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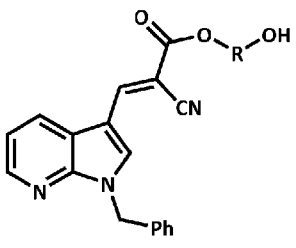
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(54) Title: COMPOUNDS FOR TREATMENT OF HAIR LOSS



(57) Abstract: Compounds represented by the Formula below are described in this disclosure. Use, methods, and medicaments related to treatment of conditions or diseases, such as for growing hair in a mammal, are also described herein.

COMPOUNDS FOR TREATMENT OF HAIR LOSS

CROSS-REFERENCE TO RELATED APPLICATIONS

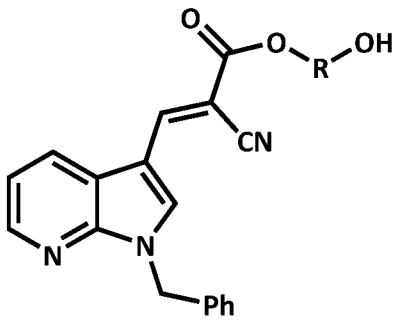
This application claims the benefit of U.S. Provisional Application No. 63/294,769, filed December 29, 2021, which is incorporated by reference herein in its entirety.

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

Some embodiments include a compound represented by Formula 1:



Formula 1

or an E/Z isomer thereof; wherein R is C_{2-12} -alkyl-, C_{4-12} -alkyl-O-alkyl-, or optionally substituted C_{6-12} -aryl-; and Ph is optionally substituted phenyl.

Some embodiments include a pharmaceutical composition comprising a compound described herein. In some embodiments, the pharmaceutical composition is for treating a disease or a disorder, such as a disease or disorder affecting or related to hair growth.

Some embodiments include a pharmaceutical composition for growing hair 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 in the area where hair growth is intended.

Some embodiments include use of a compound described herein in the manufacture of a medicament for growing hair.

Some embodiments include use of a compound described herein in the manufacture of a medicament for treating a disease or disorder.

Some embodiments include a method of growing hair comprising administering a compound described herein to a mammal in need thereof.

Some embodiments include a method of treating a disease or disorder, such as a disorder affecting hair growth comprising administering a compound described herein to a mammal in need thereof. In some embodiments, the disorder is alopecia or baldness.

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.

DETAILED DESCRIPTION

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. The E/Z isomers of the structures depicted herein are specifically contemplated.

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: $C_{1-12}H_{3-29}O_{0-4}N_{0-4}S_{0-4}F_{0-25}Cl_{0-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{1-4}N_{0-4}S_{0-4}F_{0-25}Cl_{0-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{0-4}N_{1-4}S_{0-4}F_{0-25}Cl_{0-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{0-4}N_{0-4}S_{1-4}F_{0-25}Cl_{0-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{0-4}N_{0-4}S_{0-4}F_{1-25}Cl_{0-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{0-4}N_{0-4}S_{0-4}F_{0-25}Cl_{1-5}Si_{0-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{0-4}N_{0-4}S_{0-4}F_{0-25}Cl_{0-5}Si_{1-3}P_{0-3}$, $C_{0-12}H_{0-29}O_{0-4}N_{0-4}S_{0-4}F_{0-25}Cl_{0-5}Si_{0-3}P_{1-3}$, $C_{1-6}H_{3-16}O_{0-4}N_{0-4}S_{0-4}F_{0-13}Cl_{0-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-16}O_{1-4}N_{0-4}S_{0-4}F_{0-13}Cl_{0-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-17}O_{0-4}N_{1-4}S_{0-4}F_{0-13}Cl_{0-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-17}O_{0-4}N_{0-4}S_{1-4}F_{0-13}Cl_{0-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-17}O_{0-4}N_{0-4}S_{0-4}F_{1-13}Cl_{0-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-17}O_{0-4}N_{0-4}S_{0-4}F_{0-13}Cl_{1-3}Si_{0-3}P_{0-3}$, $C_{0-6}H_{0-17}O_{0-4}N_{0-4}S_{0-4}F_{0-13}Cl_{0-3}Si_{1-3}P_{0-3}$, $C_{0-6}H_{0-17}O_{0-4}N_{0-4}S_{0-4}F_{0-13}Cl_{0-3}Si_{0-3}P_{1-3}$, $C_{1-12}H_{3-29}O_{0-4}N_{0-4}S_{0-4}F_{0-25}Cl_{0-5}P_{0-3}$, $C_{1-12}H_{3-27}O_{0-4}N_{0-2}S_{0-2}F_{0-25}Cl_{0-5}P_{0-1}$, $C_{1-12}H_{3-27}O_{0-4}N_{0-2}$, $C_{1-12}H_{3-25}O_{0-4}$, $C_{1-12}H_{3-27}N_{0-2}$, $C_{1-9}H_{3-21}O_{0-4}N_{0-2}S_{0-2}F_{0-19}Cl_{0-5}P_{0-1}$, $C_{1-9}H_{3-19}F_{0-19}$, $C_{1-9}H_{3-21}O_{0-4}N_{0-2}$, $C_{1-9}H_{3-19}O_{0-4}$, $C_{1-9}H_{3-21}N_{0-2}$, $C_{1-6}H_{3-15}O_{0-3}N_{0-2}S_{0-2}F_{0-13}Cl_{0-5}P_{0-1}$, $C_{1-6}H_{3-13}F_{0-13}$, $C_{1-6}H_{3-15}O_{0-4}N_{0-2}$, $C_{1-6}H_{3-13}O_{0-4}$, $C_{1-6}H_{3-15}N_{0-2}$, $C_{1-3}H_{3-9}O_{0-3}N_{0-2}S_{0-2}F_{0-13}Cl_{0-5}P_{0-1}$, $C_{1-3}H_{3-7}F_{0-7}$, $C_{1-3}H_{3-9}O_{0-3}N_{0-2}$, $C_{1-3}H_{3-7}O_{0-3}$, $C_{1-3}H_{3-9}N_{0-2}$, 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, hydroxyalkyl, hydroxyalkoxy, hydroxy, alkoxy, aryloxy, acyl, acyloxy, alkylcarboxylate, thiol, alkylthio, 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.

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.

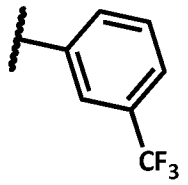
As used herein, the term "alkyl" has the broadest meaning generally understood in the art, and may include a moiety composed of carbon and hydrogen containing no double or triple bonds. Alkyl may be linear alkyl, branched alkyl, cycloalkyl, or a combination thereof, and in some embodiments, may contain 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.; and the like.

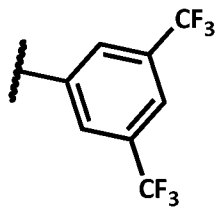
With respect to Formula 1, Ph is optionally substituted phenyl, such as phenyl substituted with 0, 1, 2, 3, 4, or 5 substituents, such as F, Cl, Br, I, OH, CN, CF_3, C_{1-6} alkyl (such as $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-C_4H_9$, $-C_5H_{11}$, $-C_6H_{13}$, etc.), or $C_{1-6}H_{3-13}O$ (such as $-C(=O)CH_3$ or $-CH_2OCH_3$).

In some embodiments, Ph is phenyl with 1, 2, 3, 4, or 5 trifluoromethyl substituents, such as 1 or 2 trifluoromethyl substituents. In some embodiments, Ph is trifluoromethylphenyl. In some embodiments, Ph is di(trifluoromethyl)phenyl.

