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(54) **Titre : NOUVELLES ERGOLINES ET PROCEDES DE TRAITEMENT DE TROUBLES DE L'HUMEUR**
(54) **Title: NOVEL ERGOLINES AND METHODS OF TREATING MOOD DISORDERS**

(57) **Abrégé/Abstract:**
The present disclosure provides ergoline compounds and their use in treating mood disorders. Pharmaceutical compositions and methods of making various ergoline compounds are provided.

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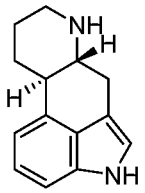
(54) Title: NOVEL ERGOLINES AND METHODS OF TREATING MOOD DISORDERS

(57) Abstract: The present disclosure provides ergoline compounds and their use in treating mood disorders. Pharmaceutical compositions and methods of making various ergoline compounds are provided.

NOVEL ERGOLINES AND METHODS OF TREATING MOOD DISORDERS

BACKGROUND

[0001] Ergolines are a diverse class of alkaloids containing the structural scaffold of the natural alkaloid ergoline.



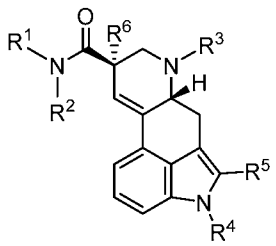
ergoline.

[0002] There are a significant number of ergoline compounds that include naturally occurring compounds, as well as synthetic and semi-synthetic chemical derivatives with similar structure. Ergolines are known to have diverse psychoactive and physiological effects. Some ergolines are serotonin 2a (5-HT_{2A}) receptor agonists and/or modulators of other serotonin receptors and are known to be psychoactive and/or induce vasoconstriction. In some cases, such compounds induce prolonged hallucinations. Other ergolines are agonists of dopamine receptors. Perhaps the most well-known ergoline is the psychedelic compound lysergic acid diethylamide (LSD). This compound is known to have significant effects on thought, perception, and behavior. However, it is currently classified as a Schedule I drug under the Controlled Substances Act due to its high abuse potential, no accepted medical use, and lack of established safety.

[0003] Accordingly, there remains a need for safe and effective ergoline compounds that can reliably be used for the treatment of mood disorders.

SUMMARY

[0004] The present disclosure includes a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, and R^6 are defined herein.

[0005] Additionally, the present disclosure includes methods of treating mood disorders comprising administering to a patient in need thereof a thereapeutically effective amound of a compound of Formula (I).

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] FIG. 1 depicts the effect of Compound 1 in the mouse head twitch response assay as quantified by the number of head twitches recorded during a 20-minute observation period. Data points represent mean ± SEM.

[0007] FIG. 2. depicts time immobile in the rat forced swim test 23.5 hours after administration of Compound 1. Data points represent mean ± SEM. Comparisons to vehicle: ** $p < 0.01$, **** $p < 0.0001$.

[0008] FIG 3. depicts the total number of marbles buried during a 30-minute observation period in the mouse marble burying test. Data points represent mean ± SEM. Comparisons to vehicle: * $p < 0.05$, **** $p < 0.0001$.

DETAILED DESCRIPTION

[0009] The features and other details of the disclosure will now be more particularly described. Before further description of the present disclosure, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

Definitions

[0010] "Treating" includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

[0011] The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon. Exemplary alkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C_1-C_6 alkyl, C_1-C_4 alkyl, and C_1-C_3 alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-butyl, 3-methyl-2-butyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

[0012] The term "alkenyl" as used herein is a branched or unbranched hydrocarbon group having a specified number of carbon atoms and containing at least one double bond. In some embodiments, alkenyl refers to a branched or unbranched saturated hydrocarbon group having three carbon atoms (C_3). In some embodiments, alkenyl refers to a branched or unbranched hydrocarbon group having six carbon atoms (C_6). In some embodiments, the term "alkenyl" includes, but is not limited to, vinyl or allyl.

[0013] The term "alkynyl" as used herein is a branched or unbranched hydrocarbon group having a specified number of carbon atoms and containing at least one triple bond. In some embodiments, alkynyl refers to a branched or unbranched saturated hydrocarbon group having three carbon atoms (C_3). In some embodiments, alkynyl refers to a branched or unbranched hydrocarbon group having six carbon atoms (C_6). In some embodiments, the term "alkynyl" includes, but is not limited to, ethynyl or propargyl.

[0014] The term "cyano" as used herein refers to the radical -CN.

[0015] The terms "cycloalkyl" or a "carbocyclic group" as used herein refers to a saturated or partially unsaturated hydrocarbon group of, for example, 3-6, or 4-6 carbons, referred to herein as C_3-C_6 cycloalkyl or C_4-C_6 cycloalkyl, respectively. Exemplary cycloalkyl groups include, but are not limited to, cyclohexyl, cyclopentyl, cyclopentenyl, cyclobutyl or cyclopropyl.

[0016] The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.

[0017] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic and bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term "aryl" may be used interchangeably with the term "aryl ring". In certain embodiments of the present disclosure, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl", as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0018] The terms "heteroaryl" and "heteroar-", used alone or as part of a larger moiety, e.g., "heteroaralkyl", or "heteroaralkoxy", refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any

quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar-", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-b]-l,4-oxazin-3(4H)-one. A heteroaryl group may be mono- or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic", any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0019] The terms “heterocyclyl” or “heterocyclic group” are art-recognized and refer to saturated or partially unsaturated, 4-10 membered ring structures, including bridged or fused rings, and whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, heterocyclyl rings may be linked to the adjacent radical through carbon or nitrogen. Examples of heterocyclyl groups include, but are not limited to, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, oxetane, azetidine, tetrahydrofuran or dihydrofuran etc.

[0020] The terms “hydroxy” and “hydroxyl” as used herein refers to the radical -OH.

[0021] “Pharmaceutically or pharmacologically acceptable” include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

[0022] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[0023] The term "pharmaceutical composition" as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

[0024] "Individual," "patient," or "subject" are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds of the present disclosure can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, *e.g.,* domestic animals (*e.g.,* dogs, cats, and the like), farm animals (*e.g.,* cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.,* rats, mice, guinea pigs, and the like). The mammal treated in the methods of the present disclosure is desirably a mammal in which treatment of psychiatric disease or disorder is desired. "Modulation" includes antagonism (*e.g.,* inhibition), agonism, partial antagonism and/or partial agonism.

[0025] In the present specification, the term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system or animal, (e.g. mammal or human) that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compounds of the present disclosure are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in a decrease in symptoms of a psychiatric disorder.

[0026] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-*bis*-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations.

Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt. In some embodiemnts the term "pharmaceutically acceptable salt(s)" as used herein refers to a hemitartrate salt. As used herein, a hemitartrate salt of a compound of Formula (I) is salt wherein the molar ratio of a compound of Formula (I) to tartaric acid is 2 : 1. In some embodiemnts the term "pharmaceutically acceptable salt(s)" as used herein refers to a tartrate salt. As used herein, a tartrate salt of a compound of Formula (I) is salt wherein the molar ratio of a compound of Formula (I) to tartaric acid is 1 : 1.

[0027] The compounds of the disclosure may contain one or more chiral centers and, therefore, exist as stereoisomers. The term “stereoisomers” when used herein consist of all enantiomers or diastereomers. These compounds may be designated by the symbols “(+),” “(-),” “R” or “S,” depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. The present disclosure encompasses various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated “(±)” in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[0028] The compounds of the disclosure may contain one or more double bonds and, therefore, exist as geometric isomers resulting from the arrangement of substituents around a carbon-carbon double bond. The symbol  denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the “*Z*” or “*E*” configuration wherein the terms “*Z*” and “*E*” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the “*E*” and “*Z*” isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as “cis” or “trans,” where “cis” represents substituents on the same side of the double bond and “trans” represents substituents on opposite sides of the double bond.

[0029] Compounds of the disclosure may contain a carbocyclic or heterocyclic ring and therefore, exist as geometric isomers resulting from the arrangement of substituents around the ring. Substituents around a carbocyclic or heterocyclic ring may also be referred to as “cis” or

"trans", where the term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[0030] Individual enantiomers and diasteriomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well known methods, such as chiral-phase liquid chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations, and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

[0031] The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the present disclosure embrace both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

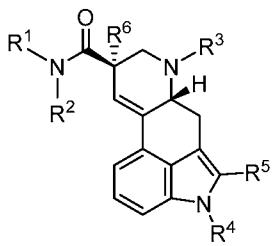
[0032] The present disclosure also embraces isotopically labeled compounds of the present disclosure which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S,

^{18}F, and ^{36}Cl, respectively. For example, a compound of the present disclosure may have one or more H atom replaced with deuterium.

[0033] Certain isotopically-labeled disclosed compounds (*e.g.*, those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H) and carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present disclosure can generally be prepared by following procedures analogous to those disclosed in the examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

I. Compounds

[0034] In some embodiments, the present disclosure provides a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein

R^1 is C_1-C_6 alkyl or 3-7 membered carbocyclyl, wherein R^1 is optionally substituted with one or more halogen or C_1-C_6 alkyl;

R^2 is hydrogen or C_1-C_6 alkyl, wherein R^2 is optionally substituted with one or more halogen or C_1-C_6 alkyl; or

wherein R^1 and R^2 can be taken together with the atom on which they are attached to form an optionally substituted 3-7 membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O, and S, wherein the heterocyclyl is optionally substituted with one or more fluoro or C_1-C_6 alkyl;

R^3 is selected from the group consisting of C_2-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, --CH_2-(cyclopropyl), and 3-7 membered cycloalkyl,

wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, and -OMe;

or

R^3 is selected from the group consisting of -(C_1-C_2 alkyl)-phenyl and -(C_1-C_2 alkyl)-(6-membered heteroaryl),

wherein C_1-C_2 alkyl is optionally substituted with one or more fluoro, hydroxyl, and -OMe, and wherein phenyl and 6-membered heteroaryl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, -NO_2, -NH_2, -C(O)NH_2, C_1-C_4 alkyl, C_3-C_5 cycloalkyl, and C_1-C_4 alkoxy;

R^4 is hydrogen or -C(O)(C_1-C_8 alkyl);

R^5 is hydrogen or halogen;

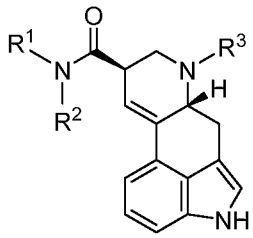
R^6 is hydrogen or deuterium;

wherein when R^1 and R^2 are both ethyl, and R^4 and R^5 are both hydrogen, R^3 is not unsubstituted linear C_2-C_6 alkyl, isopropyl, -$CH_2CH{=}CH_2$, -CH_2CH_2F, or -CH_2CH_2Ph;

wherein when R^1 and R^2 are both ethyl, R^4 is -C(O)(C_2 alkyl), and R^5 is hydrogen, R^3 is not unsubstituted ethyl;

wherein when R^1 is ethyl and R^2 is H, R^3 is not unsubstituted ethyl, unsubstituted n-propyl, or -$CH_2CH{=}CH_2$.

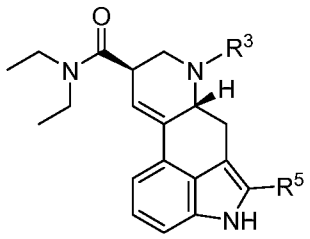
[0035] In some embodiments, the present disclosure includes a compound of formula (Ia):



(Ia),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, and R^3 are defined above and in the classes and embodiments disclosed herein.

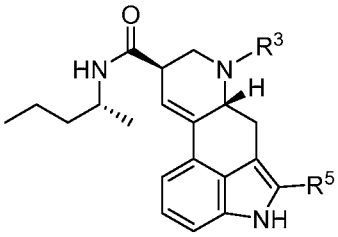
[0036] In some embodiments, the present disclosure includes a compound of formula (Ib):



(Ib),

or a pharmaceutically acceptable salt thereof, wherein R^3, and R^5 are defined above and in the classes and embodiments disclosed herein.

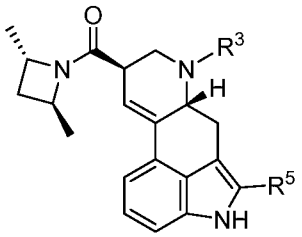
[0037] In some embodiments, the present disclosure includes a compound of formula (Ic):



(Ic),

or a pharmaceutically acceptable salt thereof, wherein R^3, and R^5 are defined above and in the classes and embodiments disclosed herein.

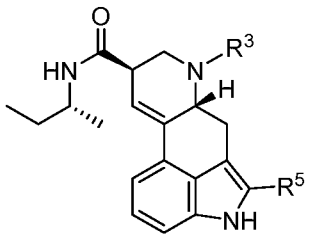
[0038] In some embodiments, the present disclosure includes a compound of formula (Id):



(Id),

or a pharmaceutically acceptable salt thereof, wherein R^3, and R^5 are defined above and in the classes and embodiments disclosed herein.

[0039] In some embodiments, the present disclosure includes a compound of formula (Ie):



(Ie),

or a pharmaceutically acceptable salt thereof, wherein R^3, and R^5 are defined above and in the classes and embodiments disclosed herein.

[0040] In some embodiments, R^1 is C_1-C_6 alkyl. In some emboidments, R^1 is linear C_1-C_6 alkyl. In some embodiments, R^1 is branched C_1-C_6 alkyl. In some emboidments, R^1 is C_2-C_5 alkyl. In some embodiments, R^1 is selected from the group consisting of ethyl, *sec*-butyl, 2-pentyl, and 3-pentyl.

[0041] In some embodiments, R^1 is C_1-C_6 alkyl or 3-7 membered carbocyclyl, wherein R^1 is optionally substituted with one or more halogen or C_1-C_6 alkyl. In some embodiments, R^1 is C_1-C_6 alkyl or 3-5 membered carbocyclyl, wherein R^1 is optionally substituted with one or more fluoro or C_1-C_4 alkyl.

[0042] In some embodiments, R^2 is hydrogen or C_1-C_6 alkyl, wherein R^2 is optionally substituted with one or more halogen or C_1-C_6 alkyl. In some embodiments, R^2 is hydrogen or C_1-C_6 alkyl. In some emodiments, R^2 is hydrogen. In some embodiments, R^2 is C_1-C_6 alkyl. In some emboidments, R^2 is linear C_1-C_6 alkyl. In some embodiments, R^2 is branched C_1-C_6 alkyl. In some emboidments, R^2 is C_2-C_5 alkyl. In some embodiments, R^2 is selected from the group consisting of hydrogen, ethyl, *sec*-butyl, 2-pentyl, and 3-pentyl.

[0043] In some embodiments, R^1 and R^2 can be taken together with the atom on which they are attached to form an optionally substituted 3-7 membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, R^1 and R^2 can be taken together with the atom on which they are attached to form an optionally substituted group selected from the group consisignt of azetidinyl, pyrrolidinyl, piperidinyl, piperizinyl, and morpholinyl. In some embodiments, R^1 and R^2 can be taken together with the atom on which they are attached to form dimethylazetidinyl.

[0044] In some emodiments, R^3 is selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, and 3-7 membered cycloalkyl, wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, 3-7 membered cycloalkyl, and phenyl, wherein cycloalkyl or phenyl are optionally substituted with one, two, or three substitutents each independently selected from the group consisting of halogen, hydroxyl, C_1-C_4 alkyl, and C_1-C_4 alkoxy. In some emodiments, R^3 is C_1-C_6 alkyl or

C_2-C_6 alkenyl, wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, 3-7 membered cycloalkyl, and phenyl, wherein cycloalkyl or phenyl are optionally substituted with one, two, or three substitutents each independently selected from the group consisting of halogen, hydroxyl, C_1-C_4 alkyl, and C_1-C_4 alkoxy. In some emodiments, R^3 is C_1-C_3 alkyl, or C_2-C_3 alkenyl, wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, 3-7 membered cycloalkyl, and phenyl, wherein cycloalkyl or phenyl are optionally substituted with one, two, or three substitutents each independently selected from the group consisting of halogen, hydroxyl, C_1-C_4 alkyl, and C_1-C_4 alkoxy. In some embodiments, R^3 is selected from the group consisting of methyl, ethyl, *n*-propyl, and allyl, wherein R^3 may be substituted with one to three substituents selected from the group consisting of fluoro, 2-methoxyphenyl, and 2-hydroxyphenyl.

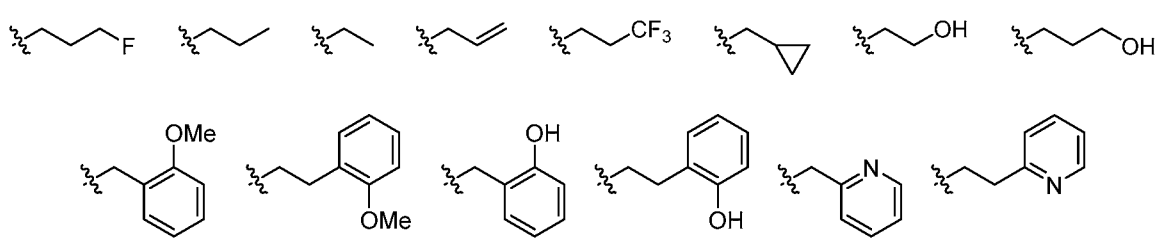
[0045] R^3 is selected from the group consisting of C_2-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -CH_2-(cyclopropyl), and 3-7 membered cycloalkyl,wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, and -OMe; or R^3 is selected from the group consisting of -(C_1-C_2 alkyl)-phenyl and -(C_1-C_2 alkyl)-(6-membered heteroaryl), wherein C_1-C_2 alkyl is optionally substituted with one or more fluoro, hydroxyl, and -OMe, and wherein phenyl and 6-membered heteroaryl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, -NO_2, -NH_2, -C(O)NH_2, C_1-C_4 alkyl, C_3-C_5 cycloalkyl, and C_1-C_4 alkoxy. In some emboidments, R^3 is selected from the group consisting of C_2-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -CH_2-(cyclopropyl), and 3-7 membered cycloalkyl,wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, and -OMe. In some embodiments, R^3 is selected from the group consisting of -(C_1-C_2 alkyl)-phenyl and -(C_1-C_2 alkyl)-(6-membered heteroaryl), wherein C_1-C_2 alkyl is optionally substituted with one or more fluoro, hydroxyl, and -OMe, and wherein phenyl and 6-membered heteroaryl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, -NO_2, -NH_2, -C(O)NH_2, C_1-C_4 alkyl, C_3-C_5 cycloalkyl, and C_1-C_4 alkoxy.

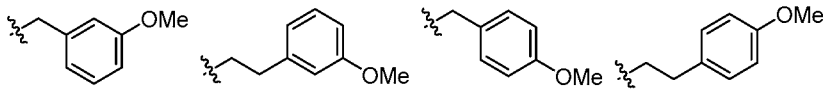
[0046] In some embodiments, R^3 is selected from the group consisting of C_2-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, -CH_2-(cyclopropyl), and 3-5 membered cycloalkyl, wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, and -OMe; or R^3 is selected from the group consisting of -(C_1-C_2 alkyl)-phenyl and -(C_1-C_2 alkyl)-(6-membered heteroaryl), wherein C_1-C_2 alkyl is optionally

substituted with one or more fluoro, and wherein phenyl and 6-membered heteroaryl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, -NO_2, -NH_2, -C(O)NH_2, C_1-C_3 alkyl, cyclopropyl, and C_1-C_3 alkoxy. In some embodiments, R^3 is selected from the group consisting of C_2-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, -CH_2-(cyclopropyl), and 3-5 membered cycloalkyl, wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, and -OMe. In some embodiments, R^3 is selected from the group consisting of -(C_1-C_2 alkyl)-phenyl and -(C_1-C_2 alkyl)-(6-membered heteroaryl), wherein C_1-C_2 alkyl is optionally substituted with one or more fluoro, and wherein phenyl and 6-membered heteroaryl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, -NO_2, -NH_2, -C(O)NH_2, C_1-C_3 alkyl, cyclopropyl, and C_1-C_3 alkoxy.

[0047] In some embodiments, R^3 is selected from the group consisting of ethyl, *n*-propyl, -$CH_2CH{=}CH_2$, cyclopropyl, and -CH_2-(cyclopropyl), wherein R^3 may be substituted with one to three instances of fluoro. In some embodiments, R^3 is selected from the group consisting of ethyl, *n*-propyl, -$CH_2CH{=}CH_2$, cyclopropyl, -CH_2-(cyclopropyl), -$CH_2CH_2CH_2F$, and -$CH_2CH_2CF_3$. In some embodiments, R^3 is selected from the group consisting of -(C_1-C_2 alkyl)-phenyl and -(C_1-C_2 alkyl)-(6-membered heteroaryl),wherein C_1-C_2 alkyl is optionally substituted with one or more fluoro, and wherein phenyl and 6-membered heteroaryl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, -NO_2, -NH_2, -C(O)NH_2, C_1-C_3 alkyl, cyclopropyl, and C_1-C_3 alkoxy. In some embodiments, R^3 is selected from the group consisting of -(C_1-C_2 alkyl)-phenyl and -(C_1-C_2 alkyl)-pyridinyl, wherein phenyl and pyridinyl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, -NO_2, -NH_2, -C(O)NH_2, C_1-C_3 alkyl, cyclopropyl, and C_1-C_3 alkoxy.

[0048] In some embodiments, R^3 is selected from the group consisting of

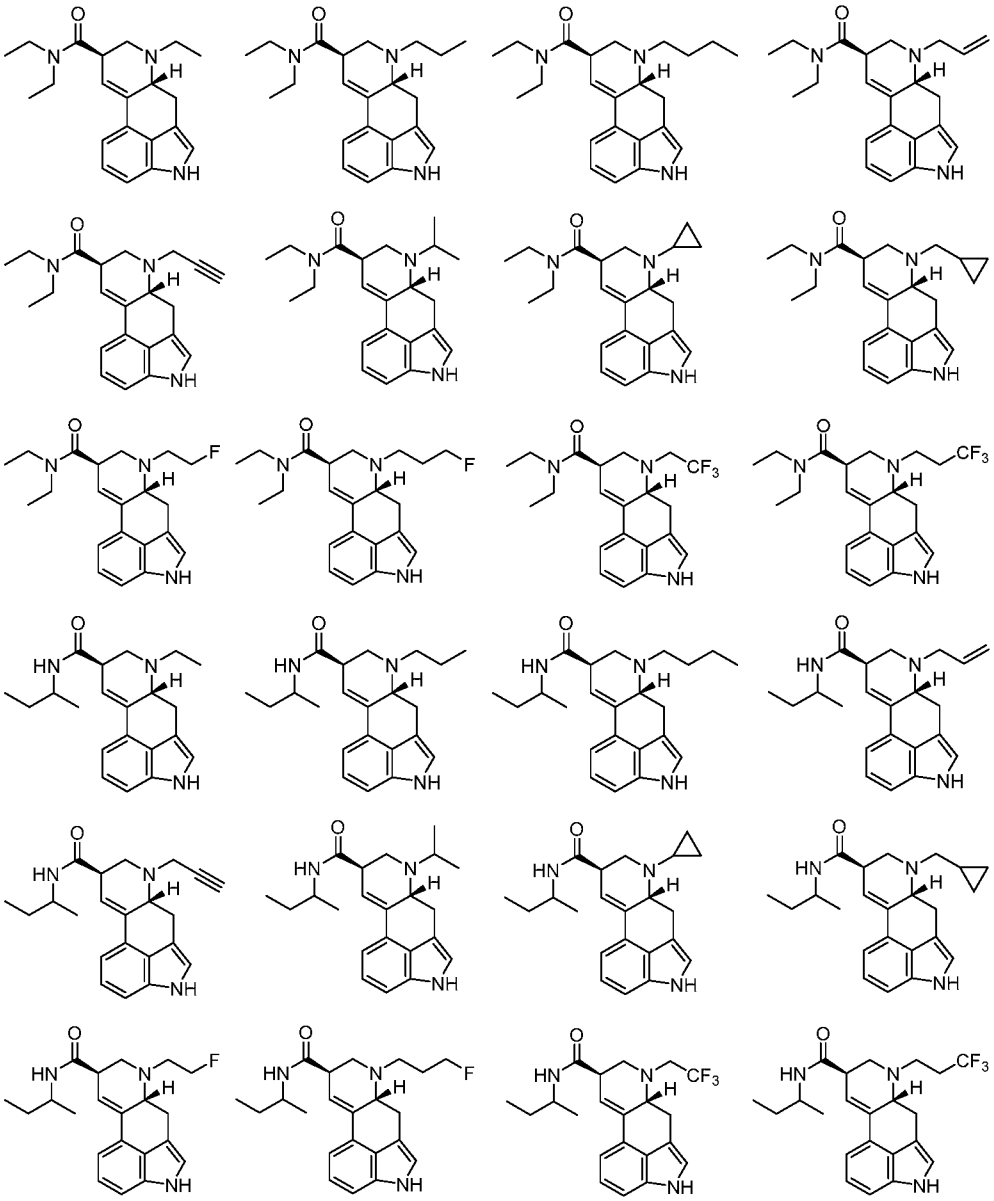


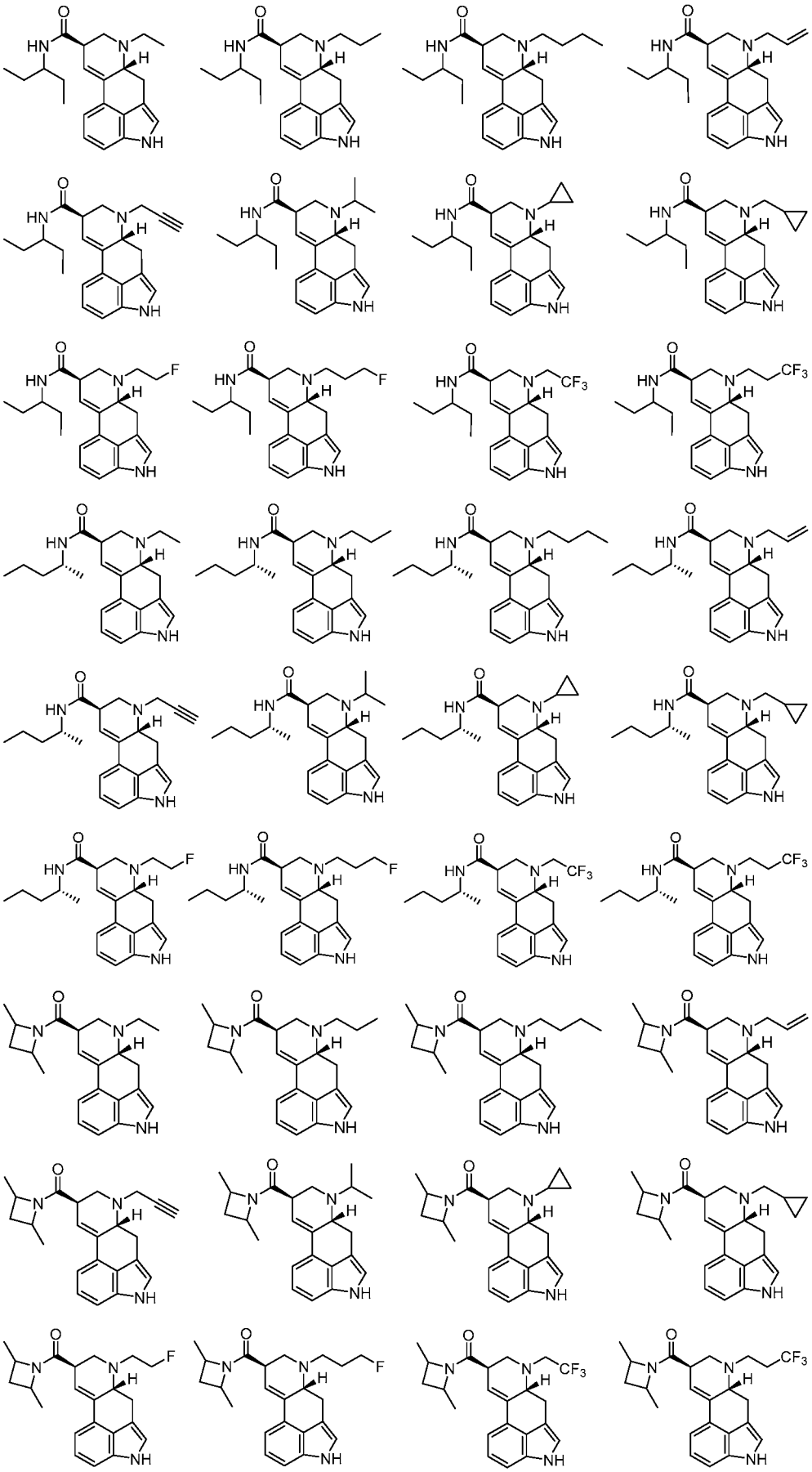


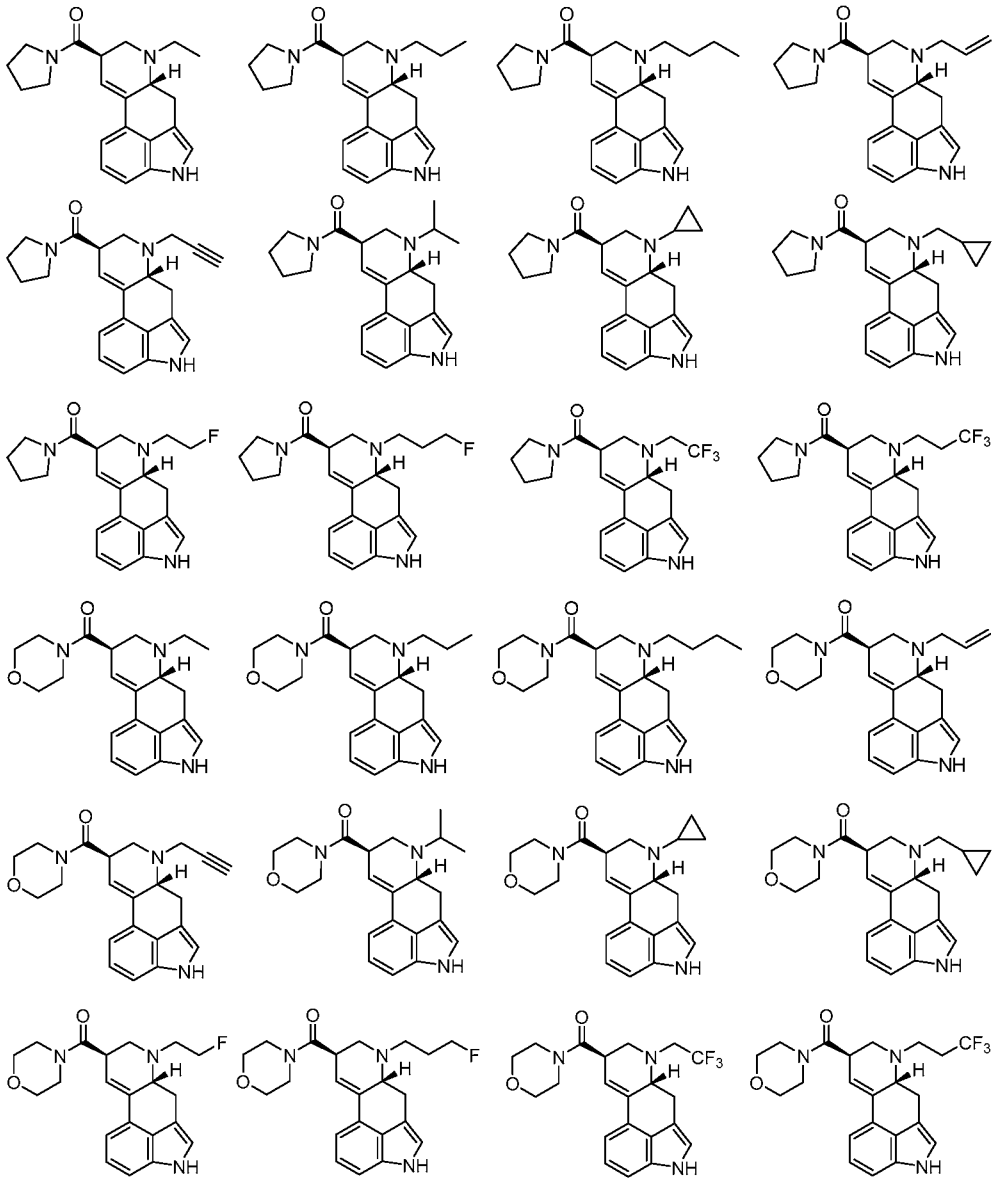
[0049] In some embodiments, R^4 is hydrogen or -C(O)(C_1-C_8 alkyl). In some embodiments, R^4 is hydrogen or -C(O)(C_1-C_3 alkyl). In some embodiments, R^4 is hydrogen. In some embodiments, R^4 is -C(O)(C_1-C_8 alkyl). In some embodiments, R^4 is -C(O)(C_1-C_3 alkyl).

[0050] In some embodiments, R^5 is hydrogen or halogen. In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is halogen. In some embodiments, R^5 is hydrogen or bromo. In some embodiments, R^5 is bromo.

