 mV to +100 mV with a duration of 400 ms. The cell was then held at +100 mV for 40 ms followed by repolarization back to holding potential 0 mV. The baseline was recorded in the pH 4.6 solution for about 1-2 minutes before cells were sequentially exposed in a series of compound concentrations from 0.005, 0.014, 0.041, 0.123, 0.370, 1.111, 3.333 to 10 μM. At each concentration, upon reaching stability for more than 30 s, the next higher concentration was applied. Data recording was filtered at 3 kHz and digitized at 10 kHz using the computer-controlled whole-cell recording patch clamp system which includes the MultiClamp 700B (or 700a) amplifier, and the Digidata 1440a amplifier. To process data, the amplitude of current was defined as the peak inward current measured with the average of 5 ms (from 0.145 to 0.150 s of each recording trace) at the end of -100 mV voltage step stimulation, which were plotted vs time over the whole experimental duration. The peak current sizes at each concentration were measured with customized macro function using Igor Pro 6.3 (WaveMetrics). Time constant measurement: the individual recording time course during compound exposure and wash off was plotted, and the wash off period, from the time point of adding wash off solution to the end of recoding, was fitted with single-exponential function with no restrictions using Igor Pro 6.3 (WaveMetrics).

[0383] Table 2-2 shows the activity of selected compounds of this invention in Ephys assays. Compounds having an activity designated as "++++" provided an EC_{50} of ≤ 0.10 μM; compounds having an activity designated as "+++" provided an EC_{50} of 0.11-0.50 μM; compounds having an activity designated as "++" provided an EC_{50} of 0.51-1.00 μM; and compounds having an activity designated as "+" provided an EC_{50} of ≥ 1.01 μM.

Table 2-2

Compound No.	EPhys EC_{50} (μM)
I-1	++++
I-2	++++

ELISA for transgene-derived human alpha synuclein

[0384] Striatal samples were lysed at a ratio of 1 ml of lysis buffer per 100 mg of tissue. The lysis buffer consisted of 1X RIPA buffer containing protease and phosphatase inhibitors (Complete

mini protease tablets, Roche, 11836153001). Samples were homogenised in ice-cold (4 °C) lysis buffer and briefly sonicated, followed by centrifugation (16,000 g_{ave} for 10 minutes at 4 °C) to produce supernatant. A portion of the supernatant (6.25 µl) was used to determine total protein levels (Pierce™ BCA Protein Assay Kit, Thermo Fisher Scientific, Waltham, MA, USA). Another portion of the supernatant, normally consisting of 1 µg of total protein, underwent ELISA procedures according to the manufacturer's instructions (BioLegend: 448607). The samples were analysed using CLARIOstar systems quantifying the colorimetric signal relative to the amount of aSyn. Levels of aSyn were expressed as ng/mg total protein.

Protein assay

[0385] Protein concentration in tissue homogenates were determined using the Pierce™ BCA Protein Assay Kit (Thermo Fisher Scientific, USA) as described in the provided kit instructions. Absorbance was measured using a POLARstar Omega plate reader (BMG LABTECH, Offenburg, Germany).

AAV alpha synuclein mouse model, AAV injection, and tissue collection

Administration of viral vectors – stereotaxic surgery:

[0386] Animals received either AAV1/2-hA53T-aSyn or empty vector (AAV1/2-EV) administered unilaterally into the right substantia nigra according to stereotaxic techniques on day 1.

[0387] AAV1/2 hA53T alpha-synuclein (aSyn) utilized the chimeric serotype 1/2. The A53T aSyn expressed by the gene delivered is of the human sequence. The control was an empty AAV1/2 vector of the same serotype and viral construction. Both were diluted in sterile PBS and were administered at a volume of 2 µl directly into the substantia nigra using stereotaxic techniques. The concentration of AAV1/2 used, 3 x 10^{12} genomic particles/ml, was previously empirically determined to produce significant behavioural and dopaminergic nigrostriatal deficits between 3 and 6 weeks following surgical delivery (Koprich et al, PLoS One, 2011 Mar 7;6(3):e17698).

[0388] All surgeries were performed using aseptic technique. On day 1, under isoflurane anaesthesia (2% with 2 L/min oxygen flow rate, isoflurane USP 99.9%) and after confirmation of loss of tail-pinch and corneal reflexes, rats were placed in a Kopf small animal stereotaxic frame with the incisor bar set 3.3 mm below the ear bars (interaural line). The animal's head was shaved,

and the skin cleaned thoroughly using disinfectant soap, isopropyl alcohol 70% USP and iodine surgical scrub (7.5% povidone iodine). An incision (~ 2 cm) was made with a sterile scalpel blade in an anteroposterior direction along the midline. After exposure of Bregma using a cotton-bud, a burr hole was drilled in the skull above the right SN at coordinates -5.2 mm AP, and -2 mm ML to Bregma (according to the atlas of Paxinos and Watson, 1986). A customized, 1 inch, 26G Hamilton needle with 45-degree bevel was lowered -7.5 mm below the skull at the injection site. The injection (2.0 µl; 0.5 µl/min) was made (for a total injection time of 4 min) and the needle was left in place for an additional 5 min to ensure complete absorption of the solution. After slow retraction of the injection needle, the incision was closed by means of wound clips and animals were administered saline (50 ml/kg, SC). The wound was coated with analgesic, antibacterial cream. Finally, animals were removed from the frame and placed in a recovery cage, positioned atop a thermostatically controlled pad, and monitored until conscious.

