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(54) Title: COMPOSITIONS AND METHODS FOR MODULATING HAIR GROWTH

(57) Abstract: The present disclosure relates to novel compounds that are capable of inhibiting the mitochondrial pyruvate carrier and promoting hair growth. The disclosure further relates to methods of promoting hair growth or treating conditions or disorders affecting hair growth, such as baldness or alopecia.

COMPOSITIONS AND METHODS FOR MODULATING HAIR GROWTH

Inventors: Daniel Lui Sun, Michael Ernest Jung, Daniel Walter Gil, William Edward Lowry, Heather Renee Christofk, Aimee Alyssa Flores, Xiaoguang Liu

CROSS-REFERENCE TO RELATED APPLICATIONS

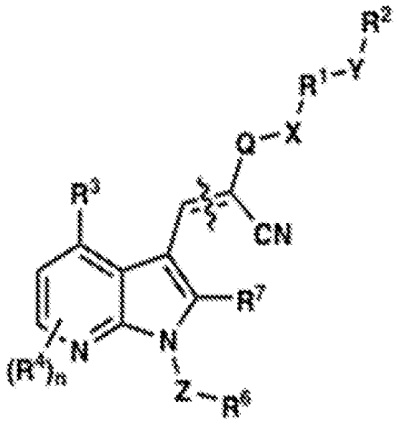
This application claims the benefit of U.S. Provisional Patent Application No. 63/046,629, filed June 30, 2020 and U.S. Provisional Patent Application No. 63/048,429, filed July 6, 2020, both of which are incorporated by reference herein in their entireties.

BACKGROUND

Hair follicle stem cells (HFSCs) undergo successive rounds of quiescence (telogen) punctuated by brief periods of proliferation correlating with the start of the hair cycle (telogen-anagen transition). Proliferation or activation of HFSCs is well known to be a prerequisite for advancement of the hair cycle. Despite advances in treatment options, baldness and alopecia continue to be conditions that cannot be successfully treated in many individuals. Some of the existing treatments are inconvenient for users, others require surgical intervention or other invasive procedures. Additional therapies are needed.

SUMMARY

Described herein are compounds of Formula 1:



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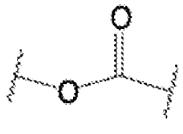
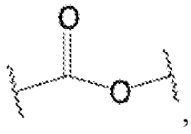
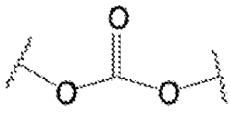
Formula 1

or a pharmaceutically acceptable salt thereof; wherein Q is —C(=O)—, —C(=S)—, —$S(=O)_2$—, —$C(=NR^5)$—, —$(C=N^+R^5R^8)$; R^1 is —, —$S(=O)_2$—, an optionally substituted $C_{1\text{-}12}$ hydrocarbon group or an optionally substituted heterocycle; R^2 is H, an optionally

substituted C_{1-6} alkyl, an optionally substituted carbocycle, or an optionally substituted heterocycle; R^3 and R^7 are independently H, F, Cl, Br, I, OH, OR^A, SH, SR^A, NR^AR^B, CF_3, CN, carboxylic acid, an optionally substituted carboxylic ester, or an optionally substituted C_{1-6} alkyl; each R^4 is independently H, F, Cl, Br, I, OH, O^-, OR^A, SH, SR^A, NR^AR^B, CF_3, CN, carboxylic acid, an optionally substituted carboxylic ester, or an optionally substituted C_{1-6} alkyl; R^A and R^B are independently H or optionally substituted C_{1-6} hydrocarbon group; n is 0, 1, or 2; X is O, S, NR^5, or $N^+R^5R^8$; R^5 and R^8 are independently H, C_{1-6} alkyl, an optionally substituted carbocycle, or an optionally substituted heterocycle, and the N, R^5 and R^1, or the N, R^5 and R^8, may together form an optionally substituted heterocyclic ring; Y is —, —O—,  ,  , or  ; Z is —, an optionally substituted —C(=O)-alkyl, an optionally substituted C_{1-12} hydrocarbon group, or optionally substituted heterocycle; R^6 is H, an optionally substituted C_{1-12} hydrocarbon group optionally substituted heterocycle; and the wavy line across the C=C bond represents an E or Z olefin.

Some embodiments include a pharmaceutical composition comprising a compound described herein.

Some embodiments include a method of growing hair, comprising: administering a compound described herein to the skin of a mammal, including a human being, in the area where hair growth is intended.

Some embodiments include a method of growing hair comprising administering an MPO inhibitor to a mammal, including a human being, in need thereof. In some embodiments, the MPO inhibitor is a compound described herein.

Some embodiments include a method of treating a disorder affecting hair growth comprising administering a compound described herein to a mammal, including a human being, in need thereof. In some embodiments, the disorder is alopecia or baldness. Some embodiments include use of a compound described herein in the manufacture of a medicament for growing hair.

Some embodiments include a kit comprising a compound described herein and a label with instructions to administer the compound for a use described herein, such as growing hair.

In certain aspects, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure and a pharmaceutically acceptable excipient.

In certain aspects, the present disclosure provides methods of enhancing lactate production in a cell, comprising contacting the cell with a compound or composition of the disclosure.

In certain aspects, the present disclosure provides methods of promoting hair growth or treating a hair growth condition or disorder such as baldness or alopecia, comprising administering to a patient a compound of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the conversion of ester prodrug (shown in gray) to the corresponding carboxylic acid API (shown in black) after 1 hour of incubation in homogenized mouse skin at 37 °C and pH 7.4.

FIG. 2 shows the conversion of ester prodrug (shown in gray) to the corresponding carboxylic acid API (shown in black) after 1 hour of incubation in homogenized minipig skin at 37 °C and pH 7.4.

FIG. 3A and 3B show the conversion of ester prodrug (shown in gray) to the corresponding carboxylic acid API (shown in black) after 1 hour of incubation in homogenized human skin at 37 °C and pH 7.4.

FIG. 4 shows a schematic for performing the LDH activity assay on human skin cell lysate.

FIG. 5A shows that pretreatment of human skin lysate with high heat kills the LDH activity.

FIG. 5B shows that treatment of human skin lysate with exemplary LDH inhibitors blocks most of the LDH activity, further confirming that the activity readout is the result of LDH activity.

FIGs. 6A and 6B, show that the treatment of human skin lysate with exemplary MPC inhibitors results in an increase in LDH activity.

FIG. 7 shows that pretreatment of human skin lysate with a carboxylesterase inhibitor (ben) prior to incubation with MPC inhibitors blocks the effect of most of the exemplary ester containing MPC inhibitors; however, the pretreatment had no effect on carboxylic containing MPC inhibitors.

FIG. 8 shows that the MPC inhibitors of the disclosure promote hair growth. Mice were shaved at day 50 when the hair cycle is dormant. Exemplary compounds were applied topically to the shaved area. Macroscopic observation led to the quantification of hair cycle staging shown where the two ester-MPC inhibitors accelerated the hair cycle compared to vehicle control.

DETAILED DESCRIPTION

Described herein are compounds, compositions, and methods for modulating hair growth. Compounds of the present disclosure include substituted 7-azaindole compounds which may be useful for modulating hair growth.

Unless otherwise indicated, any reference to a compound herein by structure, name, or any other means, includes pharmaceutically acceptable salts, such as sodium, potassium, and ammonium salts; prodrugs, such as ester prodrugs; alternate solid forms, such as polymorphs, solvates, hydrates, etc.; deuterium-modified forms; Z and E olefin isomers; tautomers; or any other chemical species that may rapidly convert to a compound described herein under conditions in which the compounds are used as described herein. In some embodiments, the compound contains more than a natural abundance of deuterium. In some embodiments, one or more of the hydrogen atoms on the compound is replaced by deuterium so that the compound is at least 50%, at least 80%, at least 90%, at least 95%, or at least 99% deuterium in that position.

Examples of pharmaceutically acceptable salts of compounds include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts described herein include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts described herein include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts. In

certain embodiments, contemplated salts described herein include, but are not limited to, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, l-ascorbic acid, l-aspartic acid, benzenesulfonic acid, benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, d-glucoheptonic acid, d-gluconic acid, d-glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, l-malic acid, malonic acid, mandelic acid, methanesulfonic acid , naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, l-pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, l-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid, and undecylenic acid acid salts.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Unless otherwise indicated, when a compound or chemical structural feature (such as alkyl or aryl) is referred to as being "optionally substituted," it includes a feature that has no substituents (i.e. unsubstituted), or a feature that is "substituted," meaning that the feature has one or more substituents. The term "substituent" has the broadest meaning known to one of ordinary skill in the art, and includes a moiety that occupies a position normally occupied by one or more hydrogen atoms attached to a parent compound or structural feature. In some embodiments, a substituent may be an ordinary organic moiety known in the art, which may have a molecular weight (e.g. the sum of the atomic masses of the atoms of the substituent) of about 15 g/mol to about 50 g/mol, about 15 g/mol to about 100 g/mol, about 15 g/mol to about 150 g/mol, about 15 g/mol to about 200 g/mol, about 15 g/mol to about 300 g/mol, or about 15 g/mol to about 500 g/mol. In some embodiments, a substituent comprises, or consists of: 0-30, 0-20, 0-10, or 0-5 carbon atoms; and 0-30, 0-20,

0-10, or 0-5 heteroatoms, wherein each heteroatom may independently be: N, O, S, P, Si, F, Cl, Br, or I; provided that the substituent includes one C, N, O, S, P, Si, F, Cl, Br, or I atom. Examples of substituents include, but are not limited to, compounds represented by an empirical formula: $C_{1-12}H_{3-29}O_{0-4}N_{0-4}S_{0-4}F_{0-25}Cl_{0-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{1-4}N_{0-4}S_{0-4}F_{0-25}Cl_{0-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{0-4}N_{1-4}S_{0-4}F_{0-25}Cl_{0-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{0-4}N_{0-4}S_{1-4}F_{0-25}Cl_{0-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{0-4}N_{0-4}S_{0-4}F_{1-25}Cl_{0-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{0-4}N_{0-4}S_{0-4}F_{0-25}Cl_{1-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{0-4}N_{0-4}S_{0-4}F_{0-25}Cl_{0-5}Si_{1-3}P_{0-3}$, $C_{1-6}H_{3-16}O_{0-4}N_{0-4}S_{0-4}F_{0-13}Cl_{0-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-16}O_{1-4}N_{0-4}S_{0-4}F_{0-13}Cl_{0-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-17}O_{0-4}N_{1-4}S_{0-4}F_{0-13}Cl_{0-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-17}O_{0-4}N_{0-4}S_{1-4}F_{0-13}Cl_{0-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-17}O_{0-4}N_{0-4}S_{0-4}F_{1-13}Cl_{0-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-17}O_{0-4}N_{0-4}S_{0-4}F_{0-13}Cl_{1-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-17}O_{0-4}N_{0-4}S_{0-4}F_{0-13}Cl_{0-3}Si_{1-3}P_{0-3}$, or $C_{0-6}H_{0-17}O_{0-4}N_{0-4}S_{0-4}F_{0-13}Cl_{0-3}Si_{0-3}P_{1-3}$, $C_{1-12}H_{3-29}O_{0-4}N_{0-4}S_{0-4}F_{0-25}Cl_{0-5}P_{0-3}$, $C_{1-12}H_{3-27}O_{0-4}N_{0-2}S_{0-2}F_{0-25}Cl_{0-5}P_{0-1}$, $C_{1-12}H_{3-27}O_{0-4}N_{0-2}$, $C_{1-12}H_{3-25}O_{0-4}$, $C_{1-12}H_{3-27}N_{0-2}$, $C_{1-9}H_{3-21}O_{0-4}N_{0-2}S_{0-2}F_{0-19}Cl_{0-5}P_{0-1}$, $C_{1-9}H_{3-19}F_{0-19}$, $C_{1-9}H_{3-21}O_{0-4}N_{0-2}$, $C_{1-9}H_{3-19}O_{0-4}$, $C_{1-9}H_{3-21}N_{0-2}$, $C_{1-6}H_{3-15}O_{0-3}N_{0-2}S_{0-2}F_{0-13}Cl_{0-5}P_{0-1}$, $C_{1-6}H_{3-13}F_{0-13}$, $C_{1-6}H_{3-15}O_{0-4}N_{0-2}$, $C_{1-6}H_{3-13}O_{0-4}$, $C_{1-6}H_{3-15}N_{0-2}$, $C_{1-3}H_{3-9}O_{0-3}N_{0-2}S_{0-2}F_{0-13}Cl_{0-5}P_{0-1}$, $C_{1-3}H_{3-7}F_{0-7}$, $C_{1-3}H_{3-9}O_{0-3}N_{0-2}$, $C_{1-3}H_{3-7}O_{0-3}$, $C_{1-3}H_{3-9}N_{0-2}$, F, Cl, Br, I, OH, OR^A, SH, SR^A, NH_2, NHR^A, NR^AR^B, CF_3, CN, carboxylic acid, optionally substituted carboxylic ester, or optionally substituted C_{1-6} alkyl, such as optionally substituted branched C_{2-6} alkyl or optionally substituted linear C_{1-6} alkyl, including optionally substituted branched or linear C_{1-3} alkyl (e.g. $–CH_3$, $–C_2H_5$, $–C_3H_7$), optionally substituted branched, linear, or cyclic C_{3-6} alkyl (e.g. $–C_3H_7$, $–C_4H_9$, $–C_5H_{11}$, $–C_6H_{13}$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, carbocycle, heterocycle, hydroxy, alkoxy (—O-alkyl), aryloxy, acyl (e.g. —C(=O)-hydrocarbyl, —C(=O)-alkyl or —C(=O)-phenyl), acyloxy (e.g. hydrocarbyl-CO_2-, alkyl-CO_2-or phenyl-CO_2-), alkylcarboxylate, thiol, alkylthio (—S-alkyl), cyano, halo, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxyl, trihalomethanesulfonyl, trihalomethanesulfonamido, etc.

With respect to any relevant structural representations, R^A is H or an optionally substituted C_{1-6} hydrocarbon group, such as optionally substituted C_{1-6} alkyl, such as optionally substituted C_{1-3} alkyl (e.g. methyl, ethyl, propyl, isopropyl), optionally substituted C_{3-6} alkyl (e.g. propyl, isopropyl, C_4H_9, cyclobutyl, C_5H_{11}, cyclopentyl, C_6H_{13},

cyclohexyl, etc.), optionally substituted C_{1-6} alkenyl, optionally substituted C_{1-6} alkynyl, optionally substituted phenyl, etc.

With respect to any relevant structural representations, R^B is H or an optionally substituted C_{1-6} hydrocarbon group, such as optionally substituted C_{1-6} alkyl, such as optionally substituted C_{1-3} alkyl (e.g. methyl, ethyl, propyl, isopropyl), optionally substituted C_{3-6} alkyl (e.g. propyl, isopropyl, C_4H_9, cyclobutyl, C_5H_{11}, cyclopentyl, C_6H_{13}, cyclohexyl, etc.), optionally substituted C_{1-6} alkenyl, optionally substituted C_{1-6} alkynyl, optionally substituted phenyl, etc.

For convenience, the term "molecular weight" is used with respect to a moiety or part of a molecule to indicate the sum of the atomic masses of the atoms in the moiety or part of a molecule, even though it may not be a complete molecule.

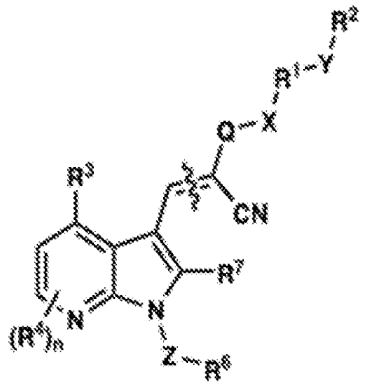
As used herein, the term "alkyl" has the broadest meaning generally understood in the art, and may include a moiety composed of carbon and hydrogen containing no double or triple bonds. Alkyl may be linear alkyl, branched alkyl, cycloalkyl, or a combination thereof, and in some embodiments, may contain from one to thirty-five carbon atoms. In some embodiments, alkyl may include C_{1-10} linear alkyl, such as methyl ($-CH_3$), ethyl ($-CH_2CH_3$), n-propyl ($-CH_2CH_2CH_3$), n-butyl ($-CH_2CH_2CH_2CH_3$), n-pentyl ($-CH_2CH_2CH_2CH_2CH_3$), n-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), etc.; C_{3-10} branched alkyl, such as C_3H_7 (e.g. iso-propyl), C_4H_9 (e.g. branched butyl isomers), C_5H_{11} (e.g. branched pentyl isomers), C_6H_{13} (e.g. branched hexyl isomers), C_7H_{15} (e.g. branched heptyl isomers), etc.; C_{3-10} cycloalkyl, such as C_3H_5 (e.g. cyclopropyl), C_4H_7 (e.g. cyclobutyl isomers such as cyclobutyl, methylcyclopropyl, etc.), C_5H_9 (e.g. cyclopentyl isomers such as cyclopentyl, methylcyclobutyl, dimethylcyclopropyl, etc.), C_6H_{11} (e.g. cyclohexyl isomers), C_7H_{13} (e.g. cycloheptyl isomers), etc.; C_{1-10} straight-chain alkyl groups; C_1-C_{10} branched-chain alkyl groups; C_1-C_6 straight-chain alkyl groups; C_1-C_6 branched-chain alkyl groups; C_1-C_4 straight-chain alkyl groups; C_1-C_4 branched-chain alkyl groups; methyl, ethyl, 1-propyl, 2-propyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl or 4-octyl and the like. The alkyl group may be optionally substituted.

With respect to an optionally substituted moiety such as optionally substituted alkyl, a phrase such as "optionally substituted C_{1-12} alkyl" refers to a C_{1-12} alkyl that may be unsubstituted, or may have 1 or more substituents, and does not limit the number of carbon

atoms in any substituent. A phrase such as "C_{1-12} optionally substituted alkyl" refers to unsubstituted C_{1-12} alkyl, or substituted alkyl wherein both the alkyl parent and all substituents have from 1-12 carbon atoms. Similar conventions may be applied to other optionally substituted moieties such as aryl and heteroaryl.

Empirical formulas, such as $C_{1-12}H_{3-25}O_{0-2}N_{0-2}F_{0-12}$, may be used to describe optionally substituted C_{1-12} alkyl chemical compositions. In some embodiments, additional elements S, Si, P, other halogens, or other heteroatoms may also be included in the empirical formula.

The compounds described herein may have any of the following structural representations:



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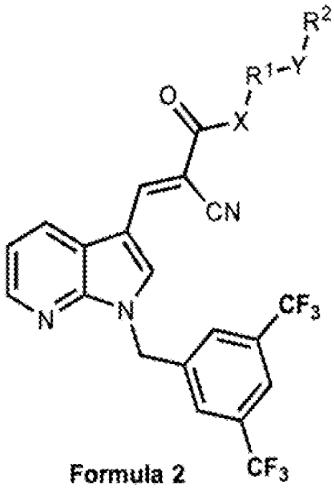
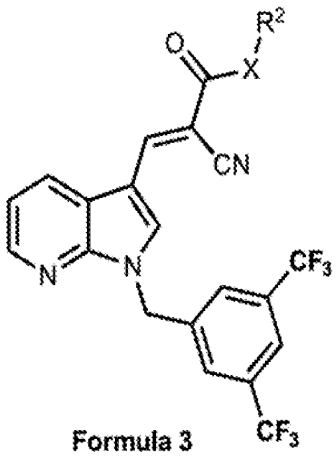
Formula 1



Formula 2

, or



Formula 3

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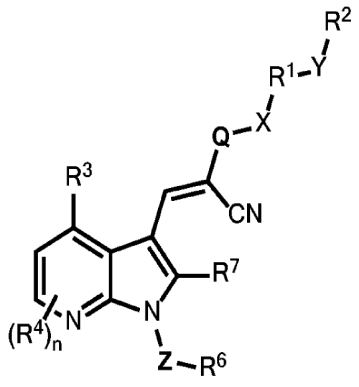
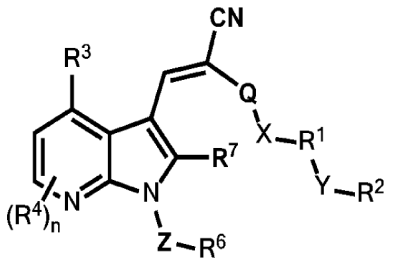
The wavy line across the C=C bond in Formula 1 represents an E or Z olefin, e.g. structures such as Formula 1C and Formula 1T.



Formula 1T



Formula 1C

With respect to any relevant structural representation, such as Formula 1, 1T, and 1C, Q is —C(=O)—, —C(=S)—, or —$S(=O)_2$—. In some embodiments, Q is —C(=O)— . In some embodiments, Q is —C(=S)— . In some embodiments, Q is —$S(=O)_2$—.

With respect to any relevant structural representation, such as Formula 1, 1C, 1T, or 2, R^1 is a bond (represented as —); —$S(=O)_2$—; an optionally substituted C_{1-12} hydrocarbon group, including optionally substituted C_{1-12} alkyl, such as optionally substituted branched C_{2-12} alkyl or optionally substituted linear C_{1-12} alkyl, including optionally substituted branched C_{2-6} alkyl or linear C_{1-6} alkyl, optionally substituted branched C_{2-3} alkyl (e.g., –$CH(CH_3)$–, –$CH(CH_2CH_3)$–, –$C(CH_3)_2$–), or linear C_{1-3} alkyl (e.g., –CH_2–, –C_2H_4–, –C_3H_6–), optionally substituted branched, linear, or cyclic C_{3-6} alkyl (e.g. –C_3H_6–, –C_4H_8–, –C_5H_{10}–, –C_6H_{12}–, –$CH(CH_2CH_3)$–, –$CH(CH_3)CH_2$–, –$C(CH_3)_2CH_2$–, –$CH_2CH(CH_3)CH_2$–, –$C(CH_3)(CH_2CH_3)$–, –$CH(CH_2CH_2CH_3)$–, –$C(CH_2CH_3)_2$–, –$C(CH_3)(CH_2CH_2CH_3)$–, –$CH(CH_2CH_2CH_2CH_3)$–, –$C(CH_3)(CH_2CH_2CH_2CH_3)$–, –$CH(CH_2CH_2CH_2CH_2CH_3)$–, –$C(CH_2CH_3)(CH_2CH_2CH_3)$–, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), optionally substituted branched, linear, or cyclic C_{6-9} alkyl (e.g., –$C(CH_3)(CH_2CH_2CH_2CH_3)$–, –$CH(CH_2CH_2CH_2CH_2CH_3)$–, –$C(CH_2CH_3)(CH_2CH_2CH_3)$–, –$C_6H_{12}$–, –$C_7H_{14}$–, –$C_8H_{16}$–, –$C_9H_{18}$–, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, etc.), optionally substituted branched, linear, or cyclic C_{9-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, optionally substituted C_{3-12} carbocycle, optionally substituted benzyl, etc.; optionally substituted carbocycle, including optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{6-9} cycloalkyl, optionally substituted C_{9-12} cycloalkyl, optionally substituted C_{3-12} cycloalkenyl, optionally substituted C_{3-6} cycloalkenyl, optionally substituted C_{6-9} cycloalkenyl, optionally substituted C_{9-12} cycloalkenyl, optionally substituted C_{3-12} cycloalkynyl, optionally substituted C_{3-6}

cycloalkynyl, optionally substituted C_{6-9} cycloalkynyl, optionally substituted C_{9-12} cycloalkynyl, optionally substituted phenyl, optionally substituted naphthyl; or optionally substituted heterocycle, such as an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 2 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally

substituted bicyclic heterocycle having 8 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 12 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), optionally substituted oxetane, optionally substituted tetrahydrofuran, optionally substituted dihydrofuran, optionally substituted furan, optionally substituted furanone, optionally substituted tetrahydropyran, optionally substituted dihydropyran, an optionally substituted pyran, optionally substituted tetrahydropyrone, optionally substituted dihydropyrone, optionally substituted pyrone, optionally substituted thietane, optionally substituted tetrahydrothiophene, optionally substituted dihydrothiophene, an optionally substituted thiophene, optionally substituted azetidine, optionally substituted pyrrolidine, optionally substituted pyrroline, optionally substituted pyrrole, optionally substituted piperidine, optionally substituted pyridine, optionally substituted oxazole, optionally substituted isoxazole, optionally substituted thiazole,

optionally substituted isothiazole, optionally substituted pyrazolidine, optionally substituted imidazolidine, optionally substituted pyrazole, optionally substituted imidazole, optionally substituted tetrazole, optionally substituted sulfolane. When X is NR^5, the N, R^1 and R^5 may together form an optionally substituted heterocyclic ring (such as optionally substituted morpholine). When X is $N^+R^1R^5$, the N, R^5 and R^1, or the N, R^5 and R^8, may together form an optionally substituted heterocyclic ring (such as optionally substituted morpholinium).

For the purposes of this disclosure, the term "alkyl" refers to both monovalent groups (such as $–CH_3$), bivalent groups (such as $–CH_2–$), or other hydrocarbon groups with higher valency that are free of double and triple bonds.

In some embodiments, R^1 is –. In some embodiments, R^1 is $C_{1\text{-}12}$ alkyl. In some embodiments, R^1 is linear $C_{1\text{-}12}$ alkyl. In some embodiments, R^1 is branched $C_{2\text{-}12}$ alkyl. In some embodiments, R^1 is $–CH_2–$, $–C_2H_4–$, $–C_3H_6–$, $–C_3H_6–$, $–C_4H_8–$, $–C_5H_{10}–$, $–C_6H_{12}–$, $–C_7H_{14}–$, $–C_8H_{16}–$, or $–C_9H_{18}–$. In some embodiments, R^1 is $–CH_2–$. In some embodiments, R^1 is $–C_2H_4–$. In some embodiments, R^1 is $–C_3H_6–$. In some embodiments, R^1 is $–C_3H_6–$. In some embodiments, R^1 is $–C_4H_8–$. In some embodiments, R^1 is $–C_5H_{10}–$. In some embodiments, R^1 is $–C_6H_{12}–$. In some embodiments, R^1 is $–C_7H_{14}–$. In some embodiments, R^1 is $–C_8H_{16}–$. In some embodiments, R^1 is $–C_9H_{18}–$. In some embodiments, R^1 is an optionally substituted linear $C_{1\text{-}12}$ alkyl. In some embodiments, R^1 is an optionally substituted branched $C_{2\text{-}12}$ alkyl. In some embodiments, R^1 is an optionally heteroatom substituted branched $C_{2\text{-}12}$ alkyl, such as a branched $C_{2\text{-}12}$ alkyl having polar substituents, including oxygen containing groups (e.g. -OH, =O, OCH_3, etc.), sulfur containing groups (e.g. -SH, $-SCH_3$, SO_2, SO_3^-, etc.), nitrogen containing groups (e.g. amino groups such as $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, quaternary ammonium salts such as $-[N(CH_3)_2]^+$, $-[N(CH_2CH_3)(CH_3)]^+$, $-NO_2$, -CN, etc.), fluorine containing groups (e.g. F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.).

In some embodiments, R^1 is an optionally substituted carbocycle. In some embodiments, R^1 is optionally substituted cyclohexyl. In some embodiments, R^1 is an optionally substituted aryl. In some embodiments, R^1 is an optionally substituted phenyl. In some embodiments, R^1 is an optionally substituted benzyl. In some embodiments, R^1 is an optionally substituted heteroaryl. In some embodiments, R^1 is an optionally substituted heterocycle. In some embodiments wherein R^1 is an optionally substituted heterocycle, a

carbon atom of the heterocycle (rather than a heteroatom of the heterocycle) is directly attached to X. In some embodiments wherein R^1 is an optionally substituted heterocycle, a carbon atom of the heterocycle ring (rather than a heteroatom of the heterocycle ring) is directly attached to Y. In some embodiments, R^1 is an optionally heteroatom substituted carbocycle, such as a carbocycle having polar substituents, including oxygen containing groups (e.g. -OH, =O, OCH_3, etc.), sulfur containing groups (e.g. -SH, $-SCH_3$, SO_2, SO_3^-, etc.), nitrogen containing groups (e.g. amino groups such as $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, quaternary ammonium salts such as $-[N(CH_3)_2]^+$, $-[N(CH_2CH_3)(CH_3)]^+$, $-NO_2$, -CN, etc.), fluorine containing groups (e.g. F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.). In some embodiments, R^1 is an optionally heteroatom substituted heterocycle, such as a heterocycle having polar substituents, including oxygen containing groups (e.g. -OH, =O, OCH_3, etc.), sulfur containing groups (e.g. -SH, $-SCH_3$, SO_2, SO_3^-, etc.), nitrogen containing groups (e.g. $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NO_2$, -CN, etc.), fluorine containing groups (F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.). In some embodiments, R^1 is an optionally heteroatom substituted benzyl, such as a benzyl having polar substituents, including oxygen containing groups (e.g. -OH, =O, OCH_3, etc.), sulfur containing groups (e.g. -SH, $-SCH_3$, SO_2, SO_3^-, etc.), nitrogen containing groups (e.g. $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NO_2$, -CN, etc.), fluorine containing groups (e.g. F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.).

In some embodiments, R^1 is an optionally substituted oxetane. In some embodiments, R^1 is an optionally substituted oxetane having a carbon atom of the oxetane ring directly attached to X.

In some embodiments, R^1 is an optionally substituted tetrahydrofuran. In some embodiments, R^1 is an optionally substituted tetrahydrofuran having a carbon atom of the tetrahydrofuran ring directly attached to X.

In some embodiments, R^1 is an optionally substituted dihydrofuran. In some embodiments, R^1 is an optionally substituted dihydrofuran having a carbon atom of the dihydrofuran ring directly attached to X.

In some embodiments, R^1 is an optionally substituted furan. In some embodiments, R^1 is an optionally substituted furan having a carbon atom of the furan ring directly attached to X.

In some embodiments, R^1 is an optionally substituted furanone. In some embodiments, R^1 is an optionally substituted furanone having a carbon atom of the furanone ring directly attached to X.

In some embodiments, R^1 is an optionally substituted tetrahydropyran. In some embodiments, R^1 is an optionally substituted tetrahydropyran having a carbon atom of the tetrahydropyran ring directly attached to X.

In some embodiments, R^1 is an optionally substituted dihydropyran. In some embodiments, R^1 is an optionally substituted dihydropyran having a carbon atom of the dihydropyran ring directly attached to X.

In some embodiments, R^1 is an optionally substituted pyran. In some embodiments, R^1 is an optionally substituted pyran having a carbon atom of the pyran ring directly attached to X.

In some embodiments, R^1 is an optionally substituted tetrahydropyrone. In some embodiments, R^1 is an optionally substituted tetrahydropyrone having a carbon atom of the tetrahydropyrone ring directly attached to X.

In some embodiments, R^1 is an optionally substituted dihydropyrone. In some embodiments, R^1 is an optionally substituted dihydropyrone having a carbon atom of the dihydropyrone ring directly attached to X.

In some embodiments, R^1 is an optionally substituted pyrone. In some embodiments, R^1 is an optionally substituted pyrone having a carbon atom of the pyrone ring directly attached to X.

In some embodiments, R^1 is an optionally substituted thietane. In some embodiments, R^1 is an optionally substituted thietane having a carbon atom of the thietane ring directly attached to X.

In some embodiments, R^1 is an optionally substituted tetrahydrothiophene. In some embodiments, R^1 is an optionally substituted tetrahydrothiophene having a carbon atom of the tetrahydrothiophene ring directly attached to X.

In some embodiments, R^1 is an optionally substituted dihydrothiophene. In some embodiments, R^1 is an optionally substituted dihydrothiophene having a carbon atom of the dihydrothiophene ring directly attached to X.

In some embodiments, R^1 is an optionally substituted thiophene. In some embodiments, R^1 is an optionally substituted thiophene having a carbon atom of the thiophene ring directly attached to X.