[0051] In some embodiments, the present disclosure includes a compound selected from the group consisting of:

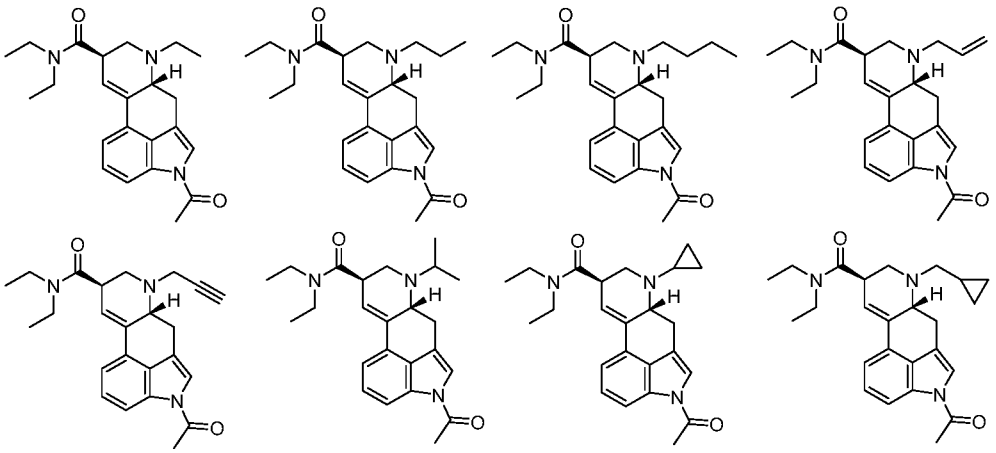


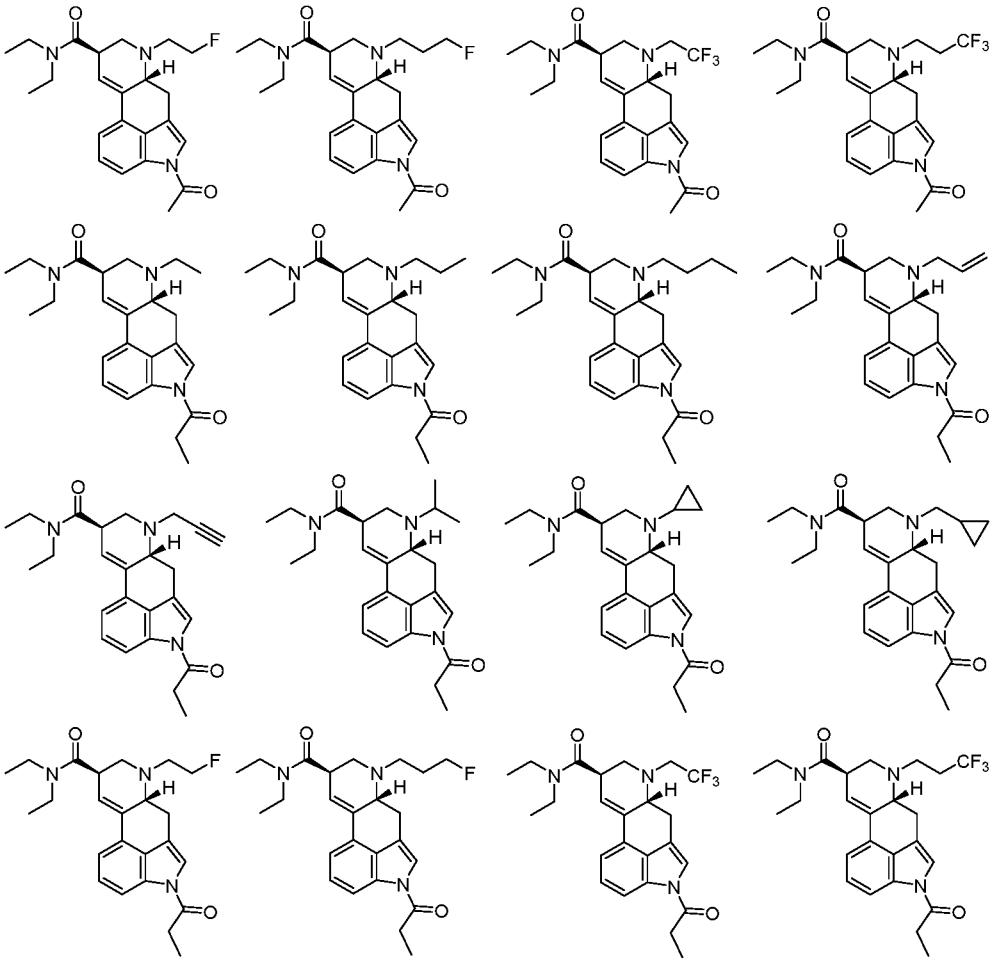




or a pharmaceutically acceptable salt thereof.

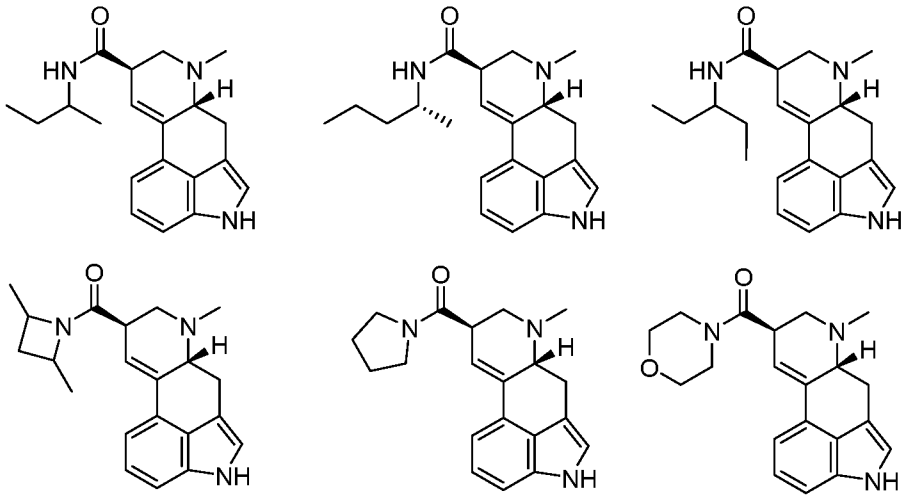
[0052] In some embodiments, the present disclosure includes a compound selected from the group consisting of:

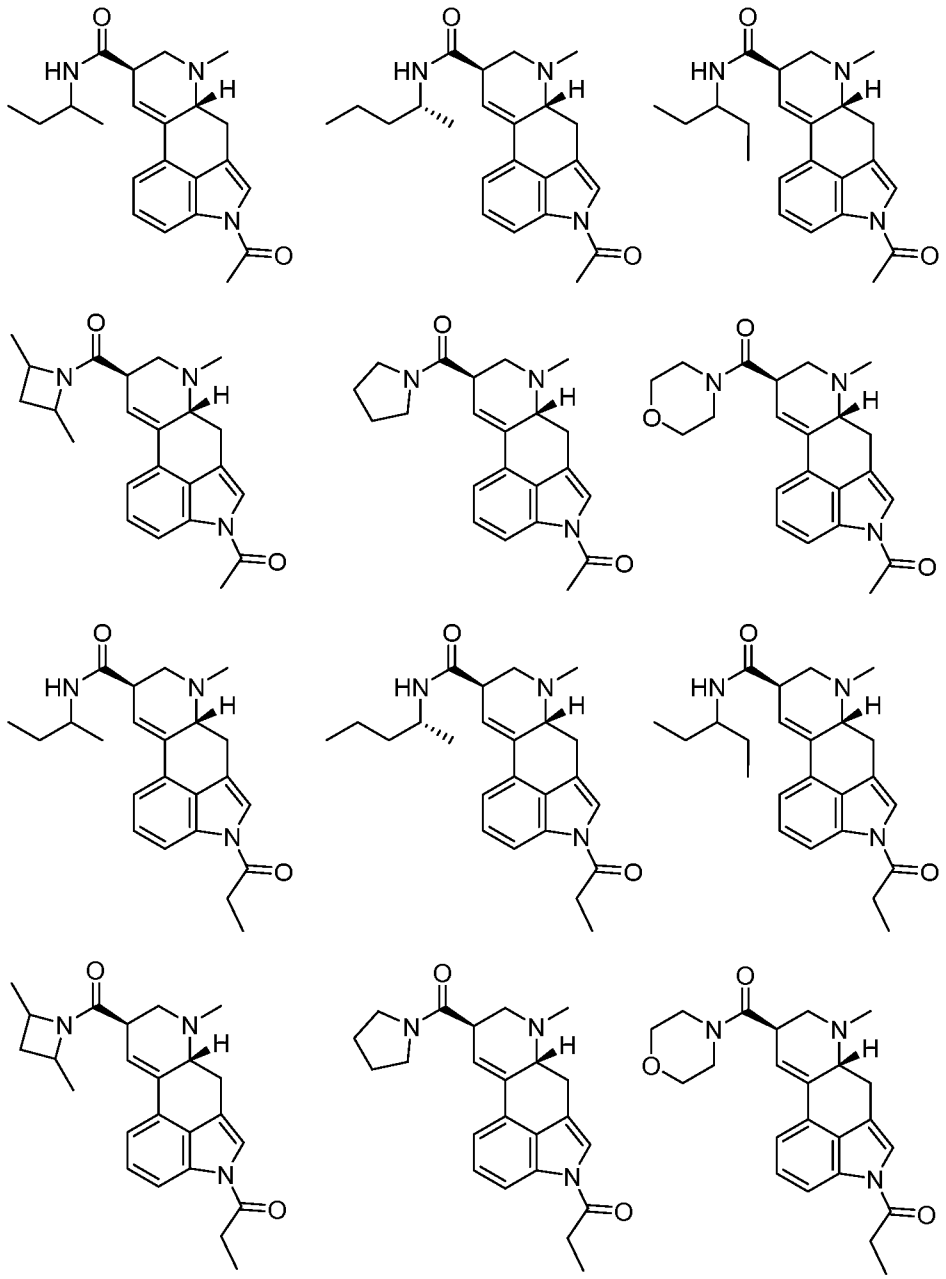




or a pharmaceutically acceptable salt thereof.

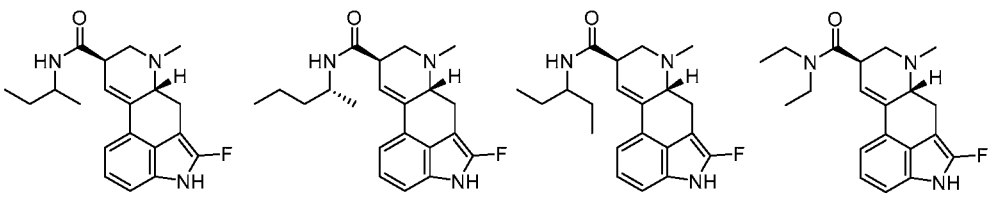
[0053] In some embodiments, the present disclosure includes a compound selected from the group consisting of:

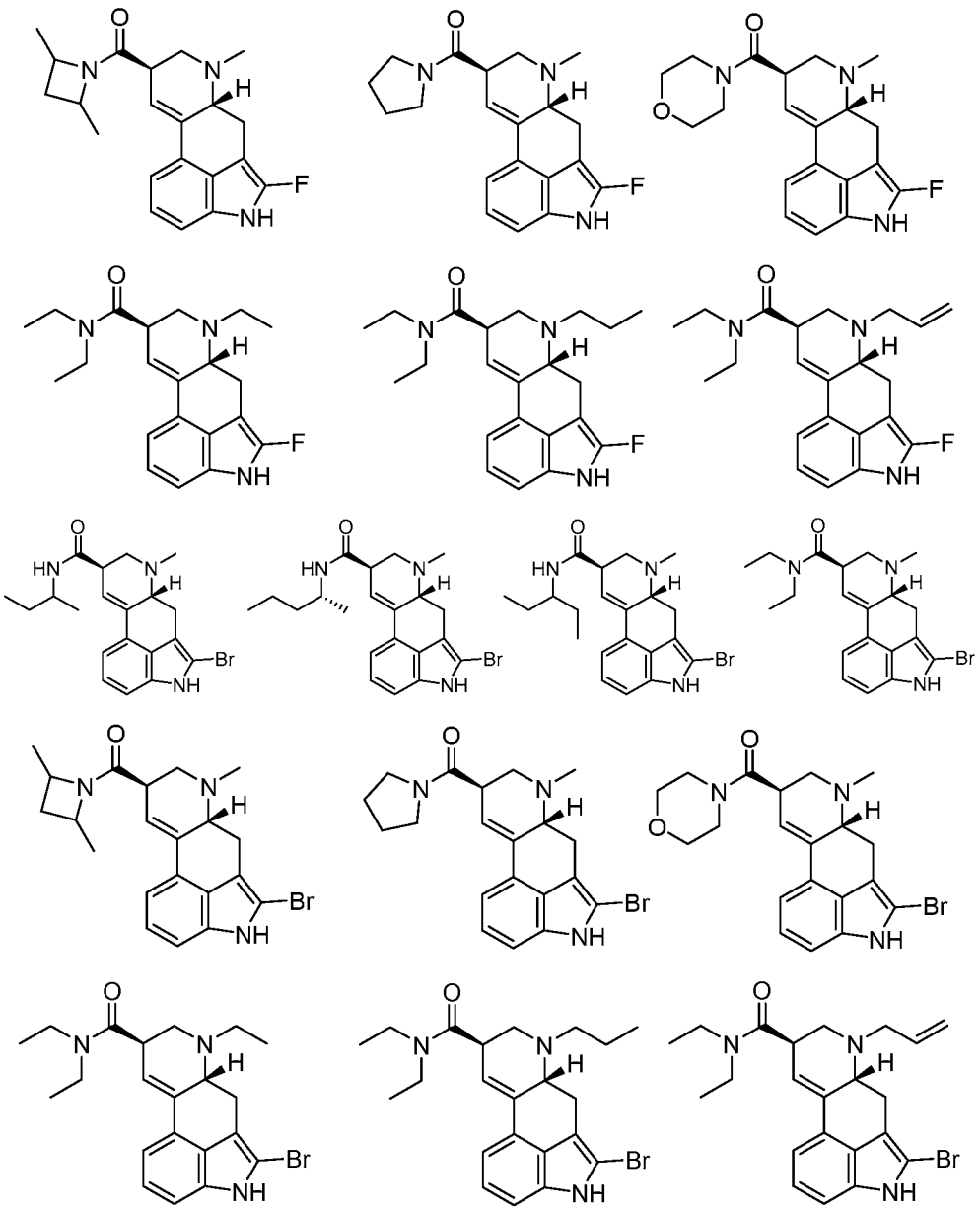




or a pharmaceutically acceptable salt thereof.

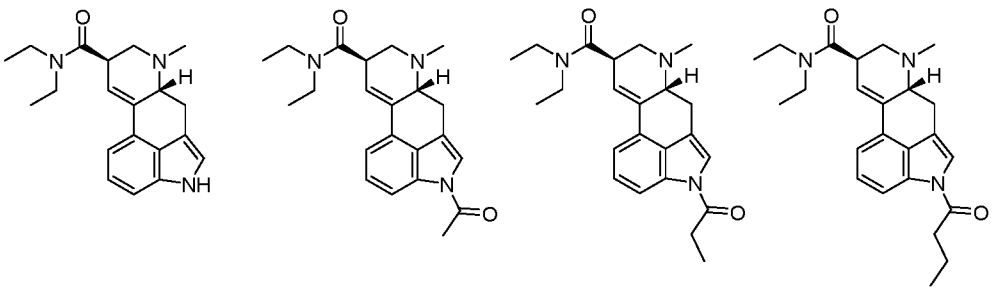
[0054] In some embodiments, the present disclosure includes a compound selected from the group consisting of:





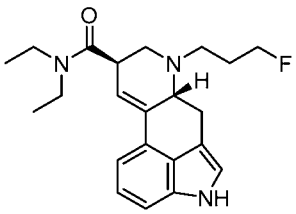
or a pharmaceutically acceptable salt thereof.

[0055] In other embodiments provided are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of a compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

[0056] In some embodiments, the present disclosure includes a compound selected from the group consisting of:



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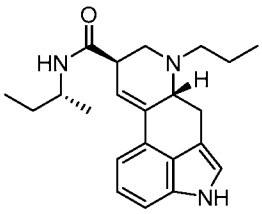

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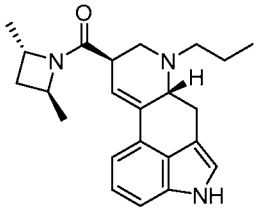

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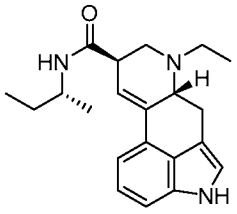

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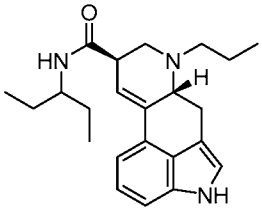

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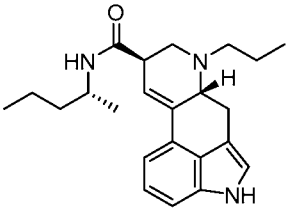

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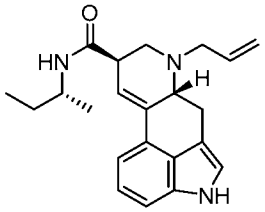

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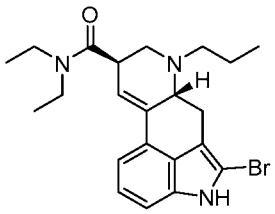

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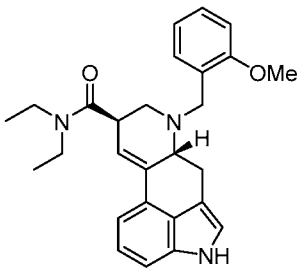

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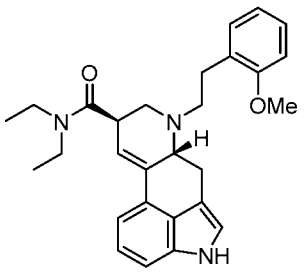

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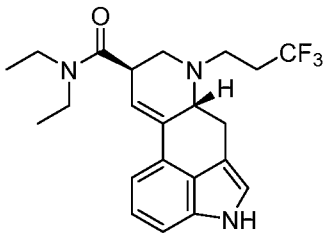

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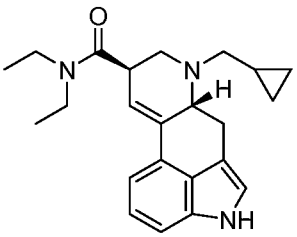

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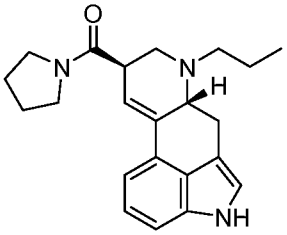

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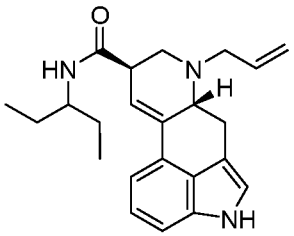

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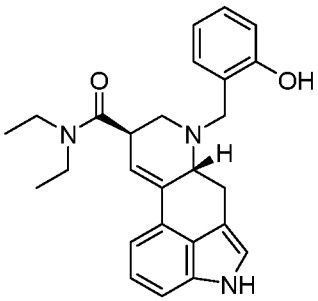

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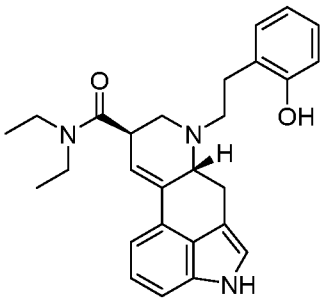

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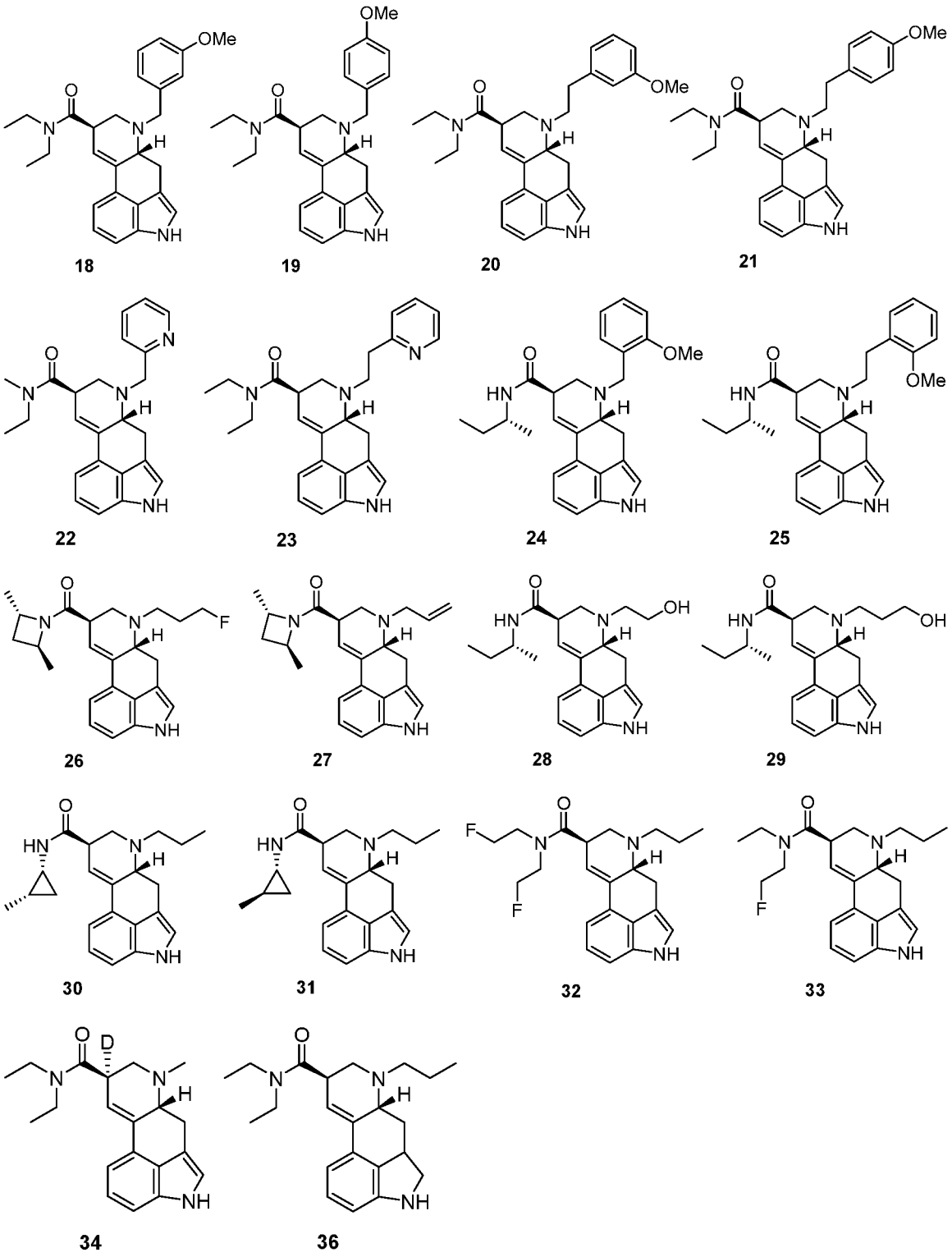


or a pharmaceutically acceptable salt thereof.

[0057] Salts of compounds of the present disclosure can be prepared by the reaction of a compound of the present disclosure with an appropriate acid or base in a suitable solvent, or mixture of solvents (such as an ether, for example, diethyl ether, or an alcohol, for example ethanol, or an aqueous solvent) using conventional procedures. Salts of compounds of General

Formula I can be exchanged for other salts by treatment using conventional ion-exchange chromatography procedures. Preferred salts of compounds of the present disclosure include tartrate, fumarate, and maleate.

[0058] Where it is desired to obtain a particular enantiomer of a compound of the present disclosure, this may be produced from a corresponding mixture of enantiomers by employing any suitable conventional procedure for resolving enantiomers. For example, diastereomeric derivatives (such as salts) can be produced by reaction of a mixture of enantiomers of a compound the present disclosure (such a racemate) and an appropriate chiral compound (such as a chiral base). The diastereomers can then be separated by any conventional means such as crystallisation, and the desired enantiomer recovered (such as by treatment with an acid in the instance where the diastereomer is a salt). Alternatively, a racemic mixture of esters can be resolved by kinetic hydrolysis using a variety of biocatalysts (for example, see Patel Steroselective Biocatalysts, Marcel Decker; New York 2000).

[0059] In another resolution process a racemate of compounds of the present disclosure can be separated using chiral High Performance Liquid Chromatography. Alternatively, a particular enantiomer can be obtained by using an appropriate chiral intermediate in one of the processes described above. Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the present disclosure.

II. Methods

[0060] Described herein are methods and compositions for treating a mood disorder by administering to a patient in need thereof a compound of the present disclosure. Also provided are pharmaceutical compositions that include a compound of the presend disclosure.

[0061] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Depressive Disorders, *e.g.*, Major Depressive Disorder, Persistent Depressive Disorder, Postpartum Depression, Premenstrual Dysphoric Disorder, Seasonal Affective Disorder, Psychotic Depression, Disruptive Mood Dysregulation Disorder, Substance/Medication-Induced Depressive Disorder, or Depressive Disorder Due to Another Medical Condition.

[0062] In embodiments, the methods, compounds, and compositions may treat mood disorders that include Bipolar and Related Disorders. In embodiments, the methods, compounds, and compositions may treat mood disorders that include Substance-Related Disorders. In embodiments, the methods, compounds, and compositions may treat mood disorders that include Anxiety Disorders. In embodiments, the methods, compounds, and

compositions may treat mood disorders that include Obsessive-Compulsive and Related Disorders. In embodiments, the methods, compounds, and compositions may treat mood disorders that include Trauma- and Stressor-Related Disorders. In embodiments, the methods, compounds, and compositions may treat mood disorders that include Feeding and Eating Disorders. In embodiments, the methods, compounds, and compositions may treat mood disorders that include Neurocognitive Disorders. In embodiments, the methods, compounds, and compositions may treat mood disorders that include Neurodevelopmental Disorders. In embodiments, the methods, compounds, and compositions may treat mood disorders that include Personality Disorders. In embodiments, the methods, compounds, and compositions may treat mood disorders that include Sexual Dysfunctions. In embodiments, the methods, compounds, and compositions may treat mood disorders that include Gender Dysphoria. In embodiments, the methods, compounds, and compositions may treat migraine or cluster headache.

[0063] Also provided herein are methods of treating refractory depression, *e.g.*, patients suffering from a depressive disorder that does not, and/or has not, responded to adequate courses of at least one, or at least two, other antidepressant compounds or therapeutics. As used herein "depressive disorder" encompasses refractory depression.

[0064] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Bipolar and Related Disorders, *e.g.*, Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder, Substance/Medication-Induced Bipolar and Related Disorder, Bipolar and Related Disorder Due to Another Medical Condition,

[0065] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Substance-Related Disorders, *e.g.*, preventing a substance use craving, diminishing a substance use craving, and/or facilitating substance use cessation or withdrawal. Substance use disorders involve abuse of psychoactive compounds such as alcohol, caffeine, cannabis, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, nicotine and tobacco. As used herein "substance" or "substances" are psychoactive compounds which can be addictive such as alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, nicotine and tobacco. For example, the methods, compounds, and compositions may be used to facilitate smoking cessation or cessation of opioid use.

[0066] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Anxiety Disorders, *e.g.*, Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic

Attack, Agoraphobia, Generalized Anxiety Disorder, Substance/Medication-Induced Anxiety Disorder, or Anxiety Disorder Due to Another Medical Condition.

[0067] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Obsessive-Compulsive and Related Disorders, *e.g.*, Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling Disorder), Excoriation (Skin-Picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, or Obsessive-Compulsive and Related Disorder Due to Another Medical Condition.

[0068] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Trauma- and Stressor-Related Disorders, *e.g.*, Reactive Attachment Disorder, Disinhibited Social Engagement Disorder, Posttraumatic Stress Disorder, Acute Stress Disorder, or Adjustment Disorders.

[0069] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Feeding and Eating Disorders, *e.g.*, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder, Pica, Rumination Disorder, or Avoidant/Restrictive Food Intake Disorder.

[0070] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Neurocognitive Disorders, *e.g.*, Delirium, Major Neurocognitive Disorder, Mild Neurocognitive Disorder, Major or Mild Neurocognitive Disorder Due to Alzheimer's Disease, Major or Mild Frontotemporal Neurocognitive Disorder, Major or Mild Neurocognitive Disorder With Lewy Bodies, Major or Mild Vascular Neurocognitive Disorder, Major or Mild Neurocognitive Disorder Due to Traumatic Brain Injury, Substance/Medication-Induced Major or Mild Neurocognitive Disorder, Major or Mild Neurocognitive Disorder Due to HIV Infection, Major or Mild Neurocognitive Disorder Due to Prion Disease, Major or Mild Neurocognitive Disorder Due to Parkinson's Disease, Major or Mild Neurocognitive Disorder Due to Huntington's Disease, Major or Mild Neurocognitive Disorder Due to Another Medical Condition, or Major or Mild Neurocognitive Disorder Due to Multiple Etiologies,

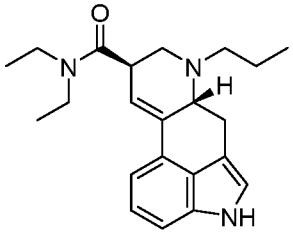
[0071] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Neurodevelopmental Disorders, *e.g.*, Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder, Stereotypic Movement Disorder, Tic Disorders, Tourette's Disorder, Persistent (Chronic) Motor or Vocal Tic Disorder, or Provisional Tic Disorder,

[0072] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Personality Disorders, *e.g.*, Borderline Personality Disorder.

[0073] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Sexual Dysfunctions, *e.g.* Delayed Ejaculation, Erectile Disorder, Female Orgasmic Disorder, Female Sexual Interest/Arousal Disorder, Genito-Pelvic Pain/Penetration Disorder, Male Hypoactive Sexual Desire Disorder, Premature (Early) Ejaculation, orSubstance/Medication-Induced Sexual Dysfunction.

[0074] In embodiments, the methods, compounds, and compositions may be used to treat a mood disorder including Gender Dysphoria, *e.g.*, Gender Dysphoria.

[0075] In embodiments provided are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of (6a*R*,9*R*)-*N*,*N*-diethyl-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**1**) or a pharmaceutically acceptable salt thereof.



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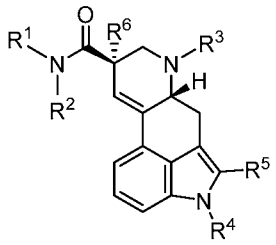
[0076] In other embodiments, provided are a method of treating a mood disorder comprising administering to a patient in need thereof a pharmaceutical composition comprising an effective amount of a compound according to Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein

R^1 is C_1-C_6 alkyl or 3-7 membered carbocyclyl, wherein R^1 is optionally substituted with one or more halogen or C_1-C_6 alkyl;

R^2 is hydrogen or C_1-C_6 alkyl, wherein R^2 is optionally substituted with one or more halogen or C_1-C_6 alkyl; or

wherein R^1 and R^2 can be taken together with the atom on which they are attached to form an optionally substituted 3-7 membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O, and S, wherein the heterocyclyl is optionally substituted with one or more fluoro or C_1-C_6 alkyl;

R^3 is selected from the group consisting of C_2-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, --CH_2-(cyclopropyl), and 3-7 membered cycloalkyl,

wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, and -OMe;

or

R^3 is selected from the group consisting of –(C_1-C_2 alkyl)-phenyl and –(C_1-C_2 alkyl)-(6-membered heteroaryl),

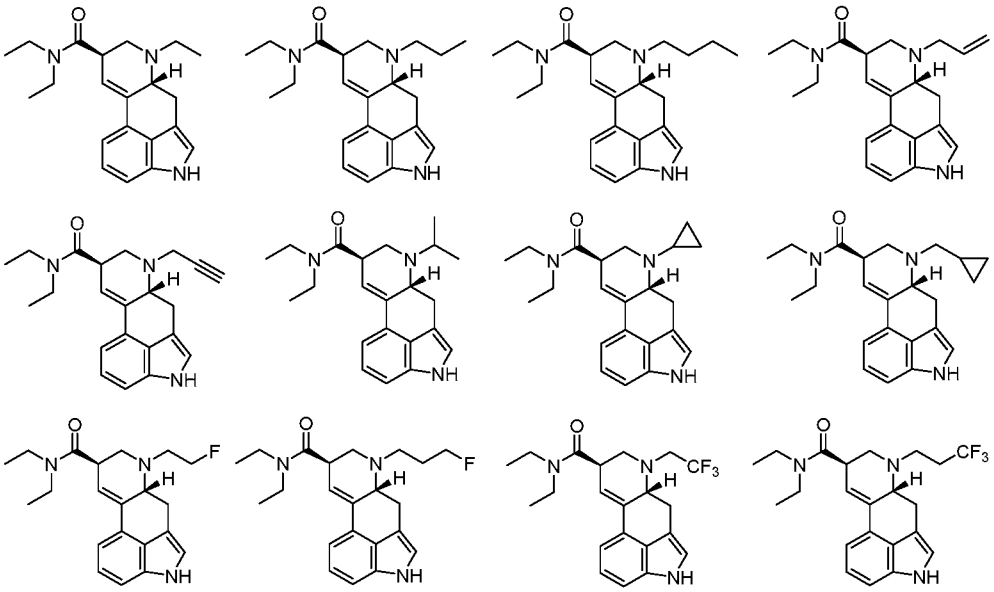
wherein C_1-C_2 alkyl is optionally substituted with one or more fluoro, hydroxyl, and -Ome, and wherein phenyl and 6-membered heteroaryl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, -NO_2, -NH_2, -C(O)NH_2, C_1-C_4 alkyl, C_3-C_5 cycloalkyl, and C_1-C_4 alkoxy;

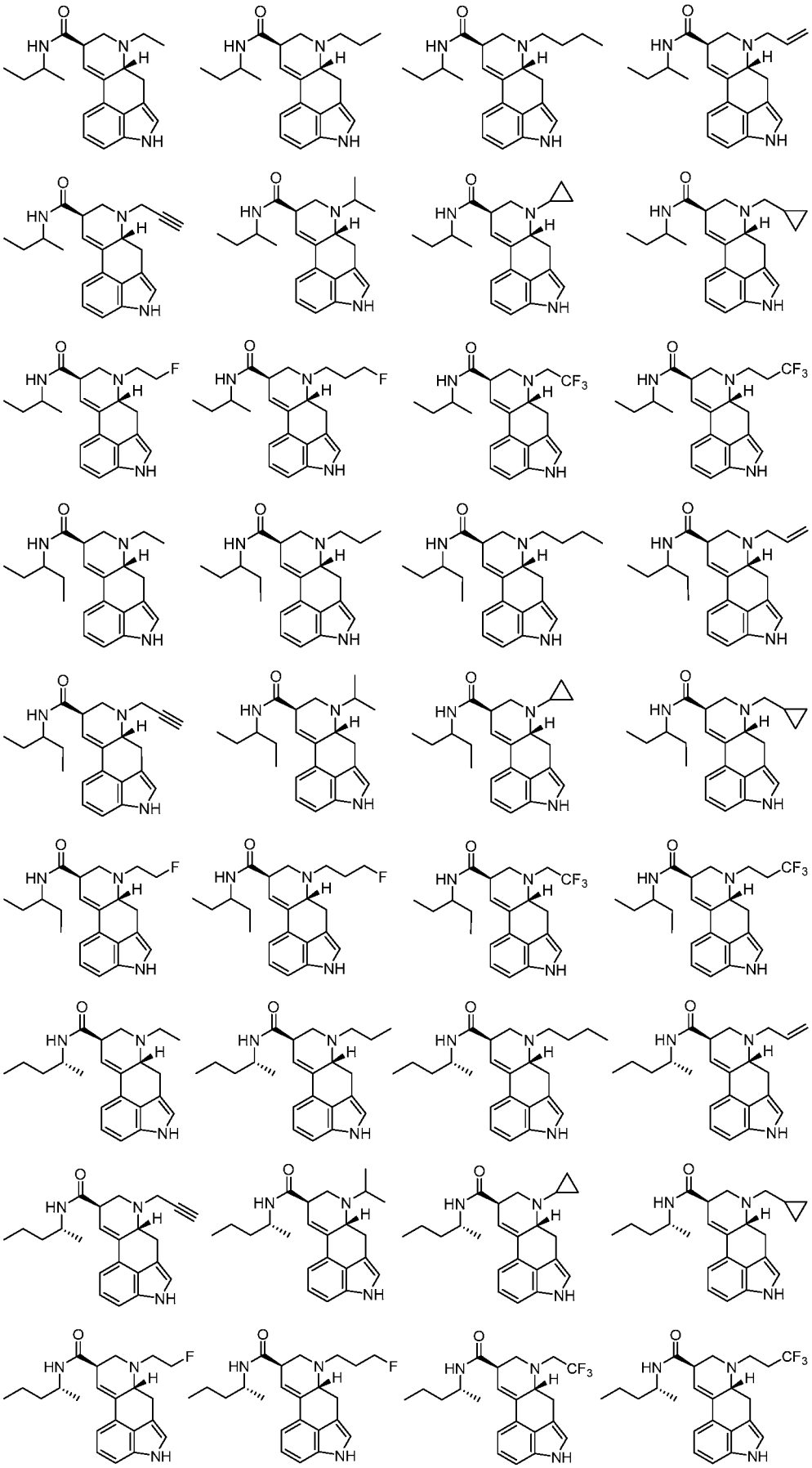
R^4 is hydrogen or -C(O)(C_1-C_8 alkyl);

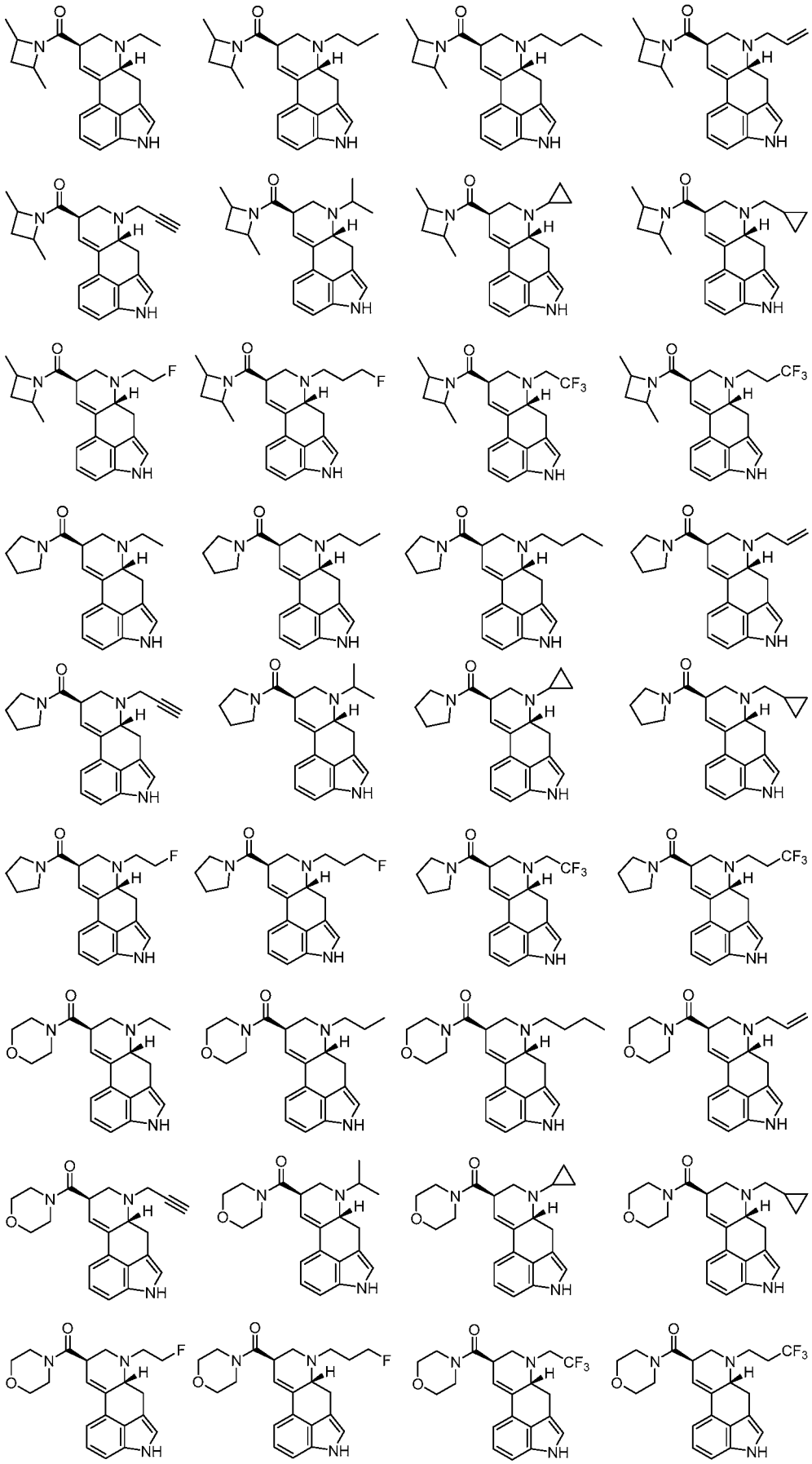
R^5 is hydrogen or halogen;

R^6 is hydrogen or deuterium.