Terminal procedure and tissue collection:

[0389] On day 43, 4 hours after test item administration, animals were deeply anaesthetised with isoflurane.

[0390] Animals were then killed via exsanguination by way of transcardial perfusion with ice-cold 0.9 % saline containing 0.2 % heparin. Brains were removed and placed, ventral up, into an ice-cold stainless steel rat brain matrix and first cut in the coronal plane at the level of the optic chiasma. The forebrain was flash frozen. A second cut was made, 1 mm posterior to the first (slice 1). The striatum from slice 1 was dissected and fresh-frozen in dry ice. A third cut, 1 mm posterior to slice 1, was then made to create slice 2. The striatum dissected from slice 2 was fresh-frozen and used for quantification of human aSyn by ELISA. The tissue was stored in a locked freezer at -80 °C.

[0391] The remainder of the caudal portion of the brain, including the mesencephalon, was immersed in 4 % paraformaldehyde (PFA) for 48 hours for fixation followed by cryoprotection in graded sucrose solutions (15 to 30 % sucrose). Tissue prepared in this manner wasused for quantification of dopamine neuron numbers in the SNc via immunohistochemistry of tyrosine hydroxylase and unbiased stereology.

[0392] Using procedures similar to those described above, Sprague Dawley rats were injected with an AAV in the substantia nigra of one brain hemisphere to overexpress human alpha-

synuclein A53T. Subsequently, the rats were treated daily with either vehicle alone, or a 10 mg/kg or 50 mg/kg dose of the compound I-2 via oral gavage. After six weeks of treatment, the striata of the injected hemisphere was isolated and the abundance of alpha-synuclein was determined using ELISA (Figure 1). Statistical significance was determined using a one-way ANOVA with uncorrected Fishers LSD test.

Tyrosine hydroxylase histology and stereological cell counting

Histology

[0393] Brains weresectioned frozen in the coronal plane at a thickness of 40 μm on a freezing sliding microtome (Leica Microsystems Inc., Richmond Hill, ON) and 6 series of sections werestored in cryoprotectant (30% glycerol, 30% ethoxyethanol, 40% PBS) at -20 °C.

[0394] A single series of sections from the midbrain was processed for visualization of tyrosine hydroxylase (TH) via the biotin-labelled antibody procedure to label dopamine neurons of the SN. Briefly, following several washes in a PBS solution containing 0.2% Triton X-100 (PBS-T), endogenous peroxidase was quenched in a 3% hydrogen peroxide solution and background staining inhibited in a 10% normal goat serum/2% bovine serum albumin solution. Tissue were then incubated with primary antibodies overnight: rabbit anti-TH antibody (1:1000, Pel-Freez, Rogers, AR). After three washes in PBS-T, sections were sequentially incubated in biotinylated goat anti-rabbit or mouse IgG (1:300; Vector, Burlingame, CA) for 1 h and the Elite avidin-biotin complex (ABC Kits; Vector, Burlingame, CA) for 1 h separated by three washes in PBS. Immunostaining was then visualized following a reaction with 3,3-diaminobenzidine (Vector, Burlingame, CA). Sections were mounted on glass slides, allowed to dry, dipped into dH20, dehydrated through graded alcohols (70%, 95%, 100%), cleared in xylenes, and coverslipped with DPX mounting medium (Electron Microscopy Sciences, Hatfield, PA).

Stereology

[0395] Estimates of TH^{+ve} neuronal number within the substantia nigra pars compacta (SNc) were performed using Stereo Investigator software (MBF Bioscience, Williston, VT) according to stereological principles. Eight sections, each separated by 240 μm from the anterior to the posterior SN, were used for counting each case. Stereology was performed using a Zeiss microscope (Carl Zeiss, Canada) coupled to a digital camera for visualization of tissue sections. The total number of

TH^{+ve} neurons was estimated from coded slides using the optical fractionator method. For each tissue section analysed, section thickness was assessed empirically and guard zones of ~2 μm thickness were used at the top and bottom of each section. The SNc was outlined under low magnification (5x) and TH^{+ve} neurons were counted under 40x magnification. Stereological parameters were empirically determined (i.e. grid size, counting frame size and dissector height) using Stereo Investigator software (MicroBrightfield, VT, USA). The acceptable coefficient of error (CE) was calculated according to the procedure of West and colleagues, known as the Gunderson CE (m=1). Gunderson values < 0.10 were accepted.