In some embodiments, R^1 is an optionally substituted azetidine. In some embodiments, R^1 is an optionally substituted azetidine having a carbon atom of the azetidine ring directly attached to X. In some embodiments, R^1 is azetidine having an optionally substituted diphenylmethyl substituent. In some embodiments, R^1 is azetidine having an optionally substituted diphenylmethyl substituent attached to the nitrogen atom of the azetidine ring.

In some embodiments, R^1 is an optionally substituted pyrrolidine. In some embodiments, R^1 is an optionally substituted pyrrolidine having a carbon atom of the pyrrolidine ring directly attached to X.

In some embodiments, R^1 is an optionally substituted pyrroline. In some embodiments, R^1 is an optionally substituted pyrroline having a carbon atom of the pyrroline ring directly attached to X.

In some embodiments, R^1 is an optionally substituted pyrrole. In some embodiments, R^1 is an optionally substituted pyrrole having a carbon atom of the pyrrole ring directly attached to X.

In some embodiments, R^1 is an optionally substituted piperidine. In some embodiments, R^1 is an optionally substituted piperidine having a carbon atom of the piperidine ring directly attached to X.

In some embodiments, R^1 is an optionally substituted pyridine. In some embodiments, R^1 is an optionally substituted pyridine having a carbon atom of the pyridine ring directly attached to X.

In some embodiments, R^1 is an optionally substituted oxazole. In some embodiments, R^1 is an optionally substituted oxazole having a carbon atom of the oxazole ring directly attached to X.

In some embodiments, R^1 is an optionally substituted isoxazole. In some embodiments, R^1 is an optionally substituted isoxazole having a carbon atom of the isoxazole ring directly attached to X.

In some embodiments, R^1 is an optionally substituted thiazole. In some embodiments, R^1 is an optionally substituted thiazole having a carbon atom of the thiazole ring directly attached to X.

In some embodiments, R^1 is an optionally substituted isothiazole. In some embodiments, R^1 is an optionally substituted isothiazole having a carbon atom of the isothiazole ring directly attached to X.

In some embodiments, R^1 is an optionally substituted pyrazolidine. In some embodiments, R^1 is an optionally substituted pyrazolidine having a carbon atom of the pyrazolidine ring directly attached to X.

In some embodiments, R^1 is an optionally substituted imidazolidine. In some embodiments, R^1 is an optionally substituted imidazolidine having a carbon atom of the imidazolidine ring directly attached to X.

In some embodiments, R^1 is an optionally substituted pyrazole. In some embodiments, R^1 is an optionally substituted pyrazole having a carbon atom of the pyrazole ring directly attached to X.

In some embodiments, R^1 is an optionally substituted imidazole. In some embodiments, R^1 is an optionally substituted imidazole having a carbon atom of the imidazole ring directly attached to X.

In some embodiments, R^1 is an optionally substituted tetrazole. In some embodiments, R^1 is an optionally substituted tetrazole having a carbon atom of the tetrazole ring directly attached to X.

In some embodiments, R^1 is an optionally substituted sulfolane. In some embodiments, R^1 is an optionally substituted sulfolane having a carbon atom of the sulfolane ring directly attached to X.

In some embodiments, R^1 is —$S(=O)_2$—.

In some embodiments, R^1 is –CH_2–, –$CH_2CH(CH_3)CH_2$–, or oxetane having a carbon atom of the oxetane ring directly attached to X. In some embodiments, R^1 is –CH_2–. In some embodiments, R^1 is –$CH_2CH(CH_3)CH_2$–. In some embodiments, R^1 is oxetane having a carbon atom of the oxetane ring directly attached to X.

In some embodiments, for a compound of Formula 1, 1C, or 1T, R^1 is —, —CH_2—, an optionally substituted C_{3-12} hydrocarbon group, or an optionally substituted heterocycle having a carbon atom directly attached to X.

In some embodiments, for a compound of Formula 2, R^1 is —, —CH_2—, an optionally substituted C_{3-12} hydrocarbon group, or an optionally substituted heterocycle having a carbon atom directly attached to X.

With respect to any relevant structural representation, such as Formula 1, 1C, 1T, 2, or 3, R^2 is H; optionally substituted C_{1-12} alkyl, optionally substituted C_{1-6} alkyl group, such as optionally substituted branched C_{3-6} alkyl or linear C_{1-6} alkyl, optionally substituted branched C_3 alkyl (e.g., $–CH(CH_3)_2$), or optionally substituted linear C_{1-3} alkyl (e.g., $–CH_3$, $–C_2H_5$, $–C_3H_7$), optionally substituted branched, linear, or cyclic C_{3-6} alkyl (e.g. $–C_3H_7$, $–C_4H_9$, $–C_5H_{11}$, $–C_6H_{13}$, $–CH(CH_3)_2$, $–CH(CH_3)(CH_2CH_3)$, $–C(CH_3)_3$, $–CH(CH_2CH_3)_2$, $–CH(CH_3)(CH_2CH_2CH_3)$, $–C(CH_3)_2(CH_2CH_3)$, $–CH_2CH_2CH_2CH(CH_3)_2$, $–CH_2CH(CH_3)CH_2CH_2CH_3$, $–CH_2CH_2CH(CH_3)CH_2CH_3$, $–CH(CH_2CH_3)(CH_2CH_2CH_3)$, $–C(CH_3)(CH_2CH_3)_2$, cycloalkyl, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.); optionally substituted carbocycle, including optionally substituted cycloalkyl, such as optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} cycloalkenyl, optionally substituted C_{3-6} cycloalkynyl, optionally substituted phenyl; or optionally substituted heterocycle such as an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring nitrogen atom, an

optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 2 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 12 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring

carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), optionally substituted oxetane, optionally substituted tetrahydrofuran, optionally substituted dihydrofuran, optionally substituted furan, optionally substituted furanone, optionally substituted tetrahydropyran, optionally substituted dihydropyran, an optionally substituted pyran, optionally substituted tetrahydropyrone, optionally substituted dihydropyrone, optionally substituted pyrone, optionally substituted thietane, optionally substituted tetrahydrothiophene, optionally substituted dihydrothiophene, an optionally substituted thiophene, optionally substituted azetidine, optionally substituted pyrrolidine, optionally substituted pyrroline, optionally substituted pyrrole, optionally substituted piperidine, optionally substituted pyridine, optionally substituted oxazole, optionally substituted isoxazole, optionally substituted thiazole, optionally substituted isothiazole, optionally substituted pyrazolidine, optionally substituted imidazolidine, optionally substituted pyrazole, optionally substituted imidazole, optionally substituted tetrazole, optionally substituted sulfolane.

In some embodiments, R^2 is H. In some embodiments, R^2 is C_{1-6} alkyl. In some embodiments, R^2 is branched C_{2-6} alkyl. In some embodiments, R^2 is $–CH_3$, $–C_2H_5$, $–C_3H_7$, $–C_4H_9$, $–C_5H_{11}$, or $–C_6H_{13}$. In some embodiments, R^2 is $–CH_3$. In some embodiments, R^2 is $–C_2H_5$. In some embodiments, R^2 is $–C_3H_7$. In some embodiments, R^2 is $–C_4H_9$. In some embodiments, R^2 is $–C_5H_{11}$. In some embodiments, R^2 is $–C_6H_{13}$. In some embodiments, R^2 is an optionally substituted linear C_{1-6} alkyl. In some embodiments, R^2 is isopropyl. In some embodiments, R^2 is isobutyl. In some embodiments, R^2 is tert-butyl. In some embodiments, R^2 is fluoro substituted C_{1-6} alkyl, including C_{1-6} perfluoralkyl. In some embodiments, R^2 is fluoro substituted branched C_{2-6} alkyl, such as branched C_{2-6} perfluoroalkyl. In some embodiments, R^2 is $–CF_3$, $–C_2F_5$, $–C_3F_7$, $–C_4F_9$, $–C_5F_{11}$, or $–C_6F_{13}$. In some embodiments, R^2 is $–CF_3$. In some embodiments, R^2 is $–C_2F_5$. In some embodiments, R^2 is $–C_3F_7$. In some embodiments, R^2 is $–C_4F_9$. In some embodiments, R^2 is $–C_5F_{11}$. In some embodiments, R^2 is $–C_6F_{13}$. In some embodiments, R^2 is CF_3. In some embodiments, R^2 is CHF_2. In some embodiments, R^2 is CH_2F. In some embodiments, R^2 is

CF_2CF_3. In some embodiments, R^2 is $CF_2CF_2CF_3$. In some embodiments, R^2 is fluoro substituted isopropyl, including perfluoroisopropyl. In some embodiments, R^2 is fluoro substituted isobutyl, including perfluoroisobutyl. In some embodiments, R^2 is fluoro substituted tert-butyl including perfluoro-tert-butyl.

In some embodiments, R^2 is an optionally substituted carbocycle. In some embodiments, R^2 is optionally substituted cyclohexyl. In some embodiments, R^2 is an optionally substituted aryl. In some embodiments, R^2 is an optionally substituted phenyl. In some embodiments, R^2 is optionally substituted benzyl. In some embodiments, R^2 is an optionally substituted heteroaryl. In some embodiments, R^2 is an optionally substituted heterocycle. In some embodiments wherein R^2 is an optionally substituted heterocycle, a carbon atom of the heterocycle (rather than a heteroatom of the heterocycle) is directly attached to Y.

In some embodiments, R^2 is an optionally substituted carbocycle, such as a carbocycle having electron-withdrawing substituents including acyl groups (e.g., -C(O)R, etc.) esters (e.g., $-CO_2R$, etc.), amides (e.g., $-C(O)NR_2$, etc.), imides (e.g., -C(O)NRC(O)R, etc.), cyano (-CN), sulfones (e.g., $-SO_2R$, etc.), sulfonamides (e.g., $-SO_2NR_2$), fluorine or fluorine containing groups (e.g., F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.), and/or nitro ($-NO_2$). In some aspects, R^2 is an electron-deficient heterocyclic moiety.

In some embodiments, R^2 is an optionally substituted oxetane. In some embodiments, R^2 is an optionally substituted oxetane having a carbon atom of the oxetane ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted tetrahydrofuran. In some embodiments, R^2 is an optionally substituted tetrahydrofuran having a carbon atom of the tetrahydrofuran ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted dihydrofuran. In some embodiments, R^2 is an optionally substituted dihydrofuran having a carbon atom of the dihydrofuran ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted furan. In some embodiments, R^2 is an optionally substituted furan having a carbon atom of the furan ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted furanone. In some embodiments, R^2 is an optionally substituted furanone having a carbon atom of the furanone ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted tetrahydropyran. In some embodiments, R^2 is an optionally substituted tetrahydropyran having a carbon atom of the tetrahydropyran ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted dihydropyran. In some embodiments, R^2 is an optionally substituted dihydropyran having a carbon atom of the dihydropyran ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted pyran. In some embodiments, R^2 is an optionally substituted pyran having a carbon atom of the pyran ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted tetrahydropyrone. In some embodiments, R^2 is an optionally substituted tetrahydropyrone having a carbon atom of the tetrahydropyrone ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted dihydropyrone. In some embodiments, R^2 is an optionally substituted dihydropyrone having a carbon atom of the dihydropyrone ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted pyrone. In some embodiments, R^2 is an optionally substituted pyrone having a carbon atom of the pyrone ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted thietane. In some embodiments, R^2 is an optionally substituted thietane having a carbon atom of the thietane ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted tetrahydrothiophene. In some embodiments, R^2 is an optionally substituted tetrahydrothiophene having a carbon atom of the tetrahydrothiophene ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted dihydrothiophene. In some embodiments, R^2 is an optionally substituted dihydrothiophene having a carbon atom of the dihydrothiophene ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted thiophene. In some embodiments, R^2 is an optionally substituted thiophene having a carbon atom of the thiophene ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted azetidine. In some embodiments, R^2 is an optionally substituted azetidine having a carbon atom of the azetidine ring directly attached to Y. In some embodiments, R^2 is azetidine having an optionally substituted diphenylmethyl substituent. In some embodiments, R^2 is azetidine having an optionally substituted diphenylmethyl substituent attached to the nitrogen atom of the azetidine ring.

In some embodiments, R^2 is an optionally substituted pyrrolidine. In some embodiments, R^2 is an optionally substituted pyrrolidine having a carbon atom of the pyrrolidine ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted pyrroline. In some embodiments, R^2 is an optionally substituted pyrroline having a carbon atom of the pyrroline ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted pyrrole. In some embodiments, R^2 is an optionally substituted pyrrole having a carbon atom of the pyrrole ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted piperidine. In some embodiments, R^2 is an optionally substituted piperidine having a carbon atom of the piperidine ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted pyridine. In some embodiments, R^2 is an optionally substituted pyridine having a carbon atom of the pyridine ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted oxazole. In some embodiments, R^2 is an optionally substituted oxazole having a carbon atom of the oxazole ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted isoxazole. In some embodiments, R^2 is an optionally substituted isoxazole having a carbon atom of the isoxazole ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted thiazole. In some embodiments, R^2 is an optionally substituted thiazole having a carbon atom of the thiazole ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted isothiazole. In some embodiments, R^2 is an optionally substituted isothiazole having a carbon atom of the isothiazole ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted pyrazolidine. In some embodiments, R^2 is an optionally substituted pyrazolidine having a carbon atom of the pyrazolidine ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted imidazolidine. In some embodiments, R^2 is an optionally substituted imidazolidine having a carbon atom of the imidazolidine ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted pyrazole. In some embodiments, R^2 is an optionally substituted pyrazole having a carbon atom of the pyrazole ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted imidazole. In some embodiments, R^2 is an optionally substituted imidazole having a carbon atom of the imidazole ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted tetrazole. In some embodiments, R^2 is an optionally substituted tetrazole having a carbon atom of the tetrazole ring directly attached to Y.

In some embodiments, R^2 is an optionally substituted sulfolane. In some embodiments, R^2 is an optionally substituted sulfolane having a carbon atom of the sulfolane ring directly attached to Y.

In some more particular but non-limiting forms, R^2 is H, $–CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, or $–C(CH_3)_3$. In some embodiments, R^2 is $-CH_2CH_3$. In some embodiments, R^2 is $-CH(CH_3)_2$.

With respect to any relevant structural representation, such as Formula 3, in some embodiments, R^2 is CH_3 or $C_{3\text{-}12}$ alkyl, such as branched C_3 alkyl (e.g., $–CH(CH_3)_2$), or linear $C_{1\text{-}3}$ alkyl (e.g., $–CH_3$, $–C_2H_5$, $–C_3H_7$), branched, linear, or cyclic $C_{3\text{-}6}$ alkyl (e.g. –

C_3H_7, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$, $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH(CH_2CH_3)_2$, $-CH(CH_3)(CH_2CH_2CH_3)$, $-C(CH_3)_2(CH_2CH_3)$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)CH_2CH_3$, $-CH(CH_2CH_3)(CH_2CH_2CH_3)$, $-C(CH_3)(CH_2CH_3)_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.).

With respect to any relevant structural representation, such as Formula 1, 1C, or 1T, R^3 is H, F, Cl, Br, I, OH, OR^A, SH, SR^A, NH_2, NHR^A, NR^AR^B, CF_3, CN, carboxylic acid, optionally substituted carboxylic ester, or optionally substituted C_{1-6} alkyl, such as optionally substituted branched C_{2-6} alkyl or optionally substituted linear C_{1-6} alkyl, including optionally substituted branched or linear C_{1-3} alkyl (e.g. $-CH_3$, $-C_2H_5$, $-C_3H_7$), optionally substituted branched, linear, or cyclic C_{3-6} alkyl (e.g. $-C_3H_7$, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.).

In some embodiments, R^3 is H. In some embodiments, R^3 is F. In some embodiments, R^3 is Cl. In some embodiments, R^3 is Br. In some embodiments, R^3 is I. In some embodiments, R^3 is OH. In some embodiments, R^3 is OR^A. In some embodiments, R^3 is SH. In some embodiments, R^3 is SR^A. In some embodiments, R^3 is NH_2. In some embodiments, R^3 is NHR^A. In some embodiments, R^3 is NR^AR^B. In some embodiments, R^3 is CF_3. In some embodiments, R^3 is CN. In some embodiments, R^3 is CO_2H. In some embodiments, R^3 is CO_2R^2. In some embodiments, R^3 is C_{1-6} alkyl. In some embodiments, R^3 is branched C_{2-6} alkyl. In some embodiments, R^3 is $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-C_4H_9$, $-C_5H_{11}$, or $-C_6H_{13}$. In some embodiments, R^3 is an optionally substituted C_{1-6} alkyl. In some embodiments, R^3 is an optionally heteroatom substituted linear C_{1-6} alkyl, such as a linear C_{1-6} alkyl having polar substituents, including oxygen containing groups (e.g. -OH, =O, OCH_3, etc.), sulfur containing groups (e.g. -SH, $-SCH_3$, SO_2, SO_3^-, etc.), nitrogen containing groups (e.g. $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NO_2$, -CN, etc.), fluorine containing groups (F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.), etc. In some embodiments, R^3 is an optionally substituted branched C_{3-6} alkyl. In some embodiments, R^3 is an optionally heteroatom substituted branched C_{3-6} alkyl, such as a branched C_{3-6} alkyl having polar substituents, including oxygen containing groups (e.g. -OH, =O, OCH_3, etc.), sulfur containing groups (e.g. -SH, $-SCH_3$, SO_2, SO_3^-, etc.), nitrogen containing groups (e.g. $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NO_2$, -CN, etc.), fluorine containing groups (F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.), etc. In some embodiments, R^3 is H.

With respect to any relevant structural representation, such as Formula 1, 1C, or 1T, each R^4 is independently H, F, Cl, Br, I, OH, O^- (when R^4 is attached to the nitrogen atom at position 7), OR^A, SH, SR^A, NH_2, NHR^A, NR^AR^B, CF_3, CN, carboxylic acid (CO_2H), optionally substituted carboxylic ester (such as optionally substituted C_{1-6} alkyl carboxylic ester, such as optionally substituted branched C_{2-6} alkyl or linear C_{1-6} alkyl carboxylic ester, optionally substituted branched C_3 alkyl carboxylic ester (e.g., $–CO_2-C(CH_3)_2$), or linear C_{1-3} alkyl carboxylic ester (e.g., $–CO_2-CH_3$, $–CO_2-C_2H_5$, $–CO_2-C_3H_7$), optionally substituted branched, linear, or cyclic C_{3-6} alkyl carboxylic ester (e.g. $–CO_2-C_3H_7$, $–CO_2-C_4H_9$, $–CO_2-C_5H_{11}$, $–CO_2-C_6H_{13}$, $–CO_2-CH(CH_3)_2$, $–CO_2-CH(CH_3)(CH_2CH_3)$, $–CO_2-CH(CH_2CH_3)_2$, $–CO_2-CH(CH_3)(CH_2CH_2CH_3)$, $–CO_2-C(CH_3)_2(CH_2CH_2CH_3)$, $–CO_2-C(CH_3)(CH_2CH_2CH_2CH_3)$, $–CO_2-CH(CH_2CH_3)(CH_2CH_2CH_3)$, –$CO_2$-cyclopropyl, –$CO_2$-cyclobutyl, –$CO_2$-cyclopentyl, –$CO_2$-cyclohexyl, etc.), or optionally substituted C_{1-6} alkyl, such as optionally substituted branched C_{2-6} alkyl or linear C_{1-6} alkyl, optionally substituted branched C_3 alkyl (e.g., $–C(CH_3)_2$), or linear C_{1-3} alkyl (e.g., $–CH_3$, $–C_2H_5$, $–C_3H_7$), optionally substituted branched, linear, or cyclic C_{3-6} alkyl (e.g. $–C_3H_7$, $–C_4H_9$, $–C_5H_{11}$, $–C_6H_{13}$, $–CH(CH_3)_2$, $–CH(CH_3)(CH_2CH_3)$, $–CH(CH_2CH_3)_2$, $–CH(CH_3)(CH_2CH_2CH_3)$, $–C(CH_3)_2(CH_2CH_2CH_3)$, $–C(CH_3)(CH_2CH_2CH_2CH_3)$, $–CH(CH_2CH_3)(CH_2CH_2CH_3)$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.).

In some embodiments, an R^4 is H. In some embodiments, an R^4 is F. In some embodiments, an R^4 is Cl. In some embodiments, an R^4 is Br. In some embodiments, an R^4 is I. In some embodiments, an R^4 is OH. In some embodiments, an R^4 is OR^A. In some embodiments, an R^4 is SH. In some embodiments, an R^4 is SR^A. In some embodiments, an R^4 is NH_2. In some embodiments, an R^4 is NHR^A. In some embodiments, an R^4 is NR^AR^B. In some embodiments, an R^4 is CF_3. In some embodiments, an R^4 is CN. In some embodiments, an R^4 is CO_2H. In some embodiments, an R^4 is CO_2R^A. In some embodiments, an R^4 is C_{1-6} alkyl. In some embodiments, an R^4 is branched C_{2-6} alkyl. In some embodiments, an R^4 is $–CH_3$, $–C_2H_5$, $–C_3H_7$, $–C_4H_9$, $–C_5H_{11}$, or $–C_6H_{13}$. In some embodiments, an R^4 is an optionally substituted C_{1-6} alkyl. In some embodiments, an R^4 is an optionally heteroatom substituted linear C_{1-6} alkyl, such as a linear C_{1-6} alkyl having polar substituents, including oxygen containing groups (e.g. -OH, =O, OCH_3, etc.), sulfur containing groups (e.g. -SH, $-SCH_3$, SO_2, SO_3^-, etc.), nitrogen containing groups (e.g. $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NO_2$, -CN, etc.), fluorine containing groups (F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.). In some embodiments, an R^4 is an optionally substituted branched

C_{2-6} alkyl. In some embodiments, an R^4 is an optionally heteroatom substituted branched C_{2-6} alkyl, such as a branched C_{2-6} alkyl having polar substituents, including oxygen containing groups (e.g. -OH, =O, OCH_3, etc.), sulfur containing groups (e.g. -SH, -SCH_3, SO_2, SO_3^-, etc.), nitrogen containing groups (e.g. -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -NO_2, -CN, etc.), fluorine containing groups (F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.).

In some embodiments, an R^4 is H.

With respect to any relevant structural representation, such as Formula 1, 1C, or 1T, n is 0, 1, or 2. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

With respect to any relevant structural representation, such as Formula 1, 1C, 1T, 2, or 3, X is —, an oxygen atom (O), a sulfur atom (S), or a substituted nitrogen atom (NR^5 or $N^+R^5R^8$). In some embodiments, X is —. In some embodiments, X is O. In some embodiments, X is NR^5. In some embodiments, X is $N^+R^5R^8$.

In some embodiments, R^5 is H; optionally substituted C_{1-6} alkyl, such as optionally substituted branched C_{2-6} alkyl or linear C_{1-6} alkyl, optionally substituted branched C_3 alkyl (e.g., $–C(CH_3)_2$), or linear C_{1-3} alkyl (e.g., $–CH_3$, $–C_2H_5$, $–C_3H_7$), optionally substituted branched, linear, or cyclic C_{3-6} alkyl (e.g. $–C_3H_7$, $–C_4H_9$, $–C_5H_{11}$, $–C_6H_{13}$, $–CH(CH_3)_2$, $–CH(CH_3)(CH_2CH_3)$, $–C(CH_3)_3$, $–CH(CH_2CH_3)_2$, $–CH(CH_3)(CH_2CH_2CH_3)$, $–C(CH_3)_2(CH_2CH_3)$, $–CH_2CH_2CH_2CH(CH_3)_2$, $–CH_2CH(CH_3)CH_2CH_2CH_3$, $–CH_2CH_2CH(CH_3)CH_2CH_3$, $–CH(CH_2CH_3)(CH_2CH_2CH_3)$, $–C(CH_3)(CH_2CH_3)_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.); optionally substituted carbocycle, including optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} cycloalkenyl, optionally substituted C_{3-6} cycloalkynyl, optionally substituted phenyl; or optionally substituted heterocycle such as an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle

having 5 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 2 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 12 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 2 ring

heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), optionally substituted oxetane, optionally substituted tetrahydrofuran, optionally substituted dihydrofuran, optionally substituted furan, optionally substituted furanone, optionally substituted tetrahydropyran, optionally substituted dihydropyran, an optionally substituted pyran, optionally substituted tetrahydropyrone, optionally substituted dihydropyrone, optionally substituted pyrone, optionally substituted thietane, optionally substituted tetrahydrothiophene, optionally substituted dihydrothiophene, an optionally substituted thiophene, optionally substituted azetidine, optionally substituted pyrrolidine, optionally substituted pyrroline, optionally substituted pyrrole, optionally substituted piperidine, optionally substituted pyridine, optionally substituted oxazole, optionally substituted isoxazole, optionally substituted thiazole, optionally substituted isothiazole, optionally substituted pyrazolidine, optionally substituted imidazolidine, optionally substituted pyrazole, optionally substituted imidazole, optionally substituted tetrazole, optionally substituted sulfolane.

In some embodiments, R^5 is H. In some embodiments, R^5 is CH_3.

In some embodiments, when X is a substituted nitrogen atom, the N, R^1, and R^5 may together form an optionally substituted heterocyclic ring. In some embodiments, N, R^1, and R^5 may together form an optionally substituted morpholine ring. In some embodiments, N, R^1, and R^5 may together form an optionally substituted piperidine ring. In some embodiments, N, R^1, and R^5 may together form an optionally substituted piperazine ring.

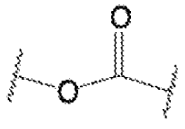
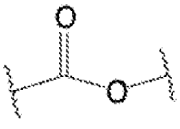
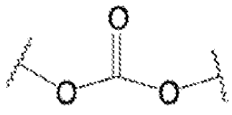
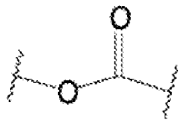
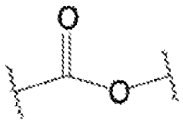
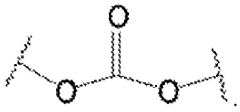
In some embodiments, R^8 is H; optionally substituted C_{1-6} alkyl, such as optionally substituted branched C_{2-6} alkyl or linear C_{1-6} alkyl, optionally substituted branched C_3 alkyl (e.g., $-C(CH_3)_2$), or linear C_{1-3} alkyl (e.g., $-CH_3$, $-C_2H_5$, $-C_3H_7$), optionally substituted branched, linear, or cyclic C_{3-6} alkyl (e.g. $-C_3H_7$, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$, $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH(CH_2CH_3)_2$, $-CH(CH_3)(CH_2CH_2CH_3)$, $-C(CH_3)_2(CH_2CH_3)$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)CH_2CH_3$, $-CH(CH_2CH_3)(CH_2CH_2CH_3)$, $-C(CH_3)(CH_2CH_3)_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.); optionally substituted carbocycle, including optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} cycloalkenyl, optionally substituted C_{3-6} cycloalkynyl, optionally substituted phenyl; or optionally substituted heterocycle such as an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or

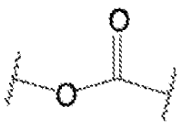
S), an optionally substituted monocyclic heterocycle having 2 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 12 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), optionally substituted oxetane, optionally substituted tetrahydrofuran, optionally substituted dihydrofuran, optionally substituted furan, optionally

substituted furanone, optionally substituted tetrahydropyran, optionally substituted dihydropyran, an optionally substituted pyran, optionally substituted tetrahydropyrone, optionally substituted dihydropyrone, optionally substituted pyrone, optionally substituted thietane, optionally substituted tetrahydrothiophene, optionally substituted dihydrothiophene, an optionally substituted thiophene, optionally substituted azetidine, optionally substituted pyrrolidine, optionally substituted pyrroline, optionally substituted pyrrole, optionally substituted piperidine, optionally substituted pyridine, optionally substituted oxazole, optionally substituted isoxazole, optionally substituted thiazole, optionally substituted isothiazole, optionally substituted pyrazolidine, optionally substituted imidazolidine, optionally substituted pyrazole, optionally substituted imidazole, optionally substituted tetrazole, optionally substituted sulfolane.

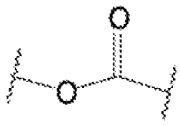
In some embodiments, R^8 is H. In some embodiments, R^8 is CH_3.

In some embodiments, when X is a substituted nitrogen atom, the N, R^5, and R^8 may together form an optionally substituted heterocyclic ring. In some embodiments, N, R^5, and R^8 may together form an optionally substituted morpholine ring. In some embodiments, N, R^5, and R^8 may together form an optionally substituted piperidine ring. In some embodiments, N, R^5, and R^8 may together form an optionally substituted piperazine ring.

With respect to any relevant structural representation, such as Formula 1, 1C, 1T, or 2, Y is —, —O—,  ,  , or  . In some embodiments, Y is —. In some embodiments, Y is —O—. In some embodiments, Y is  . In some embodiments, Y is  . In some embodiments, Y is  .

In some embodiments, Y is — or  .

In some embodiments, R^1 is alkyl, Y is O, and R^2 is alkyl.

In some embodiments, R^1 is alkyl, Y is  , and R^2 is alkyl.

In some embodiments, R^1 is —, Y is —, and R^2 is cycloalkyl.

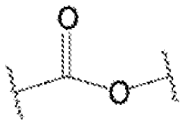
In some embodiments, R^1 is —, Y is —, and R^2 is aryl.

In some embodiments, R^1 is —, Y is —, and R^2 is heteroaryl.

In some embodiments, R^1 is alkyl, Y is —, and R^2 is aryl.

In some embodiments, R^1 is —, Y is —, and R^2 is cycloalkyl.

In some embodiments, R^1 is —, Y is —, and R^2 is a heterocycle.

In some embodiments, R^1 is alkyl, Y is  , and R^2 is alkyl.

With respect to any relevant structural representation, such as Formula 1, 1C, or 1T, Z is —; optionally substituted hydrocarbyl, such as an optionally substituted C_{1-12} hydrocarbon group, including optionally substituted alkyl, including optionally substituted C_{1-12} alkyl, such as optionally substituted branched C_{2-12} alkyl or optionally substituted linear C_{1-12} alkyl, including optionally substituted branched C_{2-6} alkyl or linear C_{1-6} alkyl, optionally substituted branched C_{2-3} alkyl (e.g., $–CH(CH_3)–$, $–CH(CH_2CH_3)–$, $–C(CH_3)_2–$), or linear C_{1-3} alkyl (e.g., $–CH_2–$, $–C_2H_4–$, $–C_3H_6–$), optionally substituted branched, linear, or cyclic C_{3-6} alkyl (e.g. $–C_3H_6–$, $–C_4H_8–$, $–C_5H_{10}–$, $–C_6H_{12}–$, $–CH(CH_2CH_3)–$, $–C(CH_3)_2–$, $–C(CH_3)(CH_2CH_3)–$, $–CH(CH_2CH_2CH_3)–$, $–C(CH_2CH_3)_2–$, $–C(CH_3)(CH_2CH_2CH_3)–$, $–CH(CH_2CH_2CH_2CH_3)–$, $–C(CH_3)(CH_2CH_2CH_2CH_3)–$, $–CH(CH_2CH_2CH_2CH_2CH_3)–$, $–C(CH_2CH_3)(CH_2CH_2CH_3)–$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), optionally substituted branched, linear, or cyclic C_{6-9} alkyl (e.g., $–C(CH_3)(CH_2CH_2CH_2CH_3)–$, $–CH(CH_2CH_2CH_2CH_2CH_3)–$, $–C(CH_2CH_3)(CH_2CH_2CH_3)–$, $–C_6H_{12}–$, $–C_7H_{14}–$, $–C_8H_{16}–$, $–C_9H_{18}–$, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, etc.), optionally substituted branched, linear, or cyclic C_{9-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, optionally substituted benzyl, etc.; optionally substituted carbocycle, including optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{6-9} cycloalkyl, optionally substituted C_{9-12} cycloalkyl, optionally substituted C_{3-12} cycloalkenyl, optionally substituted C_{3-6} cycloalkenyl, optionally substituted C_{6-9}

cycloalkenyl, optionally substituted C_{9-12} cycloalkenyl, optionally substituted C_{3-12} cycloalkynyl, optionally substituted C_{3-6} cycloalkynyl, optionally substituted C_{6-9} cycloalkynyl, optionally substituted C_{9-12} cycloalkynyl, optionally substituted phenyl, optionally substituted naphthyl, or optionally substituted heterocycle such as an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 2 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 1 ring heteroatom (N, O, or S), an

optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 12 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), optionally substituted oxetane, optionally substituted tetrahydrofuran, optionally substituted dihydrofuran, optionally substituted furan, optionally substituted furanone, optionally substituted tetrahydropyran, optionally substituted dihydropyran, an optionally substituted pyran, optionally substituted tetrahydropyrone, optionally substituted dihydropyrone, optionally substituted pyrone, optionally substituted thietane, optionally substituted tetrahydrothiophene, optionally substituted dihydrothiophene, an optionally substituted thiophene, optionally substituted azetidine, optionally substituted pyrrolidine, optionally substituted pyrroline, optionally substituted pyrrole, optionally substituted piperidine,

optionally substituted pyridine, optionally substituted oxazole, optionally substituted isoxazole, optionally substituted thiazole, optionally substituted isothiazole, optionally substituted pyrazolidine, optionally substituted imidazolidine, optionally substituted pyrazole, optionally substituted imidazole, optionally substituted tetrazole, optionally substituted sulfolane.