[0077] In other embodiments provided are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of a compound selected from the group consisting of:

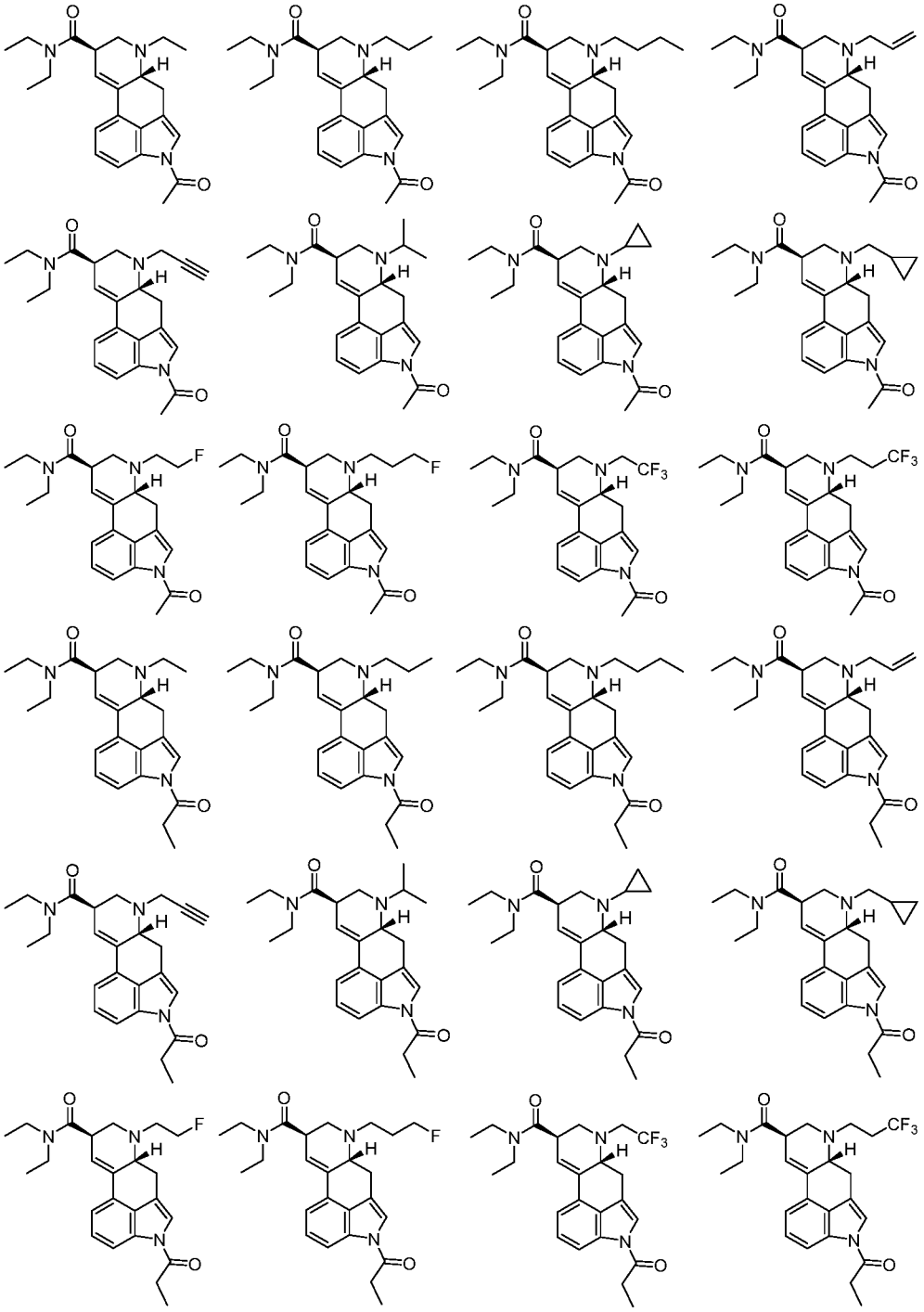






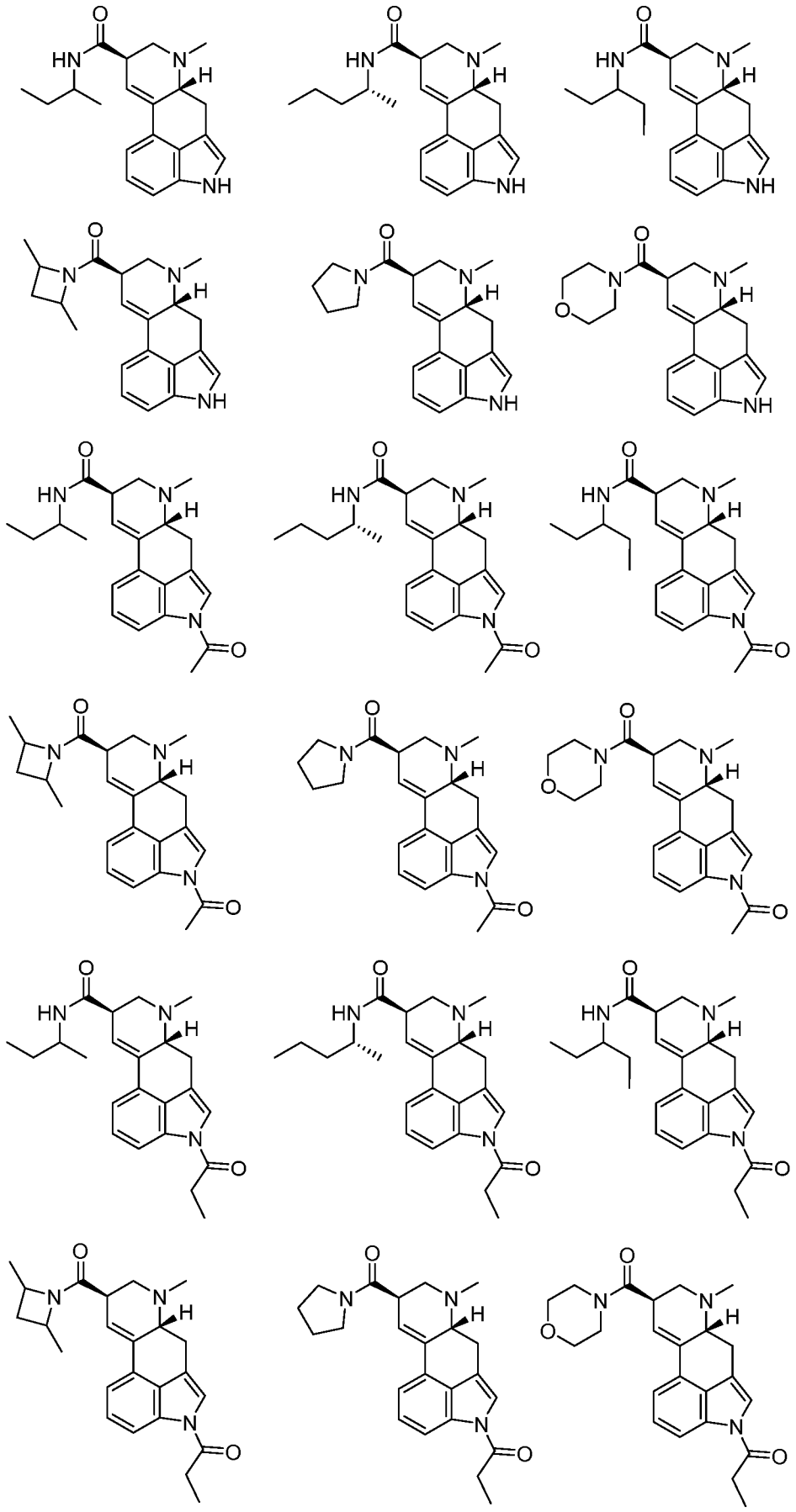
or a pharmaceutically acceptable salt thereof.

[0078] In other embodiments provided are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of a compound selected from the group consisting of:



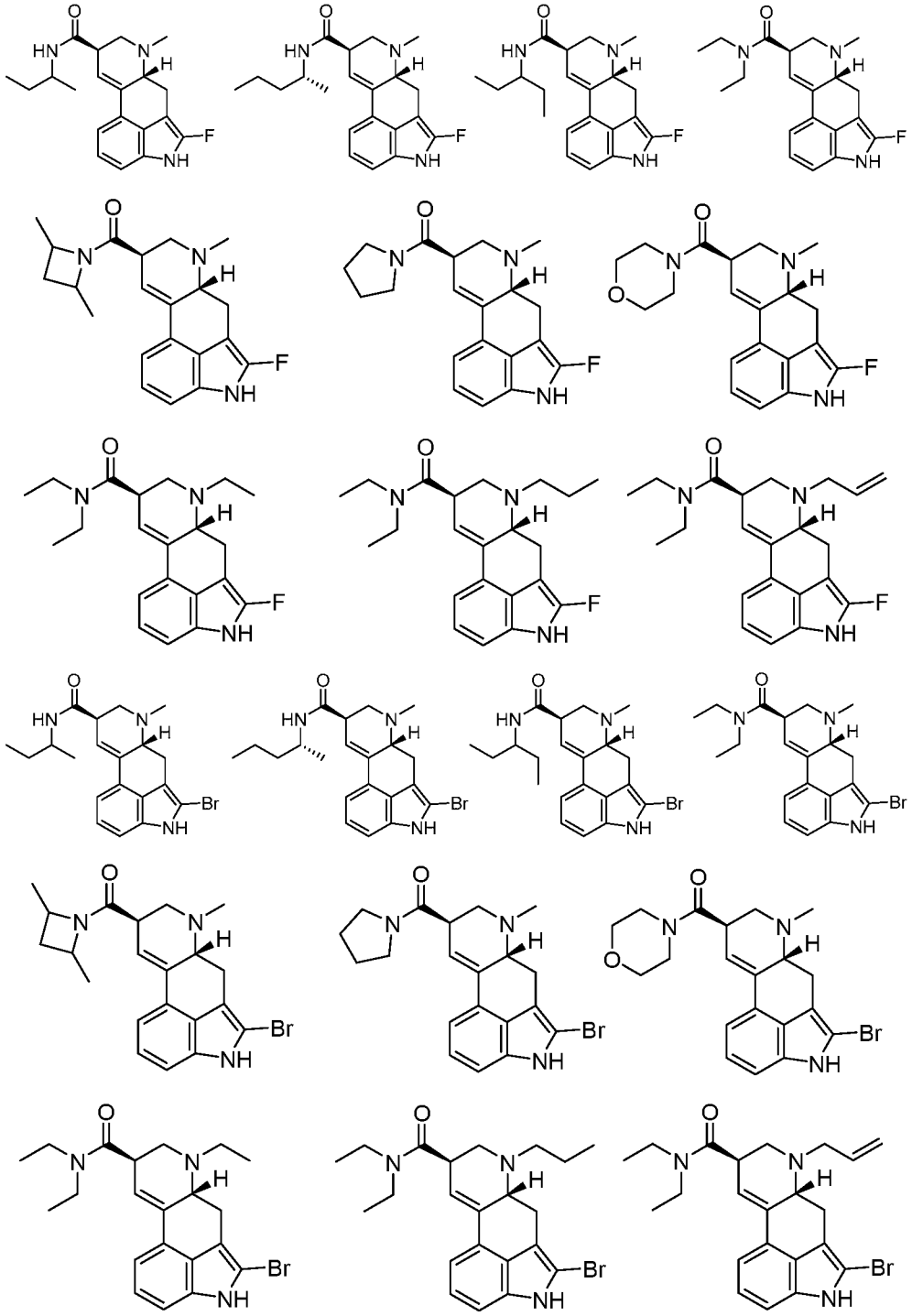
or a pharmaceutically acceptable salt thereof.

[0079] In other embodiments provided are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of a compound selected from the group consisting of:



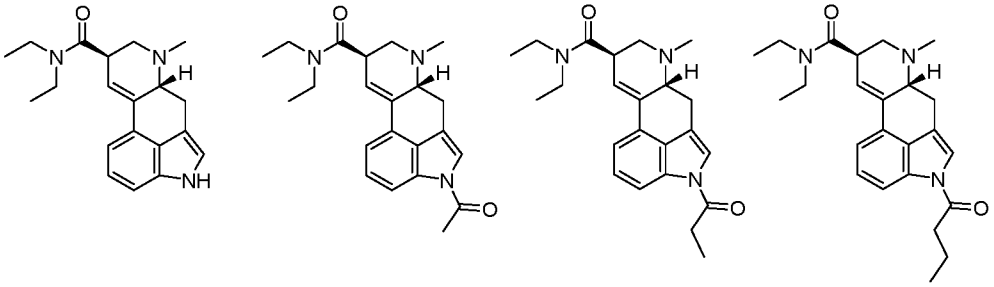
or a pharmaceutically acceptable salt thereof.

[0080] In other embodiments provided are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of a compound selected from the group consisting of:



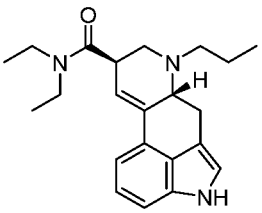
or a pharmaceutically acceptable salt thereof.

[0081] In other embodiments provided are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of a compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

[0082] In other embodiments provided are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of a compound selected from the group consisting of: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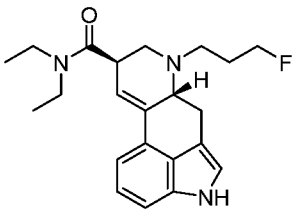
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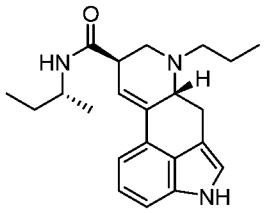
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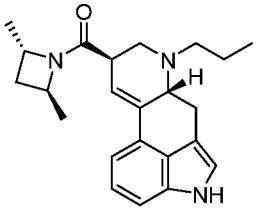
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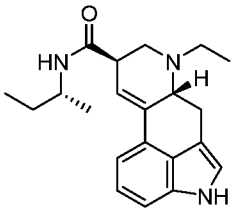
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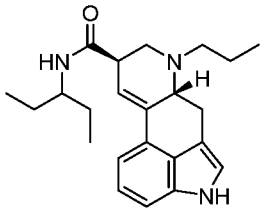
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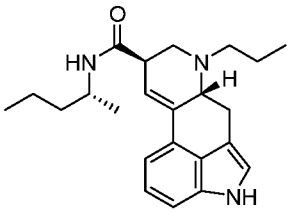
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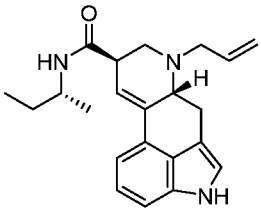
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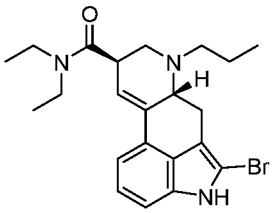
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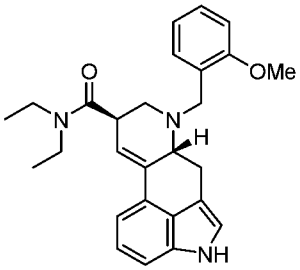
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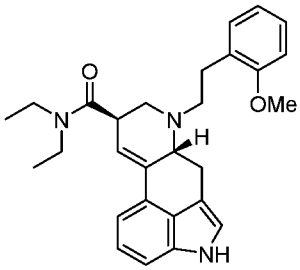
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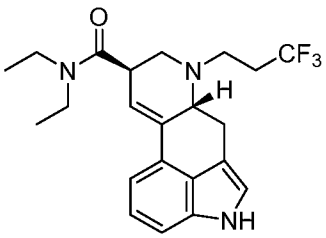
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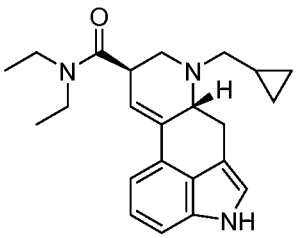
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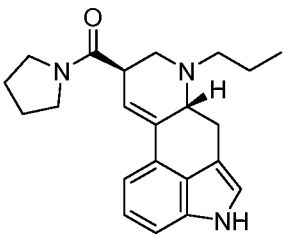
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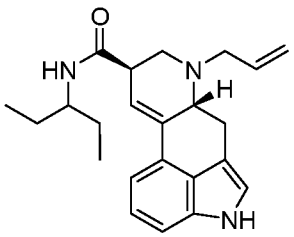
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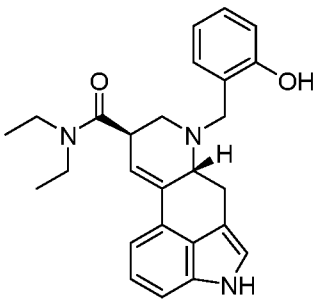
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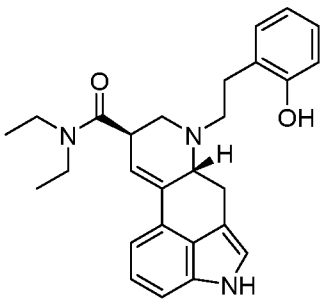
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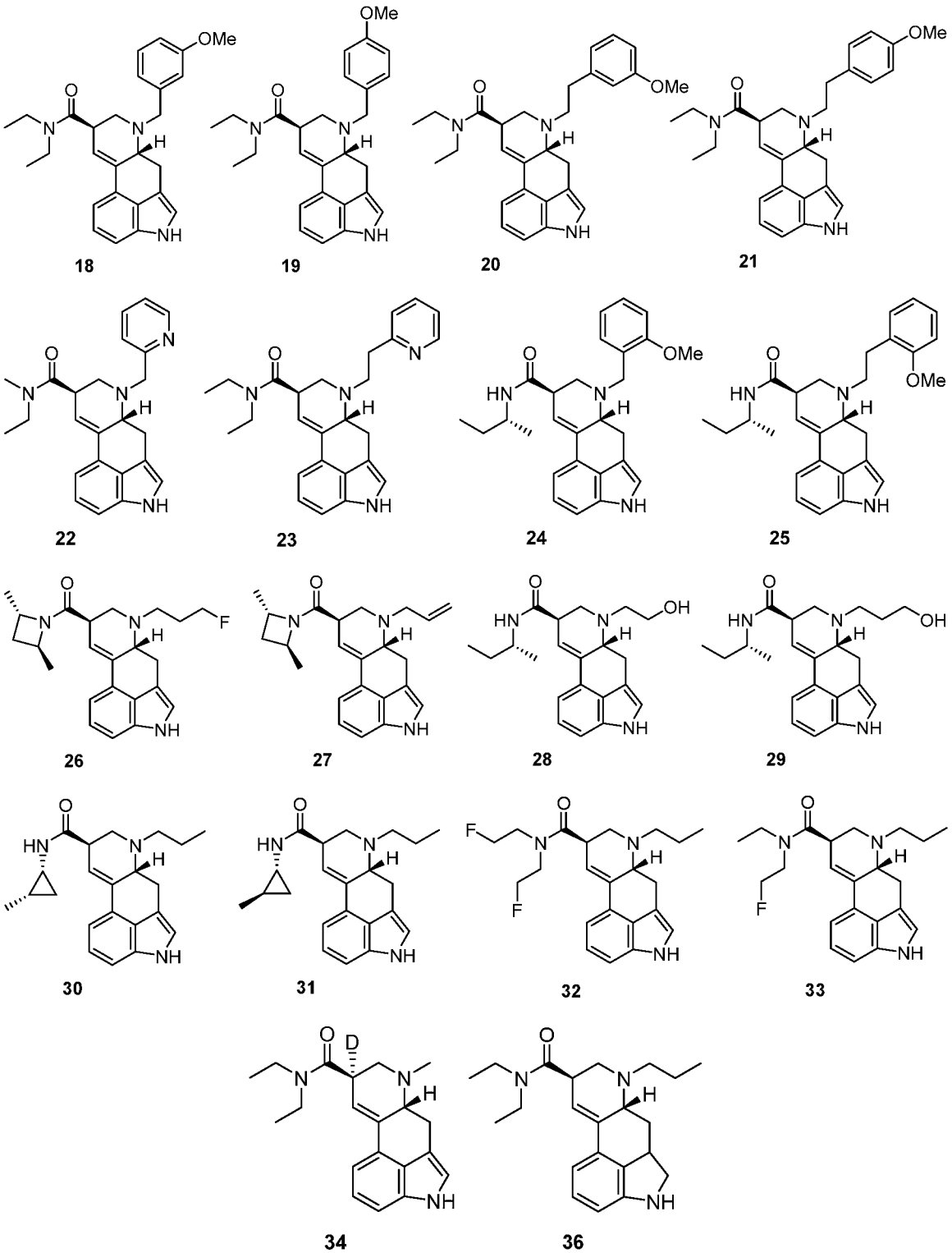


or a pharmaceutically acceptable salt thereof.

[0083] In other embodiments provided are methods and compositions for treating migraine or cluster headache by administering a therapeutically effective amount of a compound disclosed herein to a patient in need thereof.

[0084] In embodiments, methods include treating a mood disorder, *e.g.*, a depressive disorder, by administering to a patient in need thereof a pharmaceutical composition including about 0.001 mg to about 20 mg of a compound disclosed herein. In embodiments, doses may be, *e.g.*, in the range of about 0.001 to 20 mg, 0.001 to 10 mg, 0.001 to 5 mg, 0.001 to 2 mg, 0.001 to 1 mg, 0.001 to 0.5 mg, 0.001 to 0.25 mg, 0.001 to 0.15 mg, 0.001 to 0.1 mg, 0.001 to 0.075 mg, 0.001 to 0.05 mg, 0.001 to 0.025 mg, 0.001 to 0.015 mg, 0.001 to 0.01 mg, 0.01 to 5 mg, 0.01 to 2 mg, 0.01 to 1 mg, 0.01 to 0.5 mg, 0.01 to 0.25 mg, 0.01 to 0.15 mg, 0.01 to 0.1 mg, 0.01 to 0.075 mg, 0.01 to 0.05 mg, 0.01 to 0.025 mg, 0.01 to 0.015 mg, 0.025 to 2 mg, 0.025 to 1 mg, 0.025 to 0.5 mg, 0.025 to 0.25 mg, 0.025 to 0.15 mg, 0.025 to 0.1 mg, 0.025 to 0.075 mg, 0.025 to 0.05 mg, 0.05 to 2 mg, 0.05 to 1 mg, 0.05 to 0.5 mg, 0.05 to 0.25 mg, 0.05 to 0.15 mg, 0.05 to 0.1 mg, 0.05 to 0.075 mg, 0.1 to 2 mg, 0.1 to 1 mg, 0.1 to 0.5 mg, 0.1 to 0.25 mg, 0.1 to 0.15 mg, with doses of, *e.g.*, about 0.001 mg, 0.0025 mg, 0.005 mg, 0.0075 mg, 0.01 mg, 0.015 mg, 0.02 mg, 0.025 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.075 mg, 0.1 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg being examples.

[0085] In specific embodiments, dosages may include amounts of a compound disclosed herein in the range of about, *e.g.*, 0.001 to 20 mg, 0.001 to 10 mg, 0.001 to 5 mg, 0.001 to 2 mg, 0.001 to 1 mg, 0.001 to 0.5 mg, 0.001 to 0.25 mg, 0.001 to 0.15 mg, 0.001 to 0.1 mg, 0.001 to 0.075 mg, 0.001 to 0.05 mg, 0.001 to 0.025 mg, 0.001 to 0.015 mg, 0.001 to 0.01 mg, 0.01 to 5 mg, 0.01 to 2 mg, 0.01 to 1 mg, 0.01 to 0.5 mg, 0.01 to 0.25 mg, 0.01 to 0.15 mg, 0.01 to 0.1 mg, 0.01 to 0.075 mg, 0.01 to 0.05 mg, 0.01 to 0.025 mg, 0.01 to 0.015 mg, 0.025 to 2 mg, 0.025 to 1 mg, 0.025 to 0.5 mg, 0.025 to 0.25 mg, 0.025 to 0.15 mg, 0.025 to 0.1 mg, 0.025 to 0.075 mg, 0.025 to 0.05 mg, 0.05 to 2 mg, 0.05 to 1 mg, 0.05 to 0.5 mg, 0.05 to 0.25 mg, 0.05 to 0.15 mg, 0.05 to 0.1 mg, 0.05 to 0.075 mg, 0.1 to 2 mg, 0.1 to 1 mg, 0.1 to 0.5 mg, 0.1 to 0.25 mg, 0.1 to 0.15 mg, with doses of 0.001 mg, 0.0025 mg, 0.005 mg, 0.0075 mg, 0.01 mg, 0.015 mg, 0.02 mg, 0.025 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.075 mg, 0.1 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg being specific examples of doses.

[0086] Typically, dosages of a compound disclosed herein are administered once, twice, three or four times daily, every other day, every three days, twice weekly, once weekly, twice monthly, or once monthly to a patient in need thereof. In embodiments, the dosage is about, *e.g.*, 0.001-20 mg/day, or 0.001-10 mg/day, or 0.001-1 mg/day, or 0.001-0.25 mg/day, for example 20 mg/day, 5 mg/day, 1 mg/day, 0.5 mg/day, 0.25 mg/day, 0.15 mg/day, 0.1 mg/day, 0.05 mg/day, 0.025 mg/day, 0.01 mg/day, 0.005 mg/day, or 0.001 mg/day. In

embodiments, the foregoing example dose ranges may be delivered over intervals longer than one day, e.g., 0.001-20 mg/week.

[0087] In embodiments, pharmaceutical compositions for parenteral or inhalation, *e.g.*, a spray or mist, administration of a compound disclosed herein having a concentration of about 0.001 mg/mL to about 100 mg/mL. In embodiments, the compositions include a compound disclosed herein, at a concentration of, *e.g.*, about 0.05 mg/mL to about 100 mg/mL, about 0.05 mg/mL to about 50 mg/mL, about 0.05 mg/mL to about 25 mg/mL, about 0.05 mg/mL to about 10 mg/mL, about 0.05 mg/mL to about 5 mg/mL, about 0.005 mg/mL to about 1 mg/mL, about 0.005 mg/mL to about 0.25 mg/mL, about 0.005 mg/mL to about 0.05 mg/mL, about 0.005 mg/mL to about 0.025 mg/mL, about 0.001 mg/mL to about 0.05 mg/mL, about 0.001 mg/mL to about 0.025 mg/mL, about 0.001 mg/mL to about 0.01 mg/mL, or about 0.001 mg/mL to about 0.005 mg/mL.

[0088] In embodiments, the composition of a compound disclosed herein at a concentration of, *e.g.*, about 0.05 mg/mL to about 100 mg/mL, about 0.05 mg/mL to about 50 mg/mL, about 0.05 mg/mL to about 25 mg/mL, about 0.05 mg/mL to about 10 mg/mL, about 0.05 mg/mL to about 5 mg/mL, about 0.005 mg/mL to about 1 mg/mL, about 0.005 mg/mL to about 0.25 mg/mL, about 0.005 mg/mL to about 0.05 mg/mL, about 0.005 mg/mL to about 0.025 mg/mL, about 0.001 mg/mL to about 0.05 mg/mL, about 0.001 mg/mL to about 0.025 mg/mL, about 0.001 mg/mL to about 0.01 mg/mL, or about 0.001 mg/mL to about 0.005 mg/mL. In embodiments, the pharmaceutical compositions are formulated as a total volume of about, *e.g.*, 0.1 mL, 0.25 mL, 0.5 mL, 1 mL, 2 mL, 5 mL, 10 mL, 20 mL, 25 mL, 50 mL, 100 mL, 200 mL, 250 mL, or 500 mL.

[0089] Typically, dosages may be administered to a subject once, twice, three times or four times daily, every other day, every three days, twice weekly, once weekly, twice monthly, once monthly, every 2 months, every 3 months, every 4 months, every 6 months, or every 12 months. In embodiments, a compound disclosed herein is administered to a subject once in the morning, or once in the evening. In embodiments, a compound disclosed herein is administered to a subject once in the morning, and once in the evening. In embodiments, a compound disclosed herein is administered to a subject three times a day (*e.g.*, at breakfast, lunch, and dinner), at a dose, *e.g.*, of 0.005 mg/administration (*e.g.*, 0.015 mg/day).

[0090] In embodiments, an ergoline a compound disclosed herein is administered to a subject at a dose of 0.005 mg/day in one or more doses. In embodiments, a compound disclosed herein is administered to a subject at a dose of 0.01 mg/day in one or more doses. In embodiments, a compound disclosed herein is administered to a subject at a dose of 0.025 mg/day in one or more doses. In embodiments, a compound disclosed herein is administered to

a subject at a dose of 0.05 mg/day in one or more doses. In embodiments, a compound disclosed herein is administered to a subject at a dose of 0.1 mg/day in one or more doses. In embodiments, a compound disclosed herein is administered to a subject at a dose of 0.15 mg/day in one or more doses. In embodiments, a compound disclosed herein is administered to a subject at a dose of 0.2 mg/day in one or more doses. In embodiments, a compound disclosed herein is administered to a subject at a dose of 0.25 mg/day in one or more doses. In embodiments, a compound disclosed herein is administered to a subject at a dose of 0.3 mg/day in one or more doses. In embodiments, a compound disclosed herein is administered to a subject at a dose of 0.4 mg/day in one or more doses. In embodiments, a compound disclosed herein is administered to a subject at a dose of 0.5 mg/day in one or more doses.

[0091] In embodiments, the dosage of a compound disclosed herein is 0.000025-0.25 mg/kg, 0.0001-0.1 mg/kg, 0.001-0.1 mg/kg or 0.01-0.25 mg/kg once, twice, three times or four times daily. For example, in embodiments, the dosage is 0.000025 mg/kg, 0.00005 mg/kg, 0.0001 mg/kg, 0.0005 mg/kg, 0.001 mg/kg, 0.002 mg/kg, 0.003 mg/kg, 0.004 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.05 mg/kg, once, twice, three times or four times daily. In embodiments, a subject is administered a total daily dose of 0.001 mg to 20 mg of a compound disclosed herein once, twice, three times, or four times daily. In embodiments, the total amount administered to a subject in 24-hour period is, *e.g.*, 0.001 mg, 0.0025 mg, 0.005 mg, 0.0075 mg, 0.01 mg, 0.015 mg, 0.02 mg, 0.025 mg, 0.03 mg, 0.04 mg, 0.05 mg, 0.075 mg, 0.1 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, or 20 mg. In embodiments, the subject may be started at a low dose and the dosage is escalated. In embodiments, the subject may be started at a high dose and the dosage is decreased.

[0092] In embodiments, a compound disclosed herein is administered to a patient under the supervision of a healthcare provider.

[0093] In embodiments, a compound disclosed herein is administered to a patient under the supervision of a healthcare provider at a clinic specializing in the delivery of psychoactive treatments.

[0094] In embodiments, a compound disclosed herein is administered to a patient under the supervision of a healthcare provider at a high dose intended to induce a psychedelic experience in the subject, *e.g.*, 0.05 mg, 0.075 mg, 0.1 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, or 1 mg.

[0095] In embodiments, the administration to a patient of a high dose under the supervision of a healthcare provider occurs periodically in order to maintain a therapeutic effect

in the patient, *e.g.*, once weekly, twice monthly, once monthly, every 2 months, every 3 months, every 4 months, every 6 months, or every 12 months.