[0396] Using procedures similar to those described above, Sprague Dawley rats were injected with an AAV in the substantia nigra of one brain hemisphere to overexpress human alpha-synuclein A53T. Subsequently, the rats were treated daily with either vehicle alone, or a 10 mg/kg or 50 mg/kg dose of the compound I-2 via oral gavage. After six weeks of treatment, brain slices from the substantia nigra were stained for tyrosine hydrolase to determine the relative abundance of TH+ neurons in the injected hemisphere (Figure 2 and 3).

CBE survival study

Animals

[0397] C57BL/6 mice, female, 4 weeks, weighing approximately 16 g. Mice were purchased from Shanghai Lingchang Biotechnology Co., Ltd. or other certified vendors.

Animal Housing

[0398] An acclimation period of approximately one week was allowed between animal arrival and treatment in order to accustom the animals to the laboratory environment. The mice were maintained in a special pathogen-free environment and in individual ventilation cages (3 mouse per cage). All cages, bedding, and water were sterilized before use. When working in the mouse room, the investigators wore lab coats and latex or vinyl gloves. Each cage was clearly labeled with a cage card indicating number of animals, sex, strain, date received, treatment, study number, group number, and the starting date of the treatment. The cages with food and water were changed twice a week. The targeted conditions for animal room environment and photoperiod were as follows:

Temperature: 20~26 ℃

Humidity: 40~70 %

Light cycle: 12 hours light and 12 hours dark

Dietary Materials

[0399] All animals had free access to a standard certified commercial laboratory diet. Maximum allowable concentrations of contaminants in the diet were controlled and routinely analyzed by the manufacturers. Autoclaved municipal tap water, suitable for human consumption was available to the animals *ad libitum*. It is considered that there were no known contaminants in the dietary materials that could influence the efficacy.

Observations

[0400] The protocol and any amendment(s) or procedures involving the care and use of animals in this study was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) prior to conduct. During the study, the care and use of animals was conducted in accordance with the regulations of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). After treatment, the animals were checked daily for morbidity and mortality. At the time of routine monitoring, the animals were checked for any effects of treatments on normal behavior such as mobility, food and water consumption, body weight gain/loss (body weights were measured twice weekly), eye/hair matting and any other abnormal effect. Death and observed clinical signs were recorded on the basis of the numbers of animals within each subset.

Termination

[0401] 1) Body weight loss: Any animal exhibiting 20% body weight loss at any one day were humanely killed or the veterinary staff was contacted.

[0402] 2) Clinical signs: Animals were euthanized if they were found to be moribund.

[0403] Clinical examples of morbidity included:

Hunched.

Persistent recumbency and lack of response to handling or other stimuli.

Signs of severe organ or system failure.

Emaciation.

Hypothermia.

CNS deficits: convulsions.

Respiratory: rapid respiratory rate, labored breathing, coughing, rales.

GI: diarrhea lasting > 2 days, jaundice.

[0404] Any animal that exhibits the above clinical issues washumanely sacrificed by CO_2. Necropsy was not performed in the event of an unexpected death.

[0405] Using procedures similar to those described above, mice were treated daily with vehicle or 100 mg/kg Conduritol-β-epoxide (CBE) via IP and co-treated daily with CBE and 10 mg/kg or 50 mg/kg of compound I-2 via oral gavage. Resulting Kaplan Meier curves are shown in Figure 4. Statistical significance was determined using a Gehan-Breslow-Wilcoxon test. Figure 5 depicts abundance of neurofilament light chain (NfL) in the Cerebrospinal fluid (CSF) of mice after 14 days of daily treatment with vehicle, 50 mg/kg CBE (IP), 100 mg/kg CBE (IP), or daily co-treatment with CBE and 10 mg/kg or 50 mg/kg of compound I-2 via oral gavage. NfL was quantified using a Quanterix Simoa HD-x Analyzer.

Quantification of Neurofilament Light (NfL) in Mouse Samples Using a Simoa Assay

[0406] The assay required critical reagents, including Simoa NF-light Calibrators Concentrate (Quanterix, Cat# 103186) stored at ≤ -70°C and the Simoa NF-light Reagent Kit (Quanterix, Cat# 101386) stored at 2-8 °C. Additionally, non-critical reagents such as System Wash Buffers 1 and 2, discs, pipette tips, plates, and other consumables were sourced from Quanterix and stored at room temperature.

[0407] Prior to the assay, QC samples and test samples were thawed at room temperature and diluted in a sample dilution buffer at a minimum required dilution (MRD) of 1:4. If further dilution was necessary, the samples were adjusted according to the validated dilution scheme. The assay was initiated by restarting the Simoa computer, opening the instrument and software, and performing a system cleaning step using Wash Buffer 1. Once cleaned, reagents, standards, and QC samples were equilibrated to room temperature and loaded onto the assay plate. NfL calibrators and QC samples were added to pre-determined wells and mixed by gently tapping the plate.