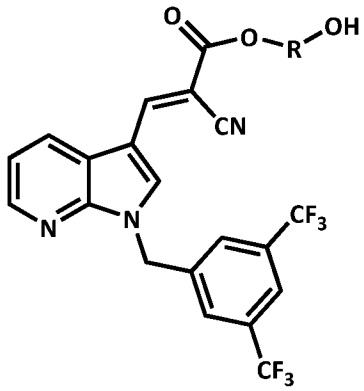
In some embodiments, Ph is:



In some embodiments, Ph is:

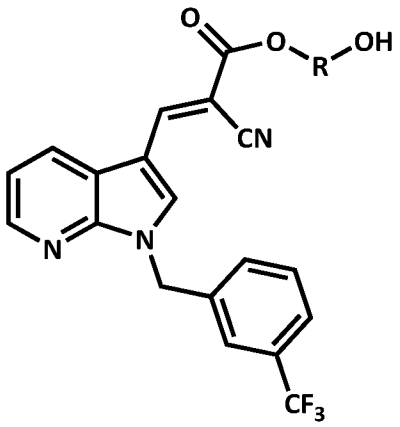


Some embodiments include compounds of Formula 2:



Formula 2

Some embodiments include compounds of Formula 3:



Formula 3

With respect to Formula 1, 2, or 3, R is C_{2-12} -alkyl-, including C_{2-5} -alkyl-, such as -C_2H_4- (e.g., -CH_2CH_2-), -C_3H_6- (e.g., -$CH_2CH_2CH_2$-), -C_4H_8- (e.g. -$CH_2CH_2CH_2CH_2$- or -$CH_2CH(CH_3)CH_2$-), -C_5H_{10}- (e.g., -$CH_2CH_2CH_2CH_2CH_2$- or -$CH_2C(CH_3)_2CH_2$-), etc., or C_{6-12} -alkyl-, such as -C_6H_{12}-, -C_7H_{14}-, -C_8H_{16}-, -C_9H_{18}-, -$C_{10}H_{20}$-, -$C_{11}H_{22}$-, -$C_{12}H_{24}$-, etc.; or C_{4-12} -alkyl-O-alkyl-, including C_{4-8} -alkyl-O-alkyl-, such as C_4 -alkyl-O-alkyl- (e.g., -$CH_2CH_2OCH_2CH_2$-), C_5 -alkyl-O-alkyl- (e.g., - $CH_2CH_2CH_2OCH_2CH_2$-), C_6 -alkyl-O-alkyl- , C_7 -alkyl-O-alkyl- , or C_{8-12} -alkyl-O-alkyl-, such as C_8 -alkyl-O-alkyl-, C_9 -alkyl-O-alkyl-, C_{10} -alkyl-O-alkyl-, C_{11} -alkyl-O-alkyl-, C_{12} -alkyl-O-alkyl-, etc.; or optionally substituted C_{6-12} aryl, such as a optionally substituted phenyl or optionally substituted naphthyl.

With respect to Formula 1, in some embodiments, R is C_{2-12} -alkyl-.

With respect to Formula 1, in some embodiments, R is C_{2-5} -alkyl-.

With respect to Formula 1, in some embodiments, R is -C_2H_4-.

With respect to Formula 1, in some embodiments, R is -C_3H_6-.

With respect to Formula 1, in some embodiments, R is -C_4H_8-.

With respect to Formula 1, in some embodiments, R is -C_5H_{10}-.

With respect to Formula 1, in some embodiments, R is -C_6H_{12}-.

With respect to Formula 1, in some embodiments, R is -C_7H_{14}-.

With respect to Formula 1, in some embodiments, R is -C_8H_{16}-.

With respect to Formula 1, in some embodiments, R is -C_9H_{18}-.

With respect to Formula 1, in some embodiments, R is -$C_{10}H_{20}$-.

With respect to Formula 1, in some embodiments, R is -$C_{11}H_{22}$-.

With respect to Formula 1, in some embodiments, R is -$C_{12}H_{24}$-.

With respect to Formula 1, in some embodiments, R is C_{4-12} -alkyl-O-alkyl-.

With respect to Formula 1, in some embodiments, R is C_{4-8} -alkyl-O-alkyl-.

With respect to Formula 1, in some embodiments, R is C_4 -alkyl-O-alkyl-.

With respect to Formula 1, in some embodiments, R is C_5 -alkyl-O-alkyl-.

With respect to Formula 1, in some embodiments, R is C_6 -alkyl-O-alkyl-.

With respect to Formula 1, in some embodiments, R is C_7 -alkyl-O-alkyl-.

With respect to Formula 1, in some embodiments, R is C_8 -alkyl-O-alkyl-.

With respect to Formula 1, in some embodiments, R is C_9 -alkyl-O-alkyl-.

With respect to Formula 1, in some embodiments, R is C_{10} -alkyl-O-alkyl-.

With respect to Formula 1, in some embodiments, R is C_{11} -alkyl-O-alkyl-.

With respect to Formula 1, in some embodiments, R is C_{12} -alkyl-O-alkyl-.

With respect to Formula 1, in some embodiments, R is optionally substituted phenyl.

With respect to Formula 1, in some embodiments, R is optionally substituted naphthyl.

With respect to Formula 2, in some embodiments, R is $C_{2\text{-}12}$ -alkyl-.

With respect to Formula 2, in some embodiments, R is $C_{2\text{-}5}$ -alkyl-.

With respect to Formula 2, in some embodiments, R is $-C_2H_4-$.

With respect to Formula 2, in some embodiments, R is $-C_3H_6-$.

With respect to Formula 2, in some embodiments, R is $-C_4H_8-$.

With respect to Formula 2, in some embodiments, R is $-C_5H_{10}-$.

With respect to Formula 2, in some embodiments, R is $-C_6H_{12}-$.

With respect to Formula 2, in some embodiments, R is $-C_7H_{14}-$.

With respect to Formula 2, in some embodiments, R is $-C_8H_{16}-$.

With respect to Formula 2, in some embodiments, R is $-C_9H_{18}-$.

With respect to Formula 2, in some embodiments, R is $-C_{10}H_{20}-$.

With respect to Formula 2, in some embodiments, R is $-C_{11}H_{22}-$.

With respect to Formula 2, in some embodiments, R is $-C_{12}H_{24}-$.

With respect to Formula 2, in some embodiments, R is $C_{4\text{-}12}$ -alkyl-O-alkyl-.

With respect to Formula 2, in some embodiments, R is $C_{4\text{-}8}$ -alkyl-O-alkyl-.

With respect to Formula 2, in some embodiments, R is C_4 -alkyl-O-alkyl-.

With respect to Formula 2, in some embodiments, R is C_5 -alkyl-O-alkyl-.

With respect to Formula 2, in some embodiments, R is C_6 -alkyl-O-alkyl-.

With respect to Formula 2, in some embodiments, R is C_7 -alkyl-O-alkyl-.

With respect to Formula 2, in some embodiments, R is C_8 -alkyl-O-alkyl-.

With respect to Formula 2, in some embodiments, R is C_9 -alkyl-O-alkyl-.

With respect to Formula 2, in some embodiments, R is C_{10} -alkyl-O-alkyl-.

With respect to Formula 2, in some embodiments, R is C_{11} -alkyl-O-alkyl-.

With respect to Formula 2, in some embodiments, R is C_{12} -alkyl-O-alkyl-.

With respect to Formula 2, in some embodiments, R is optionally substituted phenyl.

With respect to Formula 2, in some embodiments, R is optionally substituted naphthyl.