Potential substituents on Z include alkyl, such as C_{1-12} alkyl, C_{1-3} alkyl, C_{3-6} alkyl, C_{6-9} alkyl, C_{9-12} alkyl, CH_3, $–C_2H_5$, $–C_3H_7$, $–C_4H_9$, $–C_5H_{11}$, $–C_6H_{13}$, $–C_7H_{15}$, $–C_8H_{17}$, $–C_9H_{19}$, $–C_{10}H_{21}$, $–C_{11}H_{23}$, $–C_{12}H_{25}$, etc.; halo, such as F, Cl, Br, I, etc.; OH; $-CO_2H$; acyl, such as C_{1-12} -C(=O)-alkyl, C_{1-3} -C(=O)-alkyl, C_{3-6} -C(=O)-alkyl, C_{6-9} -C(=O)-alkyl, C_{9-12} -C(=O)-alkyl, $-C(=O)-CH_3$, $–C(=O)-C_2H_5$, $–C(=O)-C_3H_7$, $–C(=O)-C_4H_9$, $–C(=O)-C_5H_{11}$, $–C(=O)-C_6H_{13}$, $–C(=O)-C_7H_{15}$, $–C(=O)-C_8H_{17}$, $–C(=O)-C_9H_{19}$, $–C(=O)-C_{10}H_{21}$, $–C(=O)-C_{11}H_{23}$, $–C(=O)-C_{12}H_{25}$, $–C(=O)$-phenyl, etc.; alkoxy, such as such as C_{1-12} -O-alkyl, C_{1-3} -O-alkyl, C_{3-6} -O-alkyl, C_{6-9} -O-alkyl, C_{9-12} -O-alkyl, $-OCH_3$, $–OC_2H_5$, $–OC_3H_7$, $–OC_4H_9$, $–OC_5H_{11}$, $–OC_6H_{13}$, $–OC_7H_{15}$, $–OC_8H_{17}$, $–OC_9H_{19}$, $–OC_{10}H_{21}$, $–OC_{11}H_{23}$, $–OC_{12}H_{25}$, etc.; alkylthio, such as C_{1-12} -S-alkyl, C_{1-3} -S-alkyl, C_{3-6} -S-alkyl, C_{6-9} -S-alkyl, C_{9-12} -S-alkyl, $-SCH_3$, $–SC_2H_5$, $–SC_3H_7$, $–SC_4H_9$, $–SC_5H_{11}$, $–SC_6H_{13}$, $–SC_7H_{15}$, $–SC_8H_{17}$, $–SC_9H_{19}$, $–SC_{10}H_{21}$, $–SC_{11}H_{23}$, $–SC_{12}H_{25}$, etc.; thioester (e.g. $-C(O)SR^A$, $–SC(O)R^A$, etc.); phosphoryl; amino (e.g. NR^AR^B, where NR^AR^B may potentially form a ring, or $N^+R^AR^BR^C$, wherein R^C is H or hydrocarbyl, and $N^+R^AR^BR^C$ may potentially form a ring); amide (e.g. $-C(=O)NR^AR^B$, including where NR^AR^B form a ring); CN; $-NO_2$; azido; alkenyl, such as C_{2-12} alkenyl, C_{2-4} alkenyl, C_{4-6} alkenyl, C_{6-8} alkenyl, C_{8-10} alkenyl, C_{10-12} alkenyl, (e.g. $-CH=CH_2$, $-CH=CH_2CH_3$, etc.); alkynyl, such as C_{2-12} alkynyl, C_{2-4} alkynyl, C_{4-6} alkynyl, C_{6-8} alkynyl, C_{8-10} alkynyl, C_{10-12} alkynyl, (e.g. $-C\equiv CH$, $-C\equiv C-CH_3$, etc.); cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexyl, etc.; heterocyclylalkyl (e.g. -alkyl-heterocycle); heteroaralkyl (e.g. -alkyl-heteroaryl); sulfonamide (e.g. $-SO_2NR^AR^B$, $-NR^ASO_2R^B$, etc.); aryl; heteroaryl; heterocyclyl; aralkyl (e.g. -alkyl-aryl; etc.

In some embodiments, Z is —. In some embodiments, Z is alkyl, such as C_{1-12} alkyl. In some embodiments, Z is linear C_{1-12} alkyl. In some embodiments, Z is branched C_{2-12} alkyl. In some embodiments, Z is $–CH_2–$, $–C_2H_4–$, $–C_3H_6–$, $–C_3H_6–$, $–C_4H_8–$, $–C_5H_{10}–$, $–C_6H_{12}–$, $–C_7H_{14}–$, $–C_8H_{16}–$, or $–C_9H_{18}–$, In some embodiments, Z is an optionally substituted linear C_{1-12} alkyl. In some embodiments, Z is an optionally substituted branched C_{2-12} alkyl. In some embodiments, Z is $–CH_2–$.

In some embodiments, Z is an optionally substituted carbocycle. In some embodiments, Z is optionally substituted cyclohexyl. In some embodiments, Z is an optionally substituted aryl. In some embodiments, Z is an optionally substituted phenyl. In some embodiments, Z is an optionally substituted benzyl. In some embodiments, Z is an optionally substituted heteroaryl. In some embodiments, Z is an optionally substituted heterocycle. In some embodiments wherein Z is an optionally substituted heterocycle, a carbon atom of the heterocycle (rather than a heteroatom of the heterocycle) is directly attached to the indole nitrogen atom of the core azaindole ring. In some aspects, Z is an electron-deficient heterocyclic moiety. In some aspects, Z is an electron-deficient aryl moiety. In some aspects, Z is an electron-deficient alkyl moiety.

In some embodiments, Z is an optionally substituted benzyl. In some embodiments, Z is an optionally substituted benzyl having the carbon atom of the methylene directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted phenyl. In some embodiments, Z is an optionally substituted phenyl having a carbon atom of the phenyl directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted oxetane. In some embodiments, Z is an optionally substituted oxetane having a carbon atom of the oxetane ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted tetrahydrofuran. In some embodiments, Z is an optionally substituted tetrahydrofuran having a carbon atom of the tetrahydrofuran ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted dihydrofuran. In some embodiments, Z is an optionally substituted dihydrofuran having a carbon atom of the dihydrofuran ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted furan. In some embodiments, Z is an optionally substituted furan having a carbon atom of the furan ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted furanone. In some embodiments, Z is an optionally substituted furanone having a carbon atom of the furanone ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted tetrahydropyran. In some embodiments, Z is an optionally substituted tetrahydropyran having a carbon atom of the tetrahydropyran ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted dihydropyran. In some embodiments, Z is an optionally substituted dihydropyran having a carbon atom of the dihydropyran ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted pyran. In some embodiments, Z is an optionally substituted pyran having a carbon atom of the pyran ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted tetrahydropyrone. In some embodiments, Z is an optionally substituted tetrahydropyrone having a carbon atom of the tetrahydropyrone ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted dihydropyrone. In some embodiments, Z is an optionally substituted dihydropyrone having a carbon atom of the dihydropyrone ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted pyrone. In some embodiments, Z is an optionally substituted pyrone having a carbon atom of the pyrone ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted thietane. In some embodiments, Z is an optionally substituted thietane having a carbon atom of the thietane ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted tetrahydrothiophene. In some embodiments, Z is an optionally substituted tetrahydrothiophene having a carbon atom of the tetrahydrothiophene ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted dihydrothiophene. In some embodiments, Z is an optionally substituted dihydrothiophene having a carbon atom of the

dihydrothiophene ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted thiophene. In some embodiments, Z is an optionally substituted thiophene having a carbon atom of the thiophene ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted azetidine. In some embodiments, Z is an optionally substituted azetidine having a carbon atom of the azetidine ring directly attached to the indole nitrogen atom of the core azaindole ring. In some embodiments, Z is azetidine having an optionally substituted diphenylmethyl substituent. In some embodiments, Z is azetidine having an optionally substituted diphenylmethyl substituent attached to the nitrogen atom of the azetidine ring.

In some embodiments, Z is an optionally substituted pyrrolidine. In some embodiments, Z is an optionally substituted pyrrolidine having a carbon atom of the pyrrolidine ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted pyrroline. In some embodiments, Z is an optionally substituted pyrroline having a carbon atom of the pyrroline ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted pyrrole. In some embodiments, Z is an optionally substituted pyrrole having a carbon atom of the pyrrole ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted piperidine. In some embodiments, Z is an optionally substituted piperidine having a carbon atom of the piperidine ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted pyridine. In some embodiments, Z is an optionally substituted pyridine having a carbon atom of the pyridine ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted oxazole. In some embodiments, Z is an optionally substituted oxazole having a carbon atom of the oxazole ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted isoxazole. In some embodiments, Z is an optionally substituted isoxazole having a carbon atom of the isoxazole ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted thiazole. In some embodiments, Z is an optionally substituted thiazole having a carbon atom of the thiazole ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted isothiazole. In some embodiments, Z is an optionally substituted isothiazole having a carbon atom of the isothiazole ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted pyrazolidine. In some embodiments, Z is an optionally substituted pyrazolidine having a carbon atom of the pyrazolidine ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is an optionally substituted imidazolidine. In some embodiments, Z is an optionally substituted imidazolidine having a carbon atom of the imidazolidine ring directly attached to the indole nitrogen atom of the core azaindole ring.

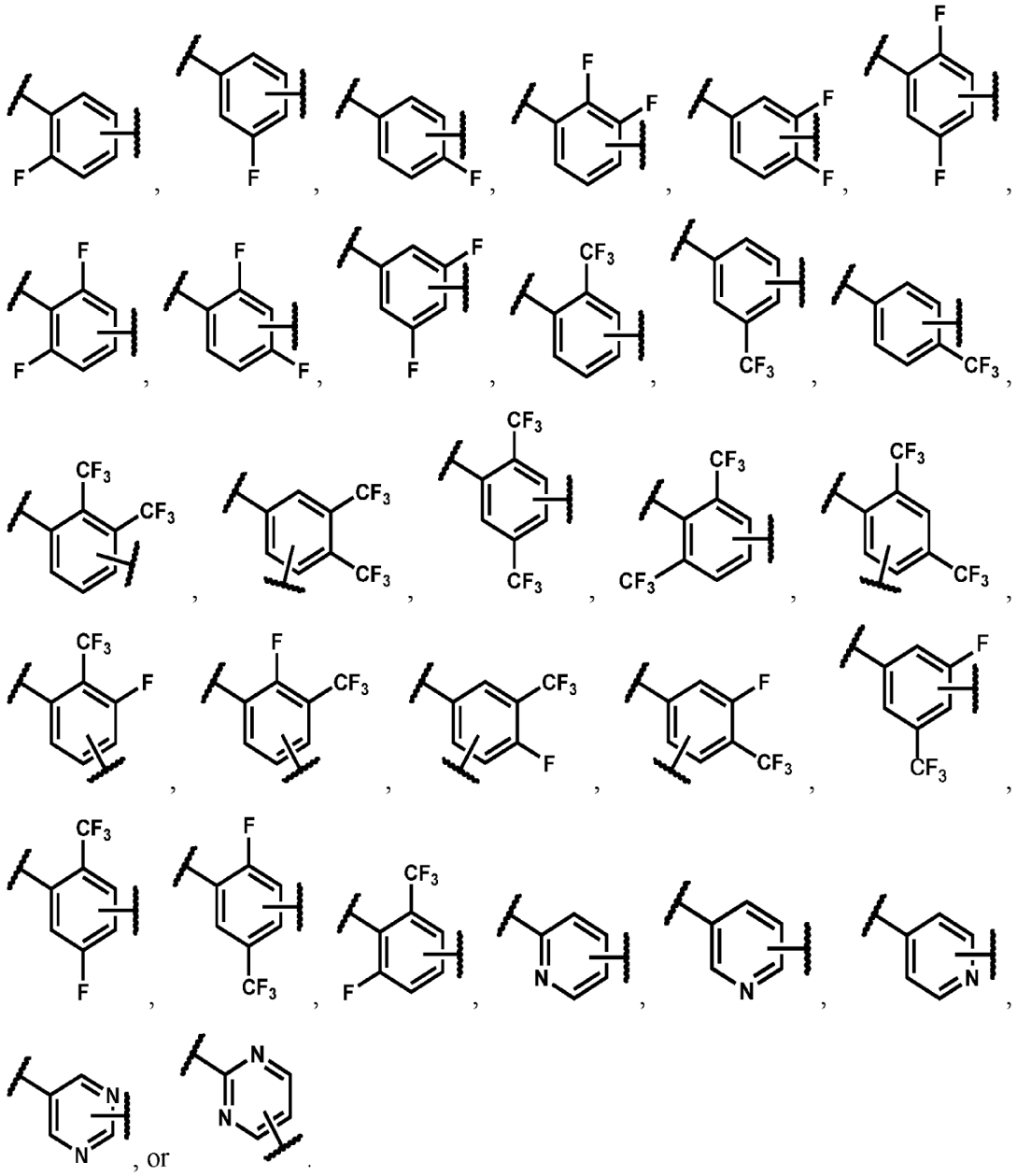
In some embodiments, Z is an optionally substituted pyrazole. In some embodiments, Z is an optionally substituted pyrazole having a carbon atom of the pyrazole ring directly attached to the indole nitrogen atom of the core azaindole ring.

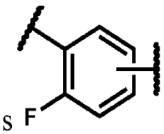
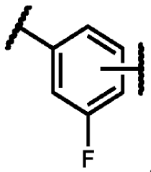
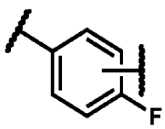
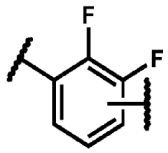
In some embodiments, Z is an optionally substituted imidazole. In some embodiments, Z is an optionally substituted imidazole having a carbon atom of the imidazole ring directly attached to the indole nitrogen atom of the core azaindole ring.

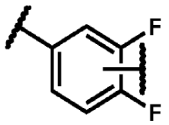
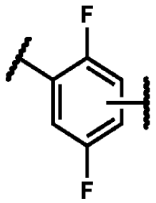
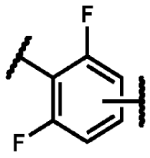
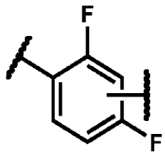
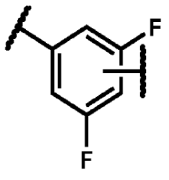
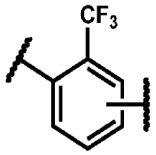
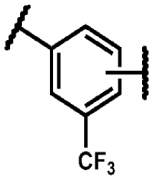
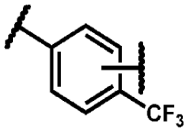
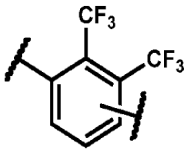
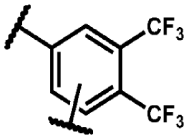
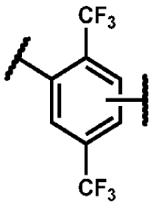
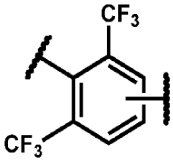
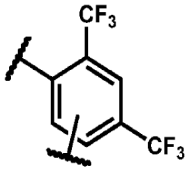
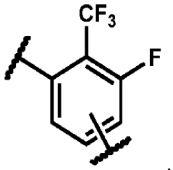
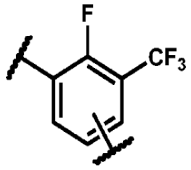
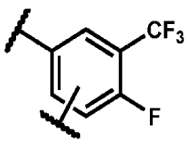
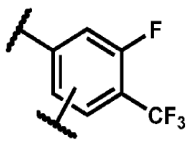
In some embodiments, Z is an optionally substituted tetrazole. In some embodiments, Z is an optionally substituted tetrazole having a carbon atom of the tetrazole ring directly attached to the indole nitrogen atom of the core azaindole ring.

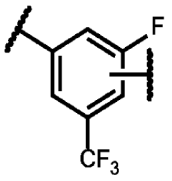
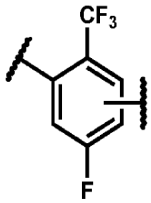
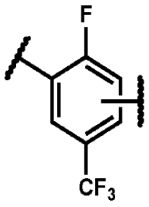
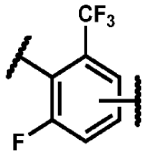
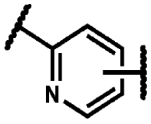
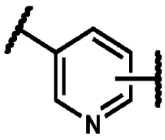
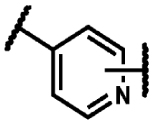
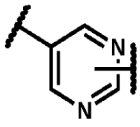
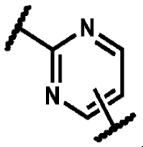
In some embodiments, Z is an optionally substituted sulfolane. In some embodiments, Z is an optionally substituted sulfolane having a carbon atom of the sulfolane ring directly attached to the indole nitrogen atom of the core azaindole ring.

In some embodiments, Z is represented by one of the following structures:



In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some

embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is. In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is  . In some embodiments, Z is


. In some embodiments, Z is 
. In some embodiments, Z is 
. In some embodiments, Z is 
. In some embodiments, Z is 
. In some embodiments, Z is 
. In some embodiments, Z is 
. In some embodiments, Z is 
. In some embodiments, Z is 
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With respect to any relevant structural representation, such as Formula 1, 1C, or 1T, R^6 is H; optionally substituted C_{1-12} hydrocarbon group, including optionally substituted C_{1-12} alkyl, such as optionally substituted branched C_{2-12} alkyl or optionally substituted linear C_{1-12} alkyl, including optionally substituted branched C_{2-6} alkyl or linear C_{1-6} alkyl, optionally substituted branched C_3 alkyl (e.g., $–C(CH_3)_2$), or linear C_{1-3} alkyl (e.g., $–CH_3$, $–C_2H_5$, $–C_3H_7$), optionally substituted branched, linear, or cyclic C_{3-6} alkyl (e.g. $–C_3H_7$, $–C_4H_9$, $–C_5H_{11}$, $–C_6H_{13}$, $–C(CH_3)_2$, $–CH(CH_3)(CH_2CH_3)$, $–CH(CH_2CH_3)_2$, $–CH(CH_3)(CH_2CH_2CH_3)$, $–CH(CH_3)(CH_2CH_2CH_2CH_3)$, $–CH(CH_2CH_3)(CH_2CH_2CH_3)$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), optionally substituted branched, linear, or cyclic C_{6-9} alkyl (e.g., $–CH(CH_3)(CH_2CH_2CH_2CH_3)$, $–CH(CH_2CH_3)(CH_2CH_2CH_3)$, $–C_6H_{13}$, $–C_7H_{15}$, $–C_8H_{17}$, $–C_9H_{19}$, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, etc.), optionally substituted branched, linear, or cyclic C_{9-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, optionally substituted benzyl, etc.; optionally substituted carbocycle, including optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{6-9} cycloalkyl, optionally substituted C_{9-12} cycloalkyl, optionally substituted C_{3-12} cycloalkenyl, optionally substituted C_{3-6} cycloalkenyl,

optionally substituted C_{6-9} cycloalkenyl, optionally substituted C_{9-12} cycloalkenyl, optionally substituted C_{3-12} cycloalkynyl, optionally substituted C_{3-6} cycloalkynyl, optionally substituted C_{6-9} cycloalkynyl, optionally substituted C_{9-12} cycloalkynyl, optionally substituted phenyl, optionally substituted naphthyl, or optionally substituted heterocycle such as an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring oxygen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring sulfur atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 7 ring carbon atoms and 1 ring nitrogen atom, an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 2 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 3 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 4 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted monocyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 1 ring

heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 12 ring carbon atoms and 1 ring heteroatom (N, O, or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 11 ring carbon atoms and 2 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 5 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 6 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 7 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 8 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 9 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), an optionally substituted bicyclic heterocycle having 10 ring carbon atoms and 3 ring heteroatoms (N, O, and/or S), optionally substituted oxetane, optionally substituted tetrahydrofuran, optionally substituted dihydrofuran, optionally substituted furan, optionally substituted furanone, optionally substituted tetrahydropyran, optionally substituted dihydropyran, an optionally substituted pyran, optionally substituted tetrahydropyrone, optionally substituted dihydropyrone, optionally substituted pyrone, optionally substituted thietane, optionally substituted tetrahydrothiophene, optionally substituted dihydrothiophene, an optionally substituted thiophene, optionally substituted azetidine, optionally substituted pyrrolidine, optionally substituted pyrroline, optionally substituted pyrrole, optionally substituted piperidine,

optionally substituted pyridine, optionally substituted oxazole, optionally substituted isoxazole, optionally substituted thiazole, optionally substituted isothiazole, optionally substituted pyrazolidine, optionally substituted imidazolidine, optionally substituted pyrazole, optionally substituted imidazole, optionally substituted tetrazole, optionally substituted sulfolane.

Potential substituents on R_6 include alkyl, such as C_{1-12} alkyl, C_{1-3} alkyl, C_{3-6} alkyl, C_{6-9} alkyl, C_{9-12} alkyl, CH_3, $–C_2H_5$, $–C_3H_7$, $–C_4H_9$, $–C_5H_{11}$, $–C_6H_{13}$, $–C_7H_{15}$, $–C_8H_{17}$, $–C_9H_{19}$, $–C_{10}H_{21}$, $–C_{11}H_{23}$, $–C_{12}H_{25}$, etc.; halo, such as F, Cl, Br, I, etc.; OH; $-CO_2H$; acyl, such as C_{1-12} -C(=O)-alkyl, C_{1-3} -C(=O)-alkyl, C_{3-6} -C(=O)-alkyl, C_{6-9} -C(=O)-alkyl, C_{9-12} -C(=O)-alkyl, $-C(=O)-CH_3$, $–C(=O)-C_2H_5$, $–C(=O)-C_3H_7$, $–C(=O)-C_4H_9$, $–C(=O)-C_5H_{11}$, $–C(=O)-C_6H_{13}$, $–C(=O)-C_7H_{15}$, $–C(=O)-C_8H_{17}$, $–C(=O)-C_9H_{19}$, $–C(=O)-C_{10}H_{21}$, $–C(=O)-C_{11}H_{23}$, $–C(=O)-C_{12}H_{25}$, $–C(=O)$-phenyl, etc.; alkoxy, such as such as C_{1-12} -O-alkyl, C_{1-3} -O-alkyl, C_{3-6} -O-alkyl, C_{6-9} -O-alkyl, C_{9-12} -O-alkyl, $-OCH_3$, $–OC_2H_5$, $–OC_3H_7$, $–OC_4H_9$, $–OC_5H_{11}$, $–OC_6H_{13}$, $–OC_7H_{15}$, $–OC_8H_{17}$, $–OC_9H_{19}$, $–OC_{10}H_{21}$, $–OC_{11}H_{23}$, $–OC_{12}H_{25}$, etc.; alkylthio, such as C_{1-12} -S-alkyl, C_{1-3} -S-alkyl, C_{3-6} -S-alkyl, C_{6-9} -S-alkyl, C_{9-12} -S-alkyl, $-SCH_3$, $–SC_2H_5$, $–SC_3H_7$, $–SC_4H_9$, $–SC_5H_{11}$, $–SC_6H_{13}$, $–SC_7H_{15}$, $–SC_8H_{17}$, $–SC_9H_{19}$, $–SC_{10}H_{21}$, $–SC_{11}H_{23}$, $–SC_{12}H_{25}$, etc.; thioester (e.g. $-C(O)SR^A$, $–SC(O)R^A$, etc.); phosphoryl; amino (e.g. NR^AR^B, where NR^AR^B may potentially form a ring, or $N^+R^AR^BR^C$, wherein R^C is H or hydrocarbyl, and $N^+R^AR^BR^C$ may potentially form a ring); amide (e.g. $-C(=O)NR^AR^B$, including where NR^AR^B form a ring); CN; $-NO_2$; azido; alkenyl, such as C_{2-12} alkenyl, C_{2-4} alkenyl, C_{4-6} alkenyl, C_{6-8} alkenyl, C_{8-10} alkenyl, C_{10-12} alkenyl, (e.g. $-CH=CH_2$, $-CH=CH_2CH_3$, etc.); alkynyl, such as C_{2-12} alkynyl, C_{2-4} alkynyl, C_{4-6} alkynyl, C_{6-8} alkynyl, C_{8-10} alkynyl, C_{10-12} alkynyl, (e.g. $-C\equiv CH$, $-C\equiv C-CH_3$, etc.); cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexyl, etc.; heterocyclylalkyl (e.g. -alkyl-heterocycle); heteroaralkyl (e.g. -alkyl-heteroaryl); sulfonamide (e.g. $-SO_2NR^AR^B$, $-NR^ASO_2R^B$, etc.); aryl; heteroaryl; heterocyclyl; aralkyl (e.g. -alkyl-aryl; etc.In some embodiments, R^6 is H. In some embodiments, R^6 is C_{1-12} alkyl. In some embodiments, R^6 is linear C_{1-12} alkyl. In some embodiments, R^6 is $–CH_3$, $–C_2H_5$, $–C_3H_7$, $–C_4H_9$, $–C_5H_{11}$, $–C_6H_{13}$, $–C_7H_{15}$, $–C_8H_{17}$, $–C_9H_{19}$, $–C_{10}H_{21}$, $–C_{11}H_{23}$, $–C_{12}H_{25}$. In some embodiments, R^6 is an optionally substituted linear C_{1-12} alkyl. In some embodiments, R^6 is branched C_{3-12} alkyl. In some embodiments, R^6 is an optionally substituted branched C_{3-12} alkyl.

In some embodiments, R^6 is an optionally substituted carbocycle, such as a carbocycle having electron-withdrawing substituents including acyl groups (e.g., -C(O)R,

etc.) esters (e.g., -CO_2R, etc.), amides (e.g., -$C(O)NR_2$, etc.), imides (e.g., -C(O)NRC(O)R, etc.), cyano (-CN), sulfones (e.g., -SO_2R, etc.), sulfonamides (e.g., -SO_2NR_2), fluorine or fluorine containing groups (e.g., F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.), and/or nitro (-NO_2). In some aspects, R^6 is an electron-deficient heterocyclic moiety. In some aspects, R^6 is an electron-deficient aryl moiety. In some aspects, R^6 is an electron-deficient alkyl moiety.

In some embodiments, R^6 is an optionally substituted carbocycle. In some embodiments, R^6 is optionally substituted cyclohexyl. In some embodiments, R^6 is an optionally substituted aryl. In some embodiments, R^6 is an optionally substituted phenyl. In some embodiments, R^6 is an optionally substituted benzyl. In some embodiments, R^6 is an optionally substituted heteroaryl. In some embodiments, R^6 is an optionally substituted heterocycle. In some embodiments wherein R^6 is an optionally substituted heterocycle, a carbon atom of the heterocycle (rather than a heteroatom of the heterocycle) is directly attached to Z.

In some embodiments, R^6 is fluoro substituted C_{1-6} alkyl, including C_{1-6} perfluoralkyl. In some embodiments, R^6 is fluoro substituted branched C_{2-6} alkyl, such as branched C_{2-6} perfluoroalkyl. In some embodiments, R^6 is $–CF_3$, $–C_2F_5$, $–C_3F_7$, $–C_4F_9$, $–C_5F_{11}$, or $–C_6F_{13}$. In some embodiments, R^6 is $–CF_3$. In some embodiments, R^6 is $–C_2F_5$. In some embodiments, R^6 is $–C_3F_7$. In some embodiments, R^6 is $–C_4F_9$. In some embodiments, R^6 is $–C_5F_{11}$. In some embodiments, R^6 is $–C_6F_{13}$. In some embodiments, R^6 is CF_3. In some embodiments, R^6 is CHF_2. In some embodiments, R^6 is CH_2F. In some embodiments, R^6 is CF_2CF_3. In some embodiments, R^6 is $CF_2CF_2CF_3$. In some embodiments, R^6 is fluoro substituted isopropyl, including perfluoroisopropyl. In some embodiments, R^6 is fluoro substituted isobutyl, including perfluoroisobutyl. In some embodiments, R^6 is fluoro substituted tert-butyl including perfluoro-tert-butyl. In some embodiments, R^6 is CF_3. In some embodiments, R^6 is CHF_2. In some embodiments, R^6 is CH_2F. In some embodiments, R^6 is CF_2CF_3. In some embodiments, R^6 is $CF_2CF_2CF_3$.

In some embodiments, R^6 is an optionally substituted oxetane. In some embodiments, R^6 is an optionally substituted oxetane having a carbon atom of the oxetane ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted tetrahydrofuran. In some embodiments, R^6 is an optionally substituted tetrahydrofuran having a carbon atom of the tetrahydrofuran ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted dihydrofuran. In some embodiments, R^6 is an optionally substituted dihydrofuran having a carbon atom of the dihydrofuran ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted furan. In some embodiments, R^6 is an optionally substituted furan having a carbon atom of the furan ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted furanone. In some embodiments, R^6 is an optionally substituted furanone having a carbon atom of the furanone ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted tetrahydropyran. In some embodiments, R^6 is an optionally substituted tetrahydropyran having a carbon atom of the tetrahydropyran ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted dihydropyran. In some embodiments, R^6 is an optionally substituted dihydropyran having a carbon atom of the dihydropyran ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted pyran. In some embodiments, R^6 is an optionally substituted pyran having a carbon atom of the pyran ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted tetrahydropyrone. In some embodiments, R^6 is an optionally substituted tetrahydropyrone having a carbon atom of the tetrahydropyrone ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted dihydropyrone. In some embodiments, R^6 is an optionally substituted dihydropyrone having a carbon atom of the dihydropyrone ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted pyrone. In some embodiments, R^6 is an optionally substituted pyrone having a carbon atom of the pyrone ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted thietane. In some embodiments, R^6 is an optionally substituted thietane having a carbon atom of the thietane ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted tetrahydrothiophene. In some embodiments, R^6 is an optionally substituted tetrahydrothiophene having a carbon atom of the tetrahydrothiophene ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted dihydrothiophene. In some embodiments, R^6 is an optionally substituted dihydrothiophene having a carbon atom of the dihydrothiophene ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted thiophene. In some embodiments, R^6 is an optionally substituted thiophene having a carbon atom of the thiophene ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted azetidine. In some embodiments, R^6 is an optionally substituted azetidine having a carbon atom of the azetidine ring directly attached to Z. In some embodiments, R^6 is azetidine having an optionally substituted diphenylmethyl substituent. In some embodiments, R^6 is azetidine having an optionally substituted diphenylmethyl substituent attached to the nitrogen atom of the azetidine ring.