[0408] The assay workflow included solubilizing the RGP substrate by heating it at 30 °C for 30 minutes with shaking at 800 rpm, vortexing the beads for 30 seconds, and loading the prepared reagents, including Bead Reagent, Detector Reagent, SBG Reagent, and Sample Diluent, into the reagent bay.

[0409] To ensure reproducibility, all calibrators, controls, and samples were allowed to reach room temperature before loading onto the Simoa HD-X Analyzer. Simoa reagents were also brought to room temperature before use unless using models equipped with a cooling reagent bay. The RGP substrate were fully solubilized by heating at 30–37 °C with vigorous shaking for at least 30 minutes. Bead Reagent was vortexed for at least 30 seconds before loading to resuspend capture beads, avoiding excessive foaming.

[0410] For data analysis, the individual instrument response (AEB) was corrected by subtracting the AEB value of the non-specific binding (NSB) for each standard point before fitting a regression model. The calculated concentration values were derived using a four-parameter logistic regression model with a $1/Y^2$ weighting factor. A minimum of six non-zero standard concentrations were required to meet the acceptance criteria of ≤20% bias and ≤20% coefficient of variation (CV) to validate the standard curve. QC samples were required to demonstrate back-calculated accuracy within ±30%, ensuring assay reliability.

Mass spectrometry quantification of Glucosylsphingosine and Clucosylceramide levels

Liquid Chromatography-Mass Spectroscopy

[0411] Instrument used was a LC-MS/MS API4000. The MS conditions used were:

ESI: positive

MRM detection

GC-C18: [M+H]+728.62/264.10 m/z; lyso-GL1: [M+H]+462.28/282.30 and 462.28/264.20 m/z;

Lyso-GL1-d5(IS): [M+H]+467.50/269.30 m/z; GC-C18-d5(IS): [M+H]+733.80/269.70 m/z

[0412] The analytes detected were Glucosylceramide (d18:1/18:0) (GC) and Glucosylsphingosine (d18:1) also know as Lyso-GL1. Internal standards were used. Lyso-GL1, 2000 ng/mL in water and GC-C18-d5) in DMSO:MeOH.

LC conditions:

Lyso-GL1 for Plasma, Liver and Brain homogenate

Mobile Phase:

Mobile Phase A: 5mM ammonium formate and 0.5% FA in ACN:MeOH:H2O(V:V:V:=1900:50:50)

Mobile Phase B: 5mM ammonium formate and 0.5% FA in ACN:MeOH:H2O(V:V:V:=100:950:950)

Time (min)	Mobile Phase B (%)
Initial	11
6.00	11

Injection: 5μL

Column: HALO 90Å HILIC, 2.7um, 4.6×75mm

Column temperature: 30 °C

Flow rate: 0.7 mL/min

GC-C18 for for Plasma, Liver and Brain homogenate

Mobile Phase:

Mobile Phase A: 5mM ammonium formate and 0.5% FA in ACN:MeOH:H2O(V:V:V:=1900:50:50)

Mobile Phase B: 5mM ammonium formate and 0.5% FA in ACN:MeOH:H2O(V:V:V:=100:950:950)

Time (min)	Mobile Phase B (%)
Initial	1
0.20	1
5.50	1
6.50	80
6.70	80
6.71	1
8.00	1

Injection: 3μL

Column: HALO 90Å HILIC, 2.7um, 4.6×150mm

Column temperature: 30 °C

Flow rate: 0.6 mL/min

With retention times:

Lyso-GL1: 4.43 min

Lyso-GL1-d5: 4.43 min

GC-C18: 3.89 min

GC-C18-d5: 3.89 min

Sample Preparation

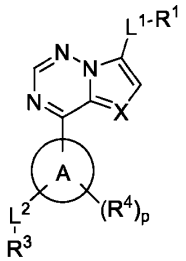
[0413] For Lyso-GL1, an aliquot of 10 uL unknown sample, calibration standard, quality control, blank and double blank samples were added to the 96-well plate, using MeOH (v:v 1:1) as an alternative matrix. Each sample (except the double blank) was quenched with 10 uL IS respectively (double blank sample was quenched with 10 uL water). All sample add 100 uL mobile phase A, and then the mixture was vortex-mixed for 5 minutes at 800 rpm and centrifuged for 15 minutes at 3220 g (4000 rpm) at 4 °C. 40 uL supernatant were directly injected for LC-MS/MS analysis.