With respect to Formula 3, in some embodiments, R is C_{2-12} -alkyl-.

With respect to Formula 3, in some embodiments, R is C_{2-5} -alkyl-.

With respect to Formula 3, in some embodiments, R is $-C_2H_4-$.

With respect to Formula 3, in some embodiments, R is $-C_3H_6-$.

With respect to Formula 3, in some embodiments, R is $-C_4H_8-$.

With respect to Formula 3, in some embodiments, R is $-C_5H_{10}-$.

With respect to Formula 3, in some embodiments, R is $-C_6H_{12}-$.

With respect to Formula 3, in some embodiments, R is $-C_7H_{14}-$.

With respect to Formula 3, in some embodiments, R is $-C_8H_{16}-$.

With respect to Formula 3, in some embodiments, R is $-C_9H_{18}-$.

With respect to Formula 3, in some embodiments, R is $-C_{10}H_{20}-$.

With respect to Formula 3, in some embodiments, R is $-C_{11}H_{22}-$.

With respect to Formula 3, in some embodiments, R is $-C_{12}H_{24}-$.

With respect to Formula 3, in some embodiments, R is C_{4-12} -alkyl-O-alkyl-.

With respect to Formula 3, in some embodiments, R is C_{4-8} -alkyl-O-alkyl-.

With respect to Formula 3, in some embodiments, R is C_4 -alkyl-O-alkyl-.

With respect to Formula 3, in some embodiments, R is C_5 -alkyl-O-alkyl-.

With respect to Formula 3, in some embodiments, R is C_6 -alkyl-O-alkyl-.

With respect to Formula 3, in some embodiments, R is C_7 -alkyl-O-alkyl-.

With respect to Formula 3, in some embodiments, R is C_8 -alkyl-O-alkyl-.

With respect to Formula 3, in some embodiments, R is C_9 -alkyl-O-alkyl-.

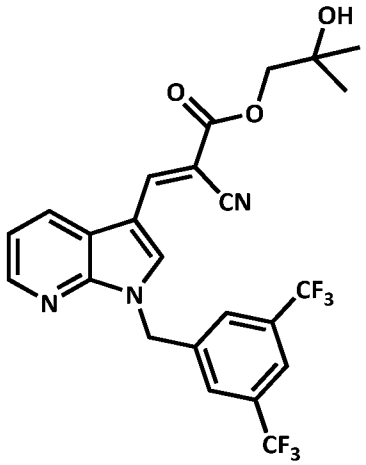
With respect to Formula 3, in some embodiments, R is C_{10} -alkyl-O-alkyl-.

With respect to Formula 3, in some embodiments, R is C_{11} -alkyl-O-alkyl-.

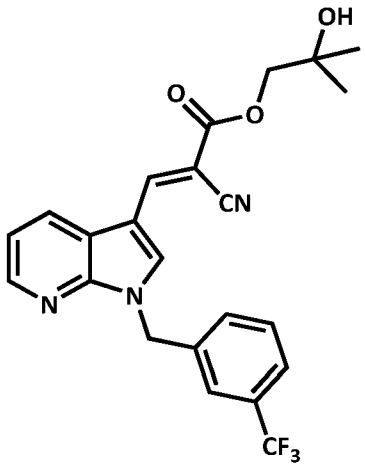
With respect to Formula 3, in some embodiments, R is C_{12} -alkyl-O-alkyl-.

With respect to Formula 3, in some embodiments, R is optionally substituted phenyl.

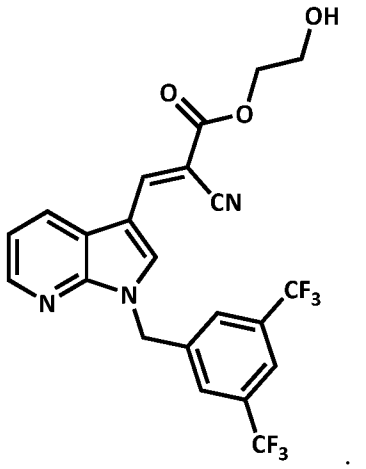
With respect to Formula 3, in some embodiments, R is optionally substituted naphthyl.



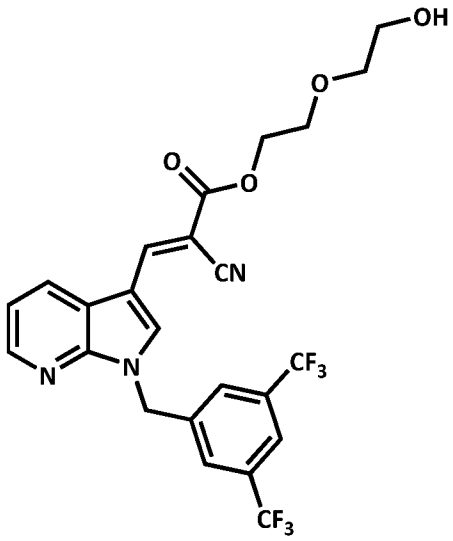
Some embodiments include the compound: .

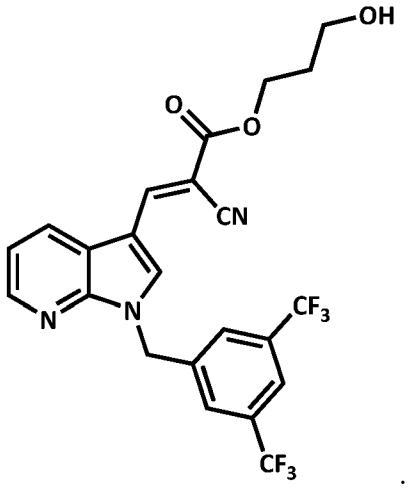


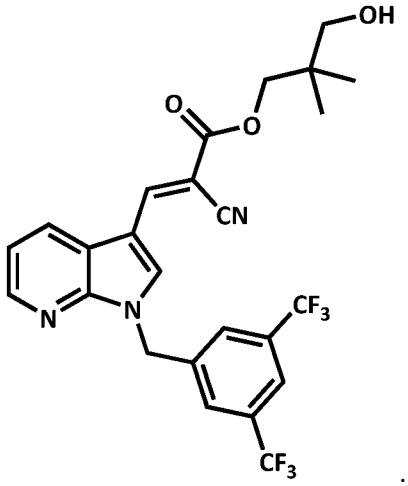
Some embodiments include the compound: .

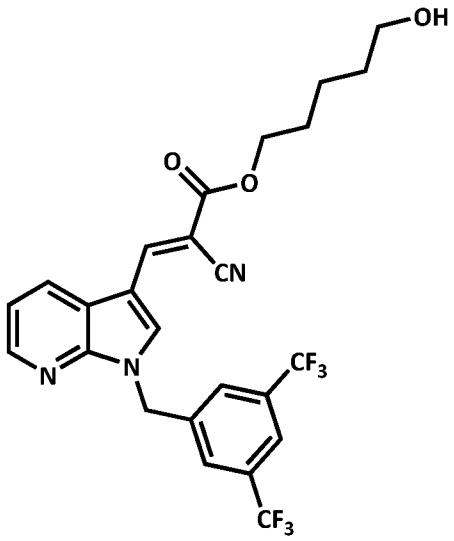


Some embodiments include the compound: .