[0096] In embodiments, a compound disclosed herein is administered by a patient on their own at home or otherwise away from the supervision of a healthcare provider.

[0097] In embodiments, a compound disclosed herein is administered by a patient on their own at home or otherwise away from the supervision of a healthcare provider at a low dose intended to be sub-perceptual or to induce threshold psychoactive effects, *e.g.*, 0.001 mg, 0.0025 mg, 0.005 mg, 0.0075 mg, 0.01 mg, 0.015 mg, 0.02 mg, 0.025 mg, 0.03 mg, or 0.04 mg.

[0098] In embodiments, the administration by a patient of a low dose on their own occurs periodically in order to maintain a therapeutic effect in the patient, *e.g.*, daily, every other day, every three days, twice weekly, once weekly, twice monthly, or once monthly.

[0099] The compounds of the present disclosure may be administered to patients (animals and humans) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. It will be appreciated that the dose required for use in any particular application will vary from patient to patient, not only with the particular compound or composition selected, but also with the route of administration, the nature of the condition being treated, the age and condition of the patient, concurrent medication or special diets then being followed by the patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician. For treating clinical conditions and diseases noted above, a compound of this present disclosure may be administered orally, subcutaneously, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Parenteral administration may include subcutaneous injections, intravenous or intramuscular injections or infusion techniques.

[00100] Treatment can be continued for as long or as short a period as desired. The compositions may be administered on a regimen of, for example, one to four or more times per day. A suitable treatment period can be, for example, at least about one week, at least about two weeks, at least about one month, at least about six months, at least about 1 year, or indefinitely. A treatment period can terminate when a desired result, for example a decrease in symptoms of a psychiatric disorder, is achieved. A treatment regimen can include a corrective phase, during which a dose sufficient to provide symptomatic relief is administered, and can be followed by a maintenance phase, during which a lower dose sufficient to prevent a return of symptoms is administered. A suitable maintenance dose is likely to be found in the lower parts of the dose ranges provided herein, but corrective and maintenance doses can readily be established for individual subjects by those of skill in the art without undue experimentation,

based on the disclosure herein. Maintenance doses can be employed to maintain remission in subjects whose symptoms have been previously controlled by other means, including treatments employing other pharmacological agents.

III. Pharmaceutical Compositions and Kits

[00101] Another aspect of the present disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with a pharmaceutically acceptable carrier. In particular, the present disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical, buccal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral or subcutaneous administration.

[00102] Exemplary pharmaceutical compositions of this present disclosure may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compounds of the present disclosure, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[00103] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, *e.g.,* conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.,* water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present disclosure, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[00104] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition 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, acetyl 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; and (10) coloring agents. In the case of capsules, tablets and pills, the 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.

[00105] 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 subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, 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.

[00106] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[00107] Suspensions, in addition to the subject composition, 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.

[00108] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[00109] Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[00110] The ointments, pastes, creams and gels may contain, in addition to a subject composition, 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.

[00111] Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00112] Compositions and compounds of the present disclosure may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[00113] Pharmaceutical compositions of this present disclosure suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous 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.

[00114] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the present disclosure 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 and cyclodextrins. Proper fluidity may 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

[00115] In another aspect, the present disclosure provides enteral pharmaceutical formulations including a disclosed compound and an enteric material; and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-

chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal collophorium, and several commercially available enteric dispersion systems (e. g. , Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives of the present disclosure.

[00116] Advantageously, the present disclosure also provides kits for use by a e.g., a consumer in need of treatment with a disclosed compound. Such kits include a suitable dosage form such as those described above and instructions describing the method of using such dosage form to treat a medical disorder, for example, a psychiatric disease or disorder. The instructions would direct the consumer or medical personnel to administer the dosage form according to administration modes known to those skilled in the art. Such kits could advantageously be packaged and sold in single or multiple kit units. An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[00117] It may be desirable to provide a memory aid on the kit, *e.g.,* in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.,* as follows "First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a first compound can consist of one

tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

[00118] Also contemplated herein are methods and compositions that include a second active agent, or administering a second active agent.

EXEMPLIFICATION

[00119] The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials.

[00120] At least some of the compounds identified as "Intermediates" herein are contemplated as compounds of the present disclosure.

General Procedures

[00121] The compounds of the present disclosure may be prepared by techniques well known in organic synthesis and familiar to a practitioner ordinarily skilled in the art. For example, the compounds may be prepared by the chemical transformations described in the following examples. However, these may not be the only means by which to synthesize or obtain the desired compounds.

Abbreviations

AcOH = acetic acid

DCM = dichloromethane

DMF = dimethyl formamide

TEA = triethylamine

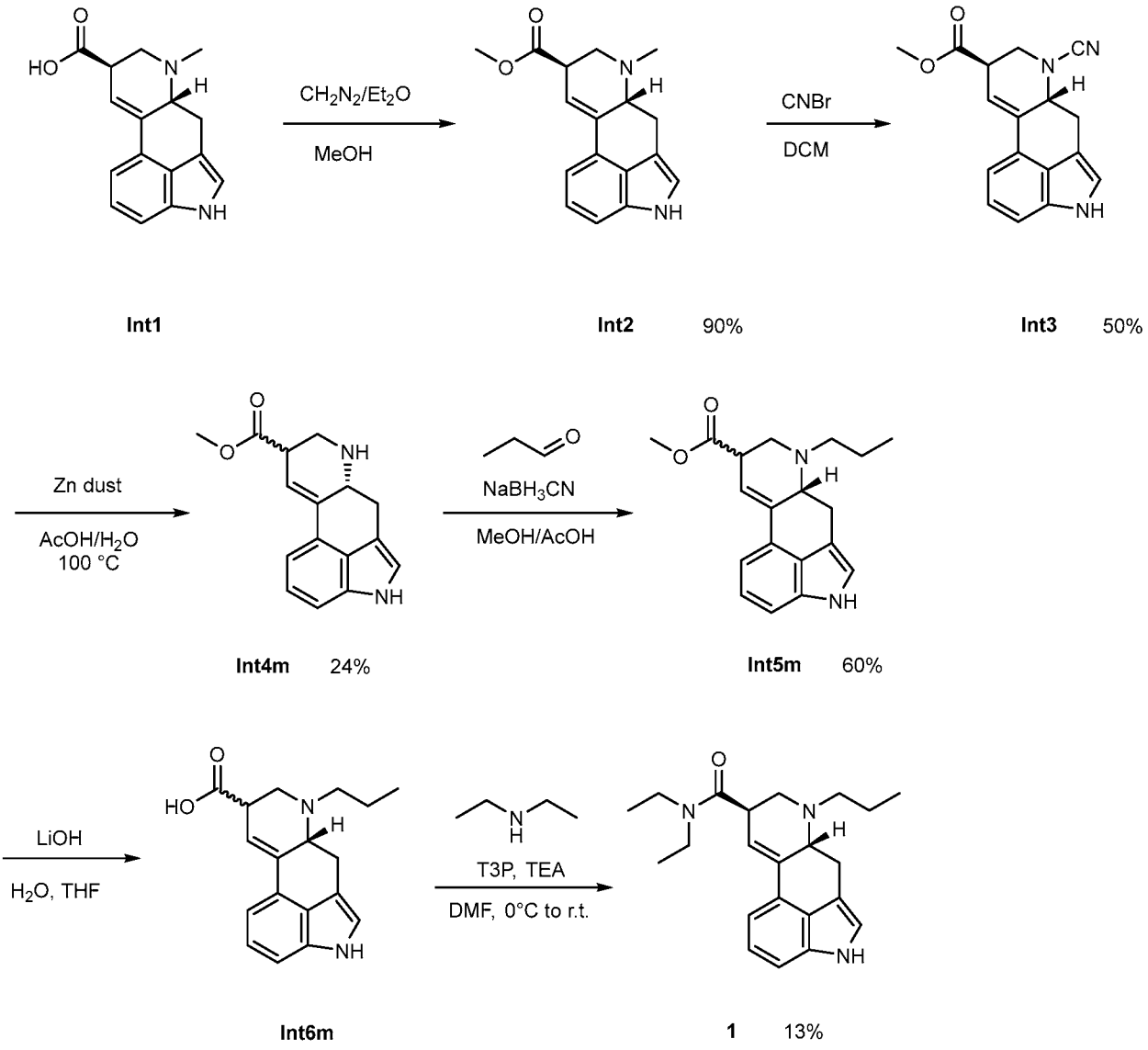
T3P = propylphosphonic anhydride

mCPBA = meta-chloroperoxybenzoic acid

HFBA = heptafluorobutyric acid

Example 1: Preparation of (6aR,9R)-N,N-diethyl-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (1)

Reaction Scheme (Method 1):



Synthetic Protocols (Method 1):

[00122] To a suspension of (6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid (**Int1**, 2.01 g, 7.5 mmol) in absolute methanol (300 mL) was added a solution of diazomethane in diethyl ether (0.5 M, 75.0 mmol, 150 mL) under vigorous stirring. The resulting mixture was stirred until it became clear, then concentrated *in vacuo* and

suspended in dichloromethane (100 mL). The solids were removed by filtration, the filter cake was washed with dichloromethane (3 x 30 mL), and the filtrate was concentrated *in vacuo* to provide methyl (6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylate (**Int2**) as an off-white foam.
Yield: 1.92 g (90%).
LC-MS purity: 98% (ELSD).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 20:80 to 100:0 + 0.1% FA in 10 min): 6.82 min.
LC-MS m/z: 283.2 $(M+H)^+$.

[00123] Methyl (6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylate (**Int2**, 564 mg, 2.0 mmol) was dissolved in dry dichloromethane (30 mL) and purged with argon. Cyanogen bromide (1.14 g, 10.72 mmol) was added in one portion and the obtained solution was stirred for 4.5 hours, at which point LC/MS showed full conversion. Silica gel (10 g) was added, and the resulting suspension was concentrated *in vacuo*. The product was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: cyclohexane/ethyl acetate 80:20 to 50:50) to give methyl (6a*R*,9*R*)-7-cyano-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylate (**Int3**) as a colorless foam.
Yield: 300 mg (50%).
LC-MS purity: 98% (ELSD).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 05:95 to 100:0 + 0.1% FA in 10 min): 8.63 min.
LC-MS m/z: 294.1 $(M+H)^+$.

[00124] Methyl (6a*R*,9*R*)-7-cyano-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylate (**Int3**, 205 mg, 0.70 mmol) was dissolved in glacial acetic acid (5 mL) and zinc dust (600 mg) and water (0.5 mL) were added. The resulting mixture was purged with argon, heated to 100 °C, and stirred for 3 hours, at which point LC/MS showed full consumption of starting material. The reaction was cooled to 0 °C, partitioned between saturated sodium bicarbonate (100 mL) and dichloromethane (100 mL), and extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 95:5 to 90:10) to afford methyl (6a*R*)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylate (**Int4m**) (mixture of diastereomers; epimers at position 9) as an off-white foam.

Yield: 51 mg (24%).
LC-MS purity: 85% (ELSD).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 05:95 to 100:0 + 0.1% FA in 10 min): 2.87 min.
LC-MS m/z: 269.2 $(M+H)^+$.

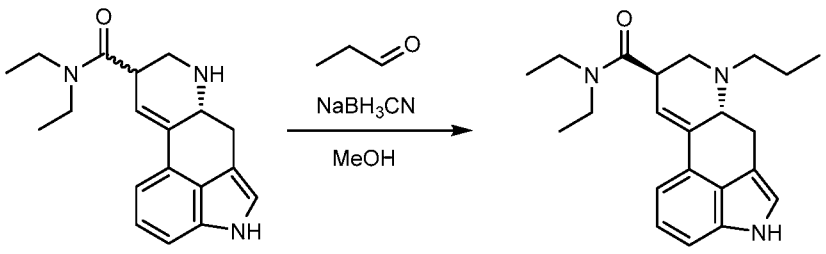
[00125] A solution of methyl (6a*R*)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylate (**Int4m**, 75 mg, 0.280 mmol; mixture of epimers at position 9) and propanal (88 µL, 1.40 mmol) in methanol (10 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (88.0 mg, 1.40 mmol) was added, the mixture was stirred for 5 minutes, and then acetic acid (300 µL) was introduced. After stirring at 0 °C for 1 hour, the solvent was evaporated, the residue was partitioned between dichloromethane (100 mL) and saturated sodium bicarbonate (100 mL), and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 99:1 to 98:2) to afford methyl (6a*R*)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylate (**Int5m**) (mixture of diastereomers; epimers at position 9) as an off-white foam.
Yield: 58 mg (67%).
LC-MS purity: 99% (ELSD), 95% (UV_{310}).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 05:95 to 100:0 + 0.1% FA in 10 min): 2.95 min.
LC-MS m/z: 311.2 $(M+H)^+$.

[00126] Methyl (6a*R*)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylate (**Int5m**, 58.7 mg, 0.189 mmol; mixture of epimers at position 9) was dissolved in freshly distilled tetrahydrofuran (10 mL) and water (1 mL) and purged with argon. Lithium hydroxide (12.46 mg, 0.297 mmol) in water (500 µL) was added and resulting mixture was stirred overnight, at which point LC/MS showed full conversion. The reaction mixture was neutralized with ice-cold methanesulfonic acid (29.2 mg, 0.297 mmol) in water (1 mL), concentrated *in vacuo*, and the obtained off-white residue (**Int6m**) (mixture of diastereomers; epimers at position 9) was used in the next step without further purification.
Yield: 58 mg (crude).
LC-MS purity: 100% (ELSD), 95% (UV_{310}).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 05:95 to 100:0 + 0.1% FA in 10 min): 7.08 min; 7.30 min.
LC-MS m/z: 297.2 $(M+H)^+$.

[00127] Crude (6a*R*)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid (**Int6m**, 55 mg; mixture of epimers at position 9) was dissolved in dry *N,N*-dimethylformamide (3 mL) and the solution was purged with argon and cooled to 0 °C. Triethylamine (106 µL, 0.760 mmol), diethylamine (60 µL, 0.570 mmol), and propanephosphonic acid anhydride (T3P, 332 µL, 0.570 mmol, 50% in DMF) were added and the resulting mixture was stirred for 1 hour. Ice-cold water (50 mL) was added, followed by ice-cold 1% ammonium hydroxide solution (5 mL), and the aqueous phase was extracted with dichloromethane (5x30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was purified by preparative LC/MS (Sinergy Polar RP C18, 5µm, 21.2 mm x 150 mm, acetonitrile/water 5:95 + 0.1% acetic acid) to give the title compound as a solution in acetonitrile/water. Freeze drying provided 10 mg of (6a*R*,9*R*)-9-(diethylcarbamoyl)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-7-ium acetate (**1**) as a beige powder.
Yield: 10 mg (13% over two steps).
^{1}H NMR spectrum (of acetate salt; acetate peak obscured by solvent peak) (300 MHz, CD_3CN, δ_H): 9.00 (s, 1H), 7.22 (dd, J = 6.8, 1.9 Hz, 1H), 7.14 – 7.05 (m, 2H), 6.98 – 6.84 (m, 2H), 6.30 (s, 1H), 3.78 – 3.68 (m, 1H), 3.56 – 3.30 (m, 6H), 3.13 (dd, J =10.9, 4.5 Hz, 1H), 2.93 – 2.82 (m, 1H), 2.69 – 2.42 (m, 4H), 1.67 – 1.43 (m, 2H), 1.21 (t, J =7.1 Hz, 3H), 1.11 (t, J =7.1 Hz, 3H), 0.94 (t, J =7.3 Hz, 3H).
LC-MS purity: 97% (ELSD), 96% (UV_{310}).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 05:95 to 100:0 + 0.1% FA in 10 min): 8.20 min.
LC-MS m/z: 352.2 $(M+H)^+$.

Reaction Scheme (Method 2):



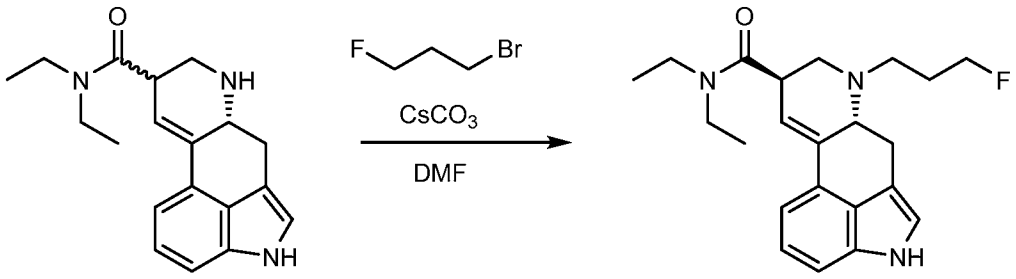
Int7m **1**

Synthetic Protocols (Method 2):

[00128] A solution of (6a*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int7m**, 45.0 mg, 0.145 mmol; mixture of epimers at position 9) and propanal (52 µL, 0.72 mmol) in methanol (10 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (46.0 mg, 0.72 mmol) was added, the mixture was stirred for 5 minutes, and then acetic acid (160 µL) was added. The reaction mixture was stirred at 0 °C for 1 hour, the solvent was removed *in vacuo*, and the residue was partitioned between dichloromethane and a 1% solution of ammonium hydroxide. The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were dried over anhydrous sodium sulfate and evaporated. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 99:1 to 98:2) to afford (6a*R*,9*R*)-*N*,*N*-diethyl-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**1**) as colorless oil.
Yield: 6 mg (11%).
^{1}H NMR spectrum (of acetate salt; acetate peak obscured by solvent peak) (300 MHz, CD_3CN, δ_H): 9.00 (s, 1H), 7.22 (dd, *J* =6.8, 1.9 Hz, 1H), 7.14 – 7.05 (m, 2H), 6.98 – 6.84 (m, 2H), 6.30 (s, 1H), 3.78 – 3.68 (m, 1H), 3.56 – 3.30 (m, 6H), 3.13 (dd, *J* =10.9, 4.5 Hz, 1H), 2.93 – 2.82 (m, 1H), 2.69 – 2.42 (m, 4H), 1.67 – 1.43 (m, 2H), 1.21 (t, *J* =7.1 Hz, 3H), 1.11 (t, *J* =7.1 Hz, 3H), 0.94 (t, *J* =7.3 Hz, 3H).
LC-MS purity: 96% (ELSD), 93% (UV_{310}).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 20:80 to 100:0 + 0.1% FA in 10 min): 5.66 min.
LC-MS m/z: 352.2 $(M+H)^+$.

Example 2: Preparation of (6aR,9R)-N,N-diethyl-7-(3-fluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (2) and (6aR,9S)-N,N-diethyl-7-(3-fluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (2a)

Reaction Scheme (Method 1):



Int7m **2** 10%

Synthetic Protocols (Method 1):

[00129] A solution of (6a*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int7m**, 60.0 mg, 0.194 mmol; mixture of epimers at position 9), cesium carbonate (139 mg, 0.426 mmol), and 1-bromo-3-fluoropropane (30.2 mg, 0.214 mmol) in *N*,*N*-dimethylformamide (1 mL) was purged with argon and stirred for 96 hours at room temperature. The reaction mixture was diluted with water (50 mL), extracted with dichloromethane (3 x 50 mL), and the combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The obtained crude product was purified by silica gel chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to afford (6a*R*,9*R*)-*N*,*N*-diethyl-7-(3-fluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**2**, faster moving fluorescent band) as a colorless foam.

Yield: 6 mg (10%).

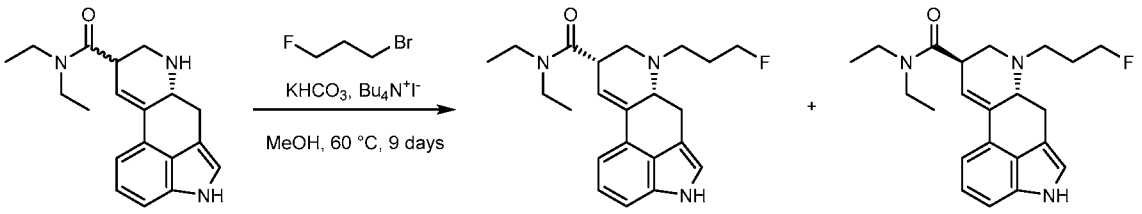
^{1}H NMR (300 MHz, $CDCl_3$, δ_H): 8.03 (s, 1H), 7.24 – 7.11 (m, 3H), 6.90 (s, 1H), 6.33 (s, 1H), 4.71 – 4.59 (m, 1H), 4.57 – 4.42 (m, 1H), 3.84 (s, 1H), 3.58 – 3.35 (m, 6H), 3.27 – 3.10 (m, 2H), 2.96 (t, J = 13.2 Hz, 1H), 2.85 – 2.64 (m, 2H), 2.13 – 1.86 (m, J = 23.6 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H).

LC-MS purity: 90% (ELSD), 81% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 5.68 min.

LC-MS m/z: 370.2 $(M+H)^+$.

Reaction Scheme (Method 2):



Int7m **2a** 12% **2** 23%

Synthetic Protocols (Method 2):

[00130] To a stirred solution of (6a*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int7m**, 45 mg, 0.145 mmol; mixture of epimers at position 9) and potassium bicarbonate (30 mg, 0.29 mmol) in methanol (2 mL) was added a solution of 1-bromo-3-fluoropropane (50 mg, 0.348 mmol) in methanol (1 mL) dropwise under argon atmosphere. Tetrabutylammonium iodide (53.5 mg, 0.145 mmol) was then introduced in one portion and the reaction was heated to 60 °C and stirred for 9 days. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (50 mL) and silica gel (10 g) was introduced. The obtained suspension was stripped of solvents *in vacuo* and subjected to silica gel chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol/ammonia 98:2:0.1) to afford (6a*R*,9*R*)-*N*,*N*-diethyl-7-(3-fluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**2**, faster moving fluorescent band) as a colorless foam and (6a*R*,9*S*)-*N*,*N*-diethyl-7-(3-fluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**2a**, slower moving fluorescent band) as a dark brownish foam.

2:

Yield: 13.9 mg (23%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 8.99 (s, 1H); 7.22 (dd, $J = J = 6.9, 1.8$, 1H); 7.14-7.03 (m, 2H); 6.95 (s, 1H); 6.30 (s, 1H); 4.75-4.58 (m, 1H); 4.57-4.41 (m, 1H); 3.79-3.65 (m, 1H); 3.57-3.29 (m, 6H); 3.18-3.01 (m, 2H); 2.71-2.45 (m, 3H); 2.02-1.82 (m, 2H); 1.20 (d, $J = J = 7.1$, 3H); 1.11 (t, $J = J = 7.1$, 3H).

LC-MS purity: 97% (ELSD), 100% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 5.47 min.

LC-MS m/z: 370.2 $(M+H)^+$.

2a:

Yield: 7.8 mg (12%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 8.98 (s, 1H); 7.20 (d, J = J = 7.3, 1H); 7.12-6.98 (m, 2H); 6.91 (s, 1H); 6.24 (s, 1H); 4.68-4.59 (m, 1H); 4.51-4.43 (m, 1H); 3.76-3.66 (m, 1H); 3.55-3.27 (m, 6H); 3.12 (dd, J = 14.6, 5.2, 1H); 3.07-2.75 (m, 5H); 1.92-1.77 (m, 2H); 1.23 (t, J = 7.1, 3H); 1.06 (t, J = 7.0, 3H).

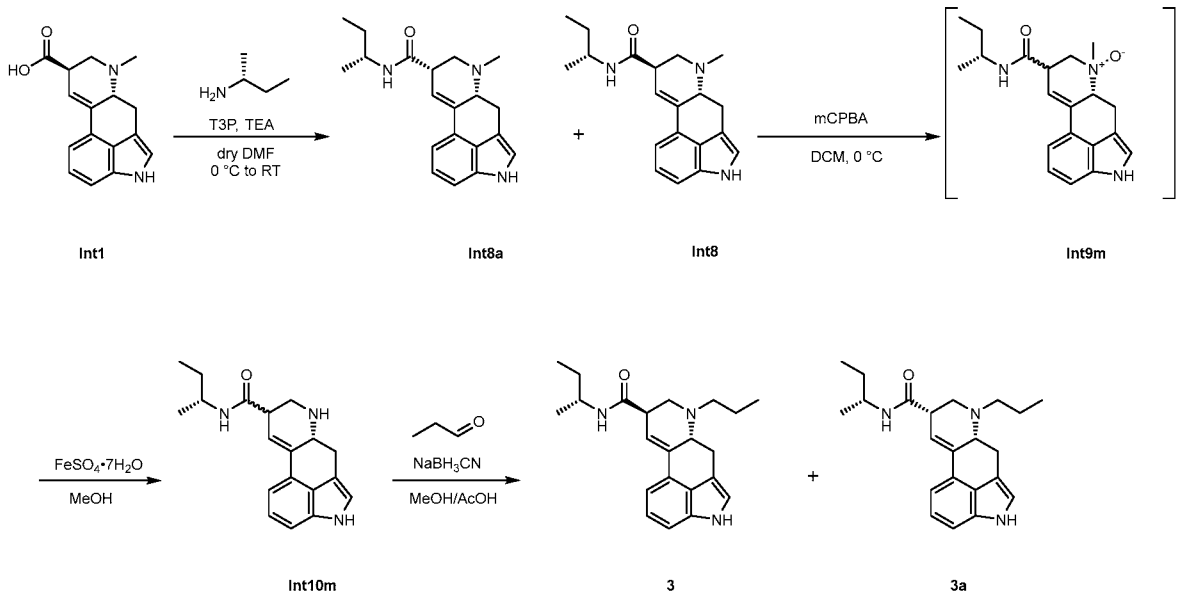
LC-MS purity: 100% (ELSD), 96% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 5.71 min.

LC-MS m/z: 370.2 $(M+H)^+$.

Example 3: Preparation of (6aR,9R)-N-((R)-sec-butyl)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (3) and (6aR,9S)-N-((R)-sec-butyl)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (3a)

Reaction Scheme:



Synthetic Protocols:

[00131] A solution of (6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid (**Int1**, 805 mg, 3.00 mmol), triethylamine (1.69 mL, 12.0 mmol), and (*R*)-butan-2-amine (329 mg, 4.50 mmol) in dry *N*,*N*-dimethylformamide (30 mL) was cooled to 0 °C and propanephosphonic acid anhydride (T3P, 5.24 mL, 9.00 mmol, 50% solution in DMF) was added dropwise over 5 minutes. The resulting mixture was stirred for 1 hour at 0 °C and then diluted with water (200 mL) and washed with ethyl acetate (3 x 150 mL). The organic phases were discarded (product is in form of salt in aqueous phase) and the aqueous phase was

basified to pH = 12 by addition of a 30% solution of ammonium hydroxide. The mixture was then extracted with dichloromethane (3 x 200 mL) and the combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 99:1 to 90:10) to afford (6a*R*,9*S*)-*N*-((*R*)-sec-butyl)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int8a**, faster, less polar isomer) as a dark-brown solid and (6a*R*,9*R*)-*N*-((*R*)-sec-butyl)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int8**, slower, more polar isomer) as a colorless solid.

Int8a:

Yield: 0.28 g (28%).

^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 8.28 (s, 1H); 8.01 (s, 1H); 7.25-7.10 (m, 3H); 6.93 (s, 1H); 6.60 (d, J = 5.7, 1H); 3.93-3.76 (m, 1H); 3.59 (dd, J = 14.5, 5.4, 1H); 3.27-3.04 (m, 2H); 2.78-2.61 (m, 2H); 2.58 (s, 3H); 1.56-1.33 (m, 2H); 1.01 (d, J = 6.6, 3H); 0.91 (d, J = 7.4, 3H).

LC-MS purity: 100% (ELSD).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 6.21 min.

LC-MS m/z: 324.2 $(M+H)^+$.

Int8:

Yield: 0.47 g (48%).

^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 8.34 (s, 1H); 7.24-7.09 (m, 3H); 6.90 (s, 1H); 6.62 (d, J = 8.0, 1H); 6.42 (dd, J = 3.7, 1.9, 1H); 3.93 (dt, J = 14.8, 6.7, 1H); 3.54-3.48 (m, 1H); 3.44-3.34 (m, 2H); 3.10 (dd, J = 11.5, 4.7, 1H); 2.83-2.68 (m, 2H); 2.60 (s, 3H); 1.56-1.37 (m, 2H); 1.13 (d, J = 6.6, 3H); 0.90 (t, J = 7.4, 3H).

LC-MS purity: 100% (ELSD).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 5.29 min.

LC-MS m/z: 324.2 $(M+H)^+$.

[00132] A solution of 3-chloroperbenzoic acid (361 mg, 1.61 mmol) in dry dichloromethane (20 mL) was added dropwise to a solution of (6a*R*)-*N*-((*R*)-sec-butyl)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int8m**, 526 mg, 1.63 mmol; mixture of epimers at position 9) in dry dichloromethane (40 mL) at 0 °C and the

resulting mixture was stirred for 1 hour. A 10% solution of sodium hydroxide (50 mL) was then added, the phases were separated, and the aqueous phase was extracted with a 10% solution of isopropanol in dichloromethane (3 x 100 mL). The combined organic phases were dried and evaporated *in* vacuo to afford (6a*R*)-9-(((*R*)-sec-butyl)carbamoyl)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline 7-oxide (**Int9m**) (mixture of diastereomers; epimers at position 9) as a dark-brownish solid, which was used in the next step without further purification.

Yield: 0.52 g (100%).

LC-MS purity: 100% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 50:50 to 100:0 + 0.1% FA in 10 min): 5.13 min.

LC-MS m/z: 340.2 $(M+H)^+$.

[00133] Crude (6a*R*)-9-(((*R*)-sec-butyl)carbamoyl)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline 7-oxide (**Int9m**, 520 mg; mixture of epimers at position 9) was dissolved in methanol (20 mL), cooled to 0 °C, and purged with argon. Iron (II) sulfate heptahydrate ($Fe_2SO_4 \cdot 7H_2O$, 895 mg, 3.22 mmol) was then added in portions to this solution and the mixture was stirred for 3 hours at 0 °C. The solvent was then removed *in vacuo* and the residue was partitioned between dichloromethane (150 mL) and a solution of EDTA (10 g) and 30% ammonium hydroxide (10 mL) in water (100 mL). The aqueous phase was further extracted with dichloromethane (3 x 100 mL) and the combined organic phases were dried and evaporated. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2 to 85:15) to afford (6a*R*)-*N*-((*R*)-sec-butyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int10m**) (mixture of diastereomers; epimers at position 9) as a dark-brownish solid.

Yield: 0.121 g (24% over 2 steps).

LC-MS purity: 100% (ELSD).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 50:50 to 100:0 + 0.1% FA in 10 min): 4.78 min (diastereomer 1); 5.15 min (diastereomer 2).

LC-MS m/z: 340.2 $(M+H)^+$.

[00134] A solution of (6a*R*)-*N*-((*R*)-sec-butyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int10m**, 55.0 mg, 0.178 mmol; mixture of epimers at position 9) and propanal (0.064 mL, 0.89 mmol) in methanol (10 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (56.0 mg, 0.89 mmol) was added, the mixture was stirred

for 5 minutes, and acetic acid (160 µL) was then added. The reaction was then stirred at 0 °C for 1 hour. The solvent was evaporated and the residue was partitioned between dichloromethane (50 mL) and a 1% solution of ammonium hydroxide (150 mL). The aqueous phase was further extracted with dichloromethane (3 x 50 mL) and the combined organic phases were dried over anhydrous magnesium sulfate and evaporated. The resulting residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 99:1 to 98:2) to afford (6a*R*,9*S*)-*N*-((*R*)-sec-butyl)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**3a**, faster, less polar diastereomer) as a colorless oil and (6a*R*,9*R*)-*N*-((*R*)-sec-butyl)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**3**, slower, more polar diastereomer) as a colorless oil.

3a:

Yield: 16 mg (26%).

^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 8.15 (br s, 1H); 7.99 (d, *J* = 5.9, 1H); 7.26-7.09 (m, 3H); 6.93 (s, 1H); 6.61 (d, *J* = 5.9, 1H); 3.85 (dt, *J* = 14.9, 6.6, 1H); 3.57 (dd, *J* = 14.5, 4.8, 1H); 3.46-3.34 (m, 1H); 3.27 (d, *J* = 11.7, 1H); 3.12 (br s, 1H); 2.92 (ddd, *J* = 13.3, 9.3, 4.6, 1H); 2.76-2.56 (m, 2H); 2.56-2.42 (m, 1H); 1.81-1.52 (m, 2H); 1.52-1.38 (m, 2H); 1.01 (d, *J* = 7.4, 3H); 1.00 (t, *J* = 7.4, 3H); 0.91 (t, *J* = 7.5, 3H).

LC-MS purity: 100% (ELSD).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.81 min.

LC-MS m/z: 352.1 $(M+H)^+$.

3:

Yield: 17 mg (27%).

^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 8.15 (br s, 1H); 7.38 (br s, 1H); 7.23-7.12 (m, 2H); 7.08 (dd, *J* = 6.9, 0.9, 1H); 6.91 (s, 1H); 6.41 (dd, *J* = 5.3, 1.6, 1H); 4.03-3.80 (m, 2H); 3.26 (dd, *J* = 14.0, 4.8, 2H); 3.03 (dd, *J* = 11.9, 4.0, 1H); 2.97-2.79 (m, 3H); 2.76-2.59 (m, 1H); 1.75-1.55 (m, 2H); 1.54-1.34 (m, 2H); 1.13 (d, *J* = 6.6, 3H); 0.98 (t, *J* = 7.3, 3H); 0.88 (t, *J* = 7.4, 3H).

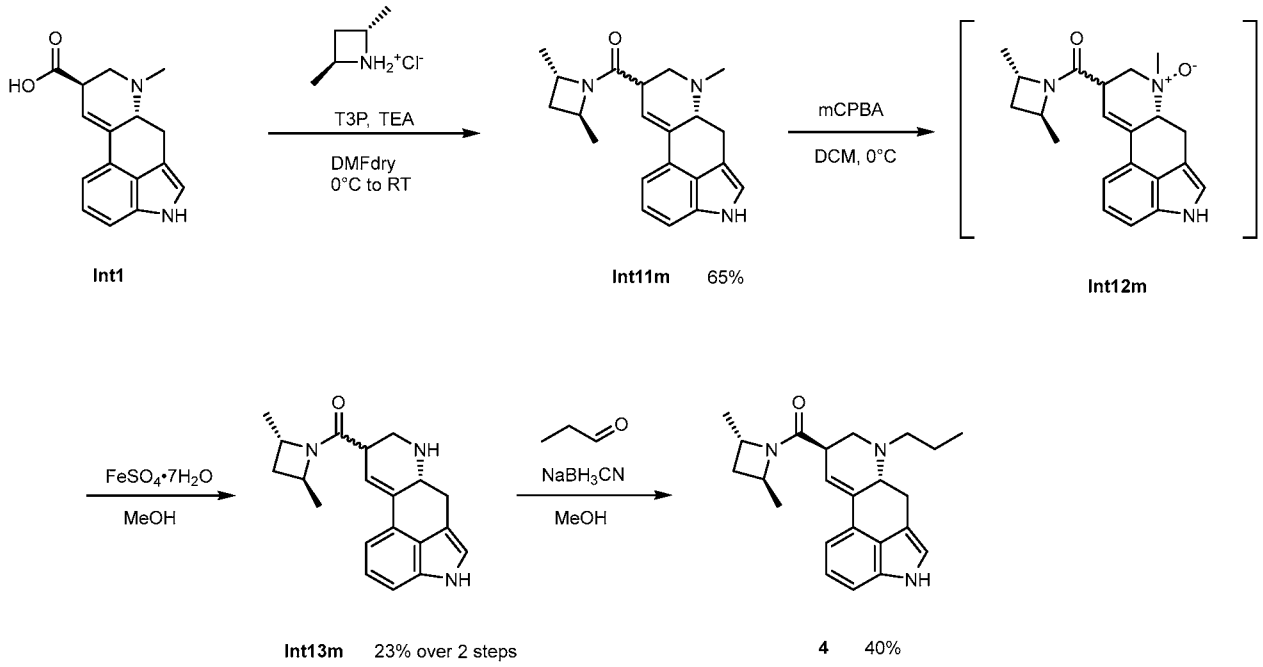
LC-MS purity: 100% (ELSD).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.00 min.