In some embodiments, R^6 is an optionally substituted pyrrolidine. In some embodiments, R^6 is an optionally substituted pyrrolidine having a carbon atom of the pyrrolidine ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted pyrroline. In some embodiments, R^6 is an optionally substituted pyrroline having a carbon atom of the pyrroline ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted pyrrole. In some embodiments, R^6 is an optionally substituted pyrrole having a carbon atom of the pyrrole ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted piperidine. In some embodiments, R^6 is an optionally substituted piperidine having a carbon atom of the piperidine ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted pyridine. In some embodiments, R^6 is an optionally substituted pyridine having a carbon atom of the pyridine ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted oxazole. In some embodiments, R^6 is an optionally substituted oxazole having a carbon atom of the oxazole ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted isoxazole. In some embodiments, R^6 is an optionally substituted isoxazole having a carbon atom of the isoxazole ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted thiazole. In some embodiments, R^6 is an optionally substituted thiazole having a carbon atom of the thiazole ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted isothiazole. In some embodiments, R^6 is an optionally substituted isothiazole having a carbon atom of the isothiazole ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted pyrazolidine. In some embodiments, R^6 is an optionally substituted pyrazolidine having a carbon atom of the pyrazolidine ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted imidazolidine. In some embodiments, R^6 is an optionally substituted imidazolidine having a carbon atom of the imidazolidine ring directly attached to Z.

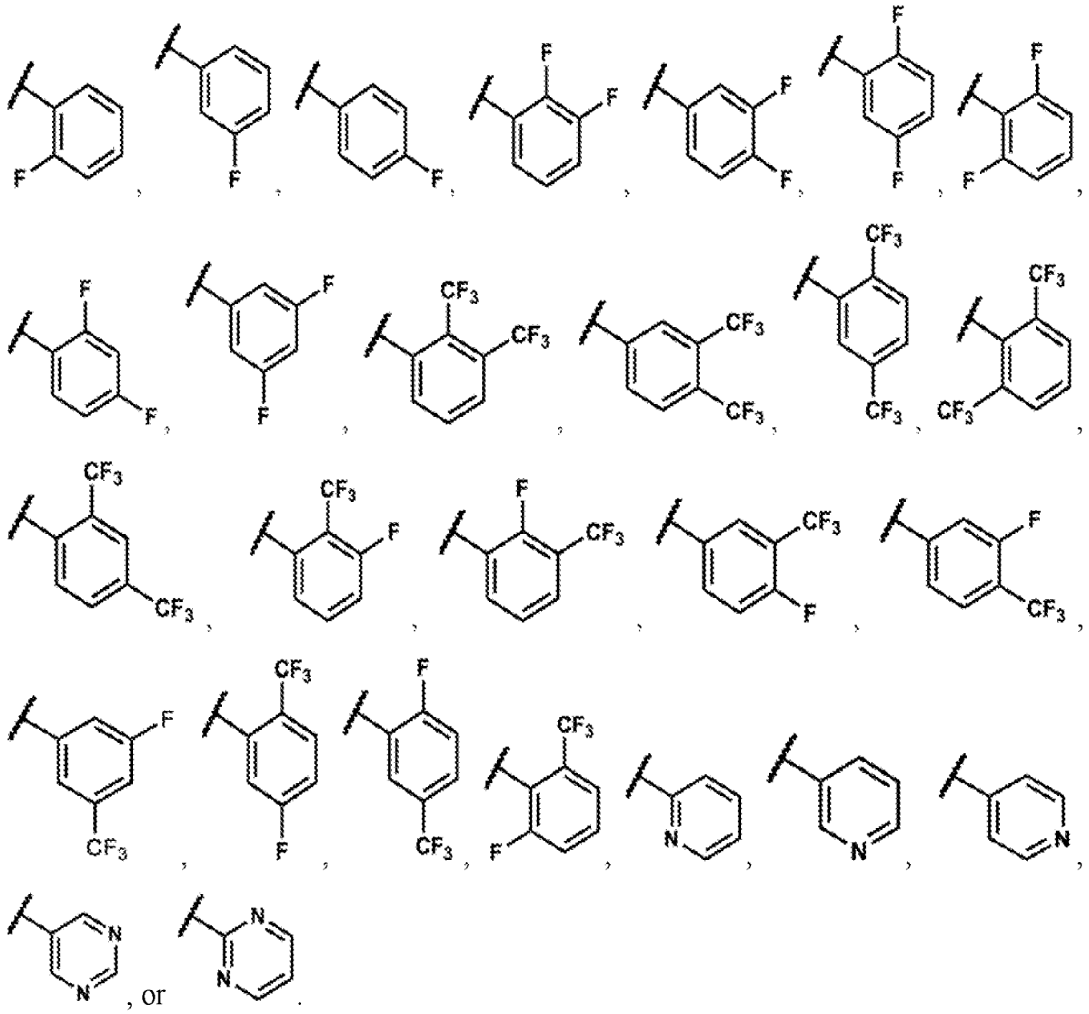
In some embodiments, R^6 is an optionally substituted pyrazole. In some embodiments, R^6 is an optionally substituted pyrazole having a carbon atom of the pyrazole ring directly attached to Z.

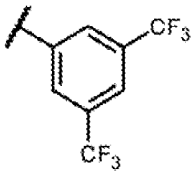
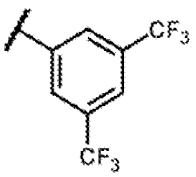
In some embodiments, R^6 is an optionally substituted imidazole. In some embodiments, R^6 is an optionally substituted imidazole having a carbon atom of the imidazole ring directly attached to Z.

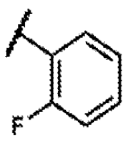
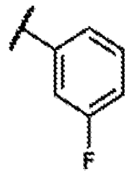
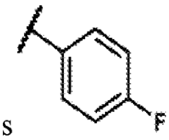
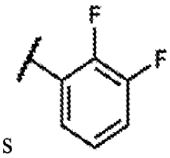
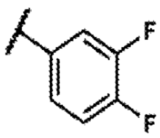
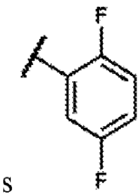
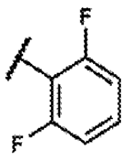
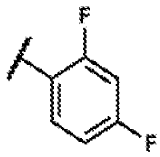
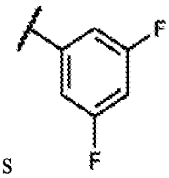
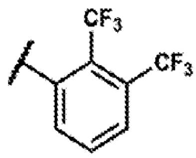
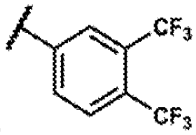
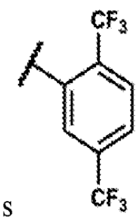
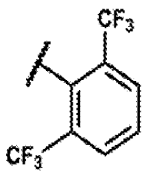
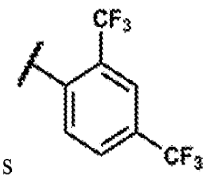
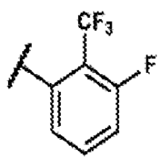
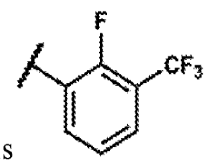
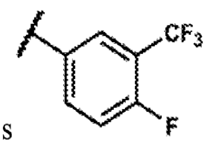
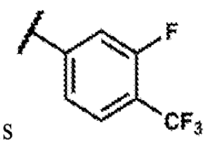
In some embodiments, R^6 is an optionally substituted tetrazole. In some embodiments, R^6 is an optionally substituted tetrazole having a carbon atom of the tetrazole ring directly attached to Z.

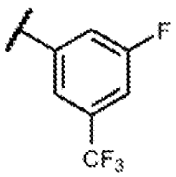
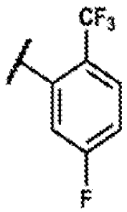
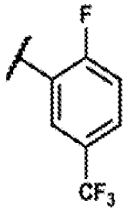
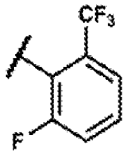
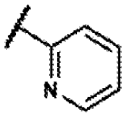
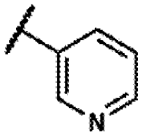
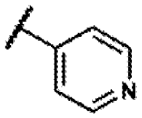
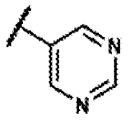
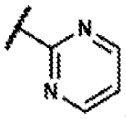
In some embodiments, R^6 is an optionally substituted sulfolane. In some embodiments, R^6 is an optionally substituted sulfolane having a carbon atom of the sulfolane ring directly attached to Z.

In some embodiments, R^6 is an optionally substituted phenyl. In some embodiments, R^6 is represented by one of the following structures:



In some embodiments, R^6 is  . In some embodiments, R^6 is not  .

In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some

embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  . In some embodiments, R^6 is  .

In some embodiments, Z is — and R^6 is an optionally substituted aryl.

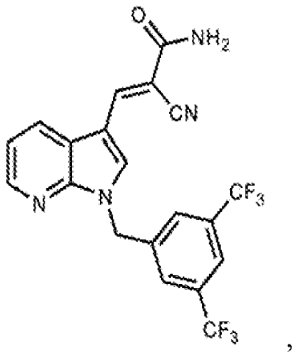
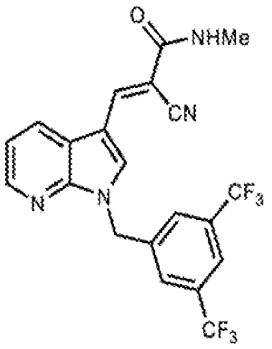
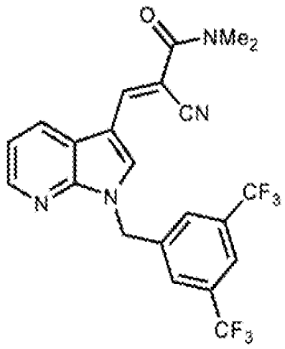
In some embodiments, Z is — and R^6 is an optionally substituted alkyl.

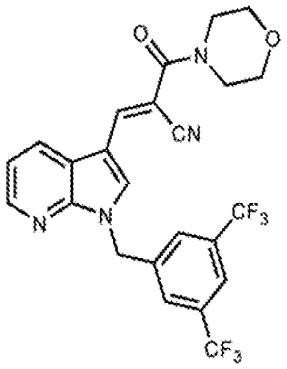
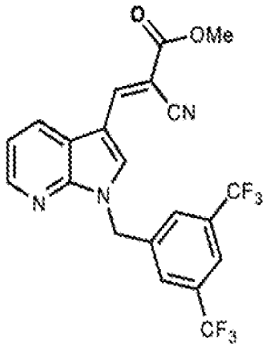
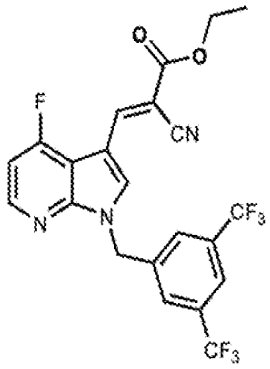
With respect to any relevant structural representation, such as Formula 1, R^7 is H, F, Cl, Br, I, OH, OR^A, SH, SR^A, NH_2, NHR^A, NR^AR^B, CF_3, CN, carboxylic acid (CO_2H), optionally substituted carboxylic ester (such as optionally substituted C_{1-6} alkyl carboxylic ester, such as optionally substituted branched C_{2-6} alkyl or linear C_{1-6} alkyl carboxylic ester, optionally substituted branched C_3 alkyl carboxylic ester (e.g., $–CO_2-C(CH_3)_2$), or linear C_{1-3} alkyl carboxylic ester (e.g., $–CO_2-CH_3$, $–CO_2-C_2H_5$, $–CO_2-C_3H_7$), optionally substituted branched, linear, or cyclic C_{3-6} alkyl carboxylic ester (e.g. $–CO_2-C_3H_7$, $–CO_2-C_4H_9$, $–CO_2-C_5H_{11}$, $–CO_2-C_6H_{13}$, $–CO_2-CH(CH_3)_2$, $–CO_2-CH(CH_3)(CH_2CH_3)$, $–CO_2-CH(CH_2CH_3)_2$, $–CO_2-CH(CH_3)(CH_2CH_2CH_3)$, $–CO_2-C(CH_3)_2(CH_2CH_2CH_3)$, $–CO_2-C(CH_3)(CH_2CH_2CH_2CH_3)$, $–CO_2-CH(CH_2CH_3)(CH_2CH_2CH_3)$, $–CO_2$-cyclopropyl, $–CO_2$-cyclobutyl, $–CO_2$-cyclopentyl, $–CO_2$-cyclohexyl, etc.), or optionally substituted C_{1-6} alkyl, such as optionally substituted branched C_{2-6} alkyl or linear C_{1-6} alkyl, optionally substituted branched C_3 alkyl (e.g., $–C(CH_3)_2$), or linear C_{1-3} alkyl (e.g., $–CH_3$, $–C_2H_5$, $–C_3H_7$), optionally substituted branched, linear, or cyclic C_{3-6} alkyl (e.g. $–C_3H_7$, $–C_4H_9$, $–C_5H_{11}$, –

C_6H_{13}, $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-CH(CH_3)(CH_2CH_2CH_3)$, $-C(CH_3)_2(CH_2CH_2CH_3)$, $-C(CH_3)(CH_2CH_2CH_2CH_3)$, $-CH(CH_2CH_3)(CH_2CH_2CH_3)$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.).

In some embodiments, R^7 is H. In some embodiments, R^7 is F. In some embodiments, R^7 is Cl. In some embodiments, R^7 is Br. In some embodiments, R^7 is I. In some embodiments, R^7 is OH. In some embodiments, R^7 is OR^A. In some embodiments, R^7 is SH. In some embodiments, R^7 is SR^A. In some embodiments, R^7 is NH_2. In some embodiments, R^7 is NHR^A. In some embodiments, R^7 is NR^AR^B. In some embodiments, R^7 is CF_3. In some embodiments, R^7 is CN. In some embodiments, R^7 is CO_2H. In some embodiments, R^7 is CO_2R^A. In some embodiments, R^7 is $C_{1\text{-}6}$ alkyl. In some embodiments, R^7 is branched $C_{2\text{-}6}$ alkyl. In some embodiments, R^7 is $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-C_4H_9$, $-C_5H_{11}$, or $-C_6H_{13}$. In some embodiments, R^7 is an optionally substituted $C_{1\text{-}6}$ alkyl. In some embodiments, R^7 is an optionally heteroatom substituted linear $C_{1\text{-}6}$ alkyl, such as a linear $C_{1\text{-}6}$ alkyl having polar substituents, including oxygen containing groups (e.g. -OH, =O, OCH_3, etc.), sulfur containing groups (e.g. -SH, $-SCH_3$, SO_2, SO_3^-, etc.), nitrogen containing groups (e.g. $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NO_2$, -CN, etc.), fluorine containing groups (F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.). In some embodiments, R^7 is an optionally substituted branched $C_{2\text{-}6}$ alkyl. In some embodiments, R^7 is an optionally heteroatom substituted branched $C_{2\text{-}6}$ alkyl, such as a branched $C_{2\text{-}6}$ alkyl having polar substituents, including oxygen containing groups (e.g. -OH, =O, OCH_3, etc.), sulfur containing groups (e.g. -SH, $-SCH_3$, SO_2, SO_3^-, etc.), nitrogen containing groups (e.g. $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NO_2$, -CN, etc.), fluorine containing groups (F, CF_3, CF_2CF_3, CHF_2, CH_2F, $CF_2CF_2CF_3$, etc.).

In some embodiments, the compound is a compound shown below, each of which may be optionally substituted:

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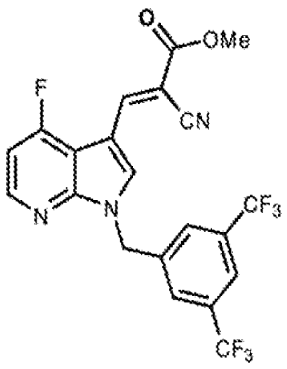
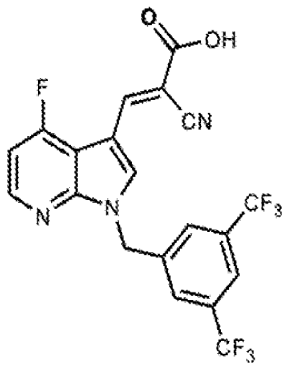
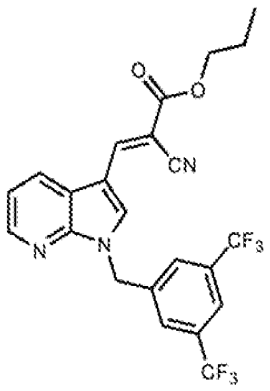

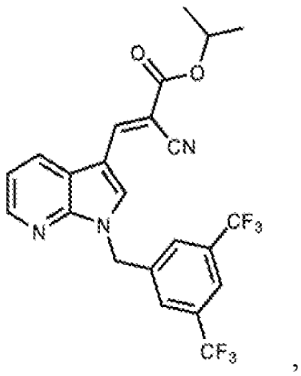

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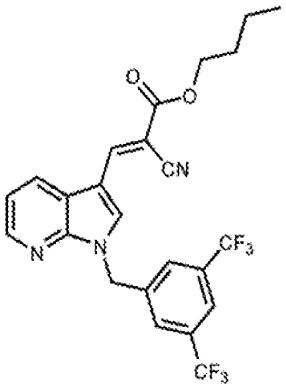
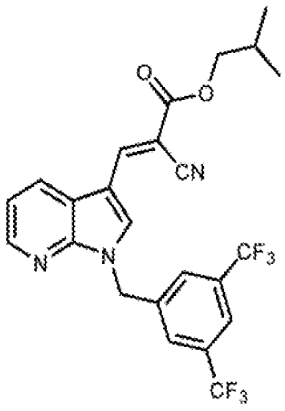

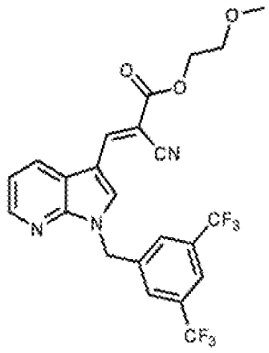
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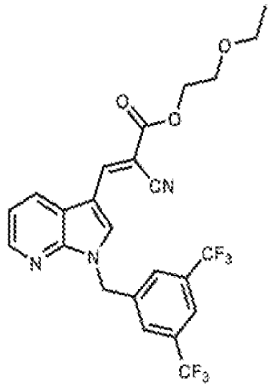
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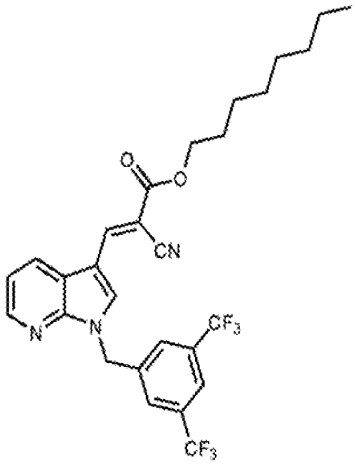
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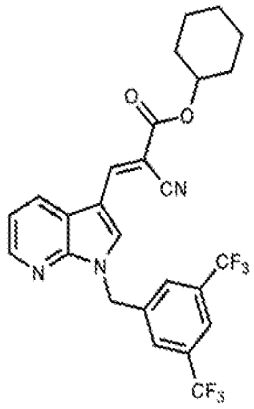
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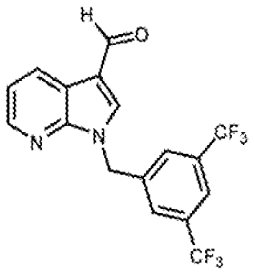
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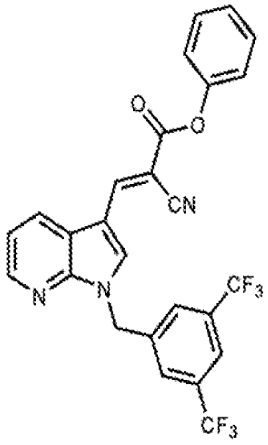
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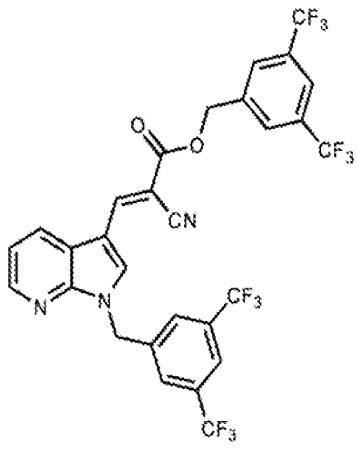
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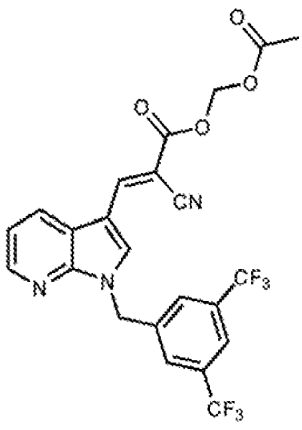
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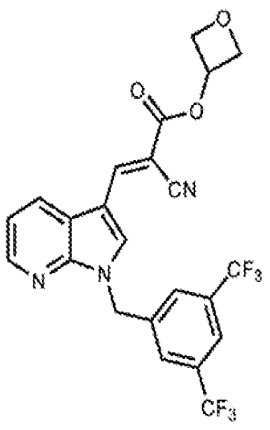
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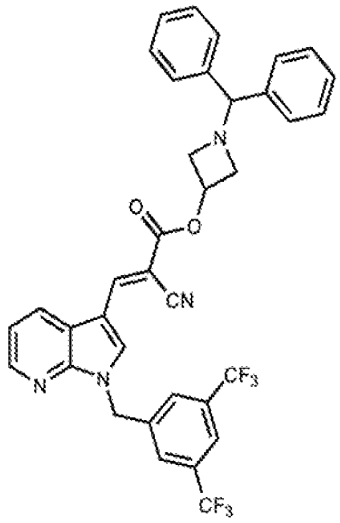
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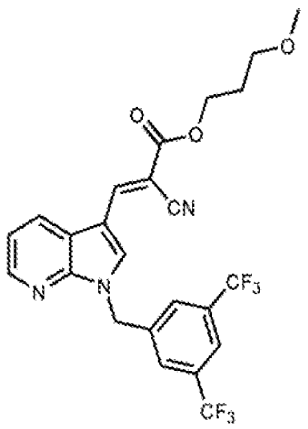
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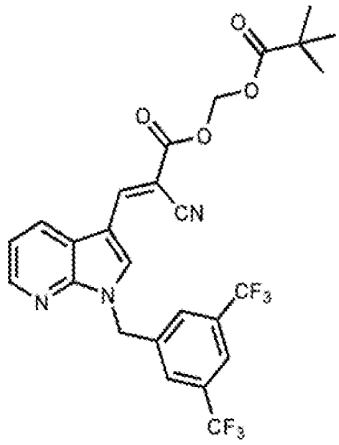
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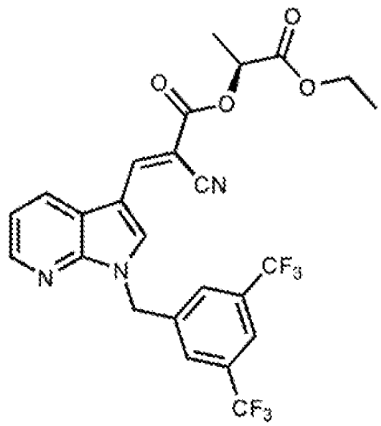
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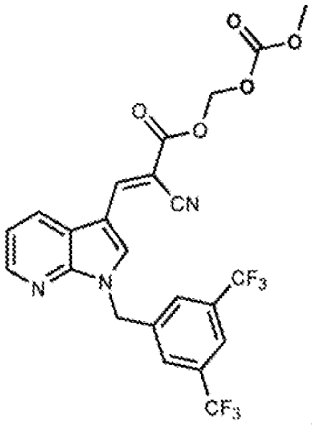
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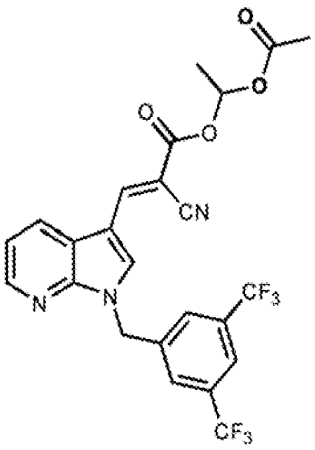
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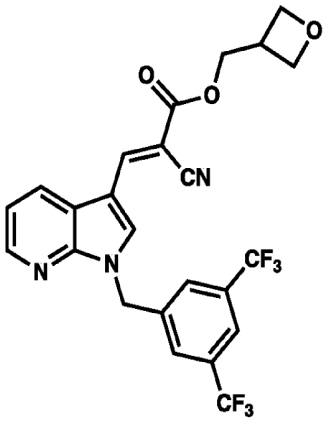
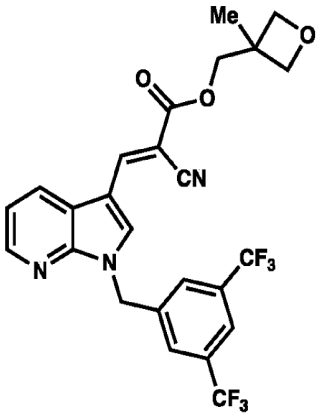
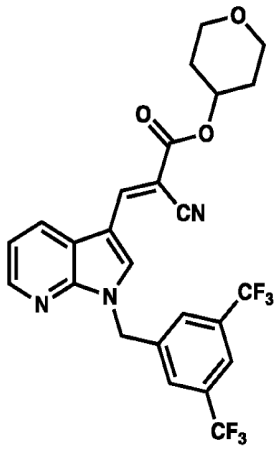
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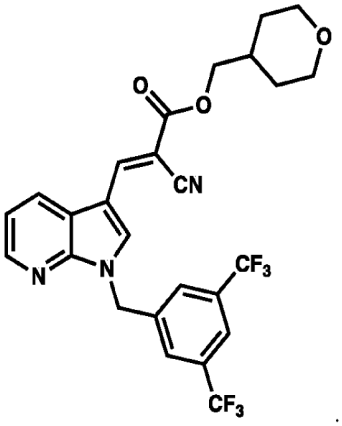

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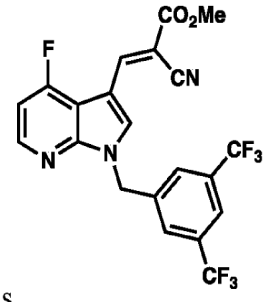
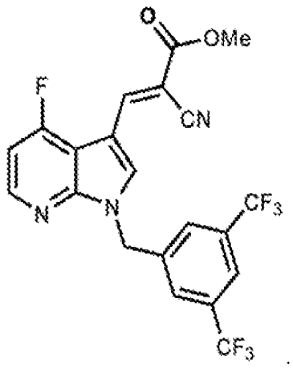
In certain aspects, the compound is 

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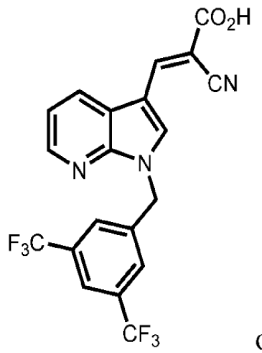
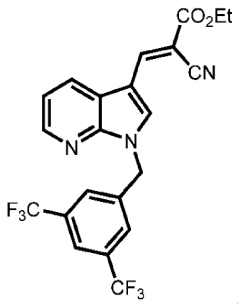
In some embodiments, the compound is not  or  .

The compound described herein are useful for growing hair. For example, a compound described herein may be administered to the skin of a mammal in the area where hair growth is intended.

In certain aspects, the present disclosure provides methods of enhancing lactate production in a cell, comprising contacting the cell with a compound or composition of the disclosure.

In certain aspects, the present disclosure provides methods of inhibiting mitochondrial pyruvate oxidation in a cell, comprising contacting the cell with a mitochondrial pyruvate oxidation (MPO) inhibitor, such as a compound of the present disclosure. In certain embodiments, the MPO inhibitor is a mitochondrial pyruvate carrier (MPC) inhibitor. In certain embodiments, inhibiting mitochondrial pyruvate oxidation in a cell has the effect of enhancing lactate production in a cell and/or enhancing the activity of LDH in a cell, and promoting hair growth, as described herein.

In certain aspects, the present disclosure provides methods of enhancing lactate production in a cell, comprising contacting the cell with an MPO inhibitor, such as a compound of the present disclosure. In certain embodiments, the MPO inhibitor is a mitochondrial pyruvate carrier (MPC) inhibitor.

In certain aspects, the present disclosure provides methods of enhancing the activity of LDH in a cell, comprising contacting the cell with an MPO inhibitor, such as a compound of the present disclosure. In certain embodiments, the MPO inhibitor is a mitochondrial pyruvate carrier (MPC) inhibitor.

In certain aspects, the present disclosure provides methods of enhancing the activity of lactic acid dehydrogenase (LDH) in a cell, comprising contacting the cell with an MPO inhibitor, such as a compound of the present disclosure. In certain embodiments, the MPO inhibitor is a mitochondrial pyruvate carrier (MPC) inhibitor. In certain aspects, the present disclosure provides methods of promoting hair growth or treating a hair growth condition or disorder such as baldness or alopecia, comprising administering to a patient a compound or composition as disclosed herein.

In certain aspects, the present disclosure provides methods of promoting hair growth or treating a hair growth condition or disorder such as baldness or alopecia, comprising administering to a patient an MPO inhibitor (e.g., topically, such as with a pharmaceutical composition formulated for topical application), such as a compound of the present disclosure. In certain embodiments, the present disclosure provides methods of promoting hair growth or treating a hair growth condition or disorder such as baldness or alopecia, comprising administering to a patient an MPC inhibitor (e.g., topically, such as with a pharmaceutical composition formulated for topical application), such a compound of the present disclosure. In certain embodiments, inhibiting mitochondrial pyruvate oxidation or the mitochondrial pyruvate carrier in a cell has the effect of enhancing lactate production and/or enhancing the activity of LDH in a cell, and promoting hair growth, as described herein.

For use in growing hair, a compound described herein may be mixed with a dermatologically compatible vehicle or carrier, e.g. so that the compound is present at an amount of about 0.001-10% or about 0.01-2%. The vehicle which may be employed for a topical dermatological composition may comprise, for example, aqueous solutions such as e.g., physiological salines, oil, solutions, ointments, gels, creams, sprays, etc. In some embodiments, the vehicle may contain a solvent such as ethanol or polyethylene glycol. In some embodiments, the vehicle may also contain a penetration enhancer, e.g. to enhance penetration into the skin, such as transcutol P. The vehicle furthermore may contain dermatologically compatible preservatives such as e.g., benzalkonium chloride, surfactants like e.g., polysorbate 80, liposomes or polymers, for example, methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid; these may be used for increasing the viscosity.

In certain aspects, the compounds of the present disclosure are mitochondrial pyruvate oxidation (MPO) inhibitors. In some embodiments, the compounds described

herein may inhibit mitochondrial pyruvate carrier (MPC). In certain embodiments, the MPO inhibitor is an MPC inhibitor. In some aspects, inhibiting MPO in a cell has the effect of enhancing lactate production in a cell and/or enhancing the activity of lactic acid dehydrogenase (LDH) in a cell, and promoting hair growth. In certain aspects, the present disclosure provides methods of promoting hair growth or treating a hair growth condition or disorder such as baldness or alopecia, comprising administering to a patient an MPO inhibitor (e.g., topically, such as with a pharmaceutical composition formulated for topical application), such as a compound of the present disclosure. In certain embodiments, the present disclosure provides methods of promoting hair growth or treating a hair growth condition or disorder such as baldness or alopecia, comprising administering to a patient an MPC inhibitor (e.g., topically, such as with a pharmaceutical composition formulated for topical application), such as a compound of the present disclosure. In some embodiments, inhibiting the MPO or the MPC in a cell has the effect of enhancing lactate production and/or enhancing the activity of LDH in a cell, and promoting hair growth.

For the purposes of this disclosure, the term "treat," "treating," or a similar term (such as "modulating"), includes cure, mitigation, treatment, or prevention of disease in man or other animals, or any other effect that would be associated with a "drug" as defined under 21 USC 321(g).