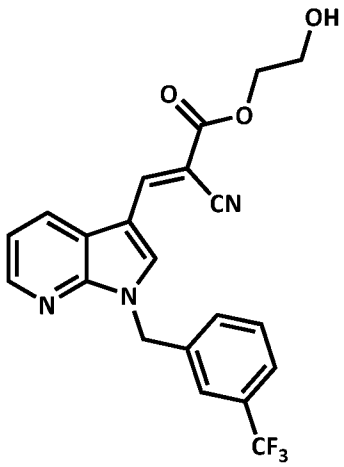
Some embodiments include the compound: .

Some embodiments include the compound: .

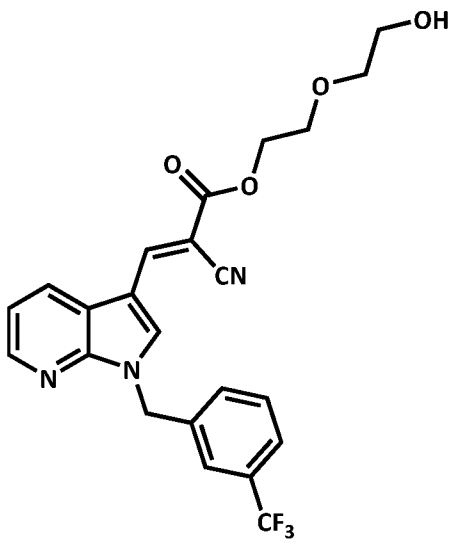
Some embodiments include the compound: .



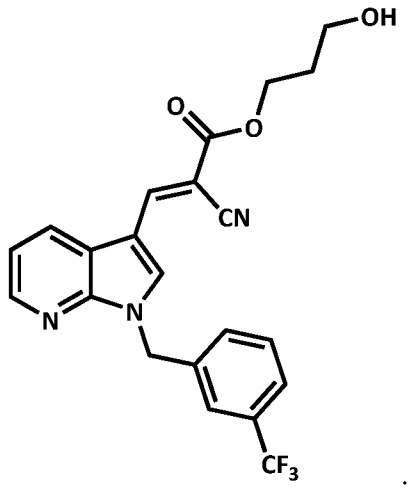
Some embodiments include the compound: .

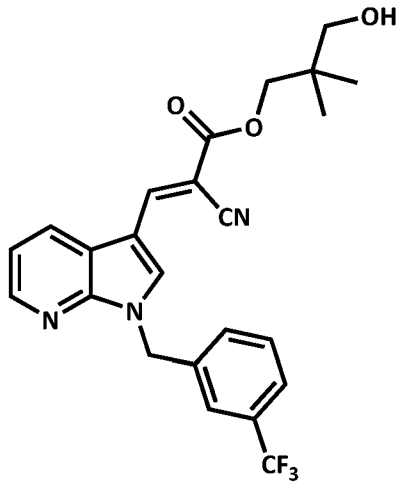


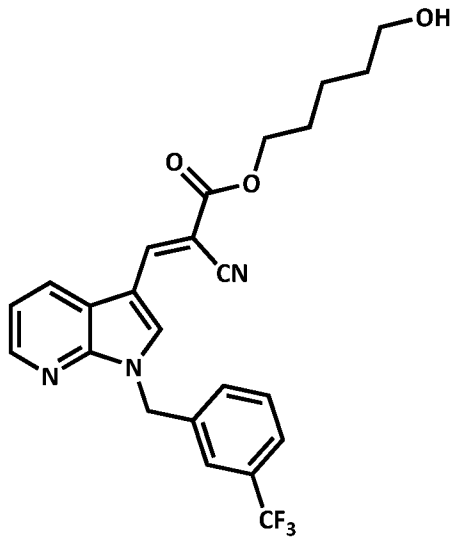
Some embodiments include the compound: .



Some embodiments include the compound: .

Some embodiments include the compound: .

Some embodiments include the compound: 

Some embodiments include the compound: .

The compounds 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 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.

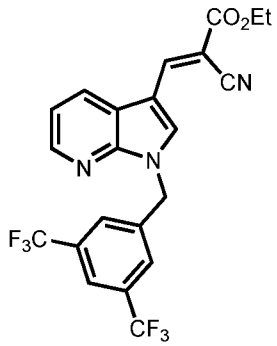
For the purposes of this disclosure, the term "treat," "treating," or a similar term (such as "modulating"), includes cure, mitigation, treatment, or prevention of disease in man or other animals, or any other effect that would be associated with a "drug" as defined under 21 USC 321(g).

In 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.

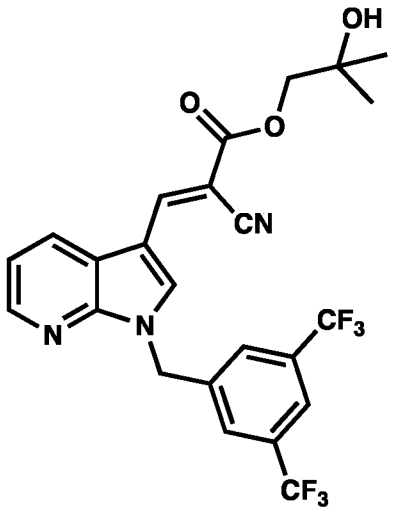
In some embodiments, the compounds of the present disclosure undergo hydrolysis to release the active free carboxylic acid. In some aspects, the compounds of the present disclosure undergo hydrolysis to release the active free carboxylic acid at a rate that is enhanced relative to conventional prodrugs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



JXL082

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.

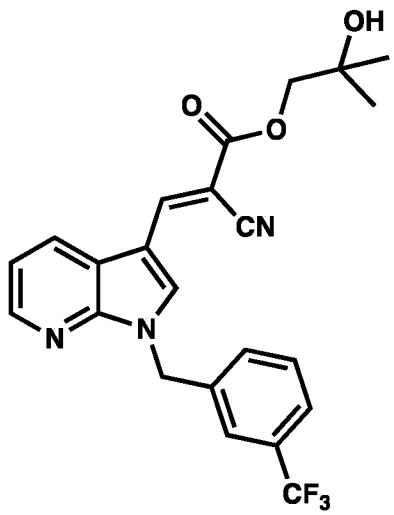
The compounds below were prepared by adapting the method described in PCT/US21/39501, filed June 29, 2021 entitled "COMPOSITIONS AND METHODS FOR MODULATING HAIR GROWTH," Attorney Docket Number UCH-22825 (32246.22825)(see Examples 5-15, pp. 73-80).



2-hydroxy-2-methylpropyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.48 (s, 1H), 8.46 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.17 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.81 (s, 1H), 7.78 (s, 2H), 7.31 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.68 (s, 2H), 4.17 (s, 2H), 2.28 (s, 1H), 1.33 (s, 6H).

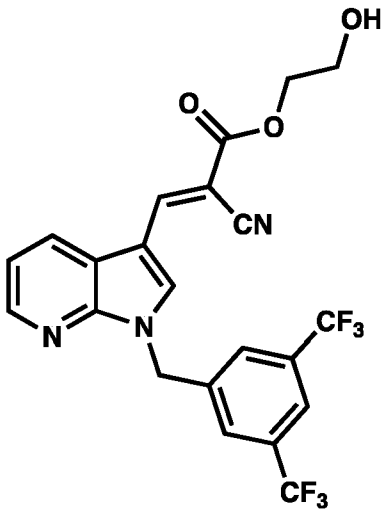
^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 147.6, 145.7, 145.5, 138.4, 133.1, 132.4 (q, $^{2}J_{C\text{-}F}$ = 33.6 Hz, 2C), 127.9 (d, $^{3}J_{C\text{-}F}$ = 4.3 Hz), 127.7, 122.9 (q, $^{1}J_{C\text{-}F}$ = 273.0 Hz, 2C), 122.4 (p, $^{3}J_{C\text{-}F}$ = 3.8 Hz, 2C), 120.3, 119.1, 117.4, 109.3, 96.2, 73.5, 69.9, 48.3, 26.1 (2C).