[0414] For GC-C18, an aliquot of 10 uL unknown sample, calibration standard, quality control, blank and double blank samples were added to the 1.5 mL EP tube, using DMSO:MeOH (v:v 1:1) as an alternative matrix. Each sample (except the double blank) was quenched with 10 uL IS respectively (double blank sample was quenched with 10 uL DMSO:MeOH (v:v = 1:1)). To all samples was added 80 uL DMSO and 400 uL mobile phase A, and then the mixture was vortex-mixed for 2 minutes at 2500 rpm and centrifuged for 5 minutes at 14000 rpm at 4 °C. 40 uL supernatant were directly injected for LC-MS/MS analysis.

[0415] The embodiments of the disclosure described above are intended to be merely exemplary, numerous variations and modifications will be apparent to those skilled in the art. All such variations and modifications are intended to be within the scope of the present invention as defined in any appended claims.

CLAIMS

1. A compound represented by formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

X is N or CR^2;

R^1 is 5- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S, C_6-C_{12} aryl, or C_3-C_{12} cycloaliphatic, wherein R^1 is optionally substituted with one or more instances of R^{1a};

each R^{1a} is independently -CN, halogen, $-OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)R^a$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_3-C_7 cycloaliphatic;

L^1 is a bond, $N(R^a)$, O, or optionally substituted C_1-C_6 aliphatic;

R^2 is H, optionally substituted C_3-C_7 cycloaliphatic, optionally substituted phenyl, optionally substituted 5- to 6-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, optionally substituted C_1-C_6 aliphatic, or optionally substituted 4- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S;

Ring A is 4- to 12-membered heterocycle comprising 1 to 4 heteroatoms selected from N, O, and S;

L^2 is -C(O)-, -C(O)O-, $-N(R^a)C(O)$-, $-C(O)N(R^a)$-, -S(O)-, $-S(O)_2$-, optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S, or optionally substituted 4- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S;

R^3 is optionally substituted C_1-C_6 aliphatic or optionally substituted 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S;

each R^4 is independently optionally substituted C_1-C_6 aliphatic;
each R^a is independently selected from H and optionally substituted C_1-C_6 aliphatic; and
p is 0, 1, 2, 3, or 4.

2. The compound of claim 1, wherein L^1 is a bond.

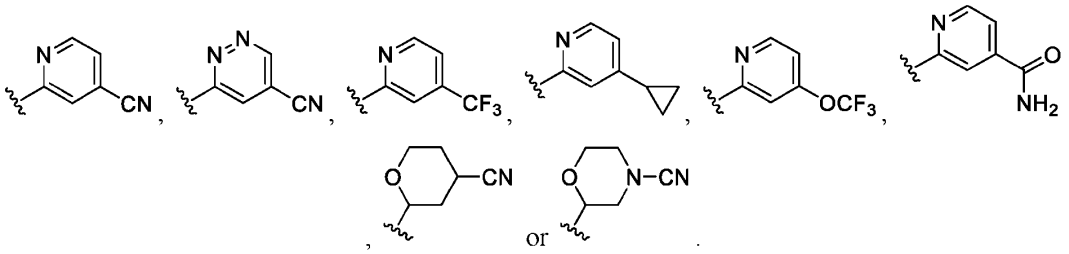
3. The compound of claims 1 or 2, wherein R^1 is 5- to 12-membered heteroaryl comprising 1 to 4 heteroatoms selected from N, O, and S, and is optionally substituted with one or more instances of R^{1a}.

4. The compound of claim 3, wherein R^1 is monocyclic 5- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S, and is substituted with one or more instances of R^{1a}.

5. The compound of claim 4, wherein R^1 is pyridinyl, substituted with R^{1a}.

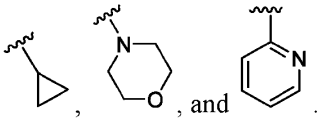
6. The compound of any one of claims 1-5, wherein R^{1a} is -CN.

7. The compound of claim 1, wherein R^1 is:



8. The compound of any one of claims 1-7, wherein R^2 is optionally substituted C_3-C_7 cycloaliphatic.

9. The compound of claim 1, wherein R^2 is selected from: -H, -CH_3, -CH_2-CH_3, -CF_3,



10. The compound of any one of claims 1-9, wherein Ring A is monocyclic 4- to 6-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

11. The compound of claim 10, wherein Ring A is piperidinyl or piperazinyl.

12. The compound of claim 11, wherein Ring A is piperidinyl.

13. The compound of any one of claims 1-9, wherein Ring A is bridged bicyclic 6- to 10-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S.

14. The compound of any one of claims 1-13, wherein p is 0.

15. The compound of any one of claims 1-13, wherein p is 1 or 2.

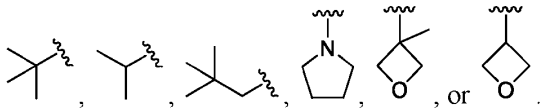
16. The compound of claim 15, wherein each R^4 is $-CH_3$.

17. The compound of any one of claims 1-16, wherein L^2 is -C(O)-, -C(O)O-*, -S(O)-, or -$S(O)_2$-, where * indicates a point of attachment to moiety R^3.