In certain aspects, the compounds of the present disclosure may be ester prodrugs. In other aspects, the compounds described herein may be thioester or amide prodrugs. In some embodiments, the compounds herein may show a higher rate of hydrolysis (such as a rate that is at least about 1.1 times higher, at least about 1.5 times higher, at least about 2 times higher, at least about 5 times higher, at least about 10 times higher, at least about 50 times higher, at least about 100 times higher, at least about 500 times higher, at least about 1,000 times higher, at least about 10,000 times higher, about 1.1-2 times higher, about 2-4 times higher, about 4-6 times higher, about 6-8 times higher, about 8-10 times higher, about 1.1-10 times higher, about 10-100 times higher, about 100-1,000 times higher, or about 1,000-10,000 times higher) relative to conventional alkyl (ethyl or methyl) esters. In some aspects, the compounds of the present disclosure may achieve a high level of hydrolyzed drug (carboxylic acid) in skin homogenate assays.

It is understood that topical delivery of an active pharmaceutical ingredient (API) for dermal indications comprises a balance of lipophilic and hydrophilic properties. It is

believed that a compound having lipophilicity as a prodrug and hydrophilicity as the corresponding free acid API may achieve the goal of reaching the desired skin layer target (e.g., a hair follicle). The rate of hydrolysis of the prodrug in the layers of the skin may be adjusted to achieve the desired result.

In some embodiments, the compounds of the present disclosure undergo hydrolysis to release the active free carboxylic acid. In some aspects, the compounds of the present disclosure undergo hydrolysis to release the active free carboxylic acid at a rate that is enhanced relative to conventional prodrugs (e.g., JXL082). In some embodiments, the rate of hydrolysis may benefit the delivery of active pharmaceutical agent to potentiate hair growth.

In some aspects, the prodrug compounds of the present disclosure undergo hydrolysis in human skin homogenate faster than known prodrugs such as JXL082. In some embodiments, the concentration of carboxylic acid (API) released by a prodrug of the present disclosure is at least about 150% greater to about 20000% greater than the amount released by a conventional prodrug such as JXL082. In some embodiments, the concentration of carboxylic acid (API) released by a prodrug of the present disclosure is at least about 150-300% greater, about 300-500% greater, about 500-1000% greater, about 1000-2000% greater, about 2000-4000% greater, about 4000-7000% greater, about 7000-10000% greater, about 10000-15000% greater, or about 15000-20000% greater, or about any value in a range bounded by any of these ranges, than the amount released by a conventional prodrug such as JXL082.

In other embodiments, the compounds of the present disclosure may enhance hair growth in their free acid form.

Pharmaceutical Compositions

The compounds of the present disclosure may be included in a pharmaceutical and a pharmaceutically acceptable excipient.

The compositions and methods described herein may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound described herein and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for

example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In preferred embodiments, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as a lotion, cream, or ointment.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound described herein. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a self-emulsifying drug delivery system or a self-microemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a therapeutic compound described herein. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

The phrase "pharmaceutically acceptable" includes those compounds, materials, compositions, and/or dosage forms which would be considered to be suitable, by a person having ordinary skill in the art, for pharmaceutical use on human beings and animals.

The phrase "pharmaceutically acceptable carrier" includes a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Acceptable carriers include those that are

compatible with the other ingredients of the formulation and acceptable for use on the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any suitable methods. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form may vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of 100%, this amount will range from about 1-99% of active ingredient, e.g. about 5-70%, about 1-10%, about 10-30%, about 30-50%, about 50-70%, about 70-99%, etc .

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound described herein, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound described herein with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations described herein suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound described herein as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. 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 sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl 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, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

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

Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

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

The phrases "parenteral administration" and "administered parenterally" include modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more

pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions described herein include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

The dosage level may depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments described herein, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

The patient receiving this treatment is any animal in need, including primates, in particular humans; and other mammals such as equines, cattle, swine, sheep, cats, and dogs; poultry; and pets in general.

In certain embodiments, compounds described herein may be used alone or conjointly administered with another type of therapeutic agent.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

The methods and techniques of the present disclosure are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout this specification. See, e.g. "Principles of Neural Science", McGraw-Hill Medical, New York, N.Y. (2000); Motulsky, "Intuitive Biostatistics", Oxford University Press, Inc. (1995); Lodish et al., "Molecular Cell Biology, 4th ed.", W. H. Freeman & Co., New York (2000); Griffiths et al., "Introduction to Genetic Analysis, 7th ed.", W. H. Freeman & Co., N.Y. (1999); and Gilbert et al., "Developmental Biology, 6th ed.", Sinauer Associates, Inc., Sunderland, MA (2000).

Chemistry terms used herein, unless otherwise defined herein, are used according to conventional usage in the art, as exemplified by "The McGraw-Hill Dictionary of Chemical Terms", Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

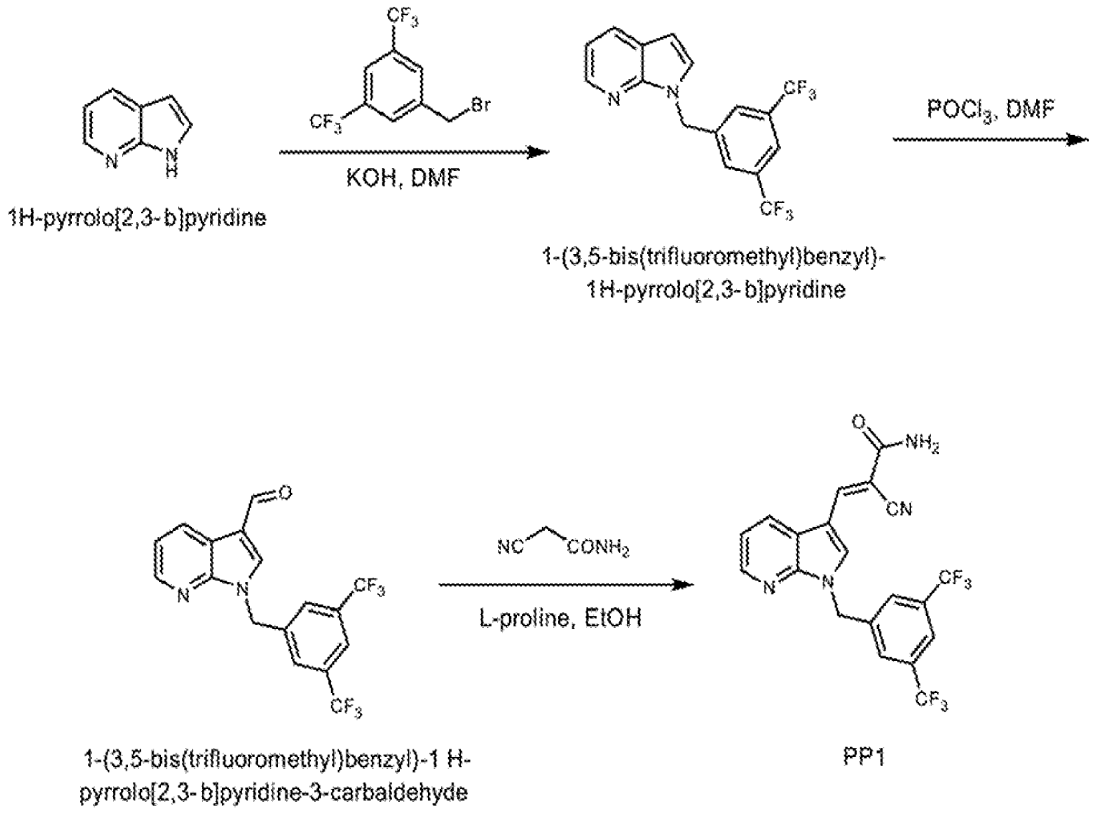
All of the above, and any other publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

A "therapeutically effective amount" or a "therapeutically effective dose" of a drug or agent is an amount of a drug or an agent that, when administered to a subject will have the intended therapeutic effect. The full therapeutic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations.

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EXAMPLES

Example 1: (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylamide (PP1)



To the solution of 1*H*-pyrrolo[2,3-*b*]pyridine (1 equiv, 3 mmol, 354.4 mg) in dry DMF (6 mL) were added 3,5-bis(trifluoromethyl)benzyl bromide (1.2 equiv, 3.6 mmol, 660 µL) and KOH (1.2 equiv, 3.6 mmol, 201.9 mg) at 0 °C. The reaction mixture was stirred at 21 °C for 2 h. After the reaction completion as shown by TLC, water (18 mL) was added to the reaction vial. The reaction mixture was extracted by dichloromethane (45 mL × 3). The combined organic layer was dried by sodium sulfate and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc = 12:1) to provide the desired product, 1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridine (yield: 75%, 774.5 mg).

$POCl_3$ (1 equiv, 1 mmol, 93 µL) was added dropwise to DMF (2 mL) at 0 °C under argon. After the mixture stirred for 10 min, a solution of 1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1 equiv, 1 mmol, 344 mg) in DMF (2 mL) was added slowly with stirring. The mixture was kept at 21 °C overnight. The reaction was quenched by adding water (5 mL) at 0 °C, then extracted with dichloromethane (10 mL × 3). The combined organic layer was dried by sodium sulfate and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc = 4:1) to provide the desired

product, 1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxaldehyde (yield 89%, 332.9 mg).

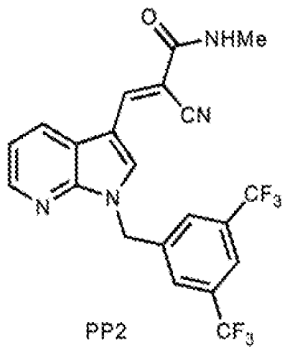
To a solution of 1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-b]pyridine-3-carbox-aldehyde (1 equiv, 0.081 mmol, 30.0 mg) in ethanol (0.8 mL) was added 2-cyanoaceta-mide (1.3 equiv, 0.10 mmol, 8.8 mg) and L-proline (40 mol%, 0.0322 mmol, 3.7 mg). The reaction was stirred at 21 °C for 12 h and yellow solid precipitated gradually. After completion of the reaction, ice-cold water (0.8 mL) was added to the reaction vial. The solid was separated by Büchner funnel filtration and washed with water (0.8 mL × 3) and dried to afford the desired product, PP1 (yield 91%, 32.2 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 0.7 Hz, 1H), 8.50 (s, 1H), 8.47 (dd, J = 4.7, 1.5 Hz, 1H), 8.24 (dd, J = 7.9, 1.5 Hz, 1H), 7.83 (s, 1H), 7.77 (s, 2H), 7.33 (dd, J = 8.0, 4.7 Hz, 1H), 6.14 (br s, 1H), 5.69 (s, 2H), 5.61 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 147.6, 145.7, 144.2, 138.5, 132.5 (q, $^2J_{C\text{-}F}$ = 33.7 Hz, 2C), 132.0, 127.9, 127.9 (d, $^3J_{C\text{-}F}$ = 2.2 Hz), 122.9 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, 2C), 122.4 (p, $^3J_{C\text{-}F}$ = 2.2 Hz, 2C), 120.2, 119.0, 118.7, 109.5, 97.1, 48.2.

The following compounds were synthesized by a route similar to that described for PP1: PP2, PP3, PP4.

Example 2: (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyano-*N*-methylacrylamide (PP2)

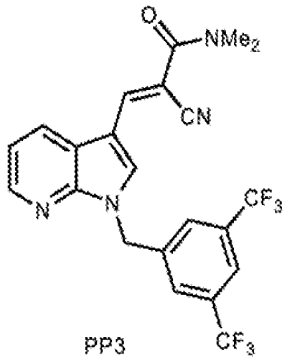


PP2

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.46 (dd, J = 4.6, 1.4 Hz, 1H), 8.45 (s, 1H), 8.24 (dd, J = 7.9, 1.4 Hz, 1H), 7.82 (s, 1H), 7.76 (s, 2H), 7.32 (ddd, J = 7.8, 4.7, 1.6 Hz, 1H), 6.20 (m, 1H), 5.68 (s, 2H), 3.01 (dd, J = 4.9, 1.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 147.6, 145.5, 142.9, 138.6, 132.4 (q, $^{2}J_{C\text{-}F}$ = 33.7 Hz, 2C), 131.5, 128.0, 127.8 (d, $^{3}J_{C\text{-}F}$ = 2.6 Hz), 123.0 (q, $^{1}J_{C\text{-}F}$ = 272.8 Hz, 2C), 122.4 (p, $^{3}J_{C\text{-}F}$ = 3.9 Hz, 2C), 120.2, 118.8, 118.7, 109.5, 98.3, 48.2, 27.2.

Example 3: (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyano-*N*,*N*-dimethylacrylamide (PP3)

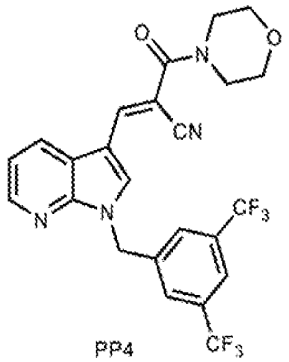


PP3

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.45 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.22 (d, *J* = 0.3 Hz, 1H), 8.14 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.75 (s, 2H), 7.30 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.68 (s, 2H), 3.25 (br s, 3H), 3.10 (br s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 147.4, 145.4, 143.8, 138.8, 132.3 (q, $^{2}J_{C\text{-}F}$ = 33.6 Hz, 2C), 130.9, 127.8 (d, $^{3}J_{C\text{-}F}$ = 3.4 Hz), 127.6, 123.0 (q, $^{1}J_{C\text{-}F}$ = 273.0 Hz, 2C), 122.3 (p, $^{3}J_{C\text{-}F}$ = 3.7 Hz, 2C), 120.2, 118.6, 118.1, 109.6, 100.1, 48.1, 39.3, 36.9.

Example 4: (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-(morpholine-4-carbonyl)acrylonitrile (PP4)

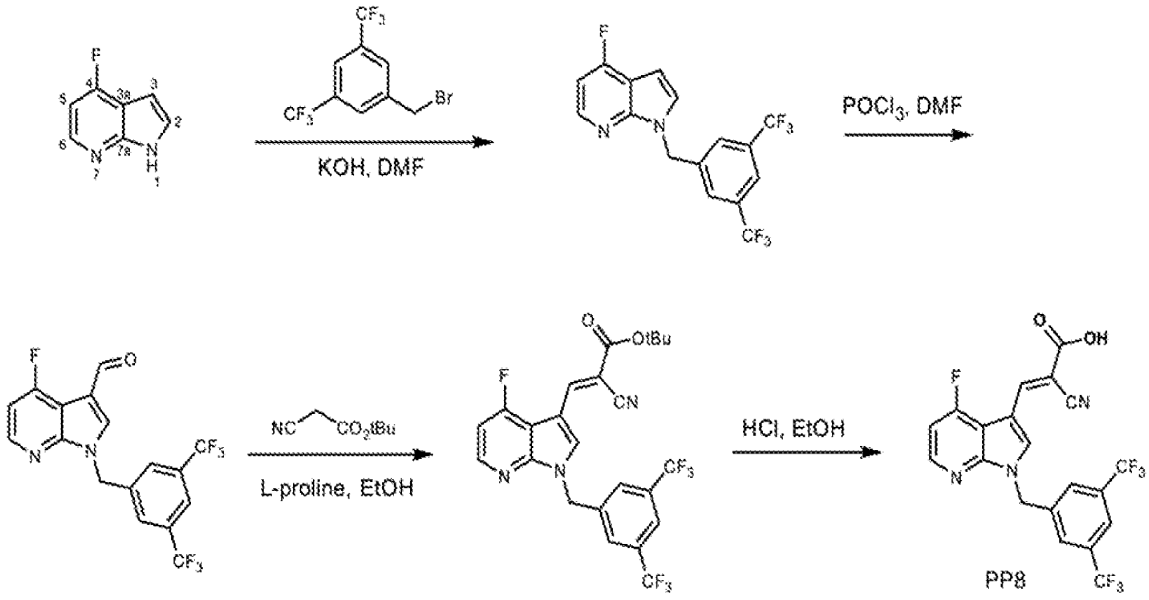


PP4

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.46 (dd, J = 4.7, 1.5 Hz, 1H), 8.23 (s, 1H), 8.15 (dd, J = 7.9, 1.5 Hz, 1H), 7.82 (s, 1H), 7.75 (s, 2H), 7.31 (dd, J = 8.0, 4.7 Hz, 1H), 5.68 (s, 2H), 3.75-3.77 (m, 8H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 147.4, 145.5, 144.5, 138.7, 132.4 (q, $^2J_{C\text{-}F}$ = 33.6 Hz, 2C), 131.2, 127.8 (d, $^3J_{C\text{-}F}$ = 2.5 Hz), 127.6, 123.0 (q, $^1J_{C\text{-}F}$ = 273.0 Hz, 2C), 122.3 (p, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 120.1, 118.7, 118.2, 109.6, 99.2, 66.7 (4C), 48.1.

Example 5: (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylic acid (PP8)



To the solution of 4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (1.0 equiv, 4 mmol, 544.5 mg) in dry DMF (8 mL) were added 3,5-bis(trifluoromethyl)benzyl bromide (1.2 equiv, 4.8 mmol, 880 μL) and KOH (1.2 equiv, 4.8 mmol, 269.3 mg) at 0 °C. The reaction mixture was stirred at 21 °C for 2 h. After the reaction completion as shown by TLC, water (24 mL) was added to the reaction vial. The reaction mixture was extracted by dichloromethane (60 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc = 12:1) to provide the desired product, 1-(3,5-bis(trifluoromethyl)benzyl)-4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (yield: 78%, 1132.0 mg).

$POCl_3$ (1.0 equiv, 1.38 mmol, 128.6 μL) was added dropwise to DMF (2.8 mL) at 0 °C under argon. After the mixture stirred for 10 min, a solution of 1-(3,5-

bis(trifluoromethyl)benzyl)-4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (1.0 equiv, 1.38 mmol, 500 mg) in DMF (2.8 mL) was added slowly with stirring. The mixture was kept at 21 °C overnight. The reaction was quenched by adding water (6.9 mL) at 0 °C, then extracted with dichloromethane (13.8 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc = 4:1) to provide the desired product, 1-(3,5-bis(trifluoromethyl)benzyl)-4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxaldehyde (yield 60%, 325.4 mg).

To the solution of 1-(3,5-bis(trifluoromethyl)benzyl)-4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxaldehyde (1.0 equiv, 0.256 mmol, 100.0 mg) in ethanol (1.0 mL) was added *tert*-butyl 2-cyanoacetate (1.3 equiv, 0.333 mmol, 41.9 µL) and L-proline (40 mol%, 0.1 mmol, 23.0 mg). The reaction was stirred at 21 °C for 12 h and yellow solid precipitated gradually. After completion of the reaction, ice-cold water (1.0 mL) was added to the reaction vial. The solid was separated by Büchner funnel filtration and washed with water (1.0 mL × 3) and the solvent was evaporated in vacuo. The powder was dissolved in chloroform and subjected to column chromatography (hexanes/EtOAc = 5:1) to provide the desired product, *tert*-butyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (yield 91%, 120.1 mg).

To a solution of *tert*-butyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (1.0 equiv, 0.1 mmol, 51.3 mg) in EtOH (1 mL) was added 12.0 M aq. HCl (120 equiv, 12.0 mmol, 1.0 mL). The reaction mixture was stirred at 21 °C for 12 h. After the reaction was complete as shown by TLC, the reaction solvent was evaporated in vacuo. The solid was washed by 1 mL of solvent mixture (hexanes/EtOAc = 5:1) 5 to 10 times and monitored by TLC until all the non-polar impurities disappeared. Finally, the product was dried in vacuo yielding the desired product, PP8 (yield 78%, 35.5 mg).

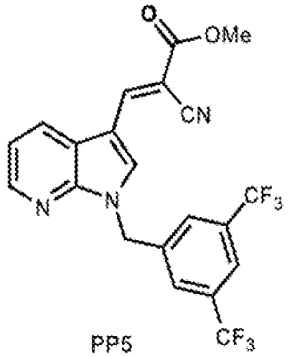
^{1}H NMR (500 MHz, DMSO-d_6) δ 13.64 (br s, 1H), 8.91 (s, 1H), 8.42-8.45 (m, 2H), 8.13 (s, 2H), 8.05 (s, 1H), 7.28 (dd, J = 10.8, 5.5 Hz, 1H), 5.86 (s, 2H).

^{13}C NMR (125 MHz, DMSO-d_6) δ 164.2, 163.0 (d, $^1J_{C\text{-}F}$ = 262.6 Hz), 150.7 (d, $^3J_{C\text{-}F}$ = 10.6 Hz), 147.6 (d, $^3J_{C\text{-}F}$ = 7.1 Hz), 146.0 (d, $^3J_{C\text{-}F}$ = 3.7 Hz), 140.3, 134.2, 130.9 (q, $^2J_{C\text{-}F}$ = 32.9 Hz, 2C), 129.5 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 123.6 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, 2C), 122.4 (p, $^3J_{C\text{-}F}$ = 3.7 Hz,

2C), 117.6, 108.9 (d, $^{2}J_{C\text{-}F}$ = 14.8 Hz), 106.7 (d, $^{4}J_{C\text{-}F}$ = 2.7 Hz), 106.3 (d, $^{2}J_{C\text{-}F}$ = 15.4 Hz),
2 98.4, 48.3.

The following compounds were synthesized by a route similar to that described for
4 PP8: PP5, PP6, PP7, PP9, PP10, PP11, PP12, PP13, PP14, PP15, PP16, PP17, PP18, PP19, PP20, PP21, PP22, PP23, PP24, PP25, PP26, PP27, PP28, PP29, and PP30.

6 **Example 6**: Methyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP5)

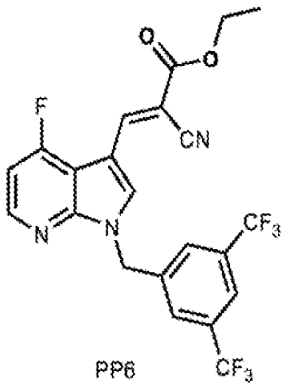


8 PP5

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.51 (d, *J* = 0.5 Hz, 1H), 8.47 (dd, *J* = 4.7, 1.4
10 Hz, 1H), 8.21 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.34 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.68 (s, 2H), 3.92 (s, 3H).

12 ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 147.6, 145.7, 145.2, 138.4, 132.9, 132.4 (q, $^{2}J_{C\text{-}F}$ = 33.7 Hz, 2C), 127.9 (d, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 127.7, 123.0 (q, $^{1}J_{C\text{-}F}$ = 272.9 Hz, 2C), 122.4 (p, $^{3}J_{C\text{-}F}$ = 3.9 Hz, 2C), 120.3, 119.1, 117.5, 109.3, 96.5, 53.1, 48.3.
14

Example 7: Ethyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-4-fluoro-1*H*-pyrrolo[2,3-
16 *b*]pyridin-3-yl)-2-cyanoacrylate (PP6)

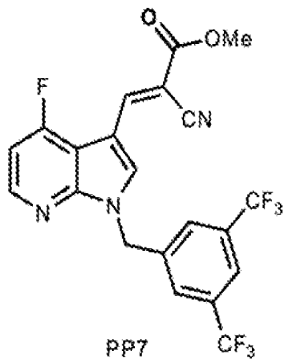


PP6

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.67 (s, 1H), 8.39 (dd, J = 7.4, 5.5 Hz, 1H), 7.83 (s, 1H), 7.77 (s, 2H), 7.03 (dd, J = 10.1, 5.4 Hz, 1H), 5.67 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, $^1J_{C\text{-}F}$ = 266.0 Hz), 162.8, 150.4 (d, $^3J_{C\text{-}F}$ = 10.6 Hz), 147.3 (d, $^3J_{C\text{-}F}$ = 6.9 Hz), 146.3 (d, $^3J_{C\text{-}F}$ = 4.1 Hz), 138.1, 132.5 (q, $^2J_{C\text{-}F}$ = 33.6 Hz, 2C), 132.2 (d, $^4J_{C\text{-}F}$ = 0.9 Hz), 127.9 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 122.9 (q, $^1J_{C\text{-}F}$ = 273.0 Hz, 2C), 122.5 (p, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 117.4, 109.2 (d, $^2J_{C\text{-}F}$ = 15.1 Hz), 108.1 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 106.1 (d, $^2J_{C\text{-}F}$ = 15.5 Hz), 98.3, 62.4, 48.7, 14.2.

Example 8: Methyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP7)

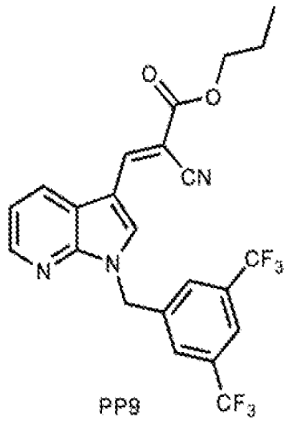


PP7

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.67 (s, 1H), 8.40 (dd, J = 7.4, 5.4 Hz, 1H), 7.83 (s, 1H), 7.77 (s, 2H), 7.04 (dd, J = 10.1, 5.4 Hz, 1H), 5.67 (s, 2H), 3.92 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, $^1J_{C\text{-}F}$ = 266.0 Hz), 163.3, 150.4 (d, $^3J_{C\text{-}F}$ = 10.7 Hz), 147.3 (d, $^3J_{C\text{-}F}$ = 7.0 Hz), 146.6 (d, $^3J_{C\text{-}F}$ = 4.0 Hz), 138.1, 132.5 (q, $^2J_{C\text{-}F}$ = 33.8 Hz, 2C), 132.3 (d, $^4J_{C\text{-}F}$ = 1.6 Hz), 127.9 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 122.9 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, 2C), 122.6 (p, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 117.4, 109.2 (d, $^2J_{C\text{-}F}$ = 15.2 Hz), 108.1 (d, $^4J_{C\text{-}F}$ = 2.8 Hz), 106.1 (d, $^2J_{C\text{-}F}$ = 15.6 Hz), 97.8, 53.1, 48.7.

Example 9: Propyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP9)

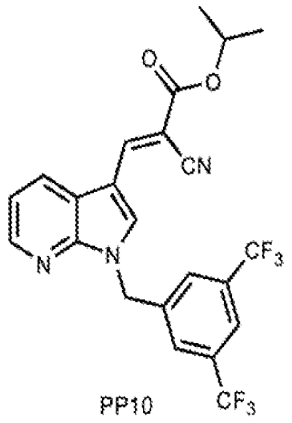


PP9

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.50 (d, J = 0.7 Hz, 1H), 8.47 (dd, J = 4.7, 1.5 Hz, 1H), 8.22 (dd, J = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.34 (dd, J = 8.0, 4.7 Hz, 1H), 5.71 (s, 2H), 4.27 (t, J = 6.7 Hz, 2H), 1.79 (heptet, J = 7.3 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 147.5, 145.6, 145.0, 138.6, 132.9, 132.5 (q, $^2J_{C\text{-}F}$ = 33.7 Hz, 2C), 128.0 (2C), 123.1 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, 2C), 122.6 (p, $^3J_{C\text{-}F}$ = 3.7 Hz, 2C), 120.6, 119.1, 117.6, 109.5, 97.4, 67.9, 48.5, 22.2, 10.5.

Example 10: Isopropyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP10)

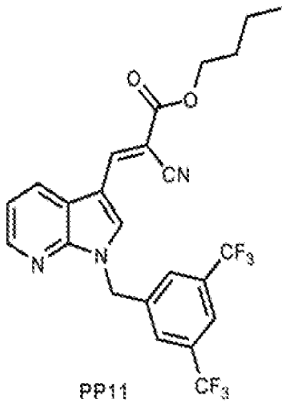


PP10

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.48 (s, 1H), 8.47 (dd, J = 4.7, 1.5 Hz, 1H), 8.21 (dd, J = 7.9, 1.5 Hz, 1H), 7.82 (s, 1H), 7.76 (s, 2H), 7.33 (dd, J = 8.0, 4.7 Hz, 1H), 5.70 (s, 2H), 5.20 (hept, J = 6.3 Hz, 1H), 1.37 (d, J = 6.3 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 147.4, 145.5, 144.7, 138.5, 132.6, 132.4 (q, $^2J_{C-F}$ = 33.7 Hz, 2C), 127.8 (d, $^3J_{C-F}$ = 4.1 Hz), 127.8, 122.9 (q, $^1J_{C-F}$ = 272.9 Hz, 2C), 122.4 (p, $^3J_{C-F}$ = 3.9 Hz, 2C), 120.4, 118.9, 117.5, 109.4, 97.7, 70.2, 48.3, 21.8 (2C).

Example 11: Butyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP11)

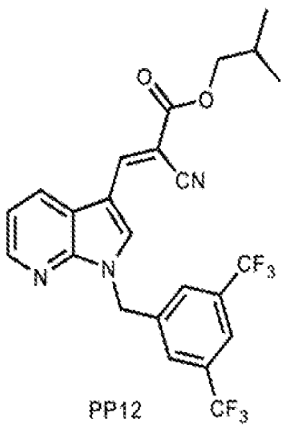


PP11

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.50 (s, 1H), 8.47 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.22 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.34 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.70 (s, 2H), 4.32 (t, *J* = 6.7 Hz, 2H), 1.72-1.77 (m, 2H), 1.47 (heptet, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 147.4, 145.5, 144.8, 138.4, 132.7, 132.4 (q, $^2J_{C-F}$ = 33.6 Hz, 2C), 127.9, 127.8, 122.9 (q, $^1J_{C-F}$ = 273.0 Hz, 2C), 122.4 (p, $^3J_{C-F}$ = 3.9 Hz, 2C), 120.4, 118.9, 117.5, 109.4, 97.2, 66.1, 48.4, 30.6, 19.1, 13.7.

Example 12: Isobutyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP12)

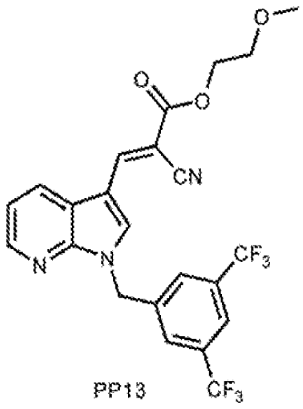


PP12

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.50 (s, 1H), 8.47 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.22 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.34 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.70 (s, 2H), 4.09 (d, *J* = 6.7 Hz, 2H), 2.08 (nonet, *J* = 6.7 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 147.4, 145.5, 144.8, 138.4, 132.7, 132.4 (q, $^2J_{C\text{-}F}$ = 33.5 Hz, 2C), 127.9 (d, $^3J_{C\text{-}F}$ = 3.9 Hz), 127.8, 122.9 (q, $^1J_{C\text{-}F}$ = 273.0 Hz, 2C), 122.4 (p, $^3J_{C\text{-}F}$ = 3.9 Hz, 2C), 120.4, 118.9, 117.4, 109.4, 97.2, 72.2, 48.4, 27.8, 19.0 (2C).

Example 13: 2-Methoxyethyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP13)

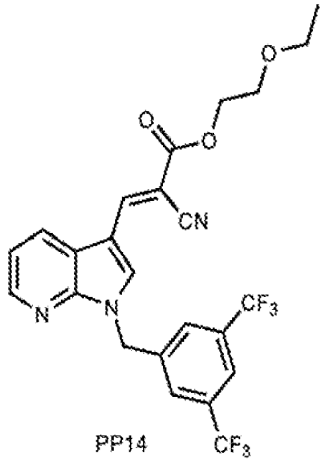


PP13

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.51 (d, *J* = 0.7 Hz, 1H), 8.47 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.22 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.34 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.70 (s, 2H), 4.45-4.47 (m, 2H), 3.70-3.72 (m, 2H), 3.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 147.4, 145.5, 145.2, 138.4, 132.9, 132.4 (q, $^2J_{C\text{-}F}$ = 33.8 Hz, 2C), 127.9, 127.8, 122.9 (q, $^1J_{C\text{-}F}$ = 273.0 Hz, 2C), 122.4 (p, $^3J_{C\text{-}F}$ = 3.9 Hz, 2C), 120.4, 119.0, 117.4, 109.4, 96.8, 70.2, 65.2, 59.2, 48.4.