2-hydroxy-2-methylpropyl (*E*)-2-cyano-3-(1-(3-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.46-8.45 (m, 2H), 8.14 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.60 (s, 1H), 7.56-7.55 (m, 1H), 7.45-7.44 (m, 2H), 7.29 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.61 (s, 2H), 4.16 (s, 2H), 2.27 (br s, 1H), 1.33 (s, 6H).

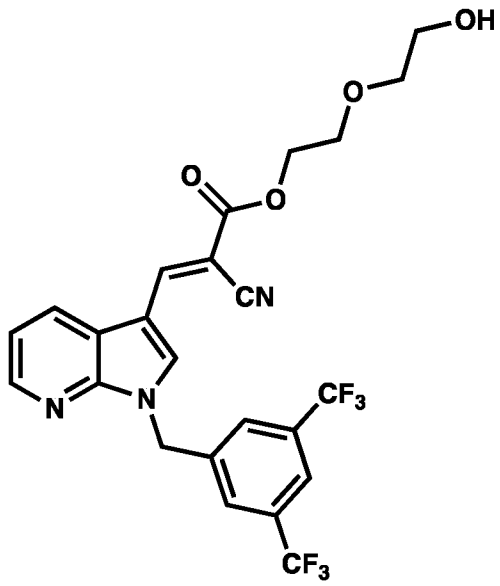
^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 147.7, 145.6, 145.5, 136.8, 133.5, 131.4 (q, $^2J_{C\text{-}F}$ = 32.1 Hz), 131.0, 129.6, 127.5, 125.2 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 124.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 123.8 (q, $^1J_{C\text{-}F}$ = 272.5 Hz), 120.3, 118.9, 117.5, 109.0, 95.6, 73.5, 69.9, 48.6, 26.1 (2C).



2-hydroxyethyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.51 (d, *J* = 0.5 Hz, 1H), 8.48 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.20 (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), 5.69 (s, 2H), 4.46-4.44 (m, 2H), 3.96-3.94 (m, 2H), 2.12-2.04 (m, 1H).

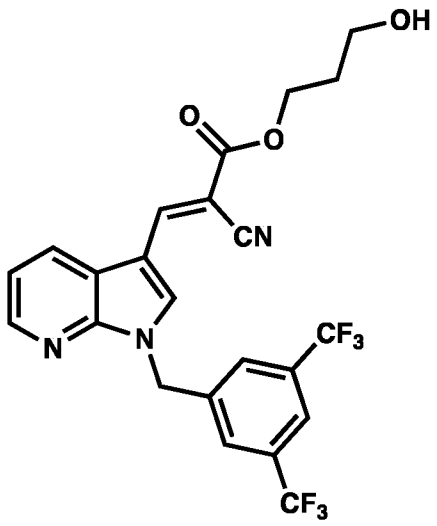
^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 147.6, 145.8, 145.6, 138.4, 133.1, 132.4 (q, $^2J_{C\text{-}F}$ = 33.4 Hz, 2C), 127.9 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 127.7, 122.9 (q, $^1J_{C\text{-}F}$ = 272.8 Hz, 2C), 122.5 (p, $^3J_{C\text{-}F}$ = 3.7 Hz, 2C), 120.3, 119.1, 117.5, 109.3, 96.2, 67.7, 61.0, 48.4.



2-(2-hydroxyethoxy)ethyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.50 (s, 1H), 8.47 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.21 (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), 4.48-4.46 (m, 2H), 3.84-3.82 (m, 2H), 3.76 (t, *J* = 4.5 Hz, 2H), 3.67 (t, *J* = 4.4 Hz, 2H), 2.17 (br s, 1H).

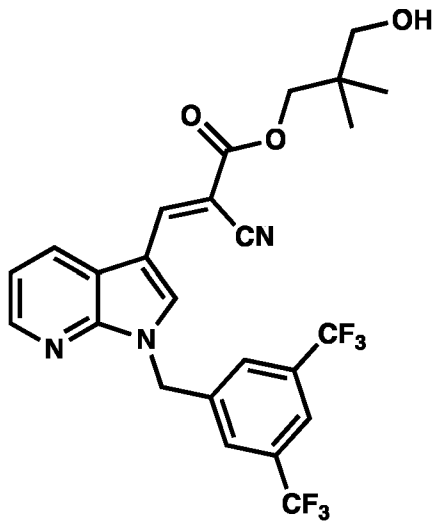
^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 147.6, 145.7, 145.4, 138.4, 133.0, 132.4 (q, $^{2}J_{C\text{-}F}$ = 33.9 Hz, 2C), 127.9 (d, $^{3}J_{C\text{-}F}$ = 2.8 Hz), 127.7, 122.9 (q, $^{1}J_{C\text{-}F}$ = 273.2 Hz, 2C), 122.4 (p, $^{3}J_{C\text{-}F}$ = 3.8 Hz, 2C), 120.3, 119.0, 117.5, 109.3, 96.5, 72.6, 68.8, 65.2, 61.8, 48.3.



3-hydroxypropyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.49 (s, 1H), 8.47 (d, *J* = 3.2 Hz, 1H), 8.19 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.33 (dd, *J* = 7.9, 4.6 Hz, 1H), 5.69 (s, 2H), 4.47 (t, *J* = 6.1 Hz, 2H), 3.79 (t, *J* = 5.9 Hz, 2H), 2.00 (p, *J* = 6.0 Hz, 2H), 1.90 (br s, 1H).

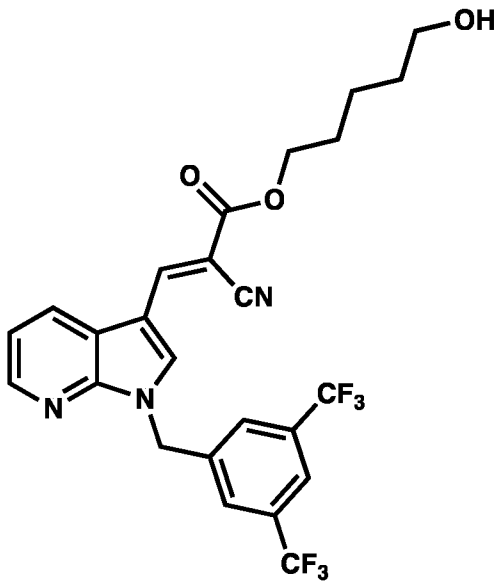
^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 147.6, 145.7, 145.3, 138.4, 133.0, 132.4 (q, $^2J_{C\text{-}F}$ = 33.9 Hz, 2C), 127.9 (d, $^3J_{C\text{-}F}$ = 2.8 Hz), 127.7, 122.9 (q, $^1J_{C\text{-}F}$ = 273.0 Hz, 2C), 122.4 (p, $^3J_{C\text{-}F}$ = 3.6 Hz, 2C), 120.3, 119.0, 117.5, 109.3, 96.5, 63.1, 59.0, 48.4, 31.6.



3-hydroxy-2,2-dimethylpropyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.49 (d, *J* = 0.5 Hz, 1H), 8.47 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.19 (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), 4.16 (s, 2H), 3.43 (s, 2H), 2.08 (br s, 1H), 1.01 (s, 6H).