LC-MS m/z: 352.1 $(M+H)^+$.

Example 4: Preparation of ((2S,4S)-2,4-dimethylazetidin-1-yl)((6aR,9R)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinolin-9-yl)methanone (4)

Reaction Scheme:



Synthetic Protocols:

[00135] A solution of (6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid (**Int1**, 460 mg, 1.71 mmol), triethylamine (1.10 mL, 7.70 mmol), and (2*S*,4*S*)-2,4-dimethylazetidine hydrochloride (250 mg, 2.05 mmol) in dry *N*,*N*-dimethylformamide (10 mL) was cooled to 0 °C under an argon atmosphere. Propanephosphonic acid anhydride (T3P, 1.20 mL, 2.05 mmol, 50% solution in DMF) was then added dropwise over 5 minutes and the resulting mixture was stirred for 1 hour at 0 °C. After the reaction was complete by LC/MS, it was quenched with ice-cold water (10 mL) and partitioned between 1M aqueous ammonium hydroxide solution (100 mL) and ethyl acetate (100 mL). The aqueous phase was further extracted with ethyl acetate (2 x 50 mL) and the combined organic phases were washed with 5% lithium chloride solution (4x50 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 100:0 to 98:2) to afford ((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)((6a*R*, 9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanone (**Int11**, faster moving fluorescent band) as an off-white solid and ((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)((6a*R*)-

7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanone (**Int11m**; mixture of diastereomers; epimers at position 9) as a dark-brown solid.
Yield: 368 mg (65%), combined isomers.
^{1}H NMR spectrum (**Int11**, pure beta isomer) (300 MHz, $CDCl_3$, δ_H): 8.24 (br s, 1H); 7.24-7.09 (m, 3H); 6.88 (s, 1H); 6.36 (s, 1H); 4.52 (dt, J = 7.5, 6.5, 2H); 3.60 (br s, 1H); 3.53 (dd, J = 14.5, 5.4, 1H); 3.31-3.17 (m, 1H); 3.07 (dd, J = 11.1, 4.9, 1H); 2.88 (t, J = 10.9, 1H); 2.70 (t, J = 12.0, 1H); 2.60 (s, 3H); 2.10-1.90 (m, 2H); 1.49 (t, J = 6.3, 6H).
LC-MS purity: 100% (combined isomers, ELSD), 98% (combined isomers, UV_{310}).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 20:80 to 100:0 + 0.1% FA in 10 min): 3.59 min (diastereomer 1); 3.95 min (diastereomer 2).
LC-MS m/z: 336.0 $(M+H)^+$.

[00136] A solution of 3-chloroperbenzoic acid (189 mg, 1.10 mmol) in dry dichloromethane (5 mL) was added dropwise to a solution of ((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)((6a*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanone (**Int11m**, 368 mg, 1.10 mmol; mixture of epimers at position 9) in dry dichloromethane (30 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 hour. A 10% solution of sodium hydroxide (100 mL) was then added to the reaction mixture and the aqueous phase was extracted with a 10% solution of isopropanol in dichloromethane (3 x 100 mL). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford (6a*R*)-9-((2*S*,4*S*)-2,4-dimethylazetidine-1-carbonyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolone 7-oxide (**Int12m**) (mixture of diastereomers; epimers at position 9) as an off-white solid, which was used to the next step without further purification.
LC-MS purity: 100% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 50:50 to 100:0 + 0.1% FA in 10 min): 1.92 min.
LC-MS m/z: 352.0 $(M+H)^+$.

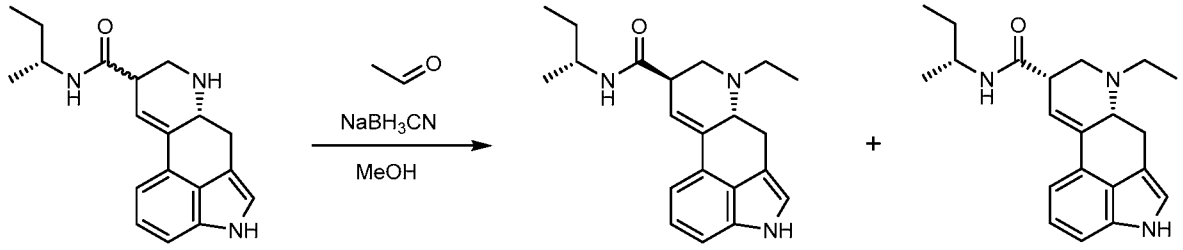
[00137] Crude (6a*R*)-9-((2*S*,4*S*)-2,4-dimethylazetidine-1-carbonyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolone 7-oxide (**Int12m**; mixture of epimers at position 9) was dissolved in methanol (75 mL), cooled to 0 °C, and purged with argon. Iron (II) sulfate heptahydrate (609 mg, 2.20 mmol) was then added and the mixture was stirred for 3 hours at 0 °C. The solvent was removed *in vacuo* and the residue was partitioned between dichloromethane (150 mL) and a solution of EDTA (10 g) and 30% ammonium hydroxide (10 mL) in water (100 mL). The aqueous phase was further extracted with dichloromethane (3 x

100 mL) and the combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2 to 90:10) to afford ((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)((6a*R*)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanone (**Int13m**) (mixture of diastereomers; epimers at position 9) as an off-white amorphous solid.
Yield: 81.5 mg (23% over 2 steps).
LC-MS purity: 88% (ELSD), 86% (UV_{310}).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 05:95 to 100:0 + 0.1% FA in 10 min): 5.87 min.
LC-MS m/z: 322.2 $(M+H)^+$.

[00138] A solution of ((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)((6a*R*)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanone (**Int13m**, 81.5 mg, 0.242 mmol; mixture of epimers at position 9) and propanal (87 µL, 1.21 mmol) in methanol (10 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (76.0 mg, 1.21 mmol) was added, the mixture was stirred for 5 minutes, and then acetic acid (300 µL) was added. After stirring at 0 °C for 1 hour, the solvent was evaporated and the residue was partitioned between dichloromethane and a 1% solution of ammonium hydroxide. The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 99:1 to 98:2) to afford ((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)((6a*R*,9*R*)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanone (**4**, faster moving fluorescent band) as an off-white foam.
Yield: 35 mg (40%).
^1H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 8.22 (br s, 1H); 7.24 – 7.06 (m, 3H); 6.89 (s, 1H); 6.34 (s, 1H); 4.66 – 4.45 (m, *J* = 13.1, 6.2 Hz, 2H); 3.73 – 3.52 (m, *J* = 18.2 Hz, 2H); 3.50 – 3.40 (m, 1H); 3.20 (dd, *J* = 10.9, 4.4 Hz, 1H); 3.04 – 2.88 (m, *J* = 12.8, 10.6 Hz, 2H); 2.86 – 2.64 (m, 2H); 2.14 – 1.89 (m, 2H); 1.74 – 1.56 (m, 2H); 1.49 (dd, 6H); 0.96 (t, *J* = 7.3 Hz, 3H).
LC-MS purity: 99% (ELSD), 96% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.51 min.
LC-MS m/z: 364.1 $(M+H)^+$.

Example 5: Preparation of (6aR,9R)-N-((R)-sec-butyl)-7-ethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (5) and (6aR,9S)-N-((R)-sec-butyl)-7-ethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (5a)

Reaction Scheme:



Int10m **5** **5a**

Synthetic Protocols:

[00139] A solution of (6a*R*)-*N*-((*R*)-sec-butyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (**Int10m**, 55.2 mg, 0.178 mmol; preparation is described in Example 3; mixture of epimers at position 9) and acetaldehyde (39.3 mg, 0.89 mmol) in methanol (10 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (56.1 mg, 0.89 mmol) was added, the mixture was stirred for 5 minutes, and acetic acid (200 µL) was then added. The reaction was stirred at 0 °C for 1 hour, the solvent was removed *in vacuo*, and the residue was partitioned between dichloromethane (50 mL) and a 1% solution of ammonium hydroxide (150 mL). The aqueous phase was further extracted with dichloromethane (3 x 50 mL) and the combined organic phases were dried over anhydrous sodium sulfate and evaporated. The resulting residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 99:1 to 98:2) to afford (6a*R*,9*S*)-N-((*R*)-sec-butyl)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**5a**, faster moving, less polar diastereomer) as a colorless oil and (6a*R*,9*R*)-N-((*R*)-sec-butyl)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**5**, slower moving, more polar diastereomer) as a colorless solid. The separated isomers were each dissolved in absolute methanol (500 µL) and treated with an equimolar amount of 1M D-(-)-tartaric acid in absolute methanol. The obtained solutions were stripped of solvents in a flow of nitrogen and dried under high vacuum to yield (6a*R*,9*S*)-9-(((*R*)-sec-butyl)carbamoyl)-7-ethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-7-ium (2*S*,3*S*)-3-carboxy-2,3-dihydroxypropanoate (**5a tartrate**) as a brown tinted amorphous solid and (6a*R*,9*R*)-9-(((*R*)-sec-butyl)carbamoyl)-7-ethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-7-ium (2*S*,3*S*)-3-carboxy-2,3-dihydroxypropanoate (**5 tartrate**) as a colorless solid.

5a:

Yield (of freebase): 12.0 mg (20%).

^{1}H NMR spectrum (of freebase) (300 MHz, $CDCl_3$, δ_H): 8.50-7.90 (m, 2 H); 7.26-7.21 (m, 1 H); 7.20-7.06 (m, 2 H); 6.92 (s, 1 H); 6.59 (d, J = 5.1 Hz, 1 H); 3.93-3.75 (m, 1 H); 3.67-3.38 (m, 2 H); 3.33-3.01 (m, 3 H); 2.91-2.41 (m, 3 H); 1.52-1.38 (m, 2 H); 1.24-1.12 (m, 3 H); 1.09-0.97 (m, 3 H); 0.91 (t, J = 7.4 Hz, 3 H).

^{1}H NMR spectrum (of tartrate) (300 MHz, MeOD, δ_H): 7.29 (dd, J = 7.0, 1.6, 1H); 7.17 (t, J = 6.9, 2H); 7.09 (s, 1H); 6.62 (d, J = 5.7, 1H); 4.47 (s, 2H); 4.31 (dd, J = 11.9, 5.3, 1H); 3.82 (dd, J = 13.2, 6.4, 2H); 3.80-3.66 (m, 2H); 3.60-3.53 (m, 1H); 3.46-3.34 (m, 2H); 3.02 (t, J = 13.0, 1H); 1.55-1.42 (m, 2H); 1.47 (t, J = 7.3, 3H); 1.19 (d, J = 7.0, 3H); 0.87 (t, J = 7.4, 3H).

LC-MS purity (of freebase): 97% (ELSD), 91% (UV, 310 nm).

LC-MS purity (of tartrate): 99% (ELSD).

LC-MS Rt (of tartrate) (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.48 min.

LC-MS m/z: 338.1 $(M+H)^+$.

5:

Yield (of freebase): 12.5 mg (21%).

^{1}H NMR spectrum (of tartrate) (300 MHz, MeOD, δ_H): 7.27 (dd, J = 6.1, 2.5, 1H); 7.19-7.09 (m, 2H); 7.07 (s, 1H); 6.49 (s, 1H); 4.44 (s, 2H); 4.37-4.24 (m, 1H); 3.85 (dd, J = 13.3, 6.6, 2H); 3.74-3.61 (m, 2H); 3.60-3.42 (m, 1H); 3.61-3.40 (m, 2H); 3.37-3.33 (m, 1H); 3.08 (t, J = 12.9, 1H); 1.61-1.50 (m, 2H); 1.42 (t, J = 7.2, 3H); 1.16 (d, J = 7.0, 3H); 0.96 (t, J = 7.4, 3H).

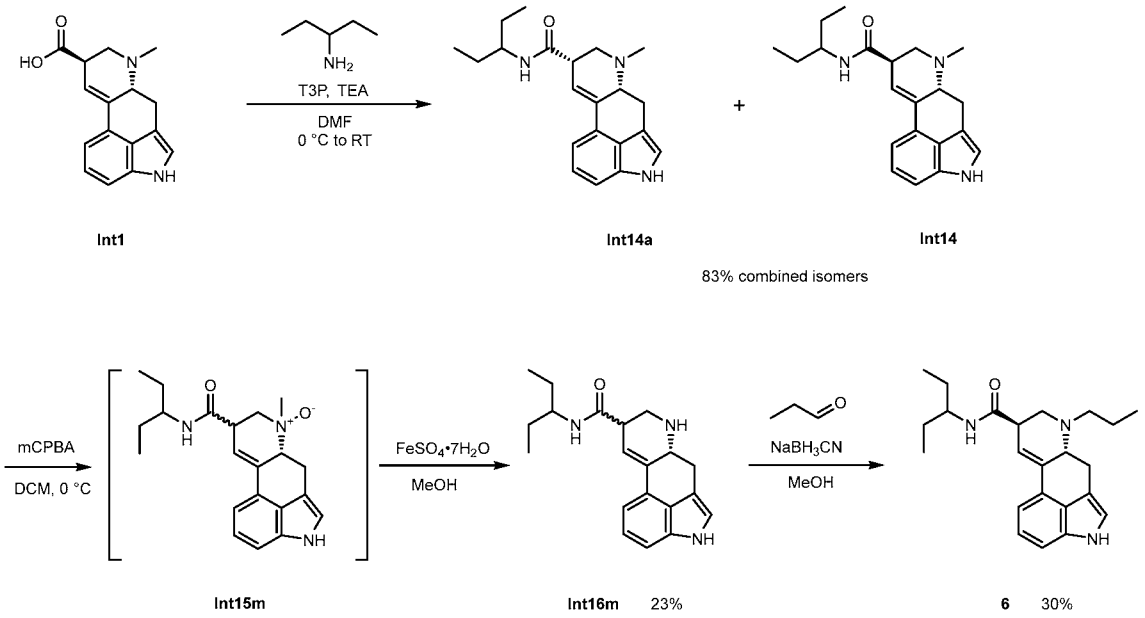
LC-MS purity (of tartrate): 91% (ELSD).

LC-MS Rt (of tartrate) (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.65 min.

LC-MS m/z: 338.1 $(M+H)^+$.

Example 6: Preparation of (6aR,9R)-N-(pentan-3-yl)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (6)

Reaction Scheme:



Synthetic Protocols:

[00140] A solution of (6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid (**Int1**, 200 mg, 0.745 mmol), triethylamine (430 µL, 3.00 mmol), and 3-pentanamine (260 µL, 2.23 mmol) in dry *N*,*N*-dimethylformamide (10 mL) was cooled to 0 °C under argon atmosphere. Propanephosphonic acid anhydride (T3P®, 1.30 mL, 2.23 mmol, 50% solution in DMF) was added dropwise over 5 minutes, and the resulting mixture was stirred for 3 hours at 0 °C and then quenched with ice-cold water (10 mL). The reaction mixture was concentrated *in vacuo* along with silica gel (10 g) and the resulting solid was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 100:0 to 98:2) to afford (6a*R*,9*S*)-7-methyl-*N*-(pentan-3-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int14a**, faster moving, less polar diastereomer) as dark brown solid and (6a*R*,9*R*)-7-methyl-*N*-(pentan-3-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int14**, slower moving, more polar diastereomer) as dark brown solid.

Yield: 208 mg (83%, combined isomers).

Int14a:

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.03 (br s, 1H); 7.87 (br d, J = 6.20 1H); 7.31-7.18 (m, 1H); 7.17-7.05 (m, 2H); 6.98 (s, 1H); 6.56 (d, J = 6.2, 1H); 3.71-3.51 (m, 2H); 3.11 (d, J = 11.7, 2H); 3.04-2.93 (m, 1H); 2.67 (dd, J = 11.8, 3.8, 1H); 2.56 (dd, J = 26.0, 1.6, 1H); 2.55 (s, 3H); 1.59-1.20 (m, 4H); 0.89 (t, J = 7.4, 3H); 0.72 (t, J = 7.4, 3H).

LC-MS purity: 100% (ELSD), 100% (UV_{310}).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 5.27 min.
LC-MS m/z: 338.2 $(M+H)^+$.

Int14:
^1H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.03 (br s, 1H); 7.22 (dt, J = 7.2, 3.6, 1H); 7.14-7.05 (m, 2H); 6.95 (s, 1H); 6.49 (br d, J = 7.1, 1H); 6.40 (s, 1H); 3.67 (qd, J = 8.5, 4.2, 1H); 3.48 (dd, J = 14.6, 5.5, 1H); 3.37 (ddd, J = 8.2, 5.6, 3.0, 1H); 3.24-3.14 (m, 1H); 3.07 (dd, J = 11.2, 5.0, 1H); 2.69-2.44 (m, 4H); 2.53 (s, 3H); 1.62-1.46 (m, 2H); 1.46-1.31 (m, 2H); 0.96-0.84 (m, 6H).
LC-MS purity: 100% (ELSD), 100% (UV_{310}).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 4.95 min.
LC-MS m/z: 338.2 $(M+H)^+$.

[00141] A solution of 3-chloroperbenzoic (77%, 138 mg, 800 µmol) acid in dry dichloromethane (5 mL) was added dropwise to a solution of (6a*R*)-7-methyl-*N*-(pentan-3-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int14m**, 208 mg, 616 µmol; mixture of epimers at position 9) in dry dichloromethane (10 mL) at 0 °C and stirred for 1 hour under argon atmosphere. A 10% aqueous solution of sodium hydroxide (100 mL) was then added to the reaction mixture and the mixture was extracted with a 10% solution of isopropanol in dichloromethane (3 x 100 mL). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford (6a*R*)-7-methyl-9-(pentan-3-ylcarbamoyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline 7-oxide (**Int15m**) (mixture of diastereomers; epimers at position 9), which was used in the next step without further purification.
LC-MS purity: 100% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.09 min.
LC-MS m/z: 354.2 $(M+H)^+$.

[00142] Crude (6a*R*)-7-methyl-9-(pentan-3-ylcarbamoyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline 7-oxide (**Int15m**, entire quantity obtained in above procedure; mixture of epimers at position 9) was dissolved in methanol (20 mL) and the solution was cooled to 0 °C under argon. Iron (II) sulfate heptahydrate (343 mg, 1.23 mmol) was then added and the resulting mixture stirred for 3 hours at 0 °C. At this time, the solvent

was removed *in vacuo* and the residue partitioned between dichloromethane (150 mL) and a solution of EDTA (10 g) and 30% ammonium hydroxide (10 mL) in water (100 mL). The aqueous phase was further extracted with dichloromethane (3 x 100 mL) and the combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2 to 90:10) to yield (6a*R*)-*N*-(pentan-3-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int16m**) (mixture of diastereomers; epimers at position 9) as an amorphous beige solid.

Yield: 50.0 mg (25% over 2 steps from Int14m).

LC-MS purity: 95% (UV_{310}).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 4.77 min.

LC-MS m/z: 324.2 $(M+H)^+$.

[00143] A solution of (6a*R*)-*N*-(pentan-3-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int16m**, 50.0 mg, 0.154 mmol; mixture of epimers at position 9) and propanal (55 µL, 0.771 mmol) in methanol (10 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (48.0 mg, 0.77 mmol) was then added and the resulting mixture stirred for 5 minutes followed by addition of glacial acetic acid (100 uL). After stirring at 0 °C for 1 hour, solvents were removed *in vacuo*, the residue partitioned between dichloromethane (200 mL) and 1% ammonium hydroxide(150 mL), and the aqueous phase was further extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Residue was purified by flash column chromatography (Silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 99:1 to 98:2) to afford (6a*R*,9*R*)-*N*-(pentan-3-yl)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**6**, slower moving fluorescent band) as a colorless foam.

Yield: 20 mg (30%).

^1H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.00 (br s, 1H); 7.21 (dd, J = 7.6, 0.8, 1H); 7.14-7.00 (m, 2H); 6.99-6.84 (m, 2H); 6.37 (dd, J = 3.8, 1.7, 1H); 3.75-3.61 (m, 1H); 3.60-3.50 (m, 1H); 3.37 (dd, J = 14.4, 5.0, 1H); 3.23-3.13 (m, 1H); 3.07 (dd, J = 11.4, 4.5, 1H); 2.79-2.58 (m, 4H); 1.65-1.45 (m, 4H); 1.44-1.24 (m, 2H); 0.98-0.81 (m, 9H).

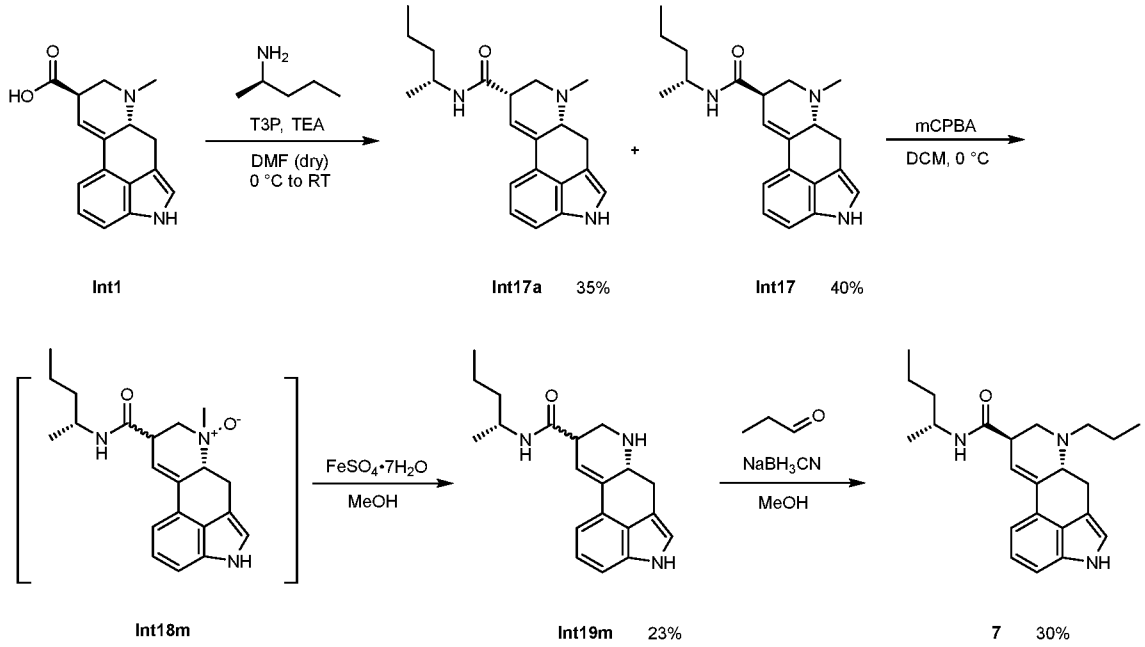
LC-MS purity: 98% (ELSD), 97% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.72 min.

LC-MS m/z: 366.2 $(M+H)^+$.

Example 7: Preparation of (6aR,9R)-N-((R)-pentan-2-yl)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (7)

Reaction Scheme:



Synthetic Protocols:

[00144] A solution of (6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid (**Int1**, 200 mg, 0.745 mmol), triethylamine (430 µL, 3.00 mmol), and (*R*)-pentan-2-amine hydrochloride (250 µg, 1.50 mmol) in dry *N*,*N*-dimethylformamide (10 mL) was cooled to 0°C under argon atmosphere. Propanephosphonic acid anhydride (T3P®, 875 µL, 1.50 mmol, 50% solution in DMF) was then added dropwise over 5 minutes. The resulting mixture was stirred for 3 hours at 0 °C and quenched with ice-cold water (1 mL). The resulting mixture was concentrated *in vacuo* along with silica gel (10 g) and purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 100:0 to 98:2) to afford (6a*R*,9*S*)-7-methyl-*N*-((*R*)-pentan-2-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int17a,** faster fluorescent band) as a dark-brown solid and (6a*R*,9*R*)-7-methyl-*N*-((*R*)-pentan-2-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int17,** slower fluorescent band) as a dark-brown solid.

Int17a:

Yield: 89 mg (35%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.07 (br s, 1H); 7.79 (br d, *J* = 6.10, 1H); 7.28-7.21 (m, 1H); 7.14-7.09 (m, 2H); 6.98 (s, 1H); 6.53 (d, *J* = 6.1, 1H); 3.89-3.73 (m, 1H); 3.61 (dd, *J* = 14.6, 5.5, 1H); 3.15 (br s, 1H); 3.12 (d, *J* = 12.0, 1H); 3.00 (br s, 1H); 2.69 (dd, *J* = 11.6, 3.4, 1H); 2.65-2.51 (m, 1H); 2.56 (s, 3H); 1.45-1.31 (m, 4H); 0.98 (d, *J* = 6.5, 3H); 0.90 (t, *J* = 6.94, H).
LC-MS purity: 95% (ELSD), 100% (UV_{310}).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 5.317 min.
LC-MS m/z: 338.2 $(M+H)^+$.

Int17:
Yield: 102 mg (40%).
^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.02 (br s, 1H); 7.23 (p, *J* = 3.8, 1H); 7.13-7.07 (m, 2H); 6.95 (s, 1H); 6.53 (br d, *J* = 6.81, 1H); 6.38 (s, 1H); 3.89 (dt, *J* = 15.0, 6.6, 1H); 3.48 (dd, *J* = 14.6, 5.5, 1H); 3.38-3.27 (m, 1H); 3.21-3.11 (m, 1H); 3.05 (dd, *J* = 11.1, 5.0, 1H); 2.64-2.54 (m, 2H); 2.51 (s, 3H); 1.48-1.29 (m, 4H); 1.11 (d, *J* = 6.6, 3H); 0.91 (t, *J* = 7.1, 3H).
LC-MS purity: 91% (ELSD), 100% (UV_{310}).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 5.06 min.
LC-MS m/z: 338.2 $(M+H)^+$.

[00145] A solution of 3-chloroperbenzoic (77%, 142.7 mg, 827 µmol) acid in dry dichloromethane (5 mL) was added dropwise to a solution of (6a*R*)-7-methyl-*N*-((*R*)-pentan-2-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int17m**, 215 mg, 630 µmol; mixture of epimers at position 9) in dry dichloromethane (10 mL) at 0 °C and the mixture was stirred at the given temperature for 1 hour under argon atmosphere. A 10% aqueous solution of sodium hydroxide (100 mL) was then added to the reaction mixture and the aqueous phase was extracted with a 10% solution of isopropanol in dichloromethane (3 x 100 mL). The combined organic phases were combined, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford (6a*R*,)-7-methyl-9-(((*R*)-pentan-2-yl)carbamoyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline 7-oxide (**Int18m**) (mixture of diastereomers, epimers at position 9), which was used in the next step without further purification.
LC-MS purity: 100% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.23 min.

LC-MS m/z: 354.1 $(M+H)^+$.

[00146] Crude (6a*R*)-7-methyl-9-(((*R*)-pentan-2-yl)carbamoyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline 7-oxide (**Int18m**, entire quantity obtained in above procedure; mixture of epimers at position 9) was dissolved in methanol (20 mL) and cooled to 0 °C under argon. Iron (II) sulfate heptahydrate (351 mg, 1.26 mmol) was then added and the resulting mixture was stirred for 3 hours at 0°C. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (150 mL) and a solution of EDTA (10 g) and 30% ammonium hydroxide (10 mL) in water (100 mL). The aqueous phase was further extracted with dichloromethane (3 x 100 mL) and the combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2 to 90:10) to yield (6a*R*)-*N*-((*R*)-pentan-2-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int19m**) (mixture of diastereomers, epimers at position 9) as an amorphous beige solid.
Yield: 47.0 mg (23% over 2 steps from Int17m).
LC-MS purity: 97% (combined diastereomers, UV_{310}).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 4.94 min, 5.19 min.
LC-MS m/z: 324.2 $(M+H)^+$.

[00147] A solution of (6a*R*)-*N*-(pentan-3-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int19m**, 47.0 mg, 0.145 mmol; mixture of epimers at position 9) and propanal (53 µL, 0.74 mmol) in methanol (10 mL) was cooled to 0 °C under argon. Sodium cyanoborohydride (46.0 mg, 0.74 mmol) was added and the resulting mixture was stirred for 5 minutes followed by addition of glacial acetic acid (100 µL). After stirring at 0 °C for 1 hour, the solvents were removed *in vacuo* and the residue partitioned between dichloromethane (200 mL) and a 1% solution of ammonium hydroxide (150 mL). The aqueous phase was further extracted with dichloromethane (3 x 50 mL) and the combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 99:1 to 98:2) to afford (6a*R*,9*R*)-7-propyl-*N*-((*R*)-pentan-2-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**7**, slower moving fluorescent band) as a dark brownish foam.
Yield: 20 mg.

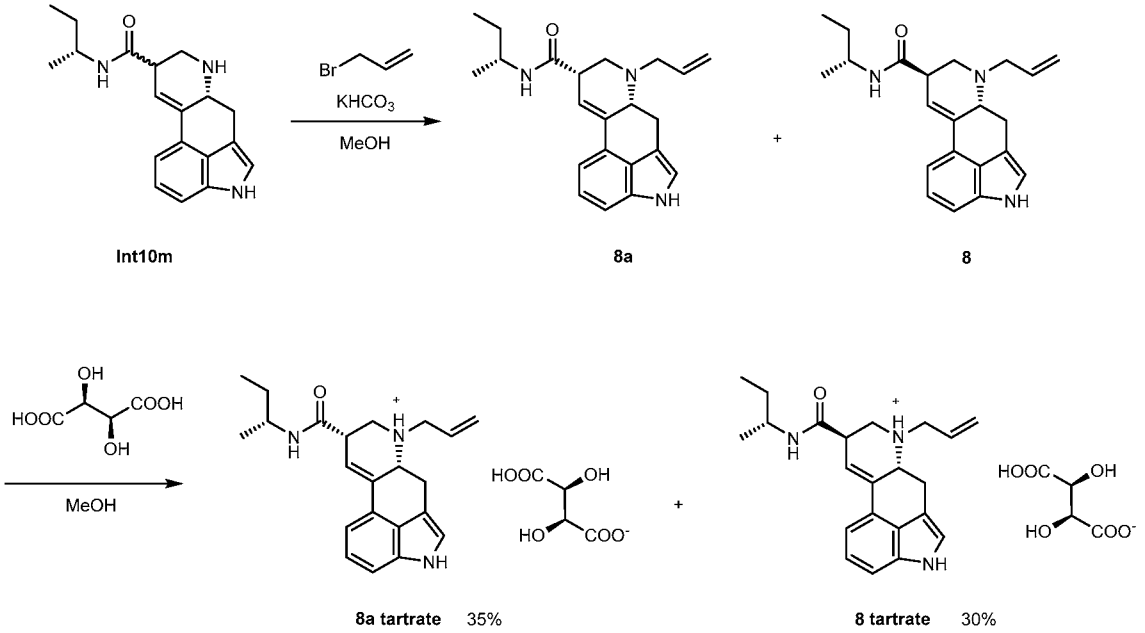
LC-MS purity: 100% (ELSD), 89% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.88 min.

LC-MS m/z: 366.2 $(M+H)^+$.

Example 8: Preparation of (6aR,9R)-7-allyl-N-((R)-sec-butyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (8) and (6aR,9S)-7-allyl-N-((R)-sec-butyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (8a)

Reaction Scheme:



Synthetic Protocols:

[00148] To a stirred solution of (6a*R*)-*N*-((*R*)-sec-butyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int10m**, 35 mg, 0.113 mmol; preparation is described in Example 3; mixture of epimers at position 9) and potassium bicarbonate (23 mg, 0.226 mmol) in methanol (2 mL) was added a solution of allylbromide (20 µL, 0.226 mmol) in methanol (1 mL) dropwise under argon. The resulting mixture was stirred for 72 hours at ambient temperature, diluted with dichloromethane (50 mL), and silica gel (10 g) was introduced. The obtained suspension was stripped of solvents *in vacuo* and subjected to silica gel chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol/ammonia 98:2:0.1) to afford (6a*R*,9*S*)-*N*-((*R*)-sec-butyl)-7-allyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**8a**, faster moving fluorescent band) as a brownish amorphous solid and (6a*R*,9*R*)-*N*-((*R*)-sec-butyl)-7-allyl-4,6,6a,7,8,9-

hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**8**, slower moving fluorescent band) as a brownish foam. The separated isomers were each dissolved in absolute methanol (500 µL) and treated with an equimolar amount of 1M D-(-)-tartaric in absolute methanol. The resulting solutions were stripped of solvents under a flow of nitrogen and dried under high vacuum to yield (6a*R*,9*S*)-7-allyl-9-(((*R*)-sec-butyl)carbamoyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-7-ium (2*S*,3*S*)-3-carboxy-2,3-dihydroxypropanoate (**8a tartrate**) as a light-brown solid and (6a*R*,9*R*)-7-allyl-9-(((*R*)-sec-butyl)carbamoyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-7-ium (2*S*,3*S*)-3-carboxy-2,3-dihydroxypropanoate (**8 tartrate**) as a light-brown solid.

8a:

Yield (of freebase): 14.1 mg (35%).

^{1}H NMR spectrum (of tartrate) (300 MHz, MeOD, δ_H): 7.26 (dt, *J* = 7.3, 3.6, 1H); 7.18-7.08 (m, 2H); 7.05 (d, *J* = 1.1, 1H); 6.57 (d, *J* = 5.6, 1H); 6.18-5.99 (m, 1H); 5.63-5.46 (m, 2H); 4.47 (s, 2H); 4.14 (dd, *J* = 13.7, 5.6, 1H); 4.02 (d, *J* = 6.8, 1H); 3.87-3.62 (m, 4H); 3.40 (br s, 1H); 3.18 (dd, *J* = 12.1, 3.5, 1H); 2.93 (t, *J* = 13.0, 1H); 1.58-1.40 (m, 2H); 1.18 (t, *J* = 7.0, 1H); 1.13 (d, *J* = 6.6, 3H); 0.89 (t, *J* = 7.4, 3H).

LC-MS purity (of freebase): 98% (ELSD), 97% (UV, 310 nm).

LC-MS purity (of tartrate): 99% (ELSD).

LC-MS Rt (of tartrate) (Sinergy Polar RP 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 6.65 min.

LC-MS m/z: 350.1 $(M+H)^+$.

8:

Yield (of freebase): 12 mg (30%).