Example 14: 2-Ethoxyethyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP14)

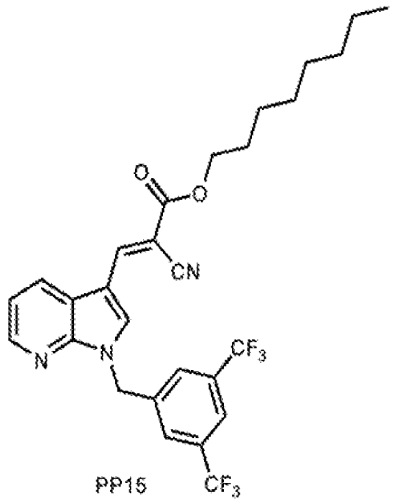


PP14

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.51 (d, J = 0.6 Hz, 1H), 8.48 (dd, J = 4.7, 1.4 Hz, 1H), 8.22 (dd, J = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.35 (dd, J = 8.0, 4.7 Hz, 1H), 5.71 (s, 2H), 4.44-4.46 (m, 2H), 3.74-3.76 (m, 2H), 3.59 (q, J = 7.0 Hz, 2H), 1.23 (t, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 147.3, 145.4, 145.1, 138.4, 132.9, 132.4 (q, $^2J_{C\text{-}F}$ = 33.7 Hz, 2C), 127.9, 127.9 (d, $^3J_{C\text{-}F}$ = 4.3 Hz), 122.9 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, 2C), 122.5 (p, $^3J_{C\text{-}F}$ = 3.6 Hz, 2C), 120.4, 119.0, 117.4, 109.4, 97.0, 68.0, 66.8, 65.4, 48.4, 15.2.

Example 15: Octyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP15)



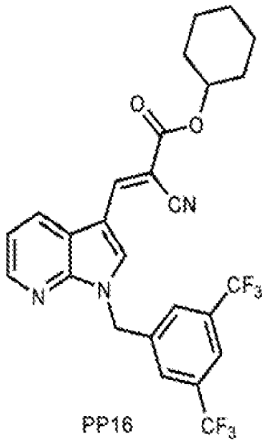
PP15

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.50 (d, J = 0.7 Hz, 1H), 8.47 (dd, J = 4.7, 1.5 Hz, 1H), 8.20 (dd, J = 7.9, 1.5 Hz, 1H), 7.82 (s, 1H), 7.76 (s, 2H), 7.33 (dd, J = 8.0, 4.7 Hz,

1H), 5.69 (s, 2H), 4.30 (t, J = 6.8 Hz, 2H), 1.72-1.78 (m, 2H), 1.28-1.45 (m, 10H), 0.88 (t, J = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 147.6, 145.7, 144.9, 138.5, 132.7, 132.4 (q, $^{2}J_{C\text{-}F}$ = 33.7 Hz, 2C), 127.8 (d, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 127.6, 122.9 (q, $^{1}J_{C\text{-}F}$ = 272.8 Hz, 2C), 122.4 (p, $^{3}J_{C\text{-}F}$ = 3.7 Hz, 2C), 120.3, 119.0, 117.5, 109.3, 97.1, 66.4, 48.3, 31.8, 29.2, 29.2, 28.6, 25.8, 22.7, 14.1.

Example 16: Cyclohexyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP16)

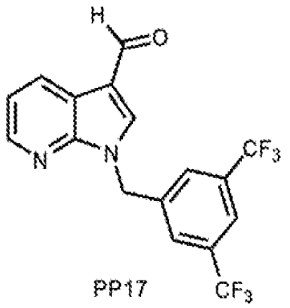


PP16

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.48 (s, 1H), 8.47 (dd, J = 4.7, 1.4 Hz, 1H), 8.22 (dd, J = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.76 (s, 2H), 7.33 (dd, J = 8.0, 4.7 Hz, 1H), 5.70 (s, 2H), 4.98 (ddd, J = 12.7, 8.9, 3.8 Hz, 1H), 1.90-1.93 (m, 2H), 1.78-1.83 (m, 2H), 1.31-1.64 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 147.5, 145.6, 144.6, 138.5, 132.6, 132.4 (q, $^{2}J_{C\text{-}F}$ = 33.5 Hz, 2C), 127.8 (d, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 127.7, 123.0 (q, $^{1}J_{C\text{-}F}$ = 272.8 Hz, 2C), 122.4 (p, $^{3}J_{C\text{-}F}$ = 3.9 Hz, 2C), 120.3, 118.9, 117.6, 109.3, 97.7, 74.8, 48.3, 31.5 (2C), 25.3 (2C), 23.5.

Example 17: 1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxaldehyde (PP17)

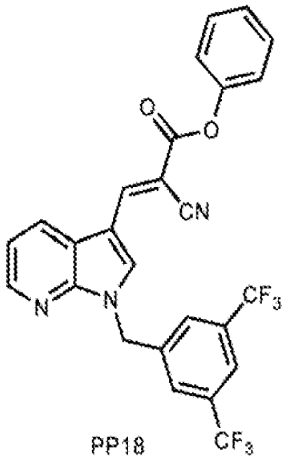


PP17

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.60 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.46 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.87 (s, 1H), 7.84 (s, 1H), 7.77 (s, 2H), 7.32 (dd, *J* = 7.9, 4.8 Hz, 1H), 5.66 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 148.3, 145.7, 138.7, 136.9, 132.5 (q, $^{2}J_{C\text{-}F}$ = 33.6 Hz, 2C), 131.0, 128.0, 127.9, 122.9 (q, $^{1}J_{C\text{-}F}$ = 272.8 Hz, 2C), 122.4 (p, $^{3}J_{C\text{-}F}$ = 3.9 Hz, 2C), 119.5, 117.6, 47.9.

Example 18: Phenyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-yl)-2-cyanoacrylate (PP18)

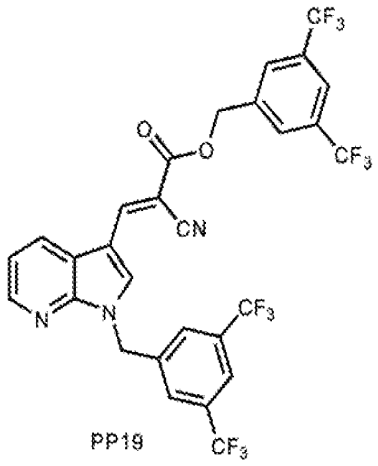


PP18

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.64 (s, 1H), 8.49 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.24 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.82 (s, 1H), 7.79 (s, 2H), 7.41-7.45 (m, 2H), 7.36 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.21-7.23 (m, 2H), 5.72 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 150.5, 147.7, 146.4, 145.9, 138.3, 133.4, 132.4 (q, $^{2}J_{C\text{-}F}$ = 33.7 Hz, 2C), 129.6 (2C), 127.9 (d, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 127.7, 126.3, 122.9 (q, $^{1}J_{C\text{-}F}$ = 272.9 Hz, 2C), 122.5 (p, $^{3}J_{C\text{-}F}$ = 3.8 Hz, 2C), 121.4 (2C), 120.3, 119.2, 117.4, 109.5, 96.0, 48.4.

Example 19: 3,5-Bis(trifluoromethyl)benzyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP19)

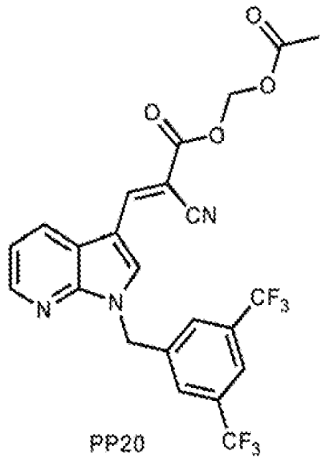


PP19

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.54 (s, 1H), 8.48 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.21 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.91 (s, 2H), 7.88 (s, 1H), 7.83 (s, 1H), 7.77 (s, 2H), 7.35 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.69 (s, 2H), 5.44 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 147.6, 146.1, 145.9, 138.3, 137.8, 133.4, 132.4 (q, $^2J_{C\text{-}F}$ = 33.3 Hz, 2C), 132.3 (q, $^2J_{C\text{-}F}$ = 33.2 Hz, 2C), 128.3 (d, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 127.9 (d, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 127.7, 123.1 (q, $^1J_{C\text{-}F}$ = 272.7 Hz, 2C), 122.9 (q, $^1J_{C\text{-}F}$ = 272.3 Hz, 2C), 122.5 (m, 2C), 120.2, 119.2, 117.2, 109.4, 95.6, 65.8, 48.4.

Example 20: Acetyloxymethyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP20)

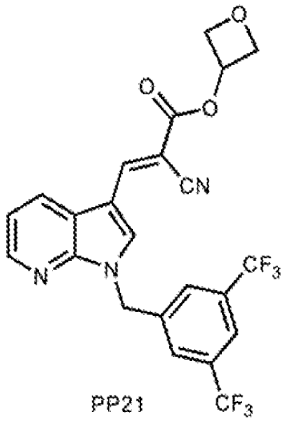


PP20

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.54 (d, J = 0.7 Hz, 1H), 8.48 (dd, J = 4.7, 1.5 Hz, 1H), 8.21 (dd, J = 8.0, 1.5 Hz, 1H), 7.83 (s, 1H), 7.77 (s, 2H), 7.35 (dd, J = 8.0, 4.7 Hz, 1H), 5.94 (s, 2H), 5.69 (s, 2H), 2.15 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 162.2, 147.6, 146.3, 145.9, 138.3, 133.6, 132.4 (q, $^2J_{C\text{-}F}$ = 33.5 Hz, 2C), 127.9 (d, $^3J_{C\text{-}F}$ = 3.4 Hz), 127.7, 122.9 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, 2C), 122.5 (p, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 120.3, 119.2, 117.0, 109.4, 95.5, 80.1, 48.4, 20.7.

Example 21: Oxetan-3-yl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP21)

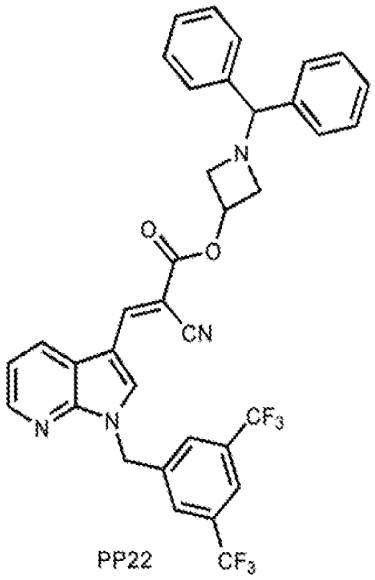


PP21

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.51 (s, 1H), 8.49 (dd, J = 4.7, 1.5 Hz, 1H), 8.21 (dd, J = 8.0, 1.5 Hz, 1H), 7.83 (s, 1H), 7.78 (s, 2H), 7.35 (dd, J = 7.9, 4.7 Hz, 1H), 5.70 (s, 2H), 5.63 (pentet, J = 5.9 Hz, 1H), 4.96 (dd, J = 7.2 Hz, 2H), 4.79 (dd, J = 8.0, 5.4 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 147.6, 145.9 (2C), 138.3, 133.3, 132.4 (q, $^2J_{C\text{-}F}$ = 33.8 Hz, 2C), 127.9 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 127.7, 122.9 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, 2C), 122.5 (p, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 120.3, 119.2, 117.2, 109.4, 95.6, 69.3 (3C), 48.4.

Example 22: 1-Benzhydrylazetidin-3-yl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP22)

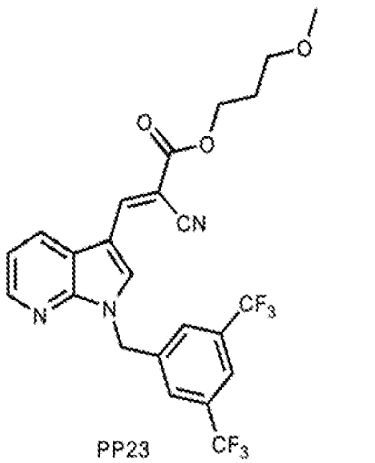


PP22

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.48 (d, J = 1.5 Hz, 1H), 8.47 (s, 1H), 8.19 (dd, J = 8.0, 1.5 Hz, 1H), 7.83 (s, 1H), 7.77 (s, 2H), 7.41-7.42 (m, 4H), 7.33 (dd, J = 8.0, 4.7 Hz, 1H), 7.28 (t, J = 7.6 Hz, 4H), 7.19 (t, J = 7.3 Hz, 2H), 5.69 (s, 2H), 5.24-5.29 (m, 1H), 4.43 (s, 1H), 3.69 (t, J = 7.7 Hz, 2H), 3.16 (t, J = 7.5 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 147.6, 145.8, 145.5, 141.7 (2C), 138.4, 133.0, 132.4 (q, $^{2}J_{C\text{-}F}$ = 33.6 Hz, 2C), 128.5 (4C), 127.9 (d, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 127.7, 127.4 (4C), 127.3 (2C), 122.9 (q, $^{1}J_{C\text{-}F}$ = 272.8 Hz, 2C), 122.5 (p, $^{3}J_{C\text{-}F}$ = 3.5 Hz, 2C), 120.3, 119.1, 117.4, 109.4, 96.2, 78.2, 65.3, 60.0 (2C), 48.4.

Example 23: 3-Methoxypropyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP23)

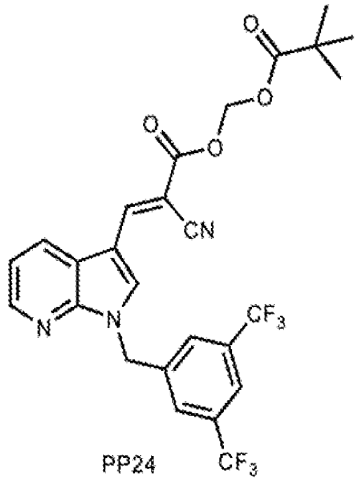


PP23

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.50 (s, 1H), 8.47 (dd, J = 4.7, 1.5 Hz, 1H), 8.21 (dd, J = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.33 (dd, J = 8.0, 4.7 Hz, 1H), 5.69 (s, 2H), 4.40 (t, J = 6.4 Hz, 2H), 3.53 (t, J = 6.1 Hz, 2H), 3.36 (s, 3H), 2.02 (pentet, J = 6.3 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 147.6, 145.7, 145.1, 138.5, 132.8, 132.3 (q, $^2J_{C\text{-}F}$ = 33.4 Hz, 2C), 127.9 (d, $^3J_{C\text{-}F}$ = 3.0 Hz), 127.7, 122.9 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, 2C), 122.4 (p, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 120.3, 119.0, 117.5, 109.3, 96.9, 68.8, 63.4, 58.8, 48.3, 28.9.

Example 24: (Pivaloyloxy)methyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP24)

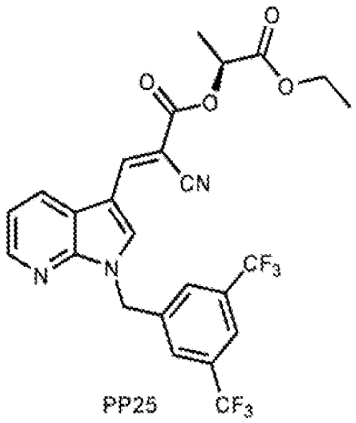


PP24

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.54 (d, J = 0.6 Hz, 1H), 8.48 (dd, J = 4.7, 1.5 Hz, 1H), 8.21 (dd, J = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.35 (dd, J = 8.0, 4.7 Hz, 1H), 5.98 (s, 2H), 5.69 (s, 2H), 1.23 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 162.1, 147.6, 146.2, 145.9, 138.3, 133.5, 132.4 (q, $^2J_{C\text{-}F}$ = 33.7 Hz, 2C), 127.9 (d, $^3J_{C\text{-}F}$ = 3.5 Hz), 127.7, 122.9 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, 2C), 122.5 (p, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 120.3, 119.2, 117.0, 109.4, 95.6, 80.5, 48.4, 38.8, 26.9 (3C).

Example 25: (*S*)-1-Ethoxy-1-oxopropan-2-yl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP25)

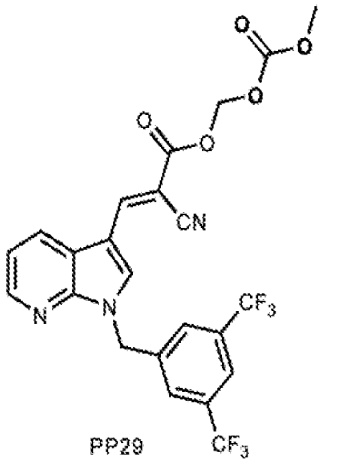


PP25

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.53 (d, J = 0.6 Hz, 1H), 8.47 (dd, J = 4.7, 1.5 Hz, 1H), 8.19 (dd, J = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.33 (dd, J = 8.0, 4.7 Hz, 1H), 5.69 (s, 2H), 5.24 (q, J = 7.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.63 (d, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 162.7, 147.6, 145.8 (2C), 138.4, 133.2, 132.4 (q, $^2J_{C-F}$ = 33.7 Hz, 2C), 127.9 (d, $^3J_{C-F}$ = 3.6 Hz), 127.7, 122.9 (q, $^1J_{C-F}$ = 272.9 Hz, 2C), 122.4 (p, $^3J_{C-F}$ = 3.8 Hz, 2C), 120.3, 119.1, 117.2, 109.4, 96.1, 70.3, 61.6, 48.4, 16.9, 14.1.

Example 26: ((Methoxycarbonyl)oxy)methyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP29)

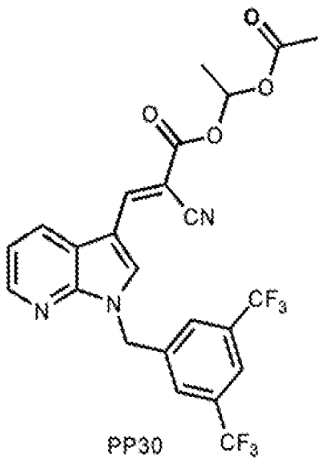


PP29

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.55 (d, J = 0.5 Hz, 1H), 8.49 (dd, J = 4.7, 1.5 Hz, 1H), 8.21 (dd, J = 8.0, 1.5 Hz, 1H), 7.83 (s, 1H), 7.78 (s, 2H), 7.35 (dd, J = 8.0, 4.7 Hz, 1H), 5.96 (s, 2H), 5.70 (s, 2H), 3.86 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 154.3, 147.6, 146.5, 145.9, 138.3, 133.6, 132.4 (q, $^{2}J_{C\text{-}F}$ = 33.5 Hz, 2C), 127.9 (d, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 127.7, 122.9 (q, $^{1}J_{C\text{-}F}$ = 272.9 Hz, 2C), 122.5 (p, $^{3}J_{C\text{-}F}$ = 3.8 Hz, 2C), 120.3, 119.3, 116.9, 109.4, 95.3, 82.8, 55.5, 48.4.

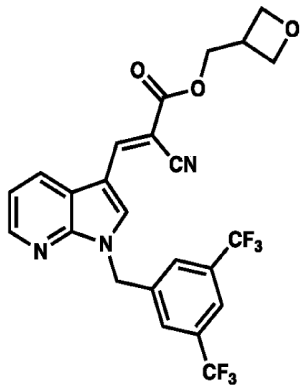
Example 27: 1-Acetyloxyethyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP30)



PP30

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.52 (d, *J* = 0.6 Hz, 1H), 8.47 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.19 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.34 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.04 (q, *J* = 5.5 Hz, 1H), 5.69 (s, 2H), 2.11 (s, 3H), 1.60 (d, *J* = 5.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 161.4, 147.6, 146.1, 145.8, 138.4, 133.3, 132.4 (q, $^{2}J_{C\text{-}F}$ = 33.6 Hz, 2C), 127.9 (d, $^{3}J_{C\text{-}F}$ = 2.9 Hz), 127.7, 122.9 (q, $^{1}J_{C\text{-}F}$ = 272.9 Hz, 2C), 122.5 (p, $^{3}J_{C\text{-}F}$ = 3.7 Hz, 2C), 120.3, 119.2, 117.1, 109.4, 95.8, 89.5, 48.4, 20.9, 19.5.

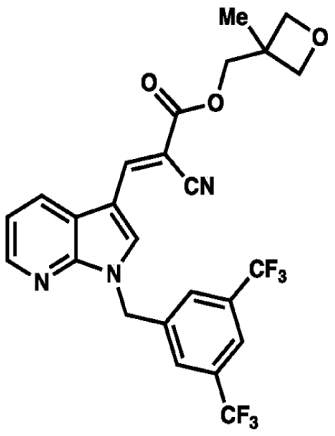


PP46

Example 28: Oxetan-3-ylmethyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP46)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.49 (d, J = 0.6 Hz, 1H), 8.46 (dd, J = 4.7, 1.5 Hz, 1H), 8.18 (dd, J = 7.9, 1.5 Hz, 1H), 7.81 (s, 1H), 7.77 (s, 2H), 7.32 (dd, J = 8.1, 4.7 Hz, 1H), 5.68 (s, 2H), 4.85 (dd, J = 7.8, 6.4 Hz, 2H), 4.51-4.55 (m, 4H), 3.36-3.44 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 147.6, 145.7, 145.5, 138.4, 133.1, 132.3 (q, $^2J_{C-F}$ = 33.9 Hz, 2C), 127.9 (d, $^3J_{C-F}$ = 4.8 Hz), 127.6, 122.9 (q, $^1J_{C-F}$ = 273.0 Hz, 2C), 122.4 (p, $^3J_{C-F}$ = 3.8 Hz, 2C), 120.3, 119.0, 117.3, 109.3, 96.2, 73.9 (2C), 66.9, 48.3, 34.2.

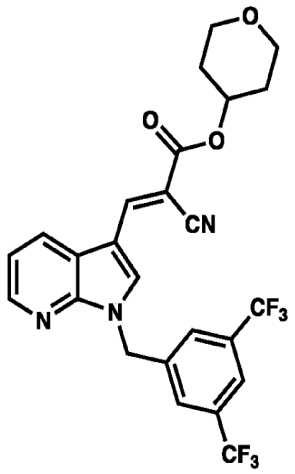


PP47

Example 29: (3-methyloxetan-3-yl)methyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP47)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.50 (d, J = 0.5 Hz, 1H), 8.46 (dd, J = 4.7, 1.5 Hz, 1H), 8.18 (dd, J = 7.9, 1.5 Hz, 1H), 7.81 (s, 1H), 7.78 (s, 2H), 7.32 (dd, J = 7.9, 4.7 Hz, 1H), 5.69 (s, 2H), 4.56 (d, J = 6.1 Hz, 2H), 4.44 (d, J = 6.3 Hz, 2H), 4.41 (s, 2H), 1.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 147.7, 145.8, 145.5, 138.6, 133.2, 132.4 (q, $^2J_{C-F}$ = 33.4 Hz, 2C), 128.0 (d, $^3J_{C-F}$ = 4.8 Hz), 127.7, 123.0 (q, $^1J_{C-F}$ = 273.0 Hz, 2C), 122.5 (p, $^3J_{C-F}$ = 3.8 Hz, 2C), 120.3, 119.1, 117.3, 109.4, 96.3, 79.5 (2C), 70.4, 48.4, 39.5, 21.1.

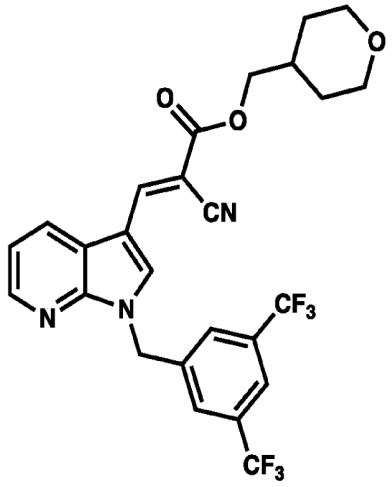


PP48

Example 30: Tetrahydro-2*H*-pyran-4-yl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP48)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.49 (d, *J* = 0.6 Hz, 1H), 8.47 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.20 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.33 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.69 (s, 2H), 5.16 (tt, *J* = 8.2, 4.0 Hz, 1H), 3.97 (ddd, *J* = 11.9, 6.0, 4.0 Hz, 2H), 3.60 (ddd, *J* = 11.6, 8.4, 3.2 Hz, 2H), 1.98-2.04 (m, 2H), 1.79-1.86 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 147.6, 145.7, 145.1, 138.5, 132.9, 132.4 (q, $^2J_{C\text{-}F}$ = 33.9 Hz, 2C), 127.9 (d, $^3J_{C\text{-}F}$ = 4.8 Hz), 127.6, 122.9 (q, $^1J_{C\text{-}F}$ = 273.0 Hz, 2C), 122.4 (p, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 120.3, 119.0, 117.4, 109.3, 97.0, 71.1, 65.1 (2C), 48.3, 31.6 (2C).



PP49

(tetrahydro-2*H*-pyran-4-yl)methyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate (PP49)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.49 (d, *J* = 0.8 Hz, 1H), 8.46 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.19 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.81 (s, 1H), 7.77 (s, 2H), 7.32 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.69 (s, 2H), 4.16 (d, *J* = 6.7 Hz, 2H), 4.00 (dd, *J* = 11.2, 3.3 Hz, 2H), 3.41 (td, *J* = 11.9, 2.0 Hz, 2H), 2.00-2.09 (m, 1H), 1.70 (dd, *J* = 12.8, 1.8 Hz, 2H), 1.43 (dd, *J* = 12.1, 4.5 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 147.6, 145.7, 145.2, 138.5, 132.9, 132.4 (q, $^2J_{C-F}$ = 33.9 Hz, 2C), 127.9 (d, $^3J_{C-F}$ = 4.8 Hz), 127.6, 122.9 (q, $^1J_{C-F}$ = 273.0 Hz, 2C), 122.4 (p, $^3J_{C-F}$ = 3.8 Hz, 2C), 120.3, 119.0, 117.4, 109.3, 96.6, 70.2, 67.4 (2C), 48.3, 34.6, 29.4 (2C).

Testing Methods

Example 31: Measurement of esterase activity of selected compounds in mouse skin homogenate.

Samples of tazarotene, tazarotenic acid, bacampicillin, ampicillin, JXL069, JXL082, PP12, PP20, PP21, PP24, PP29, PP30, and a reference blank (DMSO) were prepared at a concentration of 10 μM, and incubated with homogenized mouse skin (0.5 mg/mL) in PBS (saline) solution (total volume of 1 mL) for 1 hour at 37 °C. The samples were then quenched with UK5099 and analysis was performed using LCMS. Results are shown in FIG. 1.

Example 32: Measurement of esterase activity of selected compounds in minipig skin homogenate.

Samples of tazarotene, tazarotenic acid, bacampicillin, ampicillin, JXL069, JXL082, PP12, PP20, PP21, PP24, PP29, PP30, and a reference blank (DMSO) were prepared at a concentration of 10 μM, and incubated with homogenized minipig skin (0.5 mg/mL) in PBS (saline) solution (total volume of 1 mL) for 1 hour at 37 °C. The samples were then quenched with UK5099 and analysis was performed using LCMS. Results are shown in FIG. 2.

Example 33: Measurement of esterase activity of selected compounds in human skin homogenate.

Samples of tazarotene, tazarotenic acid, bacampicillin, ampicillin, JXL069, JXL082, PP12, PP20, PP21, PP24, PP29, PP30, PP46, PP47, PP48, and PP49 and a reference blank (DMSO) were prepared at a concentration of 10 μM, and incubated with homogenized human skin (0.5 mg/mL) in PBS (saline) solution (total volume of 1 mL) for 1 hour at 37 °C. The samples were then quenched with UK5099 and analysis was performed using LCMS. Results are shown in FIG. 3A and 3B.

Example 34: Ldh Platereader Protocol

Human skin samples were homogenized with a Benchmark BeadBlaster24R in 500 μl of Pierce RIPA Lysis and Extraction buffer (Thermo Scientific Cat No: 89900), centrifuged at 10,000 g for 15 minutes at 4 °C to remove insoluble material, and the soluble fraction quantified by Pierce BCA assay (Thermo Scientific Cat No: 23225). Lactate dehydrogenase activity was quantified using a Sigma Aldrich Lactate Dehydrogenase Activity Assay Kit (Catalog No: MAK066). Briefly, 10 μg of sample was loaded per well in a 96 well plate along with 20 uM of Pelage compounds and pre-incubated at 37 °C for 30 minutes before addition of Ldh assay master mix. Using a Biotek Synergy HTX multi-mode reader, the plate was incubated at 37 °C and absorbance measurements at 450 nm (A450) were taken every 3 minutes for 30 minutes. The LDH activity of each sample was quantified by calculating the ΔA450 over time. FIG. 4 shows a schematic for performing the LDH activity assay on human skin cell lysate.

FIG. 5A shows that pretreatment of human skin lysate with high heat kills the LDH activity.

FIG. 5B shows that treatment of human skin lysate with exemplary LDH inhibitors blocks most of the LDH activity, further confirming that the activity readout is the result of LDH activity.

FIGs. 6A and 6B show that the treatment of human skin lysate with exemplary MPC inhibitors results in an increase in LDH activity.

FIG. 7 shows that pretreatment of human skin lysate with a carboxylesterase inhibitor (benzil) prior to incubation with MPC inhibitors blocks the effect of most of the exemplary ester containing MPC inhibitors; however, the pretreatment had no effect on carboxylic containing MPC inhibitors (UK5099, indicated as “UK” in FIG. 7),

demonstrating that they act as prodrugs that are only active when converted to carboxylic acids.

FIG. 8 shows that the MPC inhibitors of the disclosure promote hair growth. Mice were shaved at day 50 when the hair cycle is dormant. Exemplary compounds were applied topically to the shaved area every other day up to day 30. Macroscopic observation led to the quantification of hair cycle staging shown where the two ester-MPC inhibitors accelerated the hair cycle compared to vehicle control.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

The terms "a," "an," "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein may be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of any claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

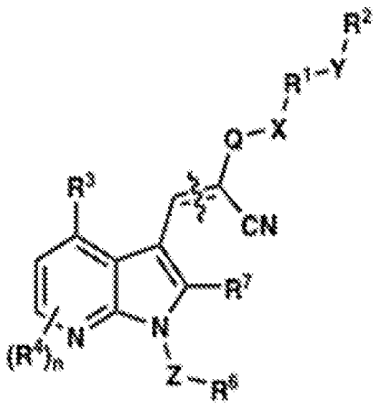
Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability.

Certain embodiments are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is contemplated unless otherwise indicated herein or otherwise clearly contradicted by context.

In closing, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments precisely as shown and described.