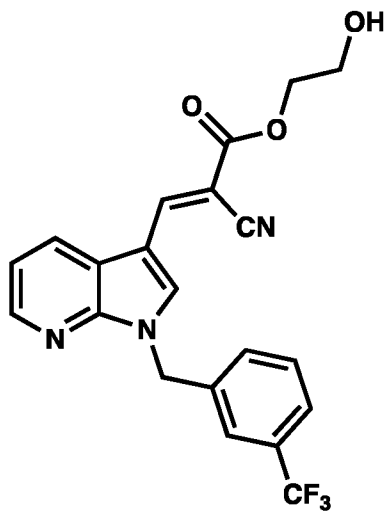
^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 147.6, 145.7, 145.4, 138.4, 132.9, 132.4 (q, $^2J_{C\text{-}F}$ = 33.9 Hz, 2C), 127.9 (d, $^3J_{C\text{-}F}$ = 4.8 Hz), 127.7, 122.9 (q, $^1J_{C\text{-}F}$ = 273.0 Hz, 2C), 122.4 (p, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 120.3, 119.1, 117.3, 109.3, 96.4, 71.0, 68.2, 48.3, 36.6, 21.4 (2C).



5-hydroxypentyl (*E*)-3-(1-(3,5-bis(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-cyanoacrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.48 (s, 1H), 8.46 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.20 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.81 (s, 1H), 7.77 (s, 2H), 7.32 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.69 (s, 2H), 4.31 (t, *J* = 6.6 Hz, 2H), 3.68 (t, *J* = 6.5 Hz, 2H), 1.79 (p, *J* = 6.9 Hz, 2H), 1.67-1.48 (m, 5H)

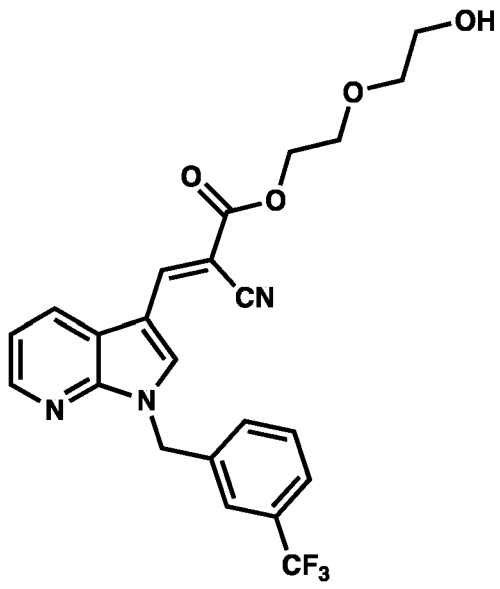
^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 147.6, 145.7, 145.0, 138.5, 132.8, 132.4 (q, $^{2}J_{C\text{-}F}$ = 33.9 Hz, 2C), 127.9 (d, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 127.7, 122.9 (q, $^{1}J_{C\text{-}F}$ = 272.8 Hz, 2C), 122.4 (p, $^{3}J_{C\text{-}F}$ = 3.8 Hz, 2C), 120.3, 119.0, 117.6, 109.3, 96.9, 66.2, 62.6, 48.3, 32.3, 28.4, 22.2.



2-hydroxyethyl (*E*)-2-cyano-3-(1-(3-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.46 (s, 2H), 8.15 (d, *J* = 7.4 Hz, 1H), 7.60 (s, 1H), 7.56-7.55 (m, 1H), 7.47-7.45 (m, 2H), 7.30 (dd, *J* = 7.9, 4.6 Hz, 1H), 5.62 (s, 2H), 4.43 (t, *J* = 4.5 Hz, 2H), 3.94 (t, *J* = 4.5 Hz, 2H), 2.36 (br s, 1H).

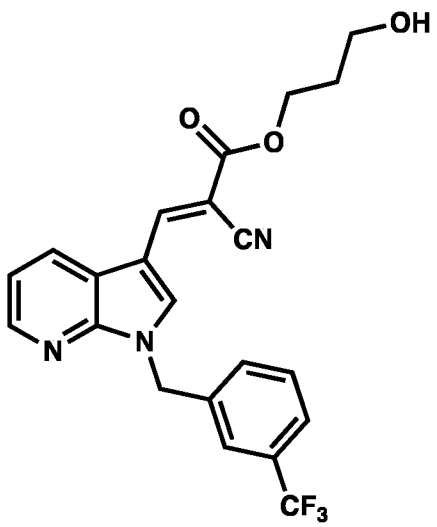
^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 147.7, 145.7, 145.6, 136.8, 133.6, 131.4 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 131.0 (d, $^4J_{C\text{-}F}$ = 0.8 Hz), 129.6, 127.5, 125.3 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 123.8 (q, $^1J_{C\text{-}F}$ = 272.5 Hz), 120.3, 118.9, 117.6, 109.0, 95.6, 67.7, 61.0, 48.6.



2-(2-hydroxyethoxy)ethyl (*E*)-2-cyano-3-(1-(3-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.49-8.46 (m, 2H), 8.19 (d, *J* = 7.6 Hz, 1H), 7.59 (s, 1H), 7.56 (d, *J* = 4.3 Hz, 1H), 7.47-7.44 (m, 2H), 7.31 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.63 (s, 2H), 4.46 (t, *J* = 4.3 Hz, 2H), 3.82 (t, *J* = 4.4 Hz, 2H), 3.76 (s, 2H), 3.67 (d, *J* = 3.9 Hz, 2H), 2.19 (br s, 1H).

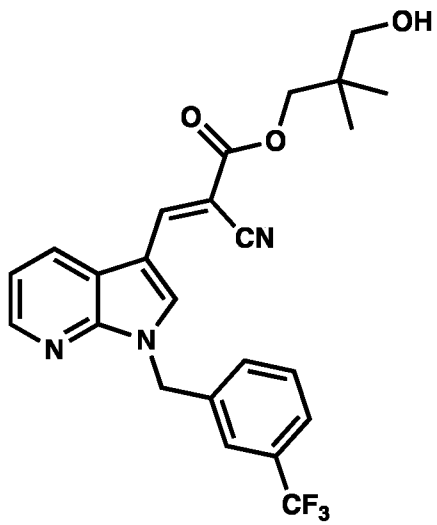
^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 147.7, 145.6 (2C), 136.9, 133.5, 131.4 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 130.9 (d, $^4J_{C\text{-}F}$ = 1.0 Hz), 129.6, 127.5, 125.2 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.6 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 123.8 (q, $^1J_{C\text{-}F}$ = 272.5 Hz), 120.3, 118.9, 117.6, 109.0, 95.8, 72.6, 68.9, 65.1, 61.8, 48.6.



3-hydroxypropyl (*E*)-2-cyano-3-(1-(3-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.48-8.46 (m, 2H), 8.17 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.59 (s, 1H), 7.57-7.55 (m, 1H), 7.47-7.44 (m, 2H), 7.30 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.63 (s, 2H), 4.46 (t, *J* = 6.0 Hz, 2H), 3.79 (t, *J* = 5.4 Hz, 2H), 2.00 (t, *J* = 6.0 Hz, 3H).