^{1}H NMR spectrum (of tartrate) (300 MHz, MeOD, δ_H): 7.25 (dd, *J* = 6.6, 2.0, 1H); 7.18-7.07 (m, 2H); 7.04 (s, 1H); 6.46 (s, 1H); 6.20-5.99 (m, 1H); 5.67-5.47 (m, 2H); 4.46 (s, 2H); 4.16-4.09 (m, 1H); 4.06 (dd, *J* = 21.2, 7.4, 1H); 3.91-3.64 (m, 4H); 3.57 (dd, *J* = 12.0, 4.8, 1H); 3.29 (t, *J* = 12.6, 1H); 3.00 (t, *J* = 12.6, 1H); 1.62-1.44 (m, 2H); 1.20 (t, *J* = 3.3, 1H); 1.17 (d, *J* = 7.0, 3H); 0.94 (t, *J* = 7.4, 3H).

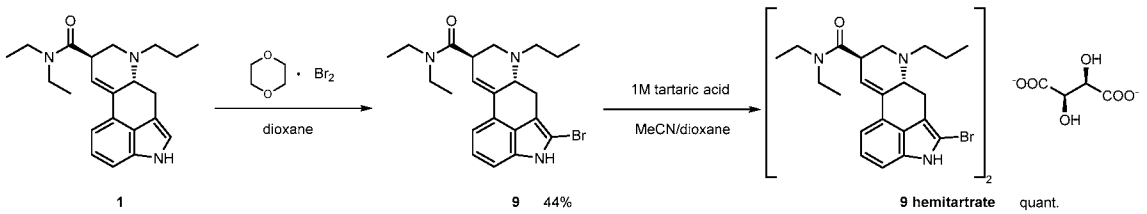
LC-MS purity (of tartrate): 98% (ELSD).

LC-MS Rt (of tartrate) (Sinergy Polar RP 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 5.47 min.

LC-MS m/z: 350.1 $(M+H)^+$.

Example 9: Preparation of (6aR,9R)-5-bromo-N,N-diethyl-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (9)

Reaction Scheme:



Synthetic Protocols:

[00149] A solution of (6a*R*,9*R*)-*N*,*N*-Diethyl-7-propyl-4,6,6a,7,8,9-hexahydroindolo[*4,3-fg*]quinoline-9-carboxamide (**1**, 53.0 mg, 0.151 mmol) in anhydrous dioxane (2.0 mL) was flushed with argon. To this solution was added a 10% v/v solution of bromine in dioxane (754 µL, 0.151 mmol) in a dropwise fashion and the resulting mixture was stirred for 48 h. The reaction mixture was filtered through a pad of silica gel. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to give (6a*R*,9*R*)-5-bromo-*N*,*N*-diethyl-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**9**) as a dark-tinted amorphous solid.

Yield: 28.4 mg (44%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.36 (s, 1H), 7.19 – 7.11 (m, 1H), 7.11 – 7.06 (m, 2H), 6.32 (s, 1H), 3.75 – 3.65 (m, 1H), 3.45 (dt, *J* = 10.8, 3.6, 2H), 3.41 – 3.29 (m, 4H), 3.13 (ddd, *J* = 11.2, 4.8, 1.0, 1H), 2.89 (ddd, *J* = 13.3, 9.0, 7.1, 1H), 2.61 (t, *J* = 10.8, 1H), 2.48 (ddd, *J* = 13.4, 8.7, 4.9, 1H), 2.40 (dd, *J* = 16.3, 12.6, 1H), 1.67 – 1.46 (m, 2H), 1.21 (t, *J* = 7.1, 3H), 1.10 (t, *J* = 7.1, 3H), 0.94 (t, *J* = 7.4, 3H).

LC-MS purity: 100% (ELSD), 97% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.20 min.

LC-MS m/z: 431.9 $(M+H)^+$.

[00150] A solution of (6a*R*,9*R*)-5-bromo-*N*,*N*-diethyl-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**9**, 28.4 mg, 66 µmol) in gradient-grade acetonitrile (5.0 mL) was treated with aqueous 1M D-(-)-tartaric acid solution (33 µL, 66 µmol) and stirred for 5 minutes. The solvent was removed *in vacuo* and the residue was re-dissolved in dioxane (5.0 mL) and then freeze dried at 0 °C to yield (6a*R*,9*R*)-5-bromo-*N*,*N*-diethyl-7-

propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**9 hemitartrate**) as a fluffy light-brown solid.

Yield: 33.2 mg (quantitative).

^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.18 (dd, J = 7.0, 1.9, 1H), 7.16 – 7.06 (m, 2H), 6.39 (s, 1H), 4.40 (s, 1H), 4.07 – 3.99 (m, 1H), 3.99 – 3.86 (m, 1H), 3.58 (dt, J = 14.1, 7.2, 2H), 3.51 – 3.36 (m, 5H), 3.27 – 3.12 (m, 2H), 3.09 – 2.93 (m, 1H), 2.77 (t, J = 12.4, 1H), 1.89 – 1.69 (m, 2H), 1.31 (t, J = 7.1, 3H), 1.19 (t, J = 7.1, 3H), 1.06 (t, J = 7.3, 3H).

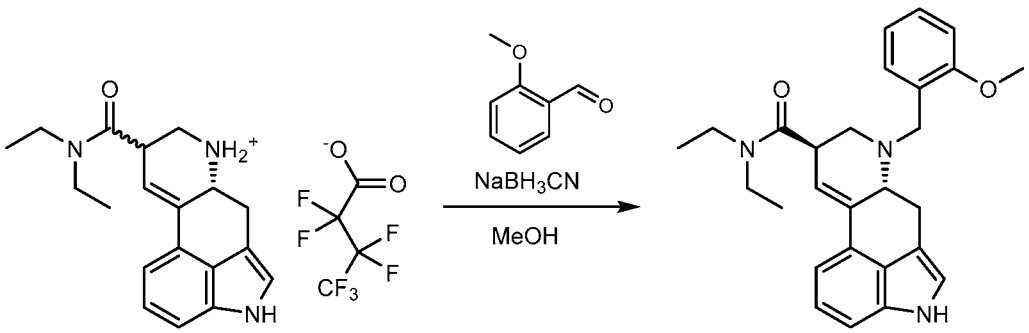
LC-MS purity: 100% (ELSD), 97% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.20 min.

LC-MS m/z: 431.9 $(M+H)^+$.

Example 10: Preparation of (6aR,9R)-N,N-diethyl-7-(2-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (10)

Reaction Scheme:



Int7m **10** 66%

Synthetic Protocols:

[00151] A solution of (6a*R*)-*N,N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide heptafluorobutanoate (**Int7m**, 40.0 mg, 0.077 mmol; mixture of epimers at position 9) and 2-methoxybenzaldehyde (32.0 mg, 0.23 mmol) in methanol (10 mL) was cooled to 0 °C under argon. Sodium cyanoborohydride (15.0 mg, 0.23 mmol) was added, the resulting mixture was stirred for 5 minutes, and then glacial acetic acid (100 µL) was added and stirring was continued at room temperature. After 48 hours, the solvents were removed *in vacuo*, the residue was partitioned between dichloromethane (200 mL) and a 1% solution of ammonium

hydroxide (150 mL), and the aqueous phase was further extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to afford (6a*R*,9*R*)-*N*,*N*-diethyl-7-(2-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**10**) as a colorless solid.

Yield: 22 mg (66%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 8.99 (br s, 1H); 7.48 (d, J = 7.4, 1H); 7.30-7.19 (m, 2H); 7.14-7.05 (m, 2H); 7.00-6.90 (m, 3H); 6.32 (s, 1H); 4.14 (d, J = 14.6, 1H); 3.80 (s, 3H); 3.75-3.63 (m, 3H); 3.47-3.26 (m, 5H); 3.05 (dd, J = 11.1, 4.4, 1H); 2.70-2.47 (m, 2H); 1.08 (dt, J = 9.4, 7.1, 6H).

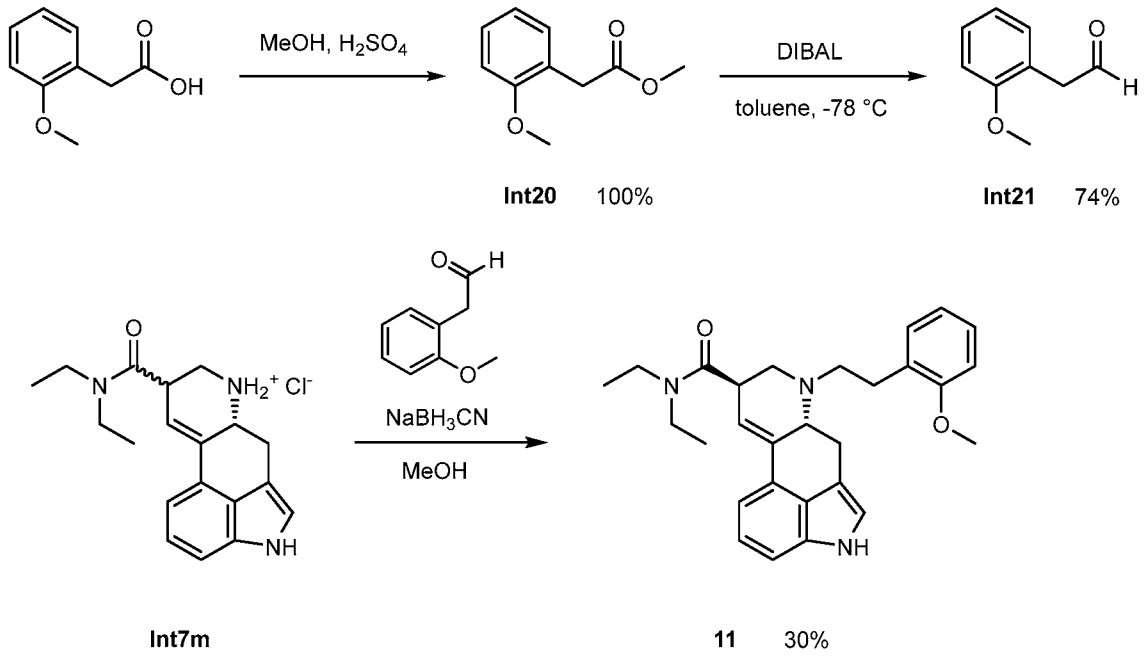
LC-MS purity: 99% (ELSD), 100% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HFBA in 10 min): 7.64 min.

LC-MS m/z: 430.2 $(M+H)^+$.

Example 11: Preparation of (6aR,9R)-N,N-diethyl-7-(2-methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (11)

Reaction Scheme:



Synthetic Protocols:

[00152] 2-(2-methoxyphenyl)acetic acid (1.66 g, 10.0 mmol) was dissolved in dry methanol (10 mL), sulfuric acid 96% (1.0 mL) was added, and the mixture was refluxed for 3 hours. The solvent was then evaporated and the residue was partitioned between ethyl acetate (50 mL) and a saturated solution of sodium bicarbonate (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield methyl 2-(2-methoxyphenyl)acetate (**Int20**) as a colorless oil.
Yield: 1.80 g (100%).
^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 7.30-7.14 (m, 2 H); 6.96-6.84 (m, 2 H); 3.82 (s, 3 H); 3.69 (s, 3 H); 3.64 (s, 2 H).

[00153] 2-(2-methoxyphenyl)acetate (**Int20**, 1.80 g, 10.0 mmol) was dissolved in dry toluene (20 mL) and cooled to -78 °C. A solution of diisobutylaluminium hydride (15.0 mL, 15 mmol, 1 M solution in hexanes) was introduced dropwise and the resulting mixture was stirred for 2 hours at -78 °C. The reaction was quenched by slow addition of methanol (5 mL), followed by additiion of a 10% solution of sodium potassium tartarate (20 mL) and ethylacetate (50 mL). The resulting mixture was then stirred for 1 hour at room temperature. The phases were separated, the aqueous phase was further extracted with ethyl acetate (2 x 50 mL), and the combined organic phases were dried over anhydrous sodium sulfate and evaporated. The residue was purified by flash column chromatography (silica gel 60, 0.040-0.063 mm; eluent: cyclohexane/ethylacetate 9:1) to afford 2-(2-methoxyphenyl)acetaldehyde (**Int21**) as a colorless oil.
Yield: 1.11 g (74%).
^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 9.68 (t, J = 2.1 Hz, 1 H); 7.30 (td, J = 8.1, 1.6 Hz, 1 H); 7.15 (dd, J = 7.3, 1.2 Hz, 1 H); 7.01-6.87 (m, 2 H); 3.83 (s, 3 H); 3.65 (d, J = 2.0 Hz, 2 H).

[00154] A solution of (6a*R*)-*N,N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hydrochloride (**Int7m**, 51.0 mg, 0.148 mmol; HCl salt; mixture of epimers at position 9) and 2-(2-methoxyphenyl)acetaldehyde (**Int21**, 111 mg, 0.74 mmol) in methanol (10 mL) was cooled to 0 °C under argon. Sodium cyanoborohydride (46.0 mg, 0.74 mmol) was added, the mixture was stirred for 5 minutes, and then glacial acetic acid (100 µL) was added and stirring was continued at 0 °C. After 1 hour, the solvents were removed *in vacuo*, the residue was partitioned between dichloromethane (200 mL) and a 1% solution of ammonium hydroxide (150 mL), and the aqueous phase was further extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm;

eluent: dichloromethane/methanol 98:2) to afford (6a*R*,9*R*)-*N*,*N*-diethyl-7-(2-methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**11**) as a colorless foam.

Yield: 20 mg (30%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.01 (br s, 1H); 7.25-7.15 (m, 3H); 7.13-7.06 (m, 2H); 6.99-6.83 (m, 3H); 6.31 (s, 1H); 3.85 (s, 3H); 3.76-3.67 (m, 1H); 3.60 (dd, J = 14.4, 5.4, 1H); 3.53-3.33 (m, 4H); 3.18 (dd, J = 11.1, 4.1, 1H); 3.13-3.02 (m, 1H); 2.97-2.69 (m, 4H); 2.46 (ddd, J = 14.2, 11.1, 1.5, 1H); 1.22 (t, J = 7.1, 3H); 1.12 (t, J = 7.1, 3H).

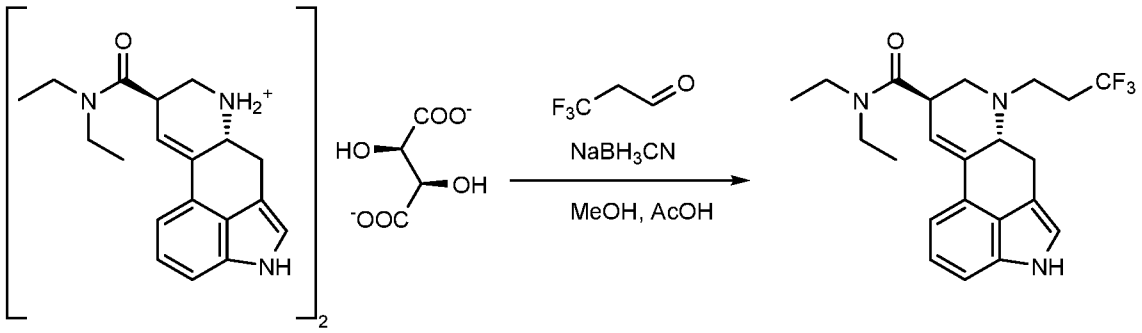
LC-MS purity: 99% (ELSD), 97% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.61 min.

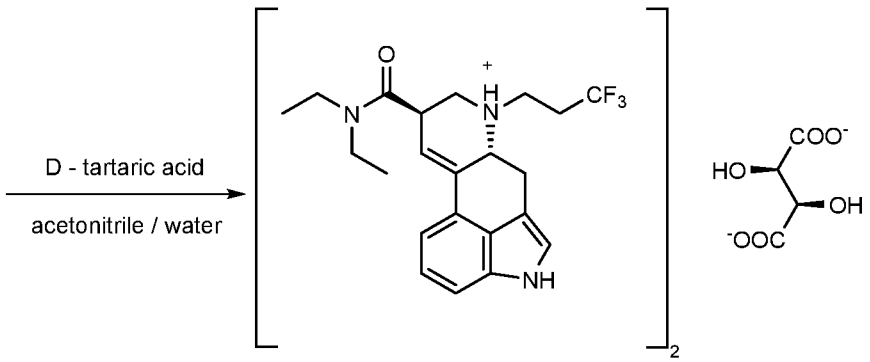
LC-MS m/z: 444.3 $(M+H)^+$.

Example 12: Preparation of (6aR,9R)-N,N-diethyl-7-(3,3,3-trifluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (12)

Reaction Scheme:



Int7 **12** 86%



12 hemitartrate quant.

Synthetic Protocols:

[00155] A solution of (6a*R*,9*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**Int7**, 30.0 mg, 78.0 μmol; 2 moles **Int7** per mole tartrate) and 3,3,3-trifluoropropanal (27.0 μL, 0.31 mmol) in methanol (2 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (20.0 mg, 0.32 mmol) was added and the resulting mixture stirred for 5 minutes followed by addition of glacial acetic acid (20 μL). After stirring at 0 °C for 3 h, the solvents were removed *in vacuo*, the residue was partitioned between dichloromethane (100mL) and a 1% aqueous solution of ammonium hydroxide (150mL), and the aqueous phase was further extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to provide (6a*R*,9*R*)-*N*,*N*-diethyl-7-(3,3,3-trifluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**12**) as a colorless foam.
Yield: 27.2 mg (86%).
^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.01 (s, 1H), 7.23 (dd, *J* = 6.8, 1.9, 1H), 7.15 – 7.03 (m, 2H), 6.96 (t, *J* = 1.8, 1H), 6.31 (s, 1H), 3.79 – 3.66 (m, 1H), 3.51 (dd, *J* = 14.5, 5.5, 1H), 3.46 (dd, *J* = 7.3, 3.2, 1H), 3.37 (m, 4H), 3.22 (ddd, *J* = 14.0, 9.1, 6.8, 1H), 3.09 (ddd, *J* = 11.1, 4.8, 1.0, 1H), 2.86 (ddd, *J* = 14.0, 8.9, 5.3, 1H), 2.73 (t, 1H), 2.57 (dd, *J* = 11.1, 1.7, 1H), 2.54 – 2.40 (m, 2H), 1.22 (t, *J* = 7.1, 3H), 1.11 (t, *J* = 7.1, 3H).
LC-MS purity: 99% (ELSD), 99% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.85 min.
LC-MS m/z: 406.0 $(M+H)^+$.

[00156] (6a*R*,9*R*)-*N*,*N*-diethyl-7-(3,3,3-trifluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**12**, 27.2 mg, 67.1 μmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (33.6 μL, 33.6 μmol). Solvents were removed *in vacuo*, and the obtained material was redissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to yield (6a*R*,9*R*)-*N*,*N*-diethyl-7-(3,3,3-trifluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**12 hemitartrate**) as a fluffy white solid.
Yield: 32.2 mg (quantitative).
^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.20 (dd, *J* = 6.3, 2.4, 1H), 7.14 – 7.05 (m, 2H), 6.98 (d, *J* = 1.2, 1H), 6.31 (s, 1H), 4.50 (s, 1H), 3.99 – 3.88 (m, 1H), 3.63 – 3.40 (m, 7H), 3.20 (dd, *J* = 11.1, 4.5, 1H), 3.11 – 2.99 (m, 1H), 2.94 (t, *J* = 10.3, 1H), 2.73 (t, *J* = 12.0, 1H), 2.58 (ddd, *J* = 16.1, 10.2, 5.5, 2H), 1.30 (t, *J* = 7.1, 3H), 1.18 (t, *J* = 7.1, 3H).

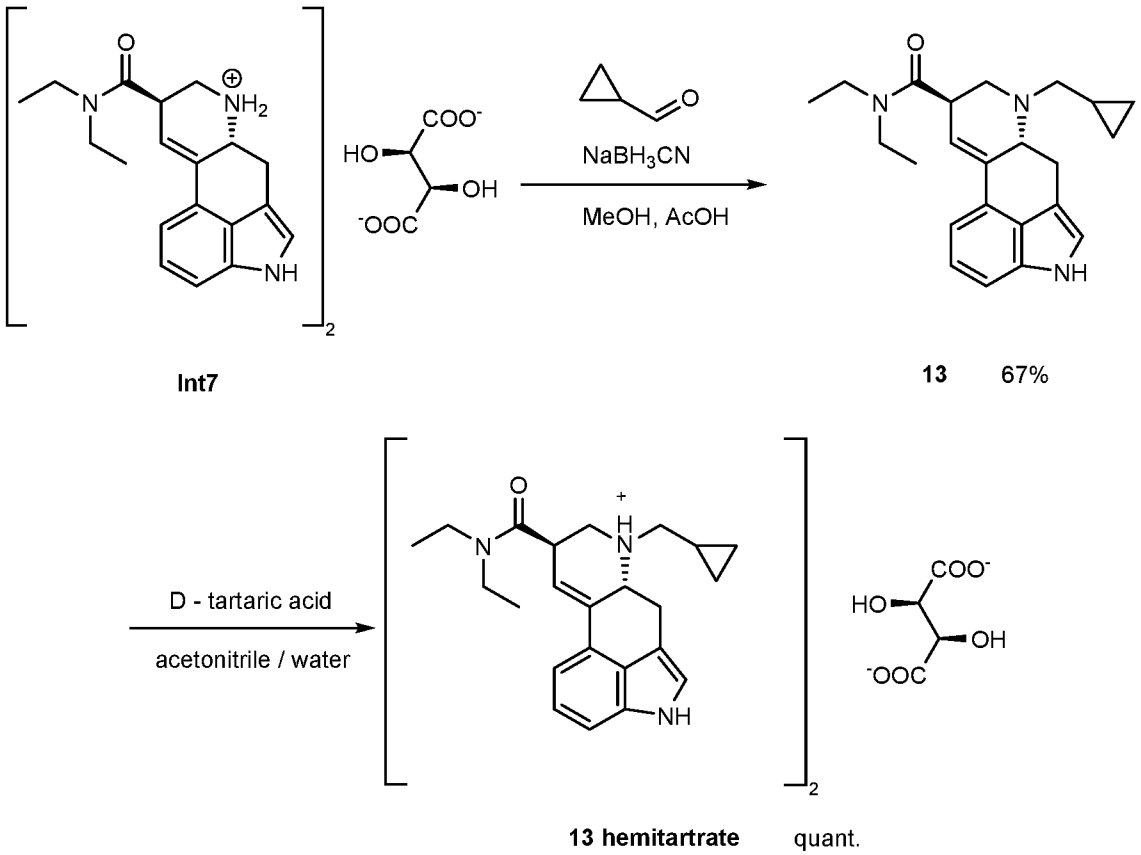
LC-MS purity: 97% (ELSD), 92% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.85 min.

LC-MS m/z: 406.0 $(M+H)^+$.

Example 13: Preparation of (6aR,9R)-N,N-diethyl-7-(cyclopropylmethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (13)

Reaction Scheme:



Int7 **13** 67%

13 hemitartrate quant.

Synthetic Protocols:

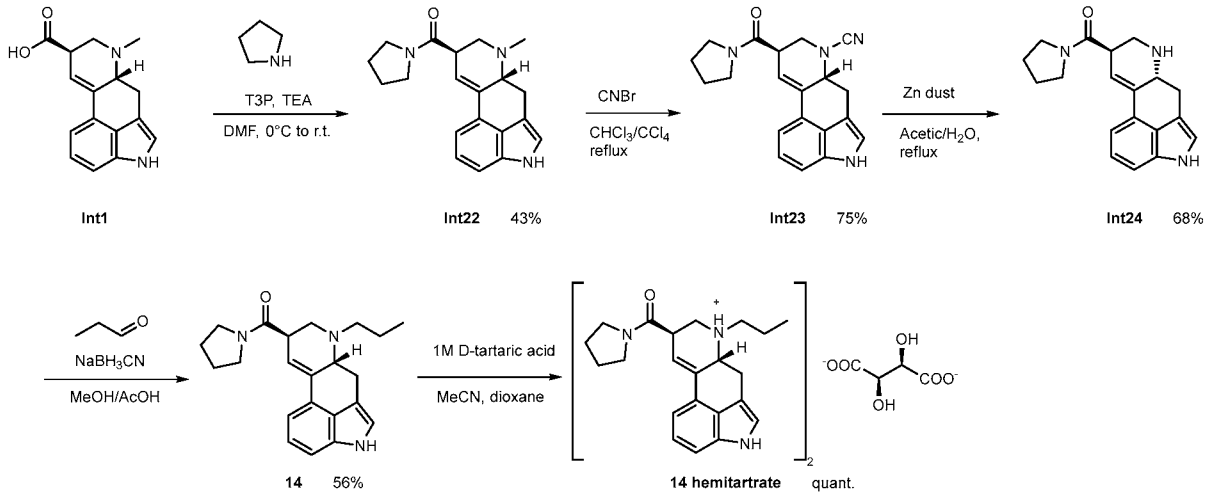
[00157] A solution of (6a*R*,9*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**Int7**, 30.0 mg, 78.0 µmol; 2 moles **Int7** per mole tartrate) and cyclopropanecarbaldehyde (23.0 µL, 0.31 mmol) in methanol (2 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (20.0 mg, 0.32 mmol) was added and the resulting mixture was stirred for 5 minutes followed by the addition of glacial acetic acid (20 uL). After stirring at 0 °C for 3 h, the solvents were removed *in vacuo*, the residue was partitioned between dichloromethane (100mL) and a 1% aqueous solution of ammonium

hydroxide (150mL), and the aqueous phase was further extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to provide (6a*R*,9*R*)-7-(cyclopropylmethyl)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**13**) as a colorless foam.
Yield: 19.0 mg (67%).
^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.17 (s, 1H), 7.27 (dd, J = 6.8, 1.9, 1H), 7.17 – 7.05 (m, 2H), 7.00 (s, 1H), 6.37 (s, 1H), 3.98 – 3.79 (m, 2H), 3.62 – 3.30 (m, 6H), 3.18 (dd, J = 11.3, 7.7, 1H), 3.01 – 2.84 (m, 2H), 2.78 (t, J = 13.1, 1H), 1.24 (t, J = 7.1, 3H), 1.13 (t, J = 7.1, 3H), 1.15 – 1.00 (m, 1H), 0.65 – 0.56 (m, 2H), 0.34 – 0.26 (m, 2H).
LC-MS purity: 99% (ELSD), 99% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.56 min.
LC-MS m/z: 364.1 $(M+H)^+$.

[00158] (6a*R*,9*R*)-7-(cyclopropylmethyl)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**13**, 19.0 mg, 52.2 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (26.2 µL, 26.2 µmol). The solvents were removed *in vacuo*, and the obtained material was redissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to yield (6a*R*,9*R*)-7-(cyclopropylmethyl)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**13 hemitartrate**) as a fluffy white solid.
Yield: 22.9 mg (quantitative).
^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.27 (p, J = 3.8, 1H), 7.17 – 7.10 (m, 2H), 7.07 (d, J = 0.8, 1H), 6.43 (dd, J = 2.8, 1.7, 1H), 4.40 (s, 1H), 4.36 – 4.24 (m, 1H), 4.15 (s, 1H), 3.77 – 3.36 (m, 8H), 3.31 – 3.22 (m, 1H), 3.02 (t, J = 12.9, 1H), 1.34 (t, J = 7.1, 3H), 1.34 – 1.16 (m, 1H), 1.20 (t, J = 7.1, 3H), 0.78 (q, J = 5.4, 2H), 0.48 (d, J = 4.3, 2H).
LC-MS purity: 100% (ELSD), 100% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.56 min.
LC-MS m/z: 364.1 $(M+H)^+$.

Example 14: Preparation of ((6aR,9R)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinolin-9-yl)(pyrrolidin-1-yl)methanone (14)

Reaction Scheme:



Synthetic Protocols:

[00159] A solution of (6a*R*,9R)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid (**Int1**, 500 mg, 1.86 mmol), triethylamine (1.05 mL, 7.44 mmol), and pyrrolidine (460 μl, 5.59 mmol) in dry *N*,*N*-dimethylformamide (10 mL) was cooled to 0 °C under an argon atmosphere. Propanephosphonic acid anhydride (T3P®, 3.26 mL, 5.59 mmol, 50% solution in DMF) was added dropwise over 5 minutes. The resulting mixture was stirred for 1 h at 0 °C. The reaction was judged to be complete by LC-MS and it was then quenched with ice-cold water (10 mL). The mixture was partitioned between 1M aqueous ammonium hydroxide solution (200 mL) and ethyl acetate (100 mL). The aqueous phase was re-extracted with ethyl acetate (2 x 150 mL). The organic phases were combined and then washed with 10% aq. lithium chloride solution (4 x 150 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 100:0 to 98:2) to afford ((6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)(pyrrolidin-1-yl)methanone (**Int22**) as a dark-brown solid.

Yield: 255 mg (43%).

LC-MS purity: 100% (ELSD), 100% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 4.59 min.

LC-MS m/z: 322.0 $(M+H)^+$.

[00160] A solution of ((6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)(pyrrolidin-1-yl)methanone (**Int22**, 52.7 mg, 0.164 mmol) in gradient-grade acetonitrile

(5.0 mL) was treated with aqueous 1M D-(-)-tartaric acid solution (81.4 µL, 0.081 mmol) and stirred for 5 min at room temperature. The solvent was removed *in vacuo*. The residue was re-dissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to yield ((6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)(pyrrolidin-1-yl)methanone hemitartrate (**Int22 hemitartrate**) as a fluffy white solid.

Yield: 69.0 mg (quantitative).

^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.24 (d, J = 7.7, 1H), 7.20 – 7.07 (m, 2H), 7.03 (s, 1H), 6.46 (s, 1H), 4.40 (s, 1H), 4.07 (dd, J = 6.5, 4.0, 1H), 3.90 – 3.79 (m, 1H), 3.76 – 3.67 (m, 1H), 3.71 (dd, J = 13.8, 6.3, 2H), 3.54 – 3.44 (m, 1H), 3.49 (dd, J = 12.7, 5.9, 2H), 3.28 – 3.16 (m, 1H), 2.94 (s, 3H), 2.95 – 2.83 (m, 1H), 2.10 – 1.90 (m, 4H).

LC-MS purity: 100% (ELSD), 100% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 4.59 min.

LC-MS m/z: 322.0 $(M+H)^+$.

[00161] To a solution of cyanogen bromide (380 mg, 3.60 mmol) in carbon tetrachloride (30 mL) under reflux was added a solution of ((6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)(pyrrolidin-1-yl)methanone (**Int22**, 255 mg, 0.795 mmol) in chloroform (10 mL) and carbon tetrachloride (70 mL) at a rate sufficient to maintain reflux. The reaction mixture was then heated under reflux for an additional 4 h. The mixture was then allowed to cool to room temperature and silica gel (silica gel 0.063-0.200 mm, 10 g) was added. The mixture was concentrated *in vacuo*. The resulting powder was added to the top of a flash chromatography column previously filled with silica gel and the product was eluted as follows (silica gel 60, 0.040–0.063 mm; eluent: cyclohexane/ethyl acetate 100:0 to 50:50) to afford (6a*R*,9*R*)-9-(pyrrolidine-1-carbonyl)-6,6a,8,9-tetrahydroindolo[4,3-*fg*]quinoline-7(4H)-carbonitrile (**Int23**) as a colorless amorphous solid.

Yield: 200 mg (75%).

^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 8.10 (s, 1H), 7.33 – 7.23 (m, 1H), 7.22 – 7.13 (m, 2H), 6.98 (s, 1H), 6.36 (s, 1H), 4.32 – 4.17 (m, 1H), 3.92 – 3.80 (m, 1H), 3.76 – 3.69 (m, 2H), 3.68 – 3.50 (m, 5H), 3.11 – 2.98 (m, 1H), 2.11 – 1.89 (m, 4H).

LC-MS purity: 98% (ELSD), 98% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.87 min.

LC-MS m/z: 333.0 $(M+H)^+$.

[00162] A solution of (6a*R*,9*R*)-9-(pyrrolidine-1-carbonyl)-6,6a,8,9-tetrahydroindolo[4,3-*fg*]quinoline-7(4H)-carbonitrile (**Int23**, 200 mg, 0.601 mmol) in acetic acid (15 mL) and water (1.5 mL) was treated with zinc dust (1000 mg). The resulting suspension was heated under reflux for 1 h. After cooling, the mixture was filtered through cotton, and the solution was basified with 10% aqueous ethylenediamine (100 mL) and stirred for 1 h. The mixture was diluted with water (100 mL) and extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and then filtered. The filtrate was treated with silica gel (silica gel 0.063-0.200 mm, 10g) and evaporated *in vacuo*. The powder was added to the top of a flash chromatography column previously filled with silica gel and the product was eluted as follows (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 100:0 to 98:2) to afford ((6a*R,9R*)-4,6,6a,7,8,9 hexahydroindolo[4,3-*fg*]quinolin-9-yl)(pyrrolidin-1-yl)methanone (**Int24**) as a dark amorphous solid.

Yield: 125 mg (68%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.08 (s, 1H), 7.28 – 7.17 (m, 1H), 7.16 – 7.06 (m, 2H), 6.95 (s, 1H), 6.39 (s, 1H), 3.71 (ddd, J = 11.4, 5.7, 2.4, 1H), 3.66 – 3.50 (m, 3H), 3.39 (td, J = 6.8, 3.7, 2H), 3.25 (dd, J = 12.9, 4.8, 1H), 3.14 (dd, J = 14.8, 5.8, 1H), 2.99 (dd, J = 12.5, 9.3, 1H), 2.67 – 2.53 (m, 1H), 2.14 (s, 1H), 1.98 – 1.91 (m, 2H), 1.90 – 1.77 (m, 2H).

LC-MS purity: 95% (ELSD), 95% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 4.22 min.

LC-MS m/z: 308.0 $(M+H)^+$.

[00163] A solution of ((6a*R*,9*R*)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)(pyrrolidin-1-yl)methanone hemitartrate (**Int24**, 40 mg, 105 µmol; 2 moles **Int24** per mole tartrate; salt prepared as described for other hemitartrates) and propanal (15 µL, 210 µmol) in methanol (2 mL) was purged with argon gas and cooled to 0 °C. Sodium cyanoborohydride (14 mg, 210 µmol) was added. The resulting mixture was stirred for 5 minutes, and then acetic acid (50 µL) was introduced. After stirring at 0 °C for 1 hour, silica gel (silica gel 0.063-0.200 mm, 10 g) was added, and the mixture was concentrated *in vacuo*. The powder was added to the top of a flash chromatography column previously filled with silica gel and the product was eluted as follows (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 99:1 to 98:2) to afford ((6a*R*,9*R*)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)(pyrrolidin-1-yl)methanone (**14**) as a colorless foam.

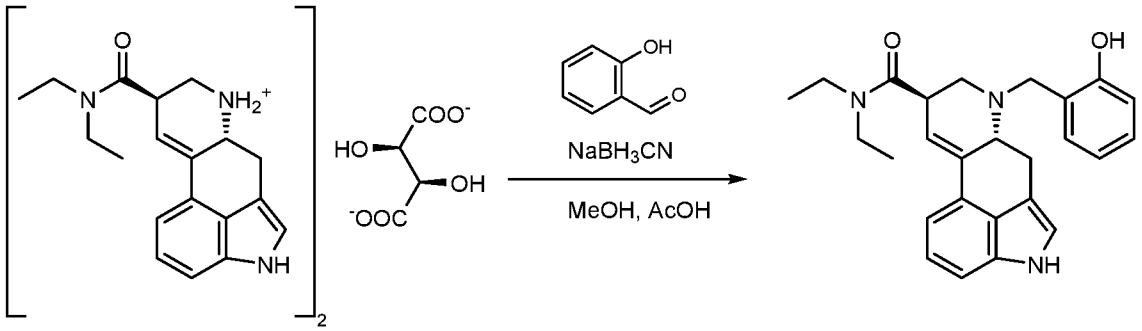
Yield: 20.5 mg (56%).