CLAIMS

1. A compound represented by a formula:



,

or a pharmaceutically acceptable salt thereof;

wherein Q is —C(=O)—, —C(=S)—, or —$S(=O)_2$—;

R^1 is —, —$S(=O)_2$—, an optionally substituted C_{1-12} hydrocarbon group or an optionally substituted heterocycle;

R^2 is H, an optionally substituted C_{1-6} alkyl, an optionally substituted carbocycle, or an optionally substituted heterocycle;

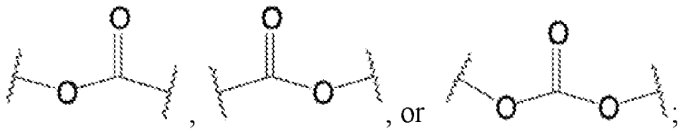
R^3 and R^7 are independently H, F, Cl, Br, I, OH, OR^A, SH, SR^A, NR^AR^B, CF_3, CN, carboxylic acid, an optionally substituted carboxylic ester, or an optionally substituted C_{1-6} alkyl;

each R^4 is independently H, F, Cl, Br, I, OH, O^-, OR^A, SH, SR^A, NR^AR^B, CF_3, CN, carboxylic acid, an optionally substituted carboxylic ester, or an optionally substituted C_{1-6} alkyl;

R^A and R^B are independently H or optionally substituted C_{1-6} hydrocarbon group;

n is 0, 1, or 2;

X is O, S, NR^5, or $N^+R^5R^8$, wherein R^5 and R^8 are independently H, C_{1-6} alkyl, an optionally substituted carbocycle, or an optionally substituted heterocycle, and the N, R^5 and R^1, or the N, R^5 and R^8, may together form an optionally substituted heterocyclic ring;

Y is —, —O—,  ;

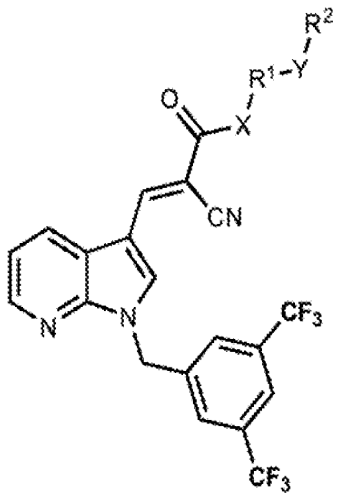
Z is —, an optionally substituted C_{1-12} hydrocarbon group, or optionally substituted heterocycle;

R^6 is H, an optionally substituted C_{1-12} hydrocarbon group, or optionally substituted heterocycle; and

the wavy line across the C=C bond represents an E or Z olefin.

2. The compound of claim 1, wherein X is O.

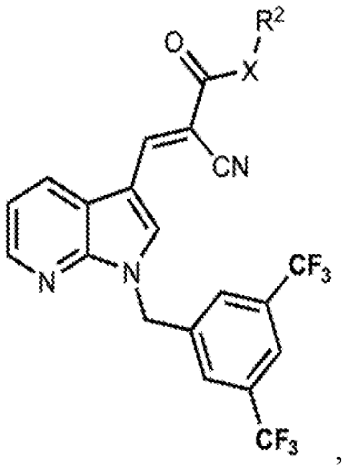
3. The compound of claim 2, further represented by a formula:



, or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3, wherein R^1 is —, —CH_2—, an optionally substituted C_{3-12} hydrocarbon group, or an optionally substituted heterocycle having a carbon atom directly attached to X.

5. The compound of claim 2, further represented by a formula:



, or a pharmaceutically acceptable salt thereof;

wherein R^2 is CH_3 or C_{3-12} alkyl.

6. The compound of claim 1, wherein X is NR^5 or $N^+R^5R^8$.

7. The compound of claim 1, 2, or 6, wherein R^1 is C_{1-12} alkyl.

8. The compound of claim 1, 2, or 6, wherein R^1 is a branched C_{2-12} alkyl.

9. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted C_{1-12} alkyl.

10. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted branched C_{2-12} alkyl.

11. The compound of claim 1, 2, or 6, wherein R^1 is an optionally heteroatom substituted branched C_{2-12} alkyl.

12. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted carbocycle.

13. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted heterocycle.

14. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted aryl.

15. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted heteroaryl.

16. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted benzyl.

17. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted heterocycle having a carbon atom directly attached to X.

18. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted oxetane.

19. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted tetrahydrofuran.

20. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted dihydrofuran.

21. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted furan.

22. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted furanone.

23. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted tetrahydropyran.

24. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted dihydropyran.

25. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted pyran.

26. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted tetrahydropyrone.

27. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted dihydropyrone.

28. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted pyrone.

29. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted thietane.

30. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted tetrahydrothiophene.

31. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted dihydrothiophene.

32. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted thiophene.

33. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted azetidine.

34. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted pyrrolidine.

35. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted pyrroline.

36. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted pyrrole.

37. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted piperidine.

38. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted pyridine.

39. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted oxazole.

40. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted isoxazole.

41. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted thiazole.

42. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted isothiazole.

43. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted pyrazolidine.

44. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted imidazolidine.

45. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted pyrazole.

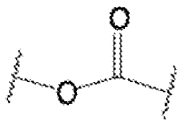
46. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted imidazole.

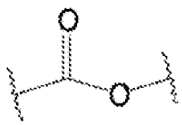
47. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted tetrazole.

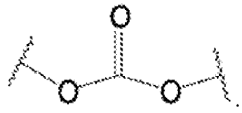
48. The compound of claim 1, 2, or 6, wherein R^1 is an optionally substituted sulfolane.

49. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48, wherein Y is —.

50. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48, wherein Y is —O—.

51. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48, wherein Y is  .

52. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48, wherein Y is  .

53. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, or 48, wherein Y is  .

54. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53, wherein R^2 is H.

55. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53, wherein R^2 is C_{1-12} alkyl.

56. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53, wherein R^2 is optionally substituted carbocycle.

57. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53, wherein R^2 is optionally substituted heterocycle.

58. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53, wherein R^2 is optionally substituted aryl.

59. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53, wherein R^2 is optionally substituted heteroaryl.

60. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, or 53, wherein R^2 is optionally substituted benzyl.

61. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60, wherein R^3 is H.

62. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60, wherein R^3 is F.

63. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is —.

64. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is optionally substituted C_{1-12} alkyl.

65. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is optionally substituted carbocycle.

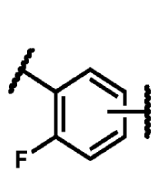
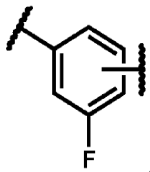
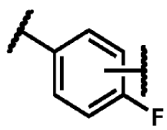
66. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is optionally substituted heterocycle.

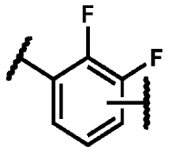
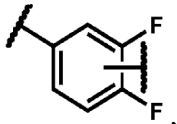
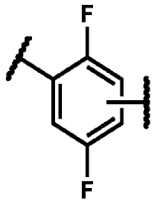
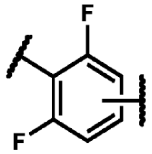
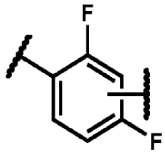
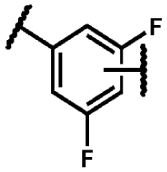
67. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is optionally substituted aryl.

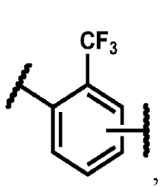
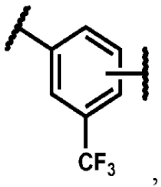
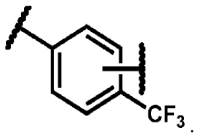
68. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42,

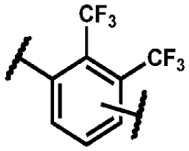
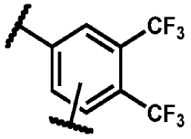
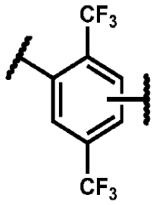
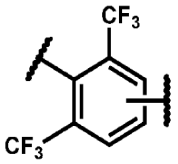
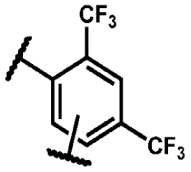
43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is optionally substituted heteroaryl.

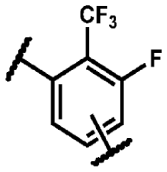
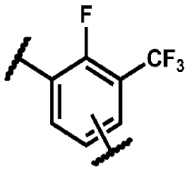
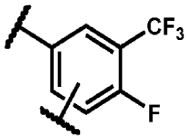
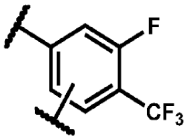
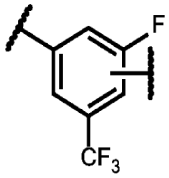
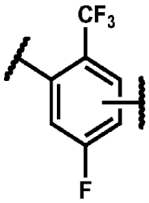
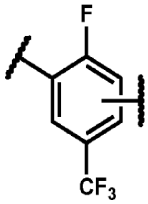
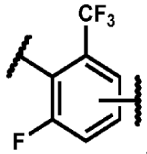
69. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is optionally substituted benzyl.

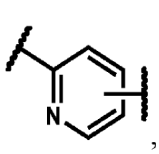
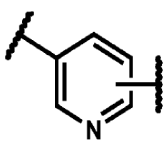
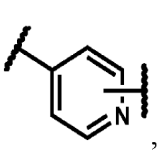
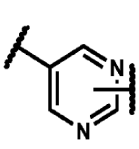
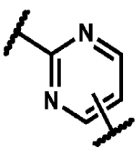
70. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is  ,  , or  .

71. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is  ,  ,  ,  ,  , or  .

72. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is  ,  , or  .

73. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is  ,  ,  ,  , or  .

74. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is  ,  ,  ,  ,  ,  ,  , or  .

75. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is  ,  ,  ,  , or  .

76. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, or 62, wherein Z is —CH_2—.

77. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is H.

78. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is optionally substituted C_{1-12} alkyl.

79. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is optionally substituted carbocycle.

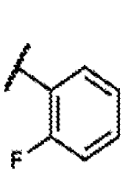
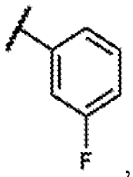
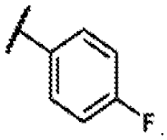
80. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is optionally substituted heterocycle.

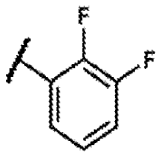
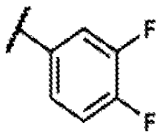
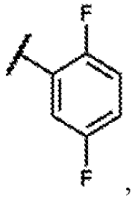
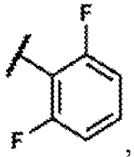
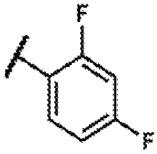
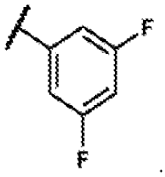
81. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is optionally substituted aryl.

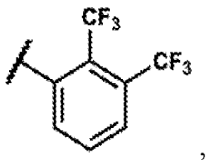
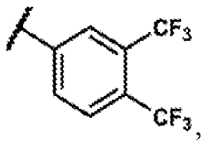
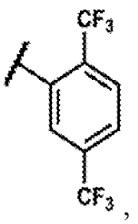
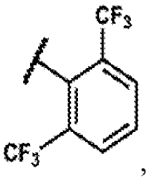
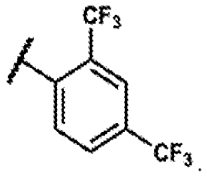
82. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is optionally substituted heteroaryl.

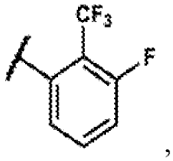
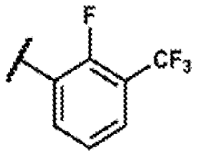
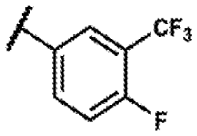
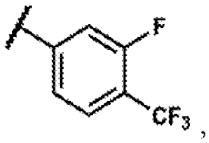
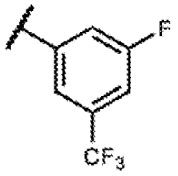
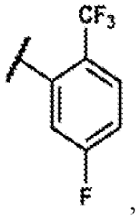
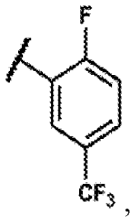
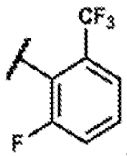
83. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65,

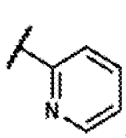
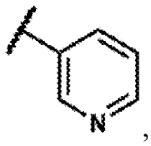
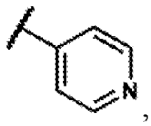
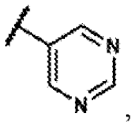
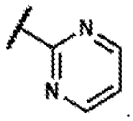
66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is optionally substituted benzyl.

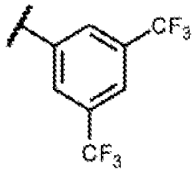
84. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is  ,  , or  .

85. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is  ,  ,  ,  ,  , or  .

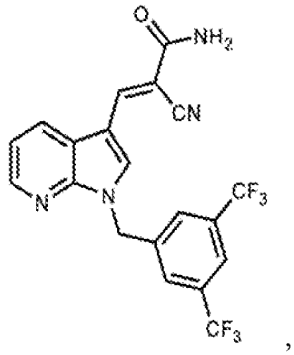
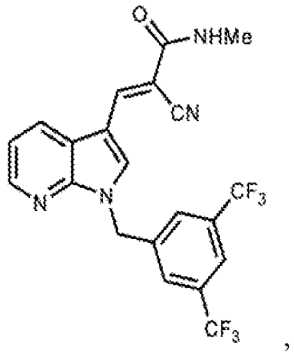
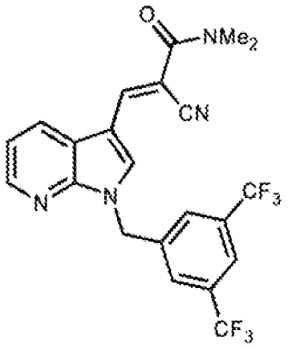
86. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is  ,  ,  ,  , or  .

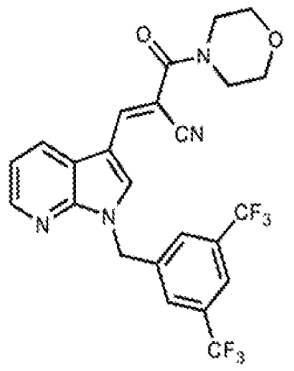
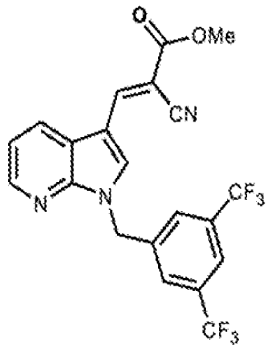
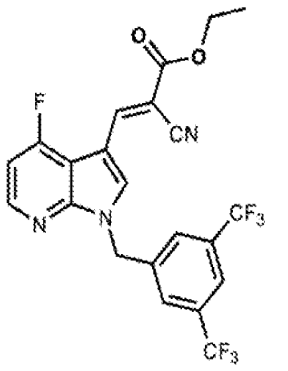
87. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is  ,  ,  ,  ,  ,  ,  , or  .

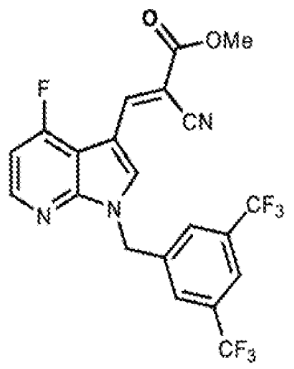
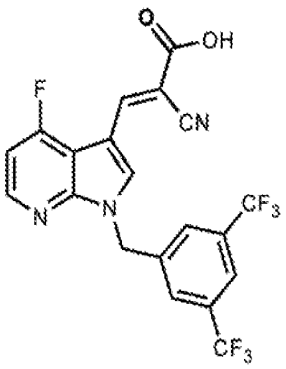
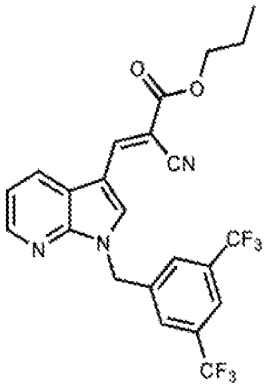
88. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is  ,  ,  ,  , or  .

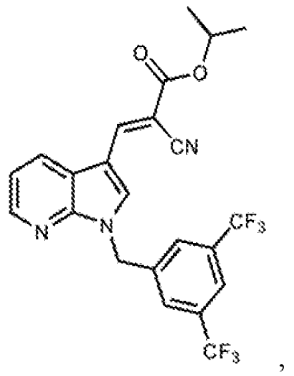
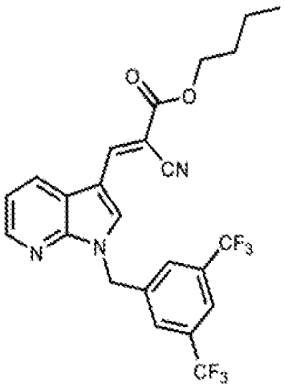
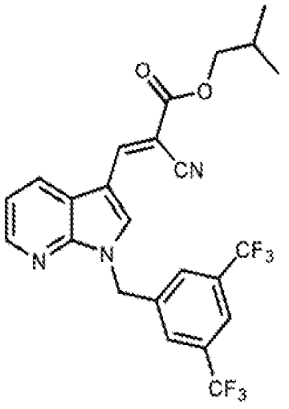
89. The compound of claim 1, 2, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein R^6 is not  .

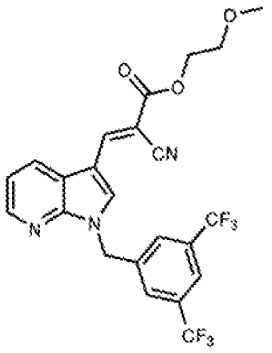
90. A compound, which is:

2  ,  ,  ,

 ,  ,  ,

4  ,  ,  ,

 ,  ,  ,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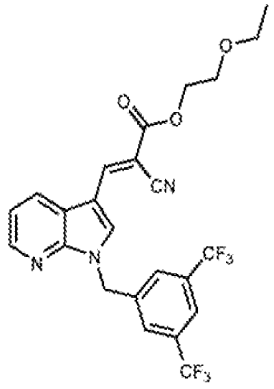
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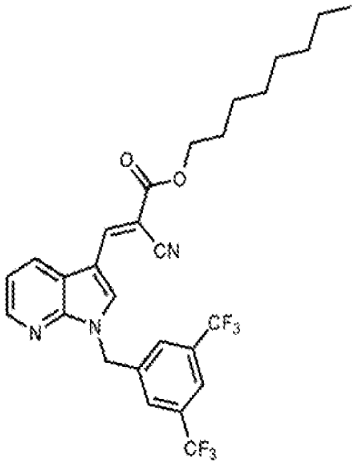
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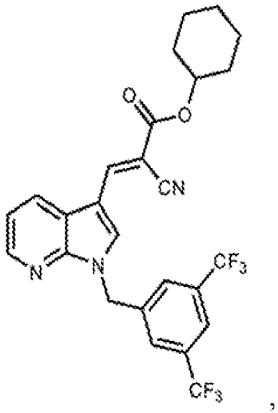
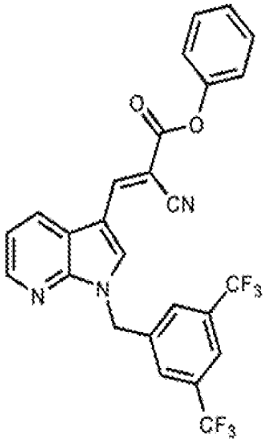

,

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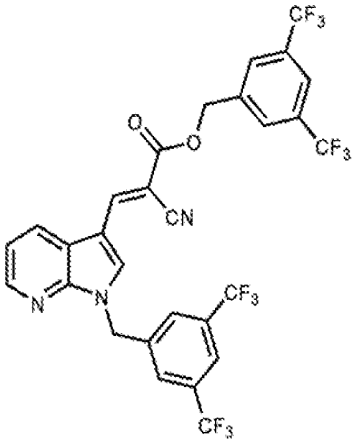
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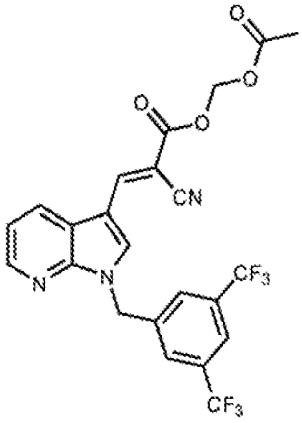
2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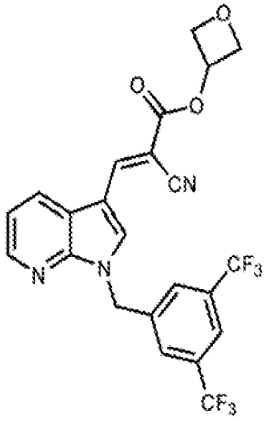
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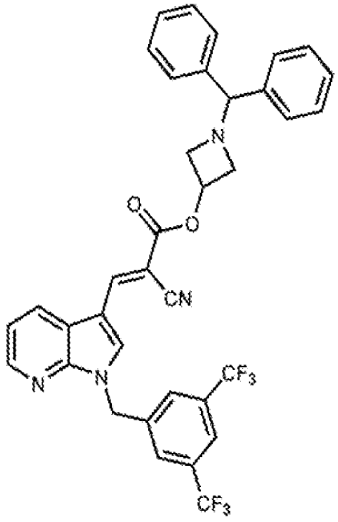
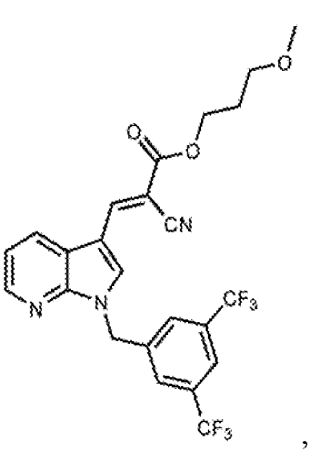

,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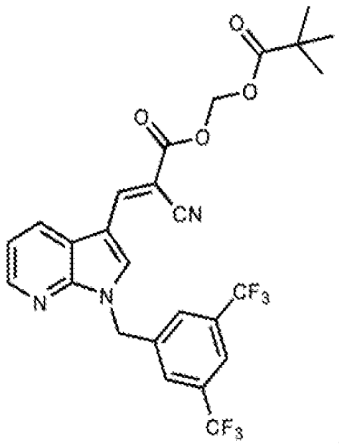
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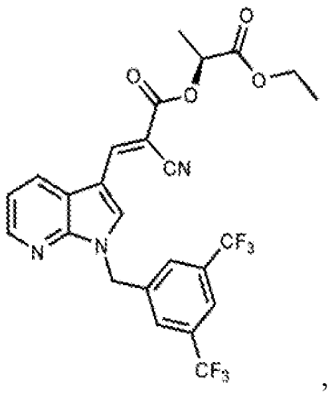
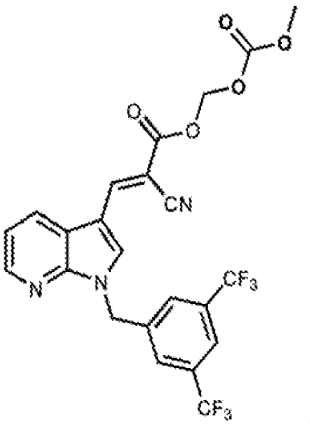

,

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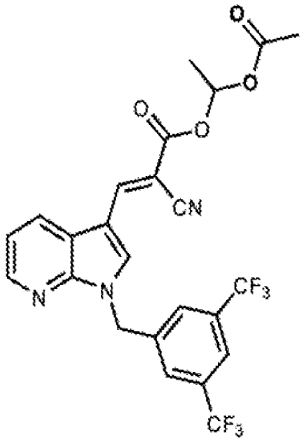
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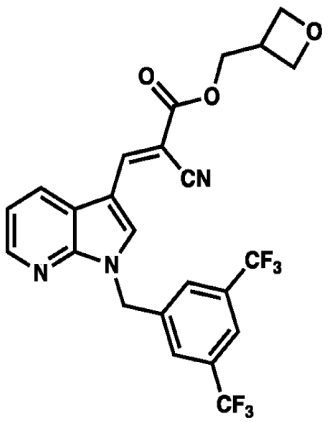
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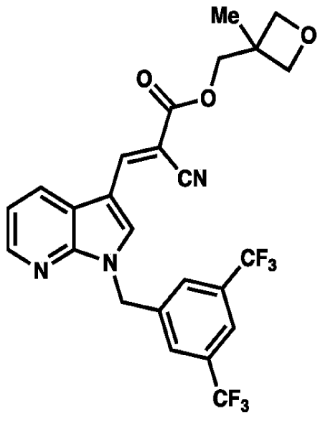
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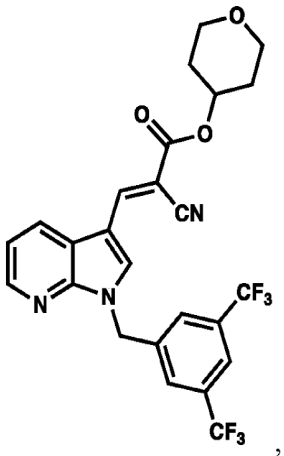
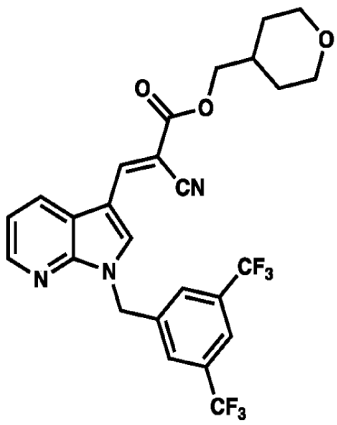

, or

.

91. A compound of any preceding claim, wherein X is O, and the compound has an ester having a rate of ester hydrolysis that is faster than a reference compound, wherein the reference compound has the same R^3, R^4, R^7, R^6, Z and n as the compound, and R^1-Y-R^2 for the reference compound is ethyl.

92. A compound of claim 91, wherein the rate of ester hydrolysis improves the delivery of the corresponding carboxylic acid product to potentiate hair growth.

93. A pharmaceutical composition comprising a compound of any preceding claim.

94. A pharmaceutical composition for growing hair comprising a compound according to any one of claims 1-92.

95. A method of growing hair, comprising: administering a compound of any preceding claim to the skin of a mammal in the area where hair growth is intended.

96. Use of a compound of according to any one of claims 1-92 in the manufacture of a medicament for growing hair.

97. A method of growing hair comprising administering an MPC inhibitor to a mammal in need thereof, wherein the MPC inhibitor is a compound according to any one of claims 1-92.

98. A method of treating a disorder affecting hair growth comprising administering a compound according to any one of claims 1-92 to a mammal in need thereof.

99. The method of claim 98, where the disorder is alopecia or baldness.

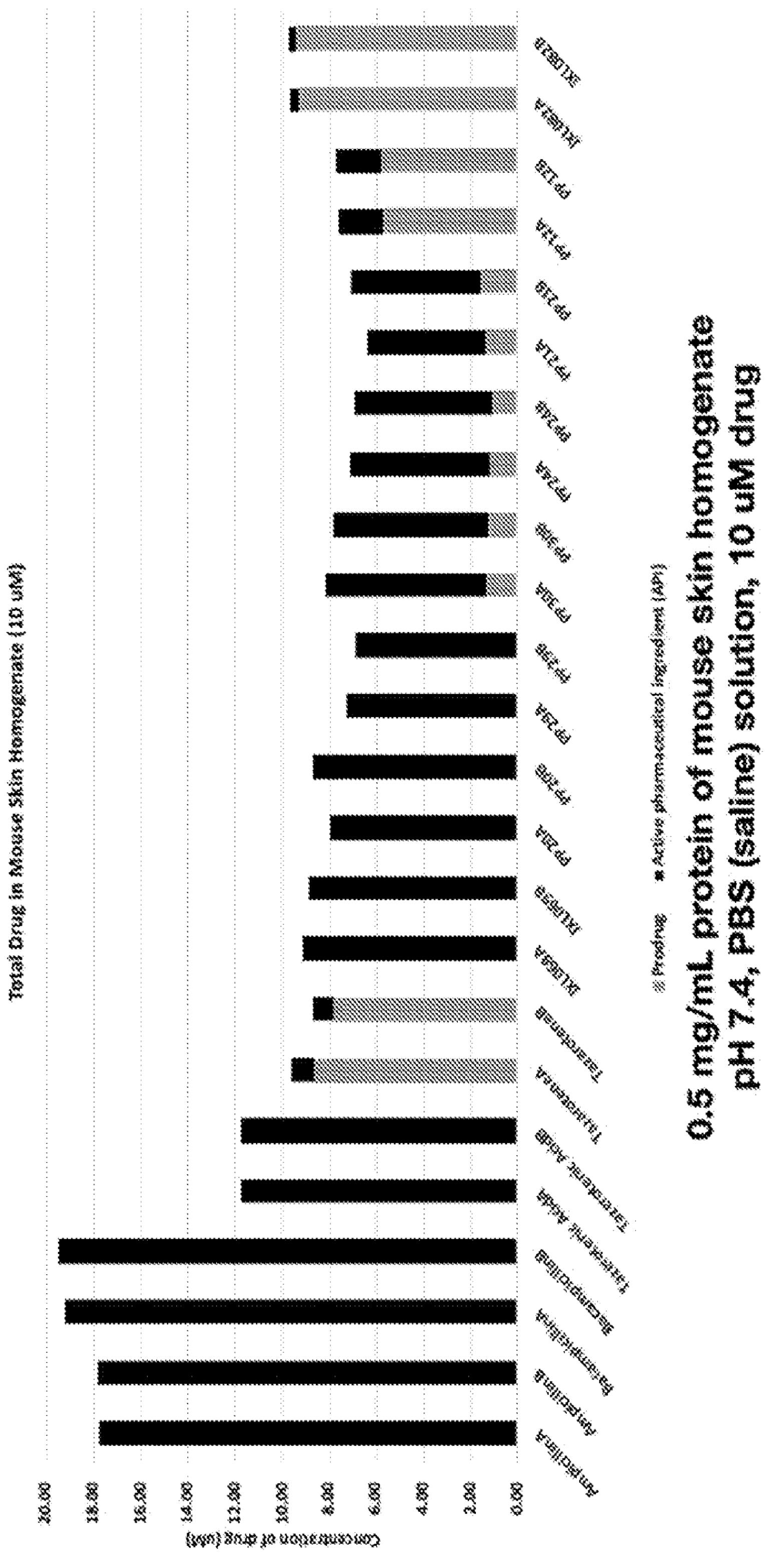

Total Drug in Mouse Skin Homogenate (10 uM)
Concentration of drug (uM)
20.00
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Prodrug
Active pharmaceutical ingredient (API)
0.5 mg/mL protein of mouse skin homogenate
pH 7.4, PBS (saline) solution, 10 uM drug

FIG. 1

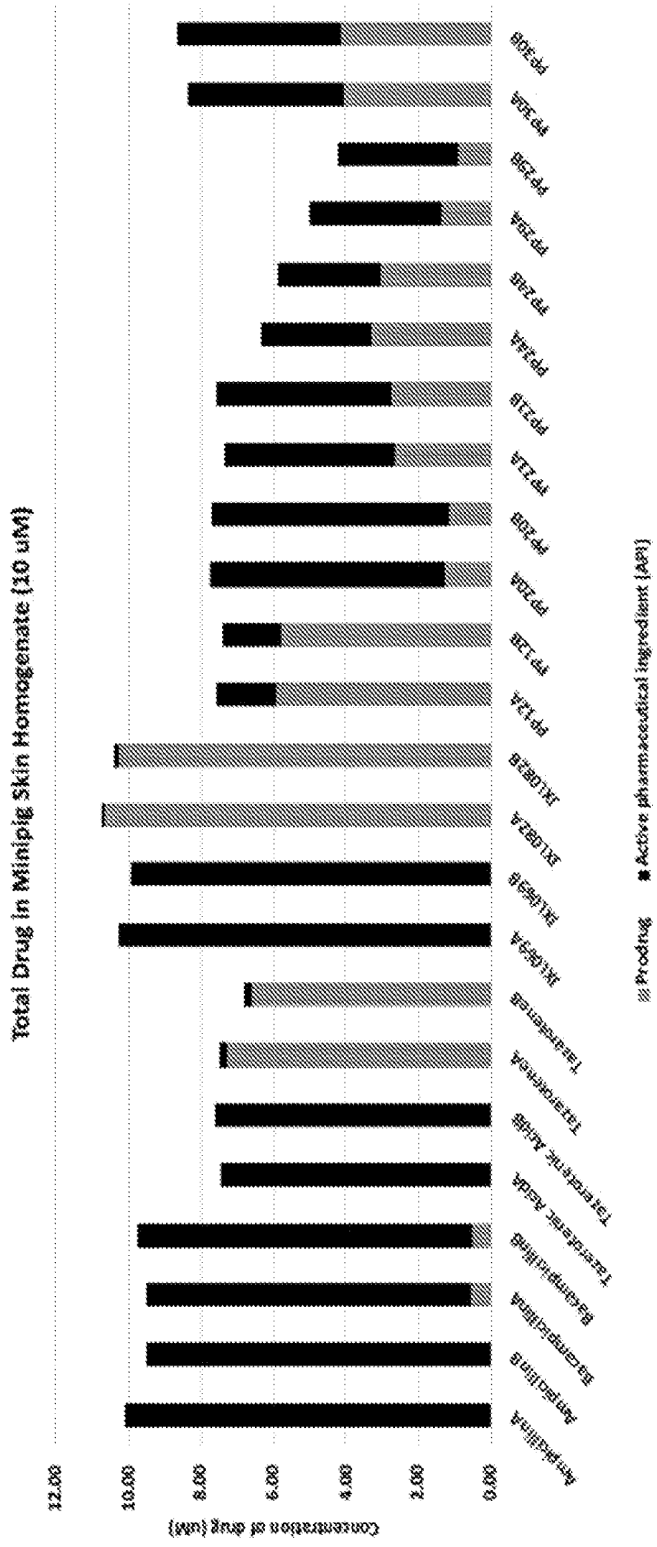

0.5 mg/mL protein of minipig skin homogenate
pH 7.4, PBS (saline) solution, 10 uM drug
Total Drug in Minipig Skin Homogenate (10 uM)
Concentration of drug (uM)
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Prodrug
Active pharmaceutical ingredient (API)
Amphotalin A
Amphotalin B
Bacampicillin
Bacampicillin B
Tazobactam Acid
Tazobactam A
Tazobactam B
JK1052A
JK1052B
JK1053A
JK1053B
JK1082A
JK1082B
PP-1A
PP-1B
PP-2A
PP-2B
PP-3A
PP-3B
PP-4A
PP-4B
PP-5A
PP-5B
PP-6A
PP-6B