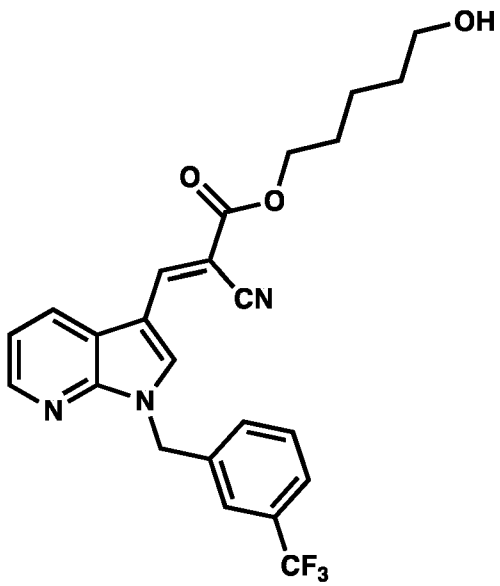
^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 147.7, 145.6, 145.5, 136.9, 133.4, 131.4 (q, $^{2}J_{C\text{-}F}$ = 32.4 Hz), 131.0 (d, $^{4}J_{C\text{-}F}$ = 1.2 Hz), 129.6, 127.5, 125.2 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 124.6 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 123.8 (q, $^{1}J_{C\text{-}F}$ = 272.3 Hz), 120.3, 118.9, 117.6, 109.0, 95.8, 63.1, 59.0, 48.6, 31.7.



3-hydroxy-2,2-dimethylpropyl (*E*)-2-cyano-3-(1-(3-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.47-8.45 (m, 2H), 8.14 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.60 (s, 1H), 7.57-7.55 (m, 1H), 7.45 (d, *J* = 5.2 Hz, 2H), 7.30 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.63 (s, 2H), 4.14 (s, 2H), 3.42 (s, 2H), 2.22 (br s, 1H), 1.00 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 147.7, 145.5, 145.5, 136.8, 133.4, 131.4 (q, $^2J_{C\text{-}F}$ = 32.9 Hz), 131.0 (d, $^4J_{C\text{-}F}$ = 1.2 Hz), 129.6, 127.5, 125.2 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 124.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 123.8 (q, $^1J_{C\text{-}F}$ = 272.5 Hz), 120.3, 118.9, 117.4, 109.0, 95.7, 70.9, 68.1, 48.6, 36.6, 21.5 (2C).



5-hydroxypentyl (*E*)-2-cyano-3-(1-(3-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acrylate

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.47-8.46 (m, 2H), 8.18 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.59 (s, 1H), 7.56-7.55 (m, 1H), 7.45-7.44 (m, 2H), 7.30 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.62 (s, 2H), 4.31 (t, *J* = 6.6 Hz, 2H), 3.69 (s, 2H), 1.82-1.48 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 147.7, 145.5, 145.2, 136.9, 133.3, 131.4 (q, $^2J_{C\text{-}F}$ = 32.7 Hz), 130.9, 129.6, 127.5, 125.2 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.5 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 123.8 (q, $^1J_{C\text{-}F}$ = 272.5 Hz), 120.3, 118.8, 117.7, 109.0, 96.2, 66.1, 62.6, 48.6, 32.3, 28.4, 22.2.

Incubation of the compounds in Human Skin Homogenate at pH 7.4 according to the procedure described in Example 17, p. 46, of PCT/US2021/039502, filed June 21, 2021 under the title "Composition and Methods for Modulating Hair Growth," attorney docket number UCH-28325, confirmed that some compounds were at least 50% hydrolyzed into the parent acid within about 1 hour. The parent acids have been shown to have hair growth properties in mammal models.

An assay similar to that described in Example 16, pp. 43-46, of PCT/US2021/039502, filed June 21, 2021 under the title "Composition and Methods for Modulating Hair Growth," attorney docket number UCH-28325, was conducted on some of the compounds described herein. The IC_{50} values at inhibiting mitochondrial oxidation for the tested compounds was less than 1 μM, and in some cases less than 100 nM.

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.

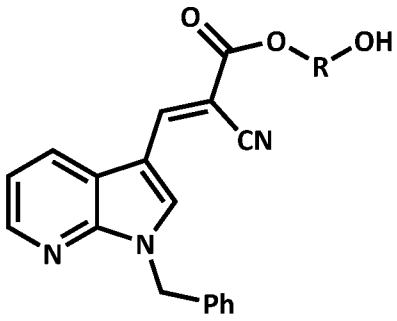
Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a 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:

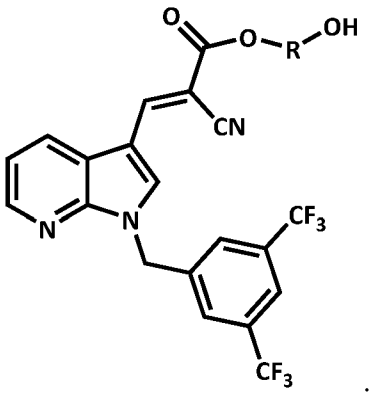


wherein R is $C_{2\text{-}12}$ -alkyl-, $C_{4\text{-}12}$ -alkyl-O-alkyl-, or optionally substituted $C_{6\text{-}12}$ -aryl-; and

Ph is optionally substituted phenyl.

2. The compound of claim 1, wherein Ph is di(trifluoromethyl)phenyl.

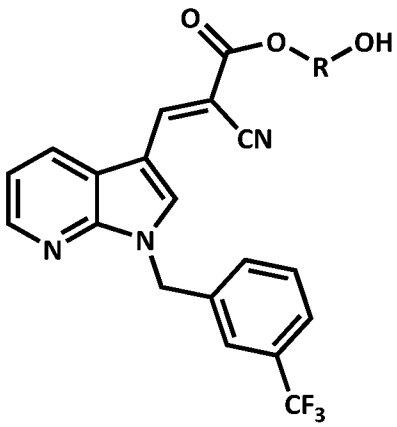
3. The compound of claim 1, further represented by a formula:



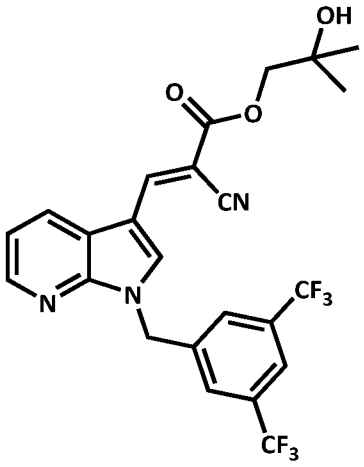
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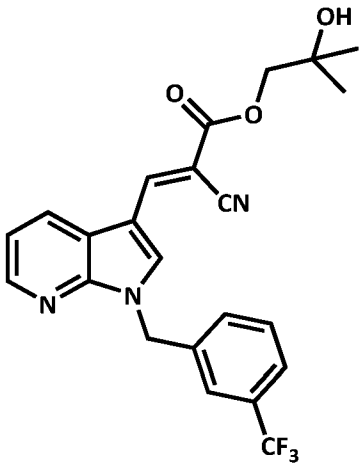
4. The compound of claim 1, wherein Ph is trifluoromethylphenyl.