LC-MS purity: 100% (ELSD), 100% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.28 min.
LC-MS m/z: 350.1 $(M+H)^+$.

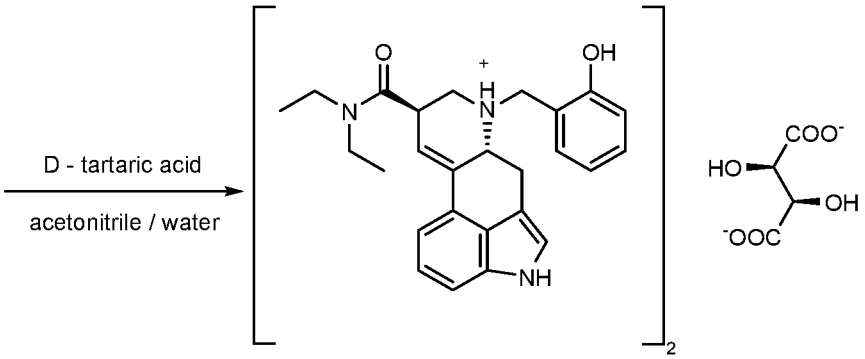
[00164] A solution of ((6a*R*,9*R*)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)(pyrrolidin-1-yl)methanone (**14**, 20.5 mg, 58.7 µmol) in gradient-grade acetonitrile (5.0 mL) was treated with aqueous 1M D-(-)-tartaric acid solution (29 µL, 29 µmol). After stirring at room temperature for 5 minutes, the solvent was removed *in vacuo*. The residue was re-dissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to afford ((6a*R*,9*R*)-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)(pyrrolidin-1-yl)methanone hemitartrate (**14 hemitartrate**) as a fluffy white solid.
Yield: 23.2 mg (quantitative).
^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.26 (dd, J = 7.2, 1.4, 1H), 7.19 – 7.09 (m, 2H), 7.06 (d, J = 1.1, 1H), 6.47 (s, 1H), 4.39 (s, 1H), 4.25 – 4.10 (m, 1H), 4.08 – 3.95 (m, 1H), 3.74 (dd, J = 6.3, 4.7, 2H), 3.70 – 3.63 (m, 2H), 3.59 – 3.47 (m, 3H), 3.47 – 3.38 (m, 1H), 3.25 – 3.11 (m, 1H), 2.99 (t, J = 12.0, 1H), 2.07 (dt, J = 11.5, 5.8, 2H), 1.97 (dt, J = 9.0, 4.6, 2H), 1.90 – 1.77 (m, 2H), 1.07 (t, J = 7.4, 3H).
LC-MS purity: 100% (ELSD), 100% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.28 min.
LC-MS m/z: 350.1 $(M+H)^+$.

Example 15: Preparation of (6aR,9R)-N,N-diethyl-7-(2-hydroxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (16)

Reaction Scheme:



Int7 **16** 43%



16 hemitartrate quant.

Synthetic Protocols:

[00165] A solution of (6a*R*,9*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**Int7**, 20.0 mg, 52.0 μmol; 2 moles **Int7** per mole tartrate) and 2-hydroxybenzaldehyde (22.0 μL, 0.208 mmol) in methanol (2 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (13.0 mg, 0.208 mmol) was introduced and the resulting mixture was stirred for 5 minutes followed by addition of glacial acetic acid (20 μL). After stirring at 0 °C for 3 h, the solvents were removed *in vacuo*, the residue was partitioned between dichloromethane (100 mL) and a aqueous 1% solution of ammonium hydroxide (150 mL), and the aqueous phase was further extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to give a material still containing impurities. This crude material was dissolved in 1M hydrochloric acid (25 mL) and methanol (5 mL), washed with diethyl ether (3 x 50 mL), basified with 24% aqueous ammonium hydroxide, and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentration *in vacuo* to provide (6a*R*,9*R*)-*N*,*N*-diethyl-7-(2-hydroxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**16**) as a colorless solid.

Yield: 9.2 mg (43%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.03 (s, 1H), 7.25 (dd, *J* = 6.1, 2.6, 1H), 7.20 – 7.06 (m, 3H), 6.96 (t, *J* = 1.7, 1H), 6.87 – 6.71 (m, 3H), 6.37 (s, 1H), 4.61 (d, *J* = 14.2, 1H), 3.79 – 3.73 (m, 1H), 3.68 (dd, *J* = 14.3, 5.1, 1H), 3.57 (d, *J* = 14.3, 1H), 3.49 (ddd, *J* = 11.5, 4.6, 2.5, 1H), 3.41 (dd, *J* = 15.0, 7.4, 1H), 3.36 – 3.25 (m, 4H), 3.08 (dd, *J* = 11.5, 4.4, 1H), 2.79 (dd, *J* = 12.0, 2.2, 1H), 2.72 (dd, *J* = 11.6, 9.2, 1H), 1.08 (dt, *J* = 14.3, 7.1, 6H).

LC-MS purity: 99% (ELSD), 99% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.85 min.

LC-MS m/z: 416.1 $(M+H)^+$.

[00166] (6a*R*,9*R*)-*N*,*N*-diethyl-7-(2-hydroxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**16**, 9.20 mg, 22.1 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (11.0 µL, 11.0 µmol). The solvents were removed *in vacuo*, and the obtained material was redissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to yield (6a*R*,9*R*)-*N*,*N*-diethyl-7-(2-hydroxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**16 hemitartrate**) as a fluffy off-white solid.

Yield: 13.3 mg (quantitative).

^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.33 – 7.18 (m, 3H), 7.16 – 7.07 (m, 2H), 7.03 (d, *J* = 1.0, 1H), 6.87 (t, *J* = 7.7, 2H), 6.37 (s, 1H), 4.67 (d, *J* = 13.6, 1H), 4.42 (s, 1H), 4.05 (d, *J* = 13.6, 1H), 4.00 – 3.91 (m, 2H), 3.86 (dd, *J* = 13.8, 5.0, 1H), 3.66 – 3.33 (m, *J* = 7.9, 1.9, 6H), 3.12 – 2.91 (m, 2H), 1.18 (t, *J* = 7.1, 3H), 1.12 (t, *J* = 7.1, 3H).

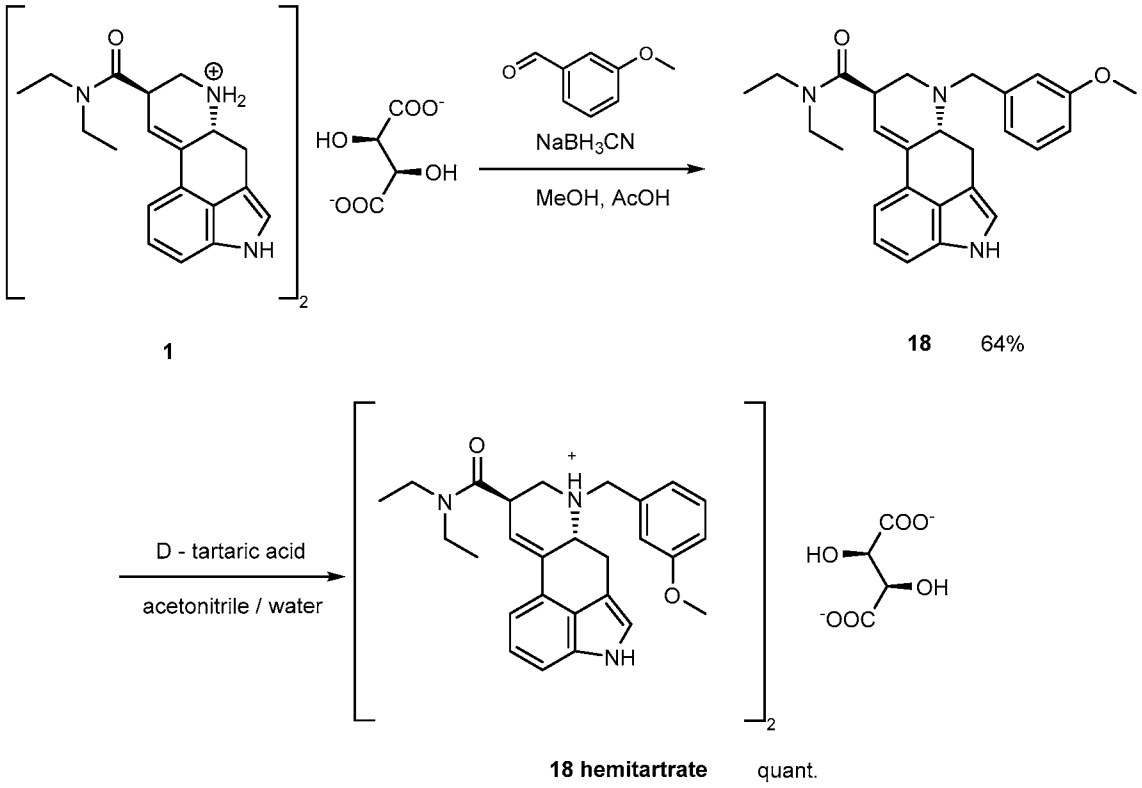
LC-MS purity: 97% (ELSD), 90% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.84 min.

LC-MS m/z: 416.1 $(M+H)^+$.

Example 16: Preparation of (6aR,9R)-N,N-diethyl-7-(3-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (18)

Reaction Scheme:



1 **18** 64%

18 hemitartrate quant.

Synthetic Protocols:

[00167] A solution of (6a*R*,9*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**Int7**, 20.0 mg, 52.0 µmol; 2 moles **Int7** per mole tartrate) and 3-methoxybenzaldehyde (28.3 µL, 0.208 mmol) in methanol (2 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (13.0 mg, 0.208 mmol) was introduced and the resulting mixture was stirred for 5 minutes followed by addition of glacial acetic acid (20 µL). After stirring at 0 °C for 3 h, the solvents were removed *in vacuo*, the residue was partitioned between dichloromethane (100 mL) and a 1% aqueous solution of ammonium hydroxide (150 mL), and the aqueous phase was further extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to provide a material still containing impurities. This crude material was dissolved in 1M hydrochloric acid (25 mL) and methanol (5 mL), washed with diethyl ether (3 x 50 mL), basified with 24% aqueous ammonium hydroxide, and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in* vacuo to give (6a*R*,9*R*)-*N*,*N*-diethyl-7-(3-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (**18**) as a colorless solid.

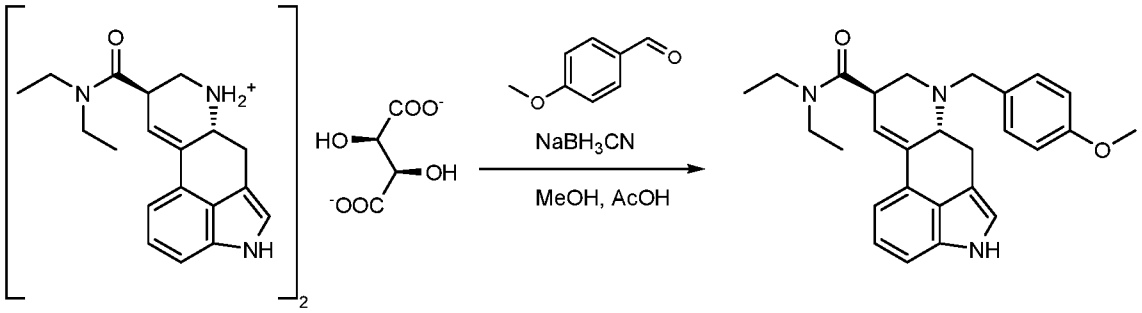
Yield: 14.2 mg (64%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.02 (s, 1H), 7.33 – 7.21 (m, 2H), 7.18 – 7.08 (m, 2H), 7.06 – 7.00 (m, 2H), 6.98 (t, *J* = 1.7, 1H), 6.88 – 6.81 (m, 1H), 6.37 (s, 1H), 4.33 (d, *J* = 14.1, 1H), 3.81 (s, 3H), 3.74 – 3.68 (m, 1H), 3.68 (dd, *J* = 14.6, 5.4, 1H), 3.49 – 3.25 (m, 6H), 3.02 (ddd, *J* = 11.1, 4.7, 1.0, 1H), 2.69 (ddd, *J* = 14.6, 11.3, 1.7, 1H), 2.56 (t, *J* = 10.5, 1H), 1.08 (td, *J* = 7.1, 2.5, 6H).
LC-MS purity: 97% (ELSD), 99% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.31 min.
LC-MS m/z: 430.1 $(M+H)^+$.

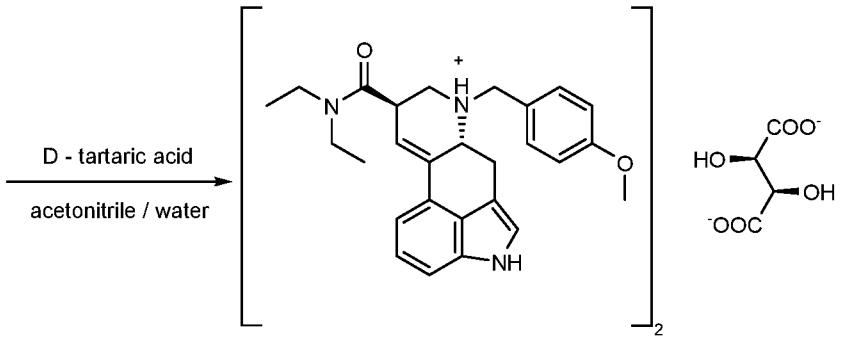
[00168] (6a*R*,9*R*)-*N*,*N*-diethyl-7-(3-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**18**, 14.2 mg, 33.0 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (16.4 µL, 16.4 µmol). The solvents were removed *in vacuo*, and the obtained material was redissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to yield (6a*R*,9*R*)-*N*,*N*-diethyl-7-(3-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**18 hemitartrate**) as a fluffy white solid.
Yield: 16.8 mg (quantitative).
^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.30 (t, *J* = 7.9, 1H), 7.22 (dd, *J* = 6.5, 2.2, 1H), 7.15 – 7.00 (m, 5H), 6.91 (dd, *J* = 8.2, 1.9, 1H), 6.35 (s, 1H), 4.46 (d, *J* = 13.1, 1H), 4.44 (s, 1H), 3.91 – 3.84 (m, 2H), 3.81 (s, 3H), 3.83 – 3.78 (m, 2H), 3.51 – 3.33 (m, 4H), 3.21 (dd, *J* = 11.4, 4.2, 1H), 2.92 (t, *J* = 13.8, 1H), 2.82 (t, *J* = 10.2, 1H), 1.13 (dt, *J* = 14.4, 7.2, 6H).
LC-MS purity: 99% (ELSD), 96% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.31 min.
LC-MS m/z: 430.1 $(M+H)^+$.

Example 17: Preparation of (6aR,9R)-N,N-diethyl-7-(4-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (19)

Reaction Scheme:



Int7 **19** 70%



19 hemitartrate quant.

Synthetic Protocols:

[00169] A solution of (6a*R*,9*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**Int7**, 20.0 mg, 52.0 µmol; 2 moles **Int7** per mole tartrate) and *p*-anisaldehyde (22.0 µL, 0.208 mmol) in methanol (2 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (13.0 mg, 0.208 mmol) was introduced and the resulting mixture was stirred for 5 minutes followed by addition of glacial acetic acid (20 µL). After stirring at 0 °C for 3 h, the solvents were removed *in vacuo*, the residue was partitioned between dichloromethane (100 mL) and a 1% aqueous solution of ammonium hydroxide (150 mL), and the aqueous phase was further extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to provide a material still containing impurities. This crude material was dissolved in 1M hydrochloric acid (25 mL) and methanol (5 mL), washed with diethyl ether (3 x 50 mL), basified with 24% aqueous ammonium hydroxide, and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentration *in vacuo* to provide (6a*R*,9*R*)-*N*,*N*-diethyl-7-(4-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**19**) as a colorless solid.

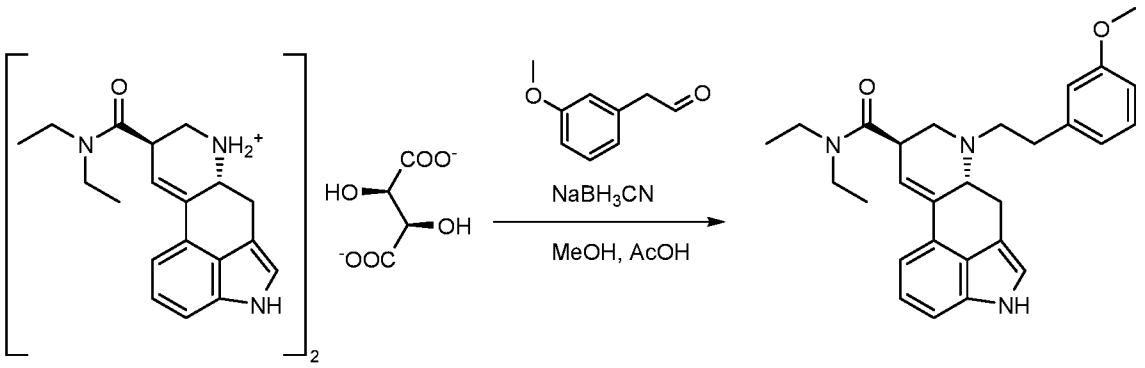
Yield: 15.6 mg (70%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.01 (s, 1H), 7.31 (d, J = 8.6, 2H), 7.23 (dd, J = 6.7, 1.9, 1H), 7.14 – 7.05 (m, 2H), 6.96 (t, J = 1.7, 1H), 6.89 (d, J = 10.9, 2H), 6.32 (s, 1H), 4.24 (d, J = 13.7, 1H), 3.77 (s, 3H), 3.69 (dd, J = 14.7, 5.3, 1H), 3.63 – 3.58 (m, 1H), 3.45 – 3.18 (m, 6H), 2.99 (ddd, J = 11.1, 4.7, 0.9, 1H), 2.66 (ddd, J = 14.5, 11.3, 1.6, 1H), 2.49 (t, J = 10.6, 1H), 1.05 (t, J = 7.1, 6H).
LC-MS purity: 97% (ELSD), 99% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.24 min.
LC-MS m/z: 430.1 $(M+H)^+$.

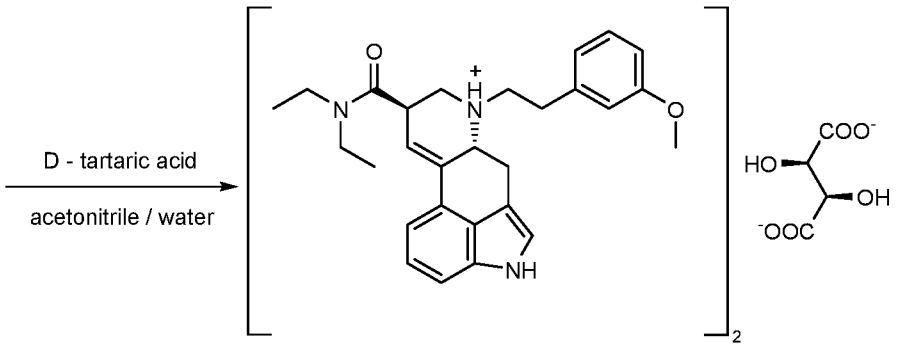
[00170] (6a*R*,9*R*)-*N*,*N*-diethyl-7-(4-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**19**, 15.6 mg, 36.3 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (18.2 µL, 18.2 µmol). The solvents were removed *in vacuo*, and the obtained material was redissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to yield (6a*R*,9*R*)-*N*,*N*-diethyl-7-(4-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**19 hemitartrate**) as a fluffy white solid.
Yield: 18.4 mg (quantitative).
^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.44 (d, J = 8.6, 2H), 7.25 (dd, J = 5.4, 3.4, 1H), 7.17 – 7.10 (m, 2H), 7.07 (d, J = 1.1, 1H), 6.98 (d, J = 8.7, 2H), 6.36 (s, 1H), 4.48 (d, J = 13.5, 1H), 4.45 (s, 1H), 4.02 – 3.97 (m, 1H), 3.97 – 3.88 (m, 3H), 3.81 (s, 3H), 3.48 (dd, J = 14.8, 7.6, 2H), 3.45 (ddd, J = 14.6, 13.5, 7.4, 2H), 3.30 – 3.27 (m, 1H), 3.09 – 2.83 (m, 2H), 1.17 (dt, J = 14.2, 7.1, 6H).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.24 min.
LC-MS m/z: 430.1 $(M+H)^+$.

Example 18: Preparation of (6aR,9R)-N,N-diethyl-7-(3-methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (20)

Reaction Scheme:



Int7 **20** 43%



20 hemitartrate quantitative

Synthetic Protocols:

[00171] A solution of (6a*R*,9*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**Int7**, 30.0 mg, 78.0 µmol; 2 moles **Int7** per mole tartrate) and 2-(3-methoxyphenyl)acetaldehyde (50.0 mg, 0.33 mmol) in methanol (2 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (20.0 mg, 0.32 mmol) was added and the resulting mixture was stirred for 5 minutes followed by addition of glacial acetic acid (20 µL). After stirring at 0 °C for 3 h, the solvents were removed *in vacuo*, the residue was partitioned between dichloromethane (100 mL0 and a 1% aqueous solution of ammonium hydroxide (150 mL), and the aqueous phase was further extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to provide a material still containing impurities. This crude material was dissolved in 1M hydrochloric acid (25 mL) and methanol (5 mL), washed with diethyl ether (3 x 50 mL), basified with 24% aqueous ammonium hydroxide, and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide (6a*R*,9*R*)-*N*,*N*-diethyl-7-(3-

methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**20**) as a colorless foam.

Yield: 14.9 mg (43%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 8.99 (s, 1H), 7.27 – 7.16 (m, 2H), 7.14 – 7.05 (m, 2H), 6.95 (t, *J* = 1.7, 1H), 6.87 (dd, *J* = 4.0, 2.2, 2H), 6.76 (ddd, *J* = 8.3, 2.5, 0.9, 1H), 6.30 (s, 1H), 3.77 (s, 3H), 3.74 – 3.65 (m, 1H), 3.55 (dd, *J* = 14.5, 5.3, 1H), 3.50 – 3.29 (m, 5H), 3.22 – 3.10 (m, 2H), 2.92 – 2.69 (m, 4H), 2.48 (ddd, *J* = 14.3, 11.0, 1.6, 1H), 1.21 (t, *J* = 7.1, 3H), 1.11 (t, *J* = 7.1, 3H).

LC-MS purity: 99% (ELSD), 99% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.58 min.

LC-MS m/z: 444.2 $(M+H)^+$.

[00172] (6a*R*,9*R*)-*N*,*N*-diethyl-7-(3-methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**20**, 14.9 mg, 33.6 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (16.8 µL, 16.8 µmol). The solvents were removed *in vacuo*, and the obtained material was redissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to yield (6a*R*,9*R*)-*N*,*N*-diethyl-7-(3-methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**20 hemitartrate**) as a fluffy off-white solid.

Yield: 17.4 mg (quantitative).

^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.28 – 7.20 (m, 2H), 7.14 – 7.08 (m, 2H), 7.02 (d, *J* = 1.0, 1H), 6.92 – 6.87 (m, 2H), 6.80 (dd, *J* = 8.3, 1.5, 1H), 6.37 (s, 1H), 4.41 (s, 1H), 4.08 – 3.96 (m, 2H), 3.79 (s, 3H), 3.68 – 3.49 (m, 5H), 3.49 – 3.38 (m, 4H), 3.10 – 2.98 (m, 2H), 2.91 (t, *J* = 12.9, 1H), 1.32 (t, *J* = 7.2, 3H), 1.19 (t, *J* = 7.1, 3H).

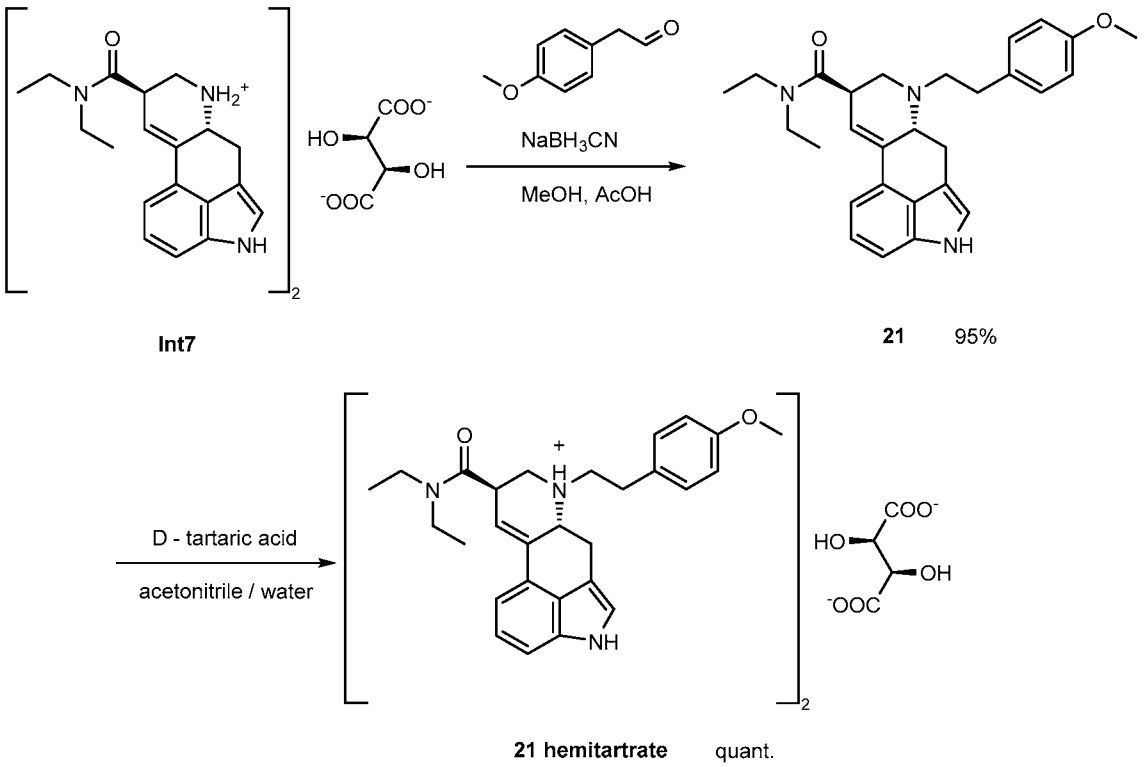
LC-MS purity: 96% (ELSD), 90% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.58 min.

LC-MS m/z: 444.1 $(M+H)^+$.

Example 19: Preparation of (6aR,9R)-N,N-diethyl-7-(4-methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (21)

Reaction Scheme:



Int7 **21** 95%

21 hemitartrate quant.

Synthetic Protocols:

[00173] A solution of (6a*R*,9*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**Int7**, 33.0 mg, 86.0 µmol; 2 moles **Int7** per mole tartrate) and 2-(4-methoxyphenyl)acetaldehyde (50.0 mg, 0.33 mmol) in methanol (2 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (20.0 mg, 0.32 mmol) was added and the resulting mixture was stirred for 5 minutes followed by addition of glacial acetic acid (20 µL). After stirring at 0 °C for 3 h, the solvents were removed *in vacuo*, the residue was partitioned between dichloromethane (100 mL) and a 1% aqueous solution of ammonium hydroxide (150 mL), and the aqueous phase was further extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to provide a material still containing impurities. This crude material was dissolved in 1M hydrochloric acid (25 mL) and methanol (5 mL), washed with diethyl ether (3 x 50 mL), basified with 24% aqueous ammonium hydroxide, and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide (6a*R*,9*R*)-*N*,*N*-diethyl-7-(4-methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**21**) as a colorless foam.

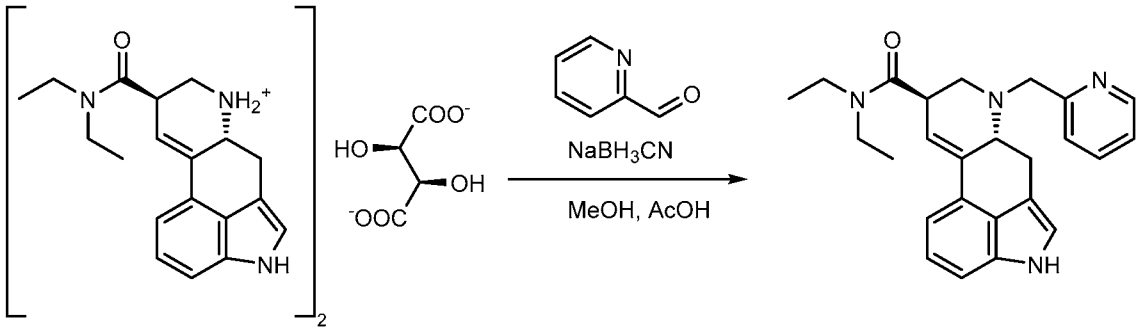
Yield: 36.2 mg (95%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.04 (s, 1H), 7.25 – 7.17 (m, 3H), 7.13 – 7.05 (m, 2H), 6.95 (t, *J* = 1.6, 1H), 6.90 – 6.81 (m, 2H), 6.32 (s, 1H), 3.80 – 3.75 (m, 1H), 3.75 (s, *J* = 3.0, 3H), 3.53 (dd, *J* = 15.8, 5.4, 1H), 3.48 – 3.32 (m, 5H), 3.23 – 3.07 (m, 2H), 2.93 – 2.74 (m, 4H), 2.55 (ddd, *J* = 15.6, 12.6, 1.6, 1H), 1.21 (t, *J* = 7.1, 3H), 1.11 (t, *J* = 7.1, 3H).
LC-MS purity: 99% (ELSD), 99% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.55 min.
LC-MS m/z: 444.2 $(M+H)^+$.

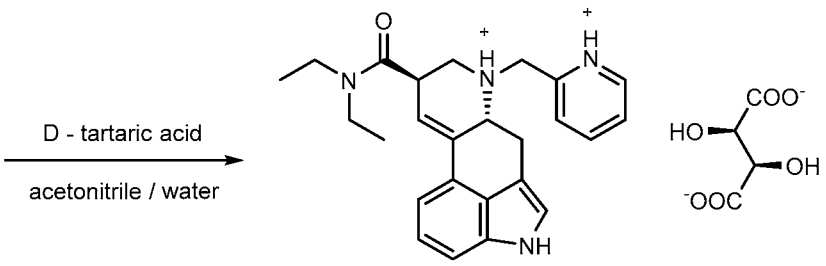
[00174] (6a*R*,9*R*)-*N*,*N*-diethyl-7-(4-methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**21**, 36.2 mg, 81.6 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (40.8 µL, 40.80 µmol). The solvents were removed *in vacuo*, and the obtained material was redissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to yield (6a*R*,9*R*)-*N*,*N*-diethyl-7-(4-methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**21 hemitartrate**) as a fluffy white solid.
Yield: 42.3 mg (quantitative).
^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.28 – 7.19 (m, 3H), 7.16 – 7.08 (m, 2H), 7.03 (d, *J* = 0.8, 2H), 6.89 (d, *J* = 8.6, 2H), 6.39 (s, 1H), 4.42 (s, 1H), 4.18 – 4.03 (m, 2H), 3.77 (s, 3H), 3.68 – 3.54 (m, 2H), 3.54 – 3.40 (m, 4H), 3.10 – 2.89 (m, 3H), 1.32 (t, *J* = 7.2, 3H), 1.20 (t, *J* = 7.1, 3H).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.57 min.
LC-MS m/z: 444.1 $(M+H)^+$.

Example 20: Preparation of (6aR,9R)-N,N-diethyl-7-(pyridin-2-ylmethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (22)

Reaction Scheme:



Int7 **22** 76%



22 tartrate quant.

Synthetic Protocols:

[00175] A solution of (6a*R*,9*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**Int7**, 20.0 mg, 52.0 µmol; 2 moles **Int7** per mole tartrate) and pyridine-2-carbaldehyde (20.0 µL, 0.208 mmol) in methanol (2 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (13.0 mg, 0.208 mmol) was introduced and the resulting mixture was stirred for 5 minutes followed by addition of glacial acetic acid (20 µL). After stirring at 0 °C for 3 h, the solvents were removed *in vacuo*, the residue was partitioned between dichloromethane (100 mL) and a 1% aqueous solution of ammonium hydroxide (150 mL), and the aqueous phase was further extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to give a material still containing impurities. This crude material was dissolved in 1M hydrochloric acid (25 mL) and methanol (5 mL), washed with diethyl ether (3 x 50 mL), basified with 24% aqueous ammonium hydroxide, and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in* vacuo to provide (6a*R*,9*R*)-*N*,*N*-diethyl-7-(pyridin-2-ylmethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**22**) as a dark-tinted amorphous solid.

Yield: 15.8 mg (76%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.02 (s, 1H), 8.51 (ddd, *J* = 4.8, 1.6, 0.8, 1H), 7.73 (td, *J* = 7.7, 1.8, 1H), 7.57 (d, *J* = 7.8, 1H), 7.22 (dt, *J* = 7.7, 3.9, 2H), 7.15 – 7.05 (m, 2H), 6.94 (t, *J* = 1.7, 1H), 6.33 (s, 1H), 4.31 (d, *J* = 14.8, 1H), 3.76 – 3.68 (m, 1H), 3.72 (d, *J* = 14.8, 1H), 3.66 (dd, *J* = 14.4, 5.1, 1H), 3.57 – 3.46 (m, 1H), 3.44 – 3.27 (m, 4H), 3.05 (dd, *J* = 10.8, 4.3, 1H), 2.69 (t, *J* = 10.5, 1H), 2.63 (ddd, *J* = 14.4, 11.2, 1.7, 1H), 1.08 (dt, *J* = 12.3, 7.1, 6H).

LC-MS purity: 99% (ELSD), 99% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.74 min.

LC-MS m/z: 401.1 $(M+H)^+$.

[00176] (6a*R*,9*R*)-*N*,*N*-diethyl-7-(pyridin-2-ylmethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**22**, 15.8 mg, 39.5 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (39.4 µL, 39.4 µmol). The solvents were removed *in vacuo*, and the obtained material was redissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to yield (6a*R*,9*R*)-*N*,*N*-diethyl-7-(pyridin-2-ylmethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide tartrate (**22 tartrate**) as a fluffy off-white solid.

Yield: 21.8 mg (quantitative).

^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 8.60 (d, *J* = 4.2, 1H), 7.91 (td, *J* = 7.7, 1.7, 1H), 7.67 (d, *J* = 7.8, 1H), 7.41 (dd, *J* = 7.0, 5.5, 1H), 7.23 (dd, *J* = 6.8, 1.9, 1H), 7.16 – 7.07 (m, 2H), 7.00 (d, *J* = 1.2, 1H), 6.39 (s, 1H), 4.63 (d, *J* = 14.7, 1H), 4.49 (s, 2H), 4.21 (d, *J* = 14.6, 1H), 4.08 – 3.93 (m, 2H), 3.73 (dd, *J* = 14.0, 5.2, 1H), 3.57 – 3.34 (m, 5H), 3.13 (dd, *J* = 11.6, 8.9, 1H), 3.03 – 2.90 (m, 1H), 1.22 (t, *J* = 7.1, 3H), 1.15 (t, *J* = 7.1, 3H).