FIG. 2

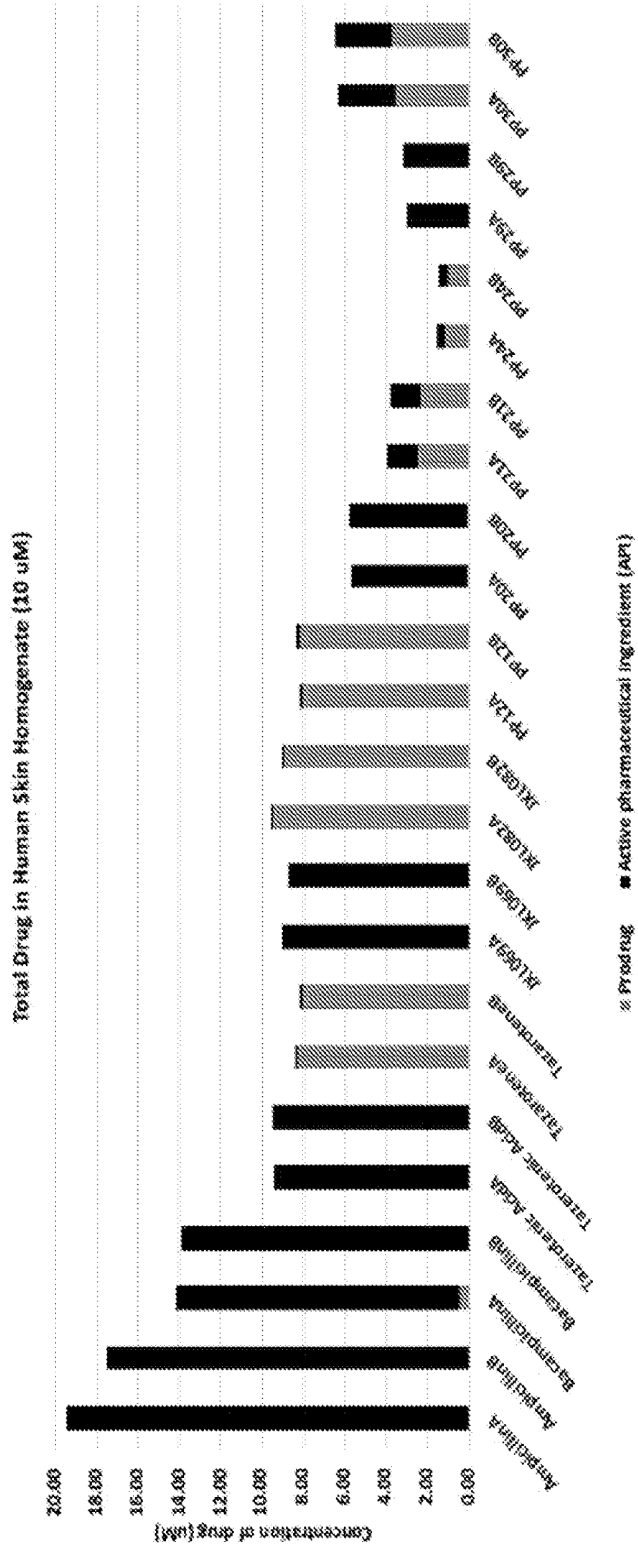

0.5 mg/mL protein of human skin homogenate
pH 7.4, PBS (saline) solution, 10 uM drug
Total Drug in Human Skin Homogenate (10 uM)
Concentration of drug (uM)
20.00
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
% Prodrug
Active pharmaceutical ingredient (API)
Amphotericin
Amphotericin B
Bacitracin/Colistin
Bacitracin/Lidocaine
Tazarotene - Acids
Tazarotene Acids
Tazarotene
Tazarotene
MK059A
MK059B
MK082A
MK082B
PP12A
PP12B
PP20A
PP20B
PP21A
PP21B
PP23A
PP23B
PP24A
PP24B
PP35A
PP35B
PP36A
PP36B

FIG. 3A

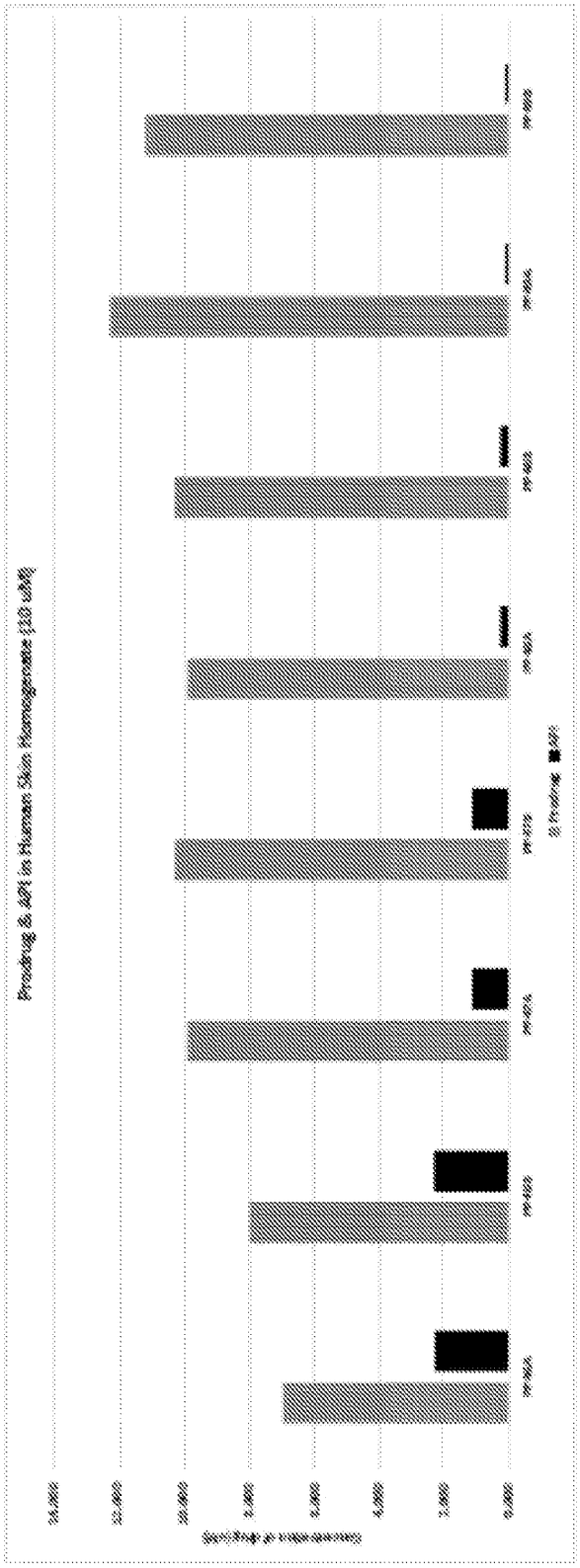


FIG. 3B

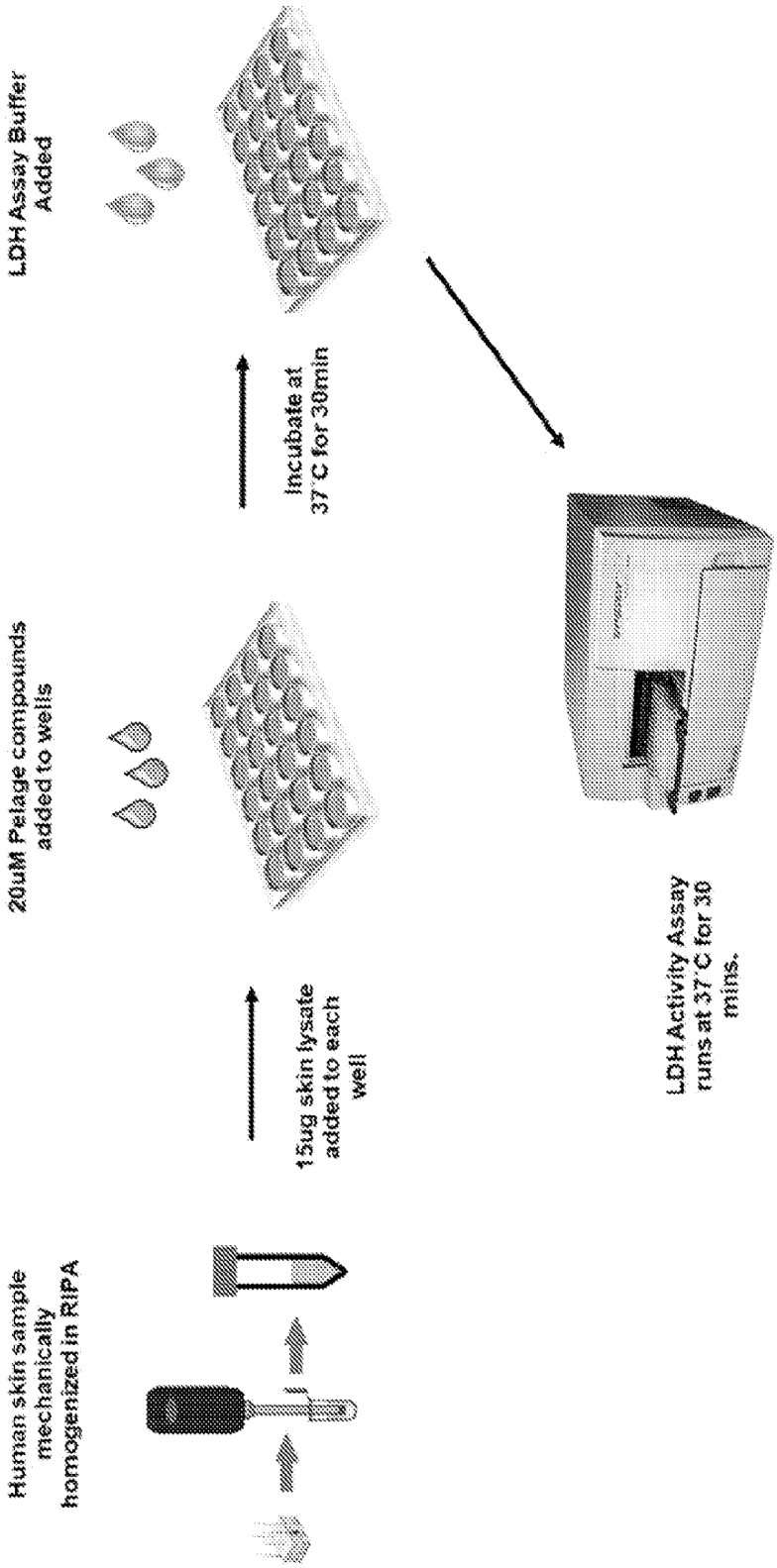

Human skin sample mechanically homogenized in RIPA
15ug skin lysate added to each well
20uM Pelage compounds added to wells
Incubate at 37˚C for 30min
LDH Assay Buffer Added
LDH Activity Assay runs at 37˚C for 30 mins.

FIG. 4

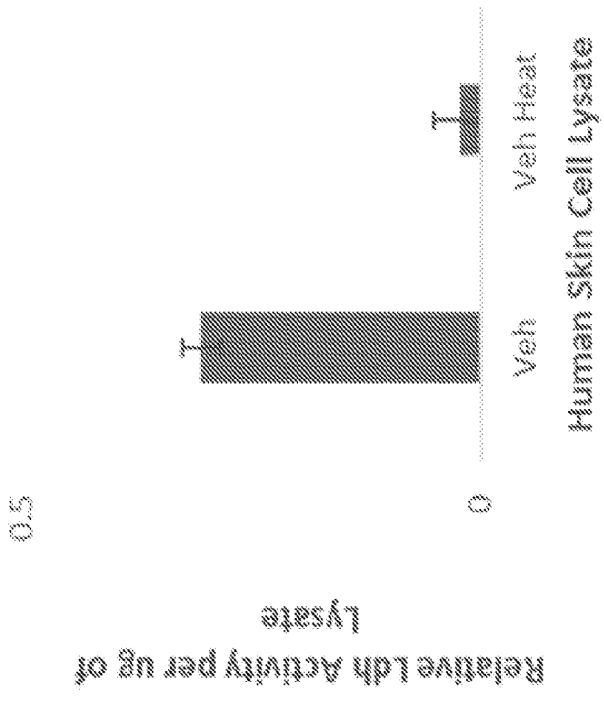

Relative Ldh Activity per ug of Lysate
0.5
0
Veh
Veh Heat
Human Skin Cell Lysate

FIG. 5A

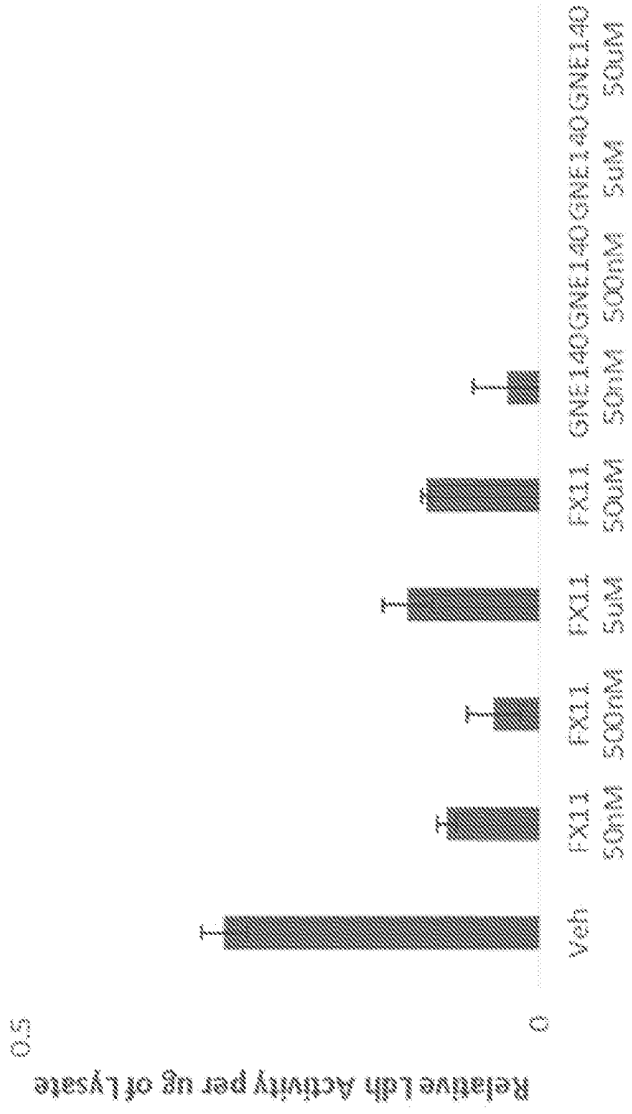

Relative Ldh Activity per ug of Lysate
0.5
0
Veh
FX11 50nM
FX11 500nM
FX11 5uM
FX11 50uM
GNE140 50nM
GNE140 500nM
GNE140 5uM
GNE140 50uM
Human Skin Cell Lysate

FIG. 5B

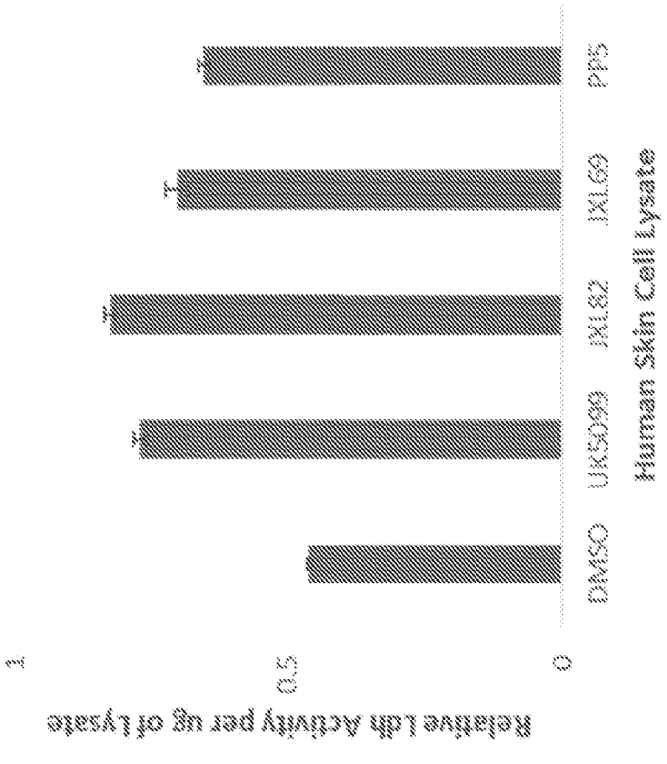

Relative Ldh Activity per ug of Lysate
1
0.5
0
DMSO
UK5099
IXL82
IXL69
PP5
Human Skin Cell Lysate

FIG. 6A

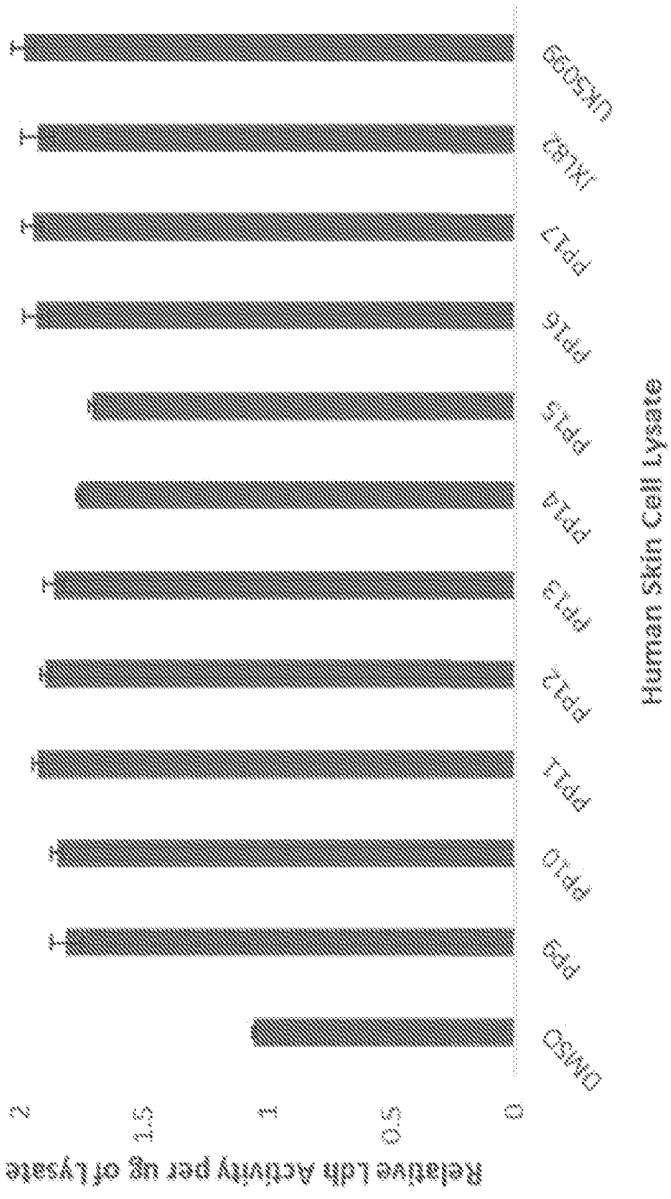

Relative Ldh Activity per ug of Lysate
0
0.5
1
1.5
2
DMSO
PP9
PP10
PP11
PP12
PP13
PP14
PP15
PP16
PP17
PP18
UK5099
Human Skin Cell Lysate

FIG. 6B

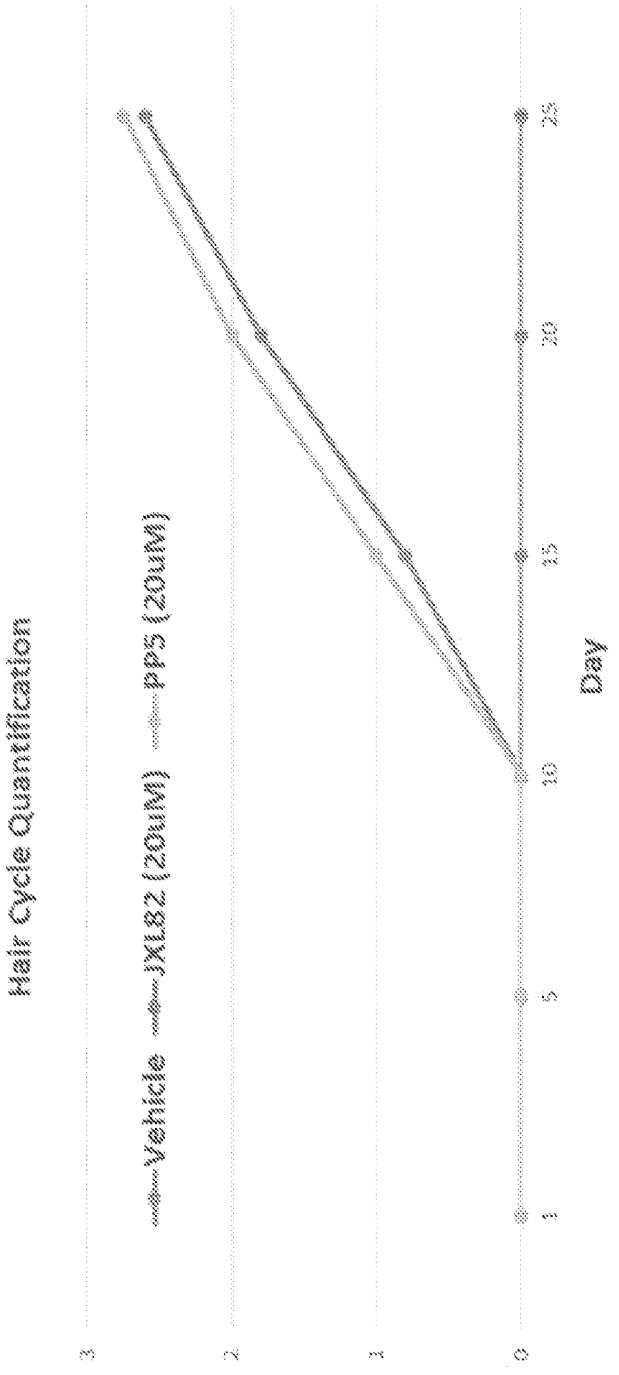

Hair Cycle Quantification
Vehicle
JXL82 (20uM)
PP5 (20uM)
Day
0
1
2
3
1
5
10
15
20
25

FIG. 7

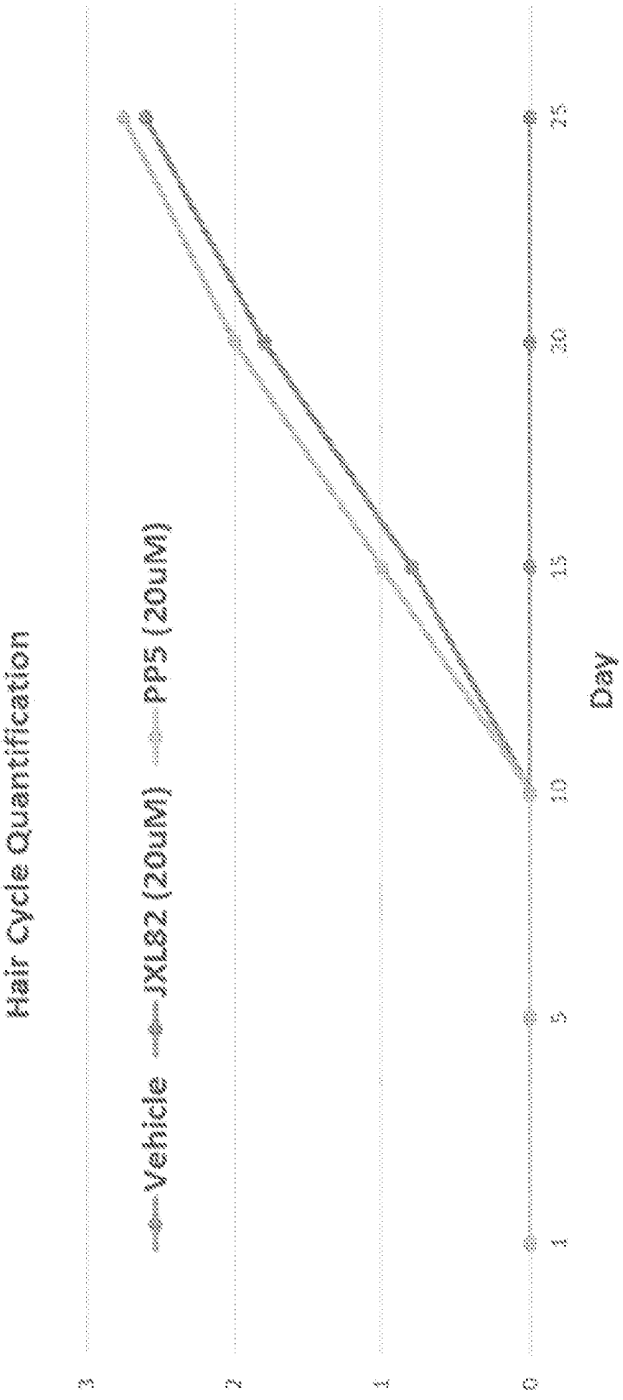

Hair Cycle Quantification
Vehicle
JXL82 (20uM)
PP5 (20uM)
Day
0
1
2
3
1
5
10
15
20
25

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/039501

A. CLASSIFICATION OF SUBJECT MATTER
IPC (20210101) C07D 471/04, A61K 31/437, A61P 17/14
CPC (20130101) C07D 471/04, A61K 31/437, A61P 17/14
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (20210101) C07D 471/04, A61K 31/437, A61P 17/14
CPC (20130101) C07D 471/04, A61K 31/437, A61P 17/14

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Databases consulted: Google Patents, CAPLUS, REGISTRY, Google Scholar, PatBase
Search terms used: alopecia, baldness, MPC inhibitor.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/006359 A1 THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US] 03 Jan 2019 (2019/01/03) JXL076, JXL077, JXL082, JXL087 and JXL088; p.18-19	1-99
X	Marsh-Armstrong, Brennan, et al. "The allosteric site on SHP2's protein tyrosine phosphatase domain is targetable with druglike small molecules." ACS omega 3.11 (2018): 15763-15770. 01 Jan 2018 (2018/01/01) Compound 7 on page 15765	1,6
X	CAS Registry Number: 677327-34-3; CA Index Name: 2-Propenamide, 2-cyano-N-ethyl-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)-; Entered STN: 28 Apr 2004; Source of Registration: Chemical Library, Supplier: TimTec, Inc 28 Apr 2004 (2004/04/28)	1,6

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 Sep 2021	30 Sep 2021

Name and mailing address of the ISA:	Authorized officer
Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Email address: pctoffice@justice.gov.il	VOLKOV Karina Telephone No. 972-73-3927136

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/039501

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Flores, A. et al. Lactate dehydrogenase activity drives hair follicle stem cell activation (Sep 2017). Nature Cell Biology, 19(9), pp.1017-1026. Published online 2017 Aug 14. Retrieved from URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5657543/>. DOI: 10.1038/ncb3575. 14 Aug 2017 (2017/08/14) whole document	1-99
A	WO 2018/039612 A1 THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US] 01 Mar 2018 (2018/03/01) whole document	1-99
P,X	WO 2021/127482 A1 THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US] 24 Jun 2021 (2021/06/24) whole document	1-99
P,X	WO 2020/142413 A1 THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US[09 Jul 2020 (2020/07/09) whole document	1-99

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2021/039501

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
WO 2019/006359 A1	03 Jan 2019	WO 2019006359 A1	03 Jan 2019
		AR 114075 A1	15 Jul 2020
		AU 2018294351 A1	05 Dec 2019
		BR 112019026080 A2	30 Jun 2020
		CA 3067746 A1	03 Jan 2019
		CL 2019003886 A1	22 May 2020
		CN 110944634 A	31 Mar 2020
		EA 202090179 A1	24 Apr 2020
		EP 3644989 A1	06 May 2020
		EP 3644989 A4	14 Jul 2021
		IL 271443 D0	30 Jan 2020
		JP 2020526484 A	31 Aug 2020
		KR 20200022480 A	03 Mar 2020
		MX 2019015475 A	19 Feb 2020
		PE 20200743 A1	24 Jul 2020
		US 2020157093 A1	21 May 2020
WO 2018/039612 A1	01 Mar 2018	WO 2018039612 A1	01 Mar 2018
		AU 2017314833 A1	25 Jul 2019
		AU 2017314836 A1	21 Mar 2019
		BR 112019015552 A2	17 Mar 2020
		CA 3034460 A1	01 Mar 2018
		CA 3050635 A1	01 Mar 2018
		CL 2019002340 A1	17 Jan 2020
		CN 109843265 A	04 Jun 2019
		CN 110300583 A	01 Oct 2019
		EA 201991988 A1	24 Jan 2020
		EP 3503871 A1	03 Jul 2019
		EP 3503871 A4	06 May 2020
		EP 3585381 A1	01 Jan 2020

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2021/039501

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		EP 3585381 A4	19 Aug 2020
		IL 268345 D0	26 Sep 2019
		JP 2020524127 A	13 Aug 2020
		KR 20190058494 A	29 May 2019
		KR 20190119118 A	21 Oct 2019
		MX 2019010101 A	15 Oct 2019
		PE 20200600 A1	10 Mar 2020
		PH 12019501722 A1	15 Jun 2020
		SG 11201906807V A	27 Aug 2019
		US 2019224182 A1	25 Jul 2019
		US 10828289 B2	10 Nov 2020
		US 2020030289 A1	30 Jan 2020
		WO 2018039615 A1	01 Mar 2018
WO 2021/127482 A1	24 Jun 2021	WO 2021127482 A1	24 Jun 2021
WO 2020/142413 A1	09 Jul 2020	WO 2020142413 A1	09 Jul 2020
		AR 117555 A1	11 Aug 2021
		AU 2019418584 A1	08 Jul 2021
		CA 3124820 A1	09 Jul 2020
		IL 284397 D0	31 Aug 2021
		SG 11202106471R A	29 Jul 2021