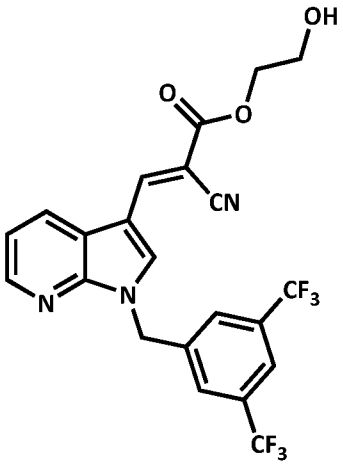
5. The compound of claim 1, further represented by a formula:

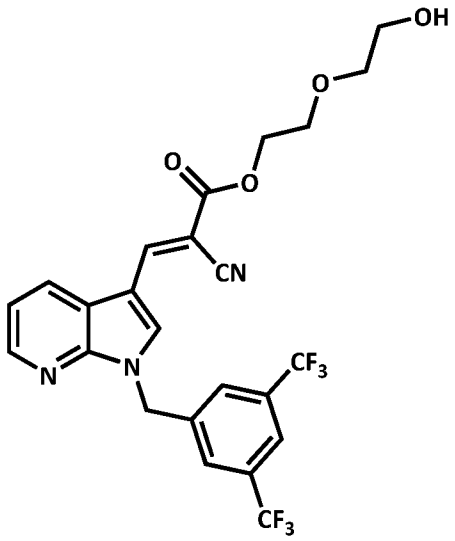


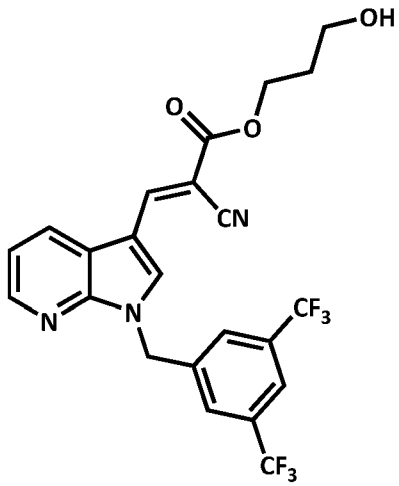
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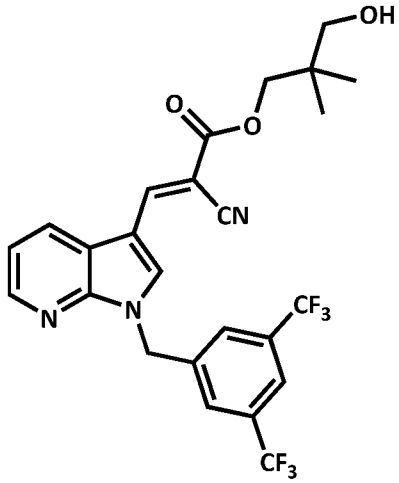
6. The compound of claim 1, which is:  .

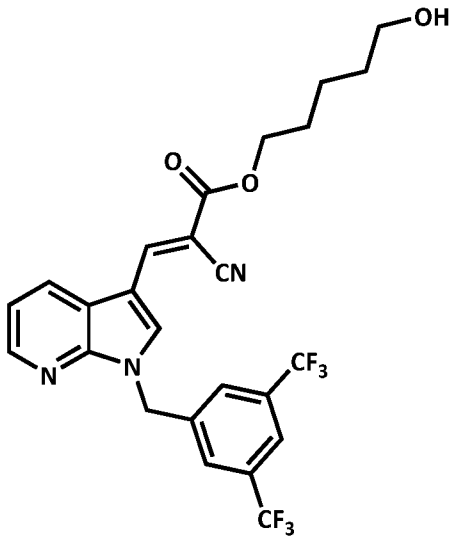
7. The compound of claim 1, which is:  .

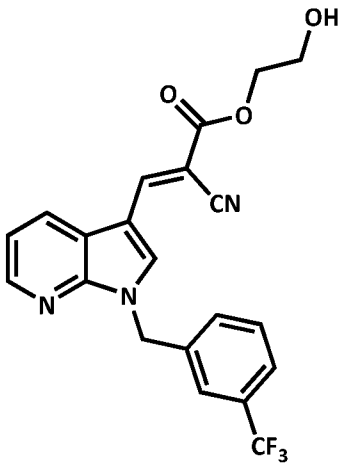
8. The compound of claim 1, which is:  .

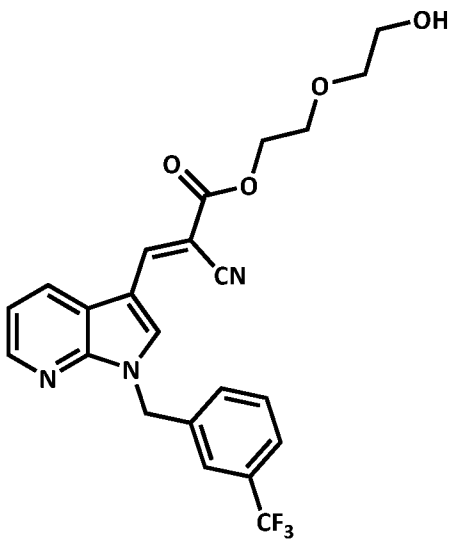
9. The compound of claim 1, which is: .

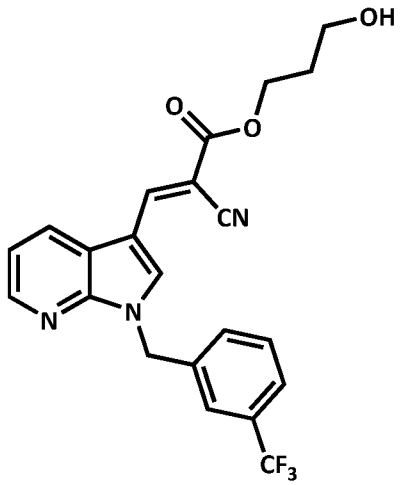
10. The compound of claim 1, which is: .

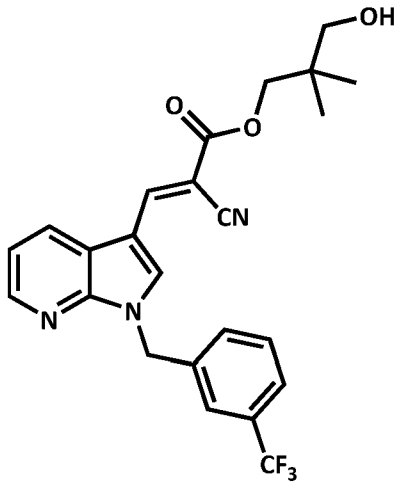
11. The compound of claim 1, which is: .

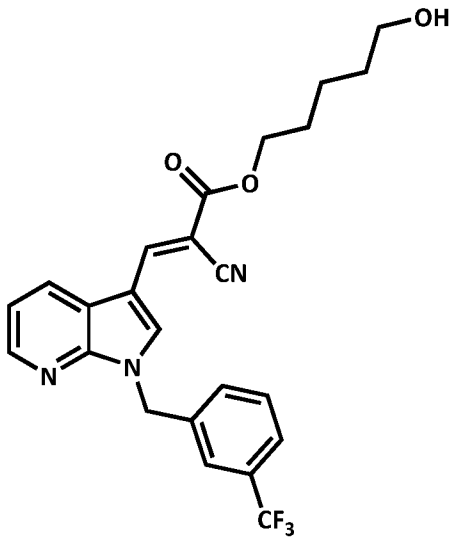
12. The compound of claim 1, which is: .

13. The compound of claim 1, which is: .

14. The compound of claim 1, which is: .

15. The compound of claim 1, which is: .

16. The compound of claim 1, which is: .

17. The compound of claim 1, which is: .

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

19. A pharmaceutical composition for growing hair comprising a compound according to any one of claims 1-17.

20. A method of growing hair, comprising: administering a compound of any one of claims 1-17 to the skin of a mammal in the area where hair growth is intended.

21. Use of a compound of according to any one of claims 1-17 in the manufacture of a medicament for growing hair.

22. A method of growing hair comprising administering a compound of any one of claims 1-17 to a mammal in need thereof.

23. A method of treating a disorder affecting hair growth comprising administering a compound according to any one of claims 1-17 to a mammal in need thereof.

24. The method of claim 23, where the disorder is alopecia or baldness.