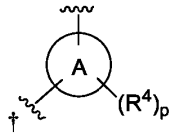
18. The compound of claim 17, wherein L^2 is -C(O)O-*, where * indicates a point of attachment to moiety R^3.

19. The compound of any one of claims 1-18, wherein R^3 is optionally substituted C_1-C_6 aliphatic.

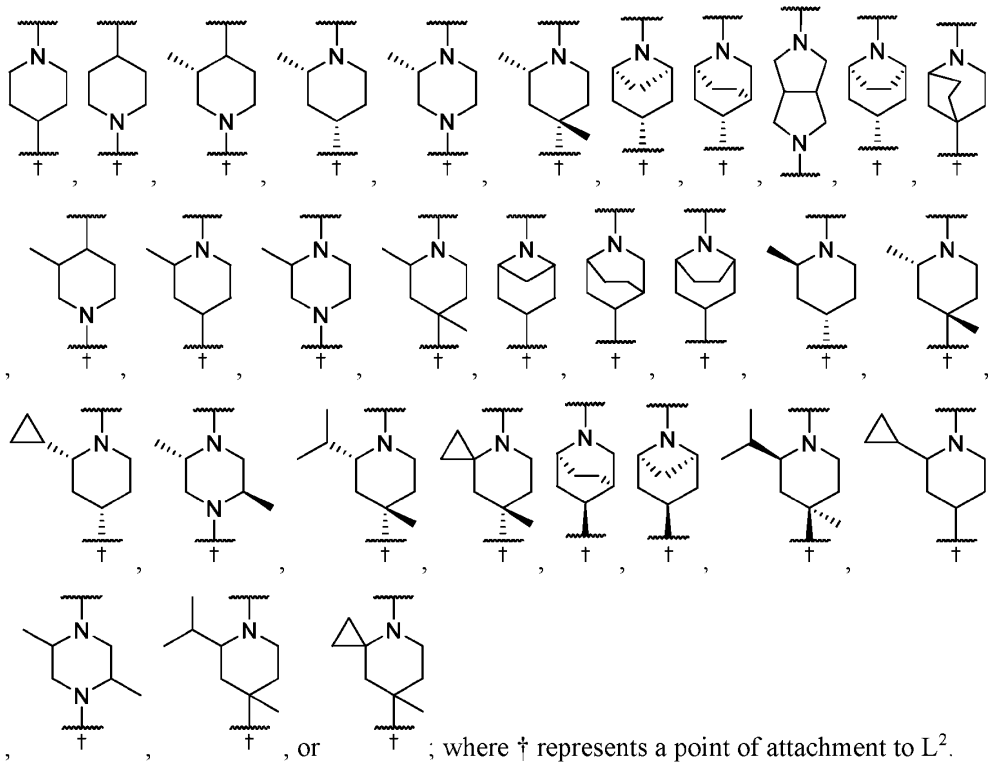
20. The compound of claim 19, wherein R^3 is:



21. The compound of claim 1, wherein moiety:

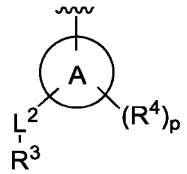


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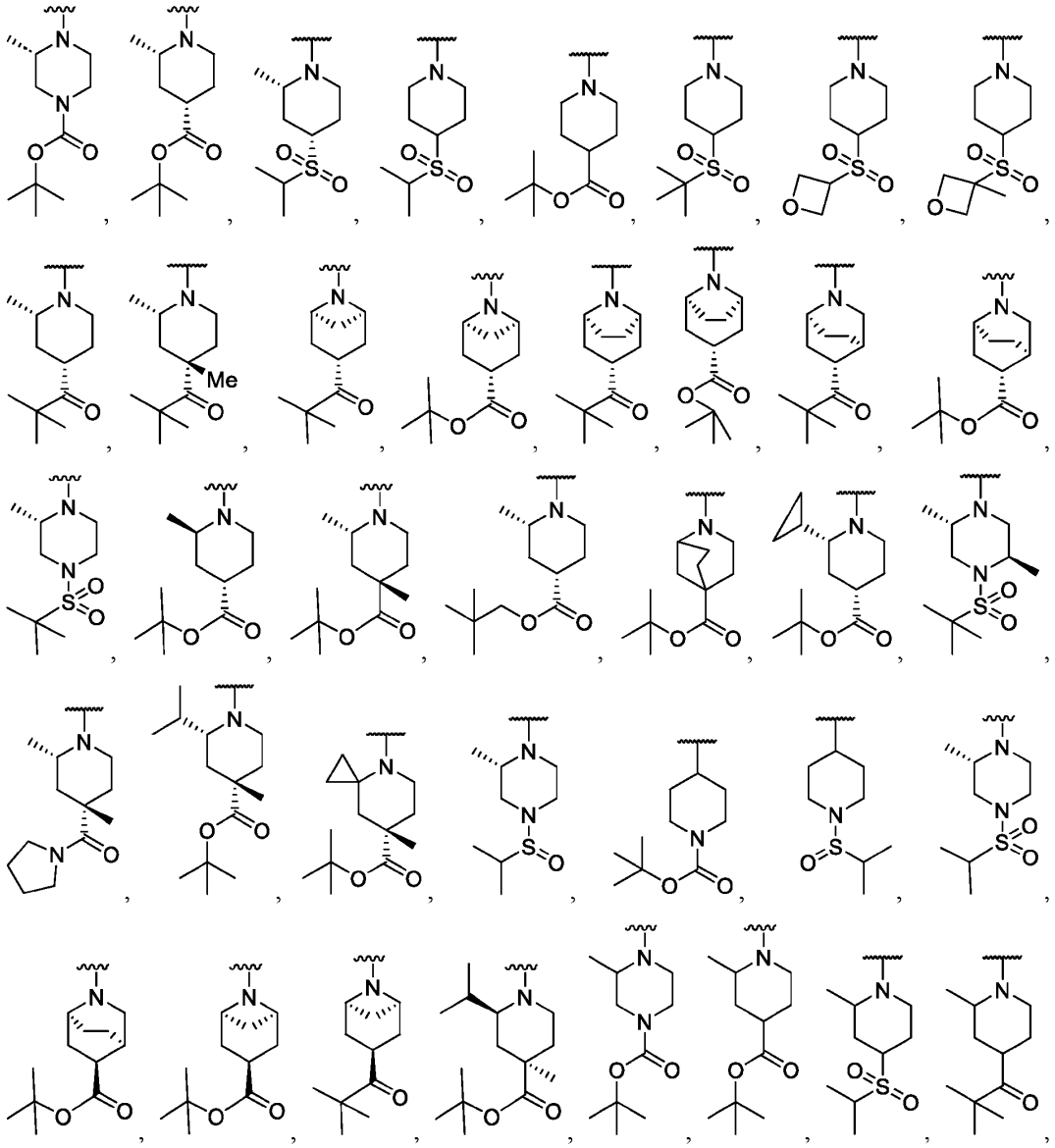


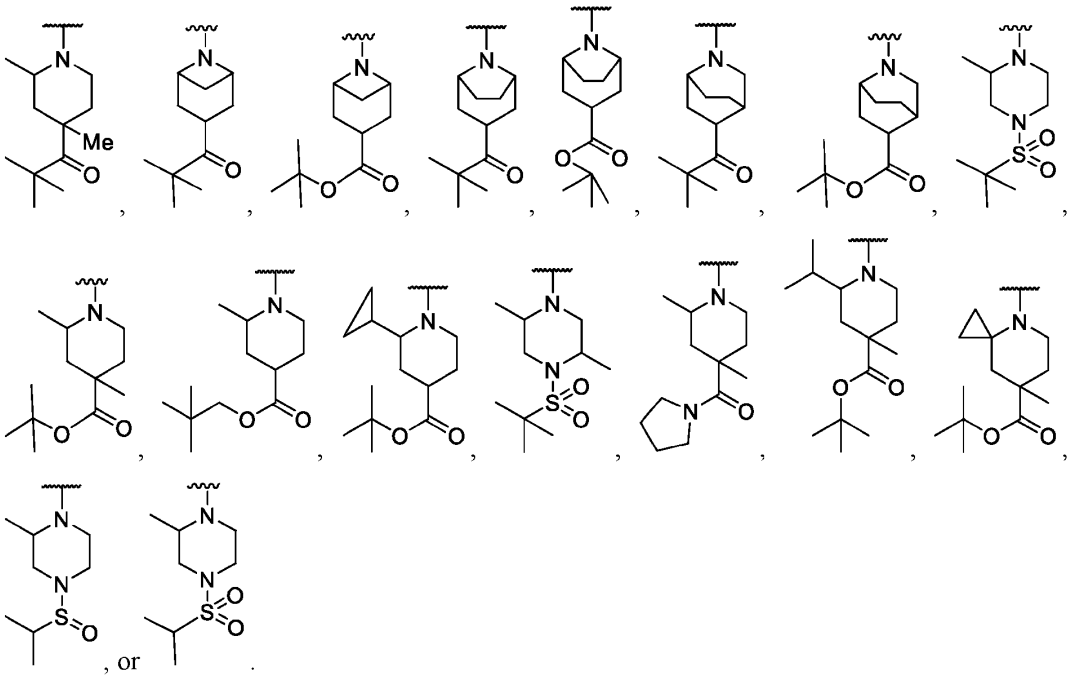
; where † represents a point of attachment to L^2.

22. The compound of claim 1, wherein moiety:

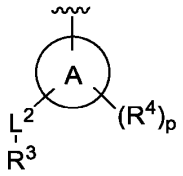


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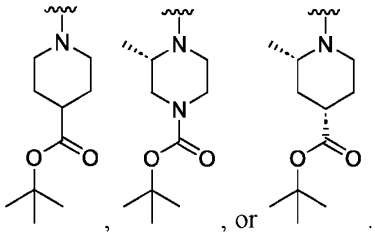




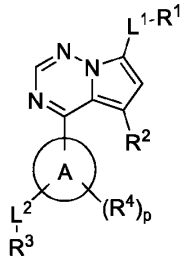
23. The compound of claim 22, wherein



is:



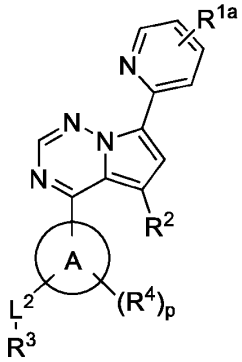
24. The compound of claim 1, wherein the compound is represented by formula I-2:



I-2

or a pharmaceutically acceptable salt thereof.

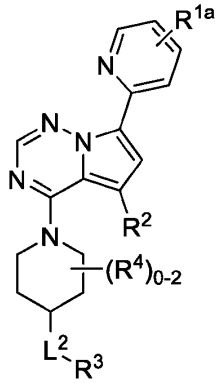
25. The compound of claim 1, wherein the compound is represented by formula II-1:



II-1

or a pharmaceutically acceptable salt thereof.

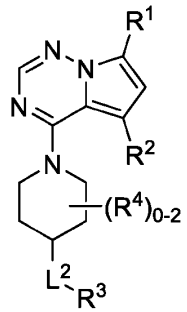
26. The compound of claim 1, wherein the compound is represented by formula II-2:



II-2

or a pharmaceutically acceptable salt thereof.

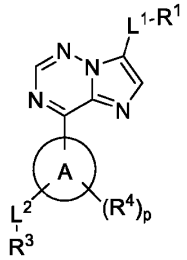
27. The compound of claim 1, wherein the compound is represented by formula III-1



III-1

or a pharmaceutically acceptable salt thereof.

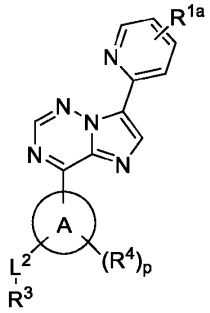
28. The compound of claim 1, wherein the compound is represented by formula IV-1



IV-1

or a pharmaceutically acceptable salt thereof.

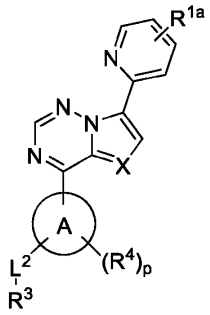
29. The compound of claim 1, wherein the compound is represented by formula IV-2



IV-2

or a pharmaceutically acceptable salt thereof.

30. The compound of claim 1, wherein the compound is represented by formula V-1



V-1

or a pharmaceutically acceptable salt thereof.

31. The compound of claim 1, wherein the compound, or a pharmaceutically acceptable salt thereof, is selected from Table 1.

32. A pharmaceutical composition comprising the compound of any one of claims 1-31, and a pharmaceutically acceptable carrier or excipient.

33. A method of modulating TRMPL in a subject comprising administering to the subject a compound of any one of claims 1-31 or a pharmaceutical composition of claim 32.

34. A method of treating a disease, disorder, or condition in a subject comprising administering to the subject a compound of any one of claims 1-31, or a pharmaceutical composition of claim 32.

35. The method of claim 34, wherein the disease, disorder, or condition is a lysosomal storage disorder.

36. The method of claim 35, wherein the lysosomal storage disorder is selected from Niemann-Pick C disease, Gaucher disease, Batten disease, cholesteryl ester storage disease, Fabry disease, and Pompe disease.

37. The method of claim 34, wherein the disease, disorder, or condition is age-related common neurodegenerative disease.

38. The method of claims 34 or 37, wherein the disease, disorder, or condition is selected from Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease.

39. The method of claim 34, wherein the disease, disorder, or condition is a type IV Mucolipidosis (ML4) neurodegenerative lysosomal storage disease caused by mutations in a TRPML.

40. The method of claim 34, wherein the disease, disorder, or condition is a muscular disease, a liver disease, a metabolic disease, an atherosclerotic disease, an inflammatory bowel disease, an atherosclerotic disease, a neurodegenerative disease, an oncological disease, or an infectious disease.

41. The method of claim 40, wherein the disease, disorder, or condition is a muscular disease.

42. The method of claim 41, wherein the muscular disease is a muscular dystrophy.

43. The method of claim 42, wherein the muscular dystrophy is Duchenne muscular dystrophy.

44. The method of claim 34, wherein the disease, disorder, or condition is an infectious disease.

45. The method of claim 44, wherein the infectious disease is an infection of *Heliobacter pylori* or *Mycobacterium tuberculosis*.