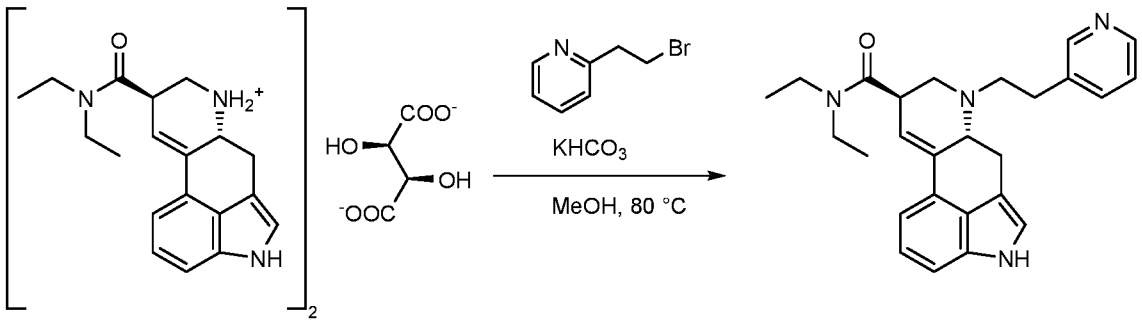
LC-MS purity: 99% (ELSD), 96% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.74 min.

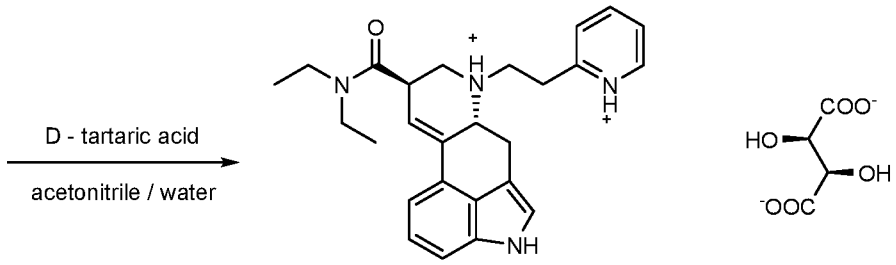
LC-MS m/z: 401.1 $(M+H)^+$.

Example 21: Preparation of (6aR,9R)-N,N-diethyl-7-(2-(pyridin-2-yl)ethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (23)

Reaction Scheme:



Int7 **23** 18%



23 tartrate quant.

Synthetic Protocols:

[00177] A solution of (6a*R*,9*R*)-*N*,*N*-diethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**Int7**, 20.0 mg, 53.0 µmol; 2 moles **Int7** per mole tartrate), potassium bicarbonate (32 mg, 0.32 mmol), and 2-(2-bromoethyl)pyridin-1-ium bromide (28.0 mg, 0.33 mmol) in methanol (2 mL) was purged with argon and stirred at 80 °C for 4 days. After LC-MS analysis showed complete consumption of starting material, the reaction mixture was concentrated on silica gel and subjected to flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2). The combined product fractions were stripped of solvents *in vacuo* to yield (6a*R*,9*R*)-*N*,*N*-diethyl-7-(2-(pyridin-2-yl)ethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (**23**) as a dark-tinted amorphous solid.

Yield: 3.8 mg (18%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 8.97 (s, 1H), 8.53 – 8.49 (m, 1H), 7.65 (td, J = 7.7, 1.9, 1H), 7.29 (d, J = 7.8, 1H), 7.22 (dd, J = 6.7, 2.0, 1H), 7.18 – 7.13 (m, 1H), 7.11 – 7.07 (m, 2H), 6.95 (t, J = 1.8, 1H), 6.29 (s, 1H), 3.71 – 3.62 (m, 1H), 3.53 (dd, J = 14.4, 5.3, 1H), 3.48 – 3.26 (m, 6H), 3.19 (dd, J = 11.1, 3.8, 1H), 3.06 – 2.93 (m, 3H), 2.73 (t, J = 10.7, 1H), 2.41 (ddd, J = 14.3, 11.0, 1.6, 1H), 1.22 (t, J = 7.1, 3H), 1.11 (t, J = 7.1, 3H).

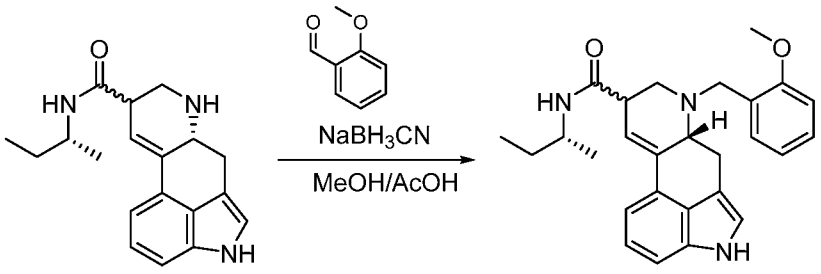
LC-MS purity: 98% (ELSD), 97% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 4.88 min.
LC-MS m/z: 415.1 $(M+H)^+$.

[00178] (6a*R*,9*R*)-*N*,*N*-diethyl-7-(2-(pyridin-2-yl)ethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**23**, 3.8 mg, 9.17 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (9.2 µL, 9.2 µmol). The solvents were removed *in vacuo*, and the obtained material was redissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to yield (6a*R*,9*R*)-*N*,*N*-diethyl-7-(2-(pyridin-2-yl)ethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide tartrate (**23 tartrate**) as a fluffy light-brown solid.
Yield: 5.2 mg (quantitative).
^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 8.52 (dd, J = 4.9, 0.8, 1H), 7.80 (td, J = 7.7, 1.8, 1H), 7.43 (d, J = 7.8, 1H), 7.31 (ddd, J = 7.5, 5.0, 0.9, 1H), 7.28 – 7.21 (m, 1H), 7.13 (dd, J = 6.7, 5.6, 2H), 7.05 (d, J = 1.0, 1H), 6.41 (dd, J = 3.6, 1.7, 1H), 4.45 (s, 2H), 4.29 – 4.18 (m, 1H), 4.13 – 4.03 (m, 1H), 3.81 – 3.35 (m, 9H), 3.01 (t, J = 12.9, 1H), 1.33 (t, J = 7.1, 3H), 1.19 (t, J = 7.1, 3H).
LC-MS purity: 95% (ELSD), 92% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 4.88 min.
LC-MS m/z: 415.1 $(M+H)^+$.

Example 22: Preparation of (6aR)-N-((R)-sec-butyl)-7-(2-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (24m)

Reaction Scheme:



Int10m **24m**

Synthetic Protocols:

[00179] A solution of (6*aR*)-*N*-((*R*)-sec-butyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int10m**, 20 mg, 46.7 µmol; mixture of epimers at position 9) and 2-methoxybenzaldehyde (27 mg, 194 µmol) in methanol (0.5 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (12 mg, 194 µmol) was added and the resulting mixture was stirred for 5 minutes. Acetic acid (20 µL) was then introduced, and the reaction mixture was stirred at 0 °C for 24 h. There was obtained a diastereomeric mixture of (6*aR*)-*N*-((*R*)-sec-butyl)-7-(2-methoxybenzyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**24m**; mixture of diastereomers; epimers at position 9) as confirmed via LC-MS analysis.

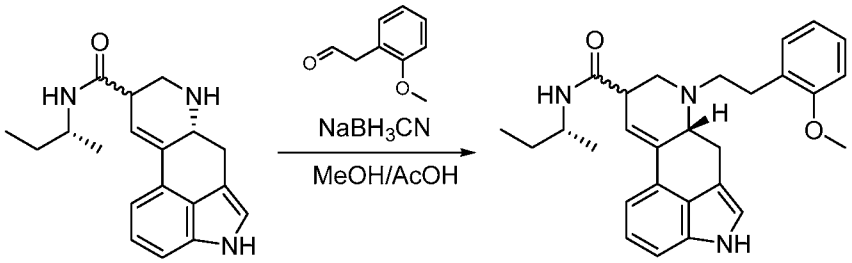
Composition by LC-MS: 87% (ELSD, faster moving isomer), 13% (ELSD, slower moving isomer).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.54 min (isomer A), 6.57 min (isomer B).

LC-MS m/z: 430.2 $(M+H)^+$.

Example 23: Preparation of (6aR)-N-((R)-sec-butyl)-7-(2-methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (25m)

Reaction Scheme:



Int10m **25m**

Synthetic Protocols:

[00180] A solution of (6*aR*)-*N*-((*R*)-sec-butyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**Int10m**, 20 mg, 46.7 µmol; mixture of epimers at position 9) and 2-(2-methoxyphenyl)acetaldehyde (29 mg, 194 µmol) in methanol (0.5 mL) was purged with argon and cooled to 0 °C. Sodium cyanoborohydride (12 mg, 194 µmol) was added and the resulting mixture was stirred for 5 minutes. Acetic acid (20 µL) was introduced and the reaction mixture was then stirred at 0 °C for 24 h. There was obtained a diastereomeric mixture of

(6*aR*)-*N*-((*R*)-sec-butyl)-7-(2-methoxyphenethyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**25m**; mixture of diastereomers; epimers at position 9) as confirmed via LC-MS analysis.

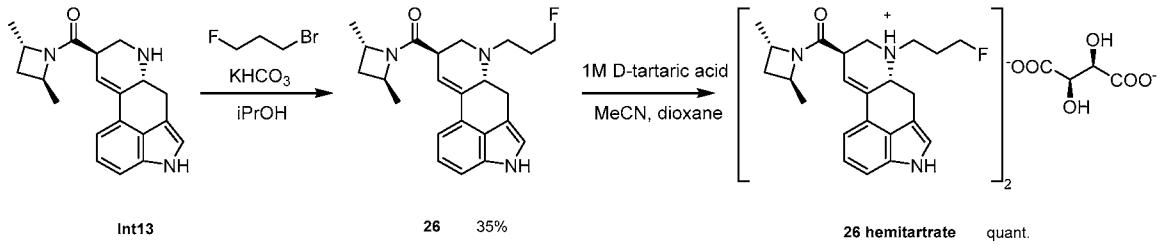
Composition by LC-MS: 87% (ELSD, faster moving isomer), 13% (ELSD, slower moving isomer).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 6.49 min (isomer A), 6.79 min (isomer B).

LC-MS m/z: 444.2 $(M+H)^+$.

Example 24: Preparation of ((2S,4S)-2,4-dimethylazetidin-1-yl)((6aR,9R)-7-(3-fluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinolin-9-yl)methanone (26)

Reaction Scheme:



Synthetic Protocols:

[00181] A solution of ((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)((6a*R*,9*R*)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanone (**Int13**, 40 mg, 0.117 mmol), potassium bicarbonate (47 mg, 0.468 mg), and 1-bromo-3-fluoropropane (33 mg, 0.234 mmol) in isopropanol (1.0 mL) was purged with argon and heated to 90 °C in a sealed glass vial. The reaction mixture was stirred for 20 hours. The vial was opened, and the solvent was removed and evaporated *in vacuo*. The crude material was redissolved in dichloromethane (25 mL), treated with silica gel (silica gel 0.063-0.200 mm, 10 g), and concentrated. The resulting powder was added to a flash column and was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 99:1 to 98:2) to afford ((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)((6a*R*,9*R*)-7-(3-fluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanone (**26**) as a colorless foam.

Yield: 15.6 mg (35%).

^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 8.99 (s, 1H), 7.22 (dd, J = 6.6, 2.1, 1H), 7.16 – 7.03 (m, 2H), 6.94 (t, J = 1.7, 1H), 6.30 (s, 1H), 4.73 – 4.55 (m, 2H), 4.55 – 4.44 (m, 1H), 4.43 – 4.33 (m, 1H), 3.50 (dd, J = 14.6, 5.1, 1H), 3.41 – 3.29 (m, 2H), 3.18 – 3.02 (m, 2H), 2.66 –

2.43 (m, 3H), 2.01 – 1.91 (m, 2H), 2.05 – 1.86 (m, 2H), 1.46 (d, *J* = 6.3, 3H), 1.39 (d, *J* = 6.3, 3H).

LC-MS purity: 100% (ELSD), 100% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.53 min.

LC-MS m/z: 382.1 $(M+H)^+$.

[00182] ((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)((6a*R*,9*R*)-7-(3-fluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanone (**26**, 15.6 mg, 40.9 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (19.6 µL, 19.6 µmol). The resulting solution was stirred for 5 min. The solvent was removed *in vacuo* and the residue was re-dissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to afford ((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)((6a*R*,9*R*)-7-(3-fluoropropyl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanone hemitartrate (**26 hemitartrate**) as a fluffy white solid.

Yield: 18.6 mg (quantitative).

^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.22 (dd, *J* = 6.9, 1.8, 1H), 7.16 – 7.06 (m, 2H), 7.00 (d, *J* = 1.2, 1H), 6.32 (s, 1H), 4.73 (dd, *J* = 13.2, 6.2, 1H), 4.70 – 4.61 (m, 1H), 4.50 (dd, *J* = 12.7, 6.3, 2H), 4.43 (s, 1H), 3.88 – 3.74 (m, 1H), 3.70 – 3.64 (m, 2H), 3.62 (dd, *J* = 14.7, 5.4, 1H), 3.38 (dd, *J* = 15.3, 4.2, 1H), 3.38 – 3.28 (m, 2H), 3.05 (t, *J* = 9.8, 1H), 2.81 (t, *J* = 12.6, 1H), 2.16 – 2.06 (m, 2H), 2.22 – 1.95 (m, 2H), 1.57 (d, *J* = 6.3, 3H), 1.47 (d, *J* = 6.3, 3H).

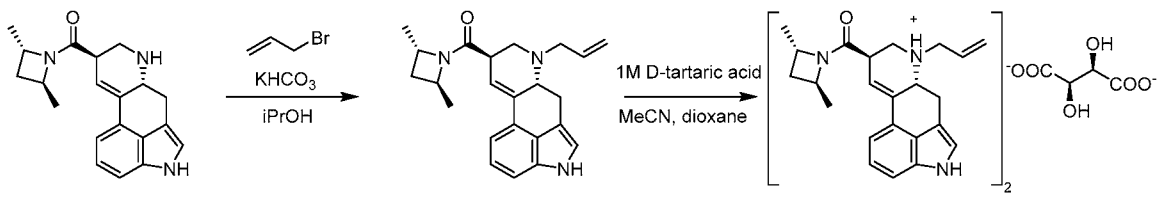
LC-MS purity: 100% (ELSD), 100% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.53 min.

LC-MS m/z: 382.1 $(M+H)^+$.

Example 25: Preparation of ((6aR,9R)-7-allyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinolin-9-yl)((2S,4S)-2,4-dimethylazetidin-1-yl)methanone (27)

Reaction Scheme:



Int13 **27** 16% **27 hemitartrate** quant.

Synthetic Protocol:

[00183] A solution of ((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)((6a*R*,9*R*)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanone (**4**, 40.0 mg, 0.117 mmol), potassium bicarbonate (47 mg, 0.468 mg), and allyl bromide (20 µL, 0.234 mmol) in isopropanol (1.0 mL) was purged with argon and heated to 90 °C. The reaction mixture was stirred for 20 h. The solvent was removed *in vacuo* and the crude material was redissolved in dichloromethane (25 mL). Silica gel (silica gel 0.063-0.200 mm, 10 g) was added and the solvent was removed *in vacuo*. The resulting powder was placed on a preloaded silica gel flash column and eluted (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 99:1 to 98:2) to afford ((6a*R*,9*R*)-7-allyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)methanone (**27**) as a colorless foam.

Yield: 14.2 mg (33%).

^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ_H): 9.03 (s, 1H), 7.29 – 7.20 (m, 1H), 7.17 – 7.08 (m, 2H), 6.97 (t, *J* = 1.8, 1H), 6.33 (s, 1H), 6.11 – 5.93 (m, 1H), 5.32 (dd, *J* = 17.2, 1.1, 1H), 5.21 (d, *J* = 10.1, 1H), 4.68 – 4.53 (m, 1H), 4.41 (dq, *J* = 12.8, 6.2, 1H), 3.74 – 3.63 (m, 1H), 3.57 (dd, *J* = 14.7, 5.2, 1H), 3.45 – 3.34 (m, 2H), 3.23 – 3.12 (m, 2H), 2.62 (t, *J* = 12.0, 1H), 2.59 – 2.47 (m, 1H), 2.09 – 1.99 (m, 2H), 1.48 (d, *J* = 6.3, 3H), 1.41 (d, *J* = 6.3, 3H).

LC-MS purity: 98% (ELSD), 91% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.42 min.

LC-MS m/z: 362.1 $(M+H)^+$.

[00184] ((6a*R*,9*R*)-7-allyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)methanone (**27**, 14.2 mg, 39.3 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (19.6 µL, 19.6 µmol). The resulting solution was stirred for 5 min and then the solvent was removed *in vacuo*. The residue was re-dissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to afford ((6a*R*,9*R*)-7-allyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)((2*S*,4*S*)-2,4-dimethylazetidin-1-yl)methanone hemitartrate (**27 hemitartrate**) as a fluffy off-white solid.

Yield: 17.1 mg (quantitative).

^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.23 (dd, *J* = 7.2, 1.5, 1H), 7.16 – 7.07 (m, 2H), 7.01 (d, *J* = 1.2, 1H), 6.33 (s, 1H), 6.14 – 5.96 (m, 1H), 5.49 (d, *J* = 17.0, 1H), 5.42 (d, *J* = 10.3, 1H), 4.77 – 4.63 (m, 1H), 4.56 – 4.44 (m, 1H), 4.44 (s, 1H), 3.92 (dd, *J* = 14.1, 5.5, 1H),

3.86 – 3.76 (m, 1H), 3.73 – 3.53 (m, 4H), 3.40 (dd, *J* = 11.5, 4.5, 1H), 3.00 (t, *J* = 10.8, 1H), 2.82 (t, *J* = 10.8, 1H), 2.20 – 2.01 (m, 2H), 1.57 (d, *J* = 6.3, 3H), 1.46 (d, *J* = 6.3, 3H).

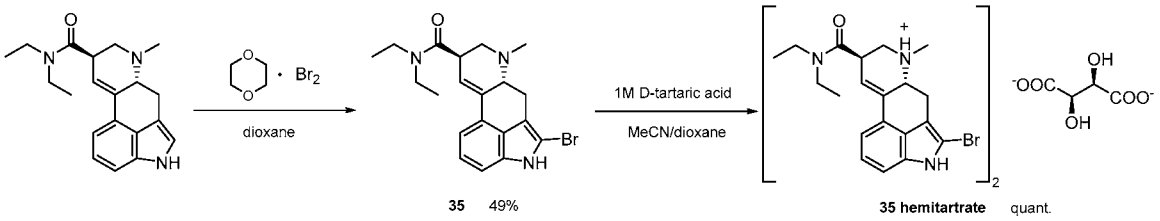
LC-MS purity: 98% (ELSD), 91% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.42 min.

LC-MS m/z: 362.1 $(M+H)^+$.

Example 26: Preparation of (6aR,9R)-5-bromo-N,N-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (35)

Reaction Scheme:



35 49% **35 hemitartrate** quant.

Synthetic Protocols:

[00185] (6a*R*,9*R*)-*N*,*N*-Diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (54.0 mg, 0.167 mmol) was dissolved in anhydrous dioxane (2.0 mL) and flushed with argon. A solution of bromine in dioxane (10% v/v, 834 µL, 0.151 mmol) was added dropwise and the resulting mixture was stirred for 2 h. The mixture was then treated with silica gel (silica gel 0.063-0.200 mm, 10g) and evaporated *in vacuo*. The resulting powder was added to the top of a flash chromatography column previously filled with silica gel and the product was eluted as follows (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to give (6a*R*,9*R*)-5-bromo-*N*,*N*-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**35**) as a dark-tinted amorphous solid.

Yield: 32.8 mg (49%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.48 (s, 1H), 7.21 – 7.05 (m, 3H), 6.33 (s, 1H), 3.88 – 3.73 (m, 1H), 3.45 (q, *J* = 7.1, 2H), 3.36 (ddd, *J* = 9.0, 6.4, 2.2, 3H), 3.11 – 3.05 (m, 1H), 3.02 (dd, *J* = 11.7, 4.4, 1H), 2.64 (t, *J* = 10.8, 1H), 2.51 (s, 3H), 2.41 (dd, *J* = 14.9, 11.3, 1H), 1.20 (t, *J* = 7.0, 3H), 1.10 (t, *J* = 7.1, 3H).

LC-MS purity: 100% (ELSD), 100% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.37 min.

LC-MS m/z: 403.9 $(M+H)^+$.

[00186] (6a*R*,9*R*)-5-bromo-*N*,*N*-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**35**, 32.8 mg, 81.5 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (40.8 µL, 40.8 µmol). The mixture was stirred at room temperature and then evaporated *in vacuo*. The residue was re-dissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to afford (6a*R*,9*R*)-5-bromo-*N*,*N*-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**35 hemitartrate**) as a fluffy light-brown solid.

Yield: 38.8 mg (quantitative).

^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.21 – 7.06 (m, 3H), 6.39 (s, 1H), 4.42 (s, 1H), 4.16 – 4.04 (m, 1H), 3.76 – 3.66 (m, 1H), 3.62 – 3.41 (m, 5H), 3.41 – 3.33 (m, 1H), 3.20 – 3.09 (m, 1H), 2.87 (s, 3H), 2.72 (dd, J = 14.5, 11.6, 1H), 1.31 (t, J = 7.1, 3H), 1.18 (t, J = 7.1, 3H).

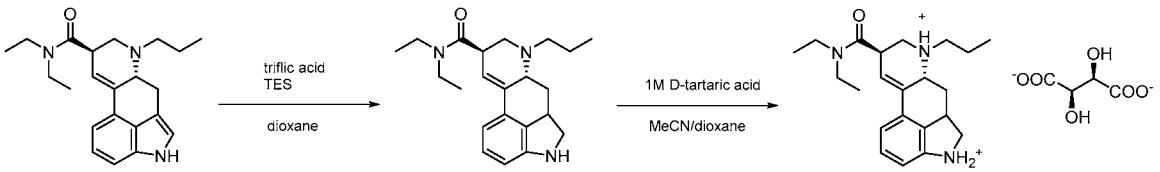
LC-MS purity: 100% (ELSD), 97% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 5.37 min.

LC-MS m/z: 403.9 $(M+H)^+$.

Example 27: (6aR,9R)-N,N-diethyl-7-propyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline-9-carboxamide (36)

Reaction Scheme:



Synthetic Protocols:

[00187] (6a*R*,9*R*)-*N*,*N*-Diethyl-7-propyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**1**, 200 mg, 0.567 mmol) was dissolved in anhydrous dioxane (10 mL) followed by the addition of triethylsilane (1 mL) and triflic acid (500 µL), and the resulting mixture was stirred at 40 °C for 96 h. The mixture was then allowed to cool to room temperature and silica gel (silica gel 0.063-0.200 mm, 10 g) was added. The mixture was concentrated *in vacuo* and the resulting powder was added to the top of a flash chromatography column previously filled

with silica gel and the product was eluted as follows (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to give (6a*R*,9*R*)-*N*,*N*-diethyl-7-propyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**36**; mixture of diastereomers; epimers at position 5a) as a dark-tinted amorphous solid.

Yield: 97.6 mg (49%).

LC-MS purity: 100% (ELSD), 98% (UV, 310 nm). LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 3.85 min.

LC-MS m/z: 354.2 $(M+H)^+$.

[00188] (6a*R*,9*R*)-*N*,*N*-diethyl-7-propyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**36**, 16.3 mg, 46.1 µmol; mixture of epimers at position 5a) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (50 µL, 50.0 µmol). The solvent was removed *in vacuo*. The residue was re-dissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to yield (6a*R*,9*R*)-*N*,*N*-diethyl-7-propyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide tartrate (**36 tartrate**; mixture of diastereomers; epimers at position 5a) as a fluffy brown solid.

Yield: 24.0 mg (quantitative).

^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.11 – 6.94 (m, 2H), 6.57 (dd, J = 5.3, 2.9, 1H), 6.37 (s, 1H), 4.42 (s, 2H), 4.22 – 4.06 (m, 2H), 3.75 – 3.67 (m, 1H), 3.66 – 3.61 (m, 2H), 3.56 (dd, J = 14.8, 7.4, 2H), 3.50 – 3.40 (m, 1H), 3.44 (dt, J = 11.5, 6.3, 2H), 3.31 – 3.22 (m, 2H), 3.21 – 3.06 (m, 2H), 2.81 – 2.67 (m, 1H), 1.93 – 1.73 (m, 2H), 1.65 (dd, J = 23.6, 11.7, 1H), 1.31 (t, J = 7.1, 3H), 1.17 (t, J = 7.1, 3H), 1.05 (t, J = 7.3, 3H).

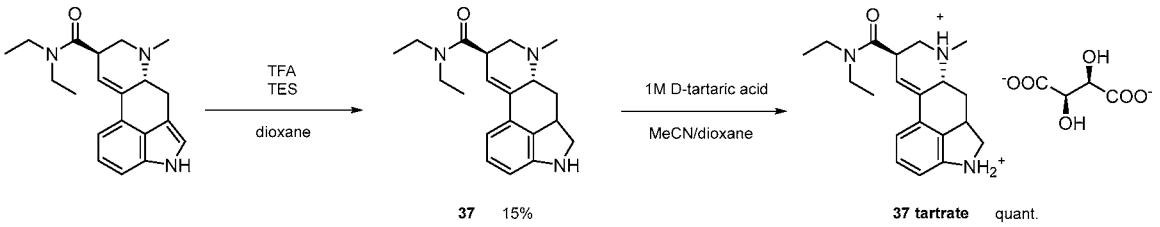
LC-MS purity: 100% (ELSD), 98% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 3.85 min.

LC-MS m/z: 354.2 $(M+H)^+$.

Example 28: Preparation of (6aR,9R)-N,N-diethyl-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline-9-carboxamide (37)

Reaction Scheme:



Synthetic Protocols:

[00189] (6a*R*,9*R*)-*N*,*N*-Diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (108 mg, 0.334 mmol) was dissolved in trifluoroacetic acid (10 mL) followed by the addition of triethylsilane (1 mL). The resulting mixture was stirred at 40 °C for 72 h. The mixture was then allowed to cool to room temperature and silica gel (silica gel 0.063-0.200 mm, 10 g) was added. The mixture was concentrated *in vacuo*. The resulting powder was added to the top of a flash chromatography column previously filled with silica gel and the product was eluted as follows (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 98:2) to give (6a*R*,9*R*)-*N*,*N*-diethyl-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**37**; mixture of diastereomers; epimers at position 5a) as a dark-tinted amorphous solid.

Yield: 16.3 mg (15%).

LC-MS purity: 92% (ELSD), 77% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 3.46 min.

LC-MS m/z: 326.1 $(M+H)^+$.

[00190] (6a*R*,9*R*)-*N*,*N*-diethyl-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**37**, 16.3 mg, 50.0 µmol; mixture of epimers at position 5a) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (50 µL, 50.0 µmol). The solvents were removed *in vacuo*, and the material was re-dissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C to afford (6a*R*,9*R*)-*N*,*N*-diethyl-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide tartrate (**37 tartrate**; mixture of diastereomers; epimers at position 5a) as a fluffy brown solid.

Yield: 24.0 mg (quantitative).

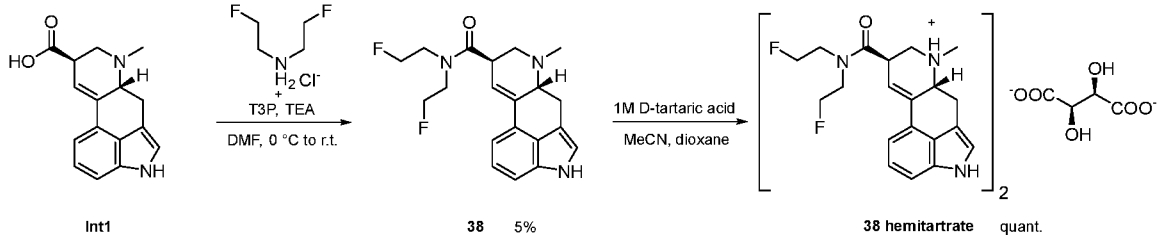
LC-MS purity: 92% (ELSD), 77% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 3.46 min.

LC-MS m/z: 326.1 $(M+H)^+$.

Example 29: Preparation of (6aR,9R)-N,N-bis(2-fluoroethyl)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide (38)

Reaction Scheme:



Synthetic Protocols:

[00191] A solution of (6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid (**Int1**, 384 mg, 1.43 mmol), triethylamine (0.93 mL, 6.43 mmol), and bis(2-fluoroethyl)amine hydrochloride (250 mg, 1.71 mmol) in dry *N*,*N*-dimethylformamide (10 mL) was cooled to 0 °C under an argon atmosphere. Propanephosphonic acid anhydride (T3P®, 0.998 mL, 1.71 mmol, 50% solution in DMF) was added dropwise over 5 minutes. The resulting mixture was stirred for 3 h at 0 °C. The reaction was judged to be complete by LC-MS and then it was quenched with ice-cold water (10 mL). The mixture was partitioned between 1M ammonium hydroxide solution (250 mL) and ethyl acetate (200 mL). The aqueous phase was re-extracted with ethyl acetate (2 x 200 mL), and the combined organic phases were washed with 10% aq. lithium chloride solution (4 x 150 mL) and dried over anhydrous magnesium sulfate. The solvent was filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60, 0.040–0.063 mm; eluent: dichloromethane/methanol 100:0 to 98:2). Leading fractions were cut to afford (6a*R*,9*R*)-*N*,*N*-bis(2-fluoroethyl)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**38**) as a colorless amorphous solid after evaporation of solvents.

Yield: 25 mg (5%).

^{1}H NMR spectrum (300 MHz, CD_3CN, δ_H): 9.01 (s, 1H), 7.23 (dd, J = 6.0, 2.7, 1H), 7.14 – 7.06 (m, 2H), 6.95 (t, J = 1.7, 1H), 6.32 (s, 1H), 4.74 – 4.62 (m, 2H), 4.59 – 4.47 (m, 2H), 3.98 – 3.86 (m, 2H), 3.80 (dd, J = 9.2, 4.6, 1H), 3.75 (td, J = 4.9, 1.9, 1H), 3.70 – 3.63 (m, 1H), 3.53 (dd, J = 14.7, 5.6, 1H), 3.12 – 3.07 (m, 1H), 3.07 – 2.98 (m, 1H), 2.63 (t, J = 10.7, 1H), 2.58 – 2.47 (m, 1H), 2.48 (s, 3H).

LC-MS purity: 100% (ELSD), 95% (UV, 310 nm).

LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 4.90 min.
LC-MS m/z: 360.1 $(M+H)^+$.

[00192] (6a*R*,9*R*)-*N*,*N*-bis(2-fluoroethyl)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (**38**, 25.0 mg, 69.6 µmol) was dissolved in gradient-grade acetonitrile (5.0 mL) and treated with aqueous 1M D-(-)-tartaric acid solution (34.8 µL, 34.8 µmol). The resulting mixture was stirred for an additional 5 minutes. The solvent was removed *in vacuo*, and the remaining material was re-dissolved in dioxane (5.0 mL) and subjected to freeze drying at 0 °C. This afforded (6a*R*,9*R*)-*N*,*N*-bis(2-fluoroethyl)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide hemitartrate (**38 hemitartrate**) as a fluffy white solid.
Yield: 30.2 mg (quantitative).
^{1}H NMR spectrum (300 MHz, MeOD, δ_H): 7.24 (dd, J = 6.8, 1.9, 1H), 7.16 – 7.07 (m, 2H), 7.02 (d, J = 1.3, 1H), 6.42 (s, 1H), 4.77 (t, J = 4.6, 1H), 4.70 (t, J = 4.9, 1H), 4.61 (t, J = 4.6, 1H), 4.55 (t, J = 4.9, 1H), 4.40 (s, 1H), 4.34 – 4.24 (m, 1H), 4.02 (dd, J = 9.7, 4.7, 1H), 3.93 (dd, J = 10.2, 4.8, 1H), 3.84 (t, J = 4.9, 1H), 3.81 – 3.73 (m, 2H), 3.72 – 3.63 (m, 2H), 3.43 (dd, J = 11.7, 4.8, 1H), 3.19 (t, J = 10.4, 1H), 2.89 (s, 3H), 2.93 – 2.82 (m, 1H).
LC-MS purity: 100% (ELSD), 95% (UV, 310 nm).
LC-MS Rt (Sinergy Polar RP, 4.6 mm x 150 mm, acetonitrile/water 30:70 to 100:0 + 0.1% HBFA in 10 min): 4.90 min.
LC-MS m/z: 360.1 $(M+H)^+$.

Example 30: 5-HT2A and 5-HT2B Receptor Binding

[00193] The binding affinities of disclosed compounds at the ketanserin binding site of the 5-HT2A receptor and the LSD binding site of the 5-HT2B receptor were determined in radioligand binding experiments.

Methods:

[00194] Affinity of the test compounds for the 5-HT2A receptor was determined in radioligand binding experiments with [^{3}H]ketanserin by WuXi AppTec (Hong Kong) Limited, using methods adapted from the literature and under conditions described in **Table 1**.

Table 1. Assay conditions for 5-HT2A receptor radioligand binding.

Receptor Source	HEK293 stable cell line

Incubation Vehicle	0.5% DMSO
Incubation Time	1 h
Incubation Temperature	25 °C
Incubation Buffer	50 mM Tris-HCl, pH 7.4
Ligand	1 nM [^{3}H]ketanserin
Non-Specific Ligand	1 μM ketanserin

[00195] Affinity of the test compounds for the 5-HT2B receptor was determined in radioligand binding experiments with [^{3}H]LSD by WuXi AppTec (Hong Kong) Limited, using methods adapted from the literature and under conditions described in **Table 2**.

Table 2. Assay conditions for 5-HT2B receptor radioligand binding.

Receptor Source	HEK293 stable cell line
Vehicle	1.0% DMSO
Incubation Time	1 h
Incubation Temperature	25 °C
Incubation Buffer	50 mM Tris-HCl, pH 7.4
Ligand	1 nM [^{3}H]LSD
Non-Specific Ligand	50 μM serotonin

Results:

[00196] Results of the radioligand binding assays are shown in **Table 3.** Tested compounds showed substantial binding affinity for the 5-HT2A and 5-HT2B receptor. Compounds having the R configuration at position 9 were much more potent at the 5-HT2A receptor than those having the S configuration at this position. Tested compounds were more selective for the 5-HT2A receptor over the 5-HT2B receptor compared to the reference compound LSD. Compounds bearing an arylalkyl or heteroarylalkyl substituent on the amine nitrogen (position 7) tended to be much more potent in binding at the 5-HT2A receptor than in the Ca^{2+} signaling assay (see **Table 4**).

Table 3. Results of 5-HT2A and 5-HT2B receptor binding affinity experiments. NT = not tested.

Compound	**5-HT2A Receptor K_i (nM)**	**5-HT2B Receptor K_i (nM)**

	([^{3}H]ketanserin)	([^{3}H]LSD)
LSD	0.89	0.42
1	1.06	NT
2a	115.05	NT
2	2.79	4.1
3a	27.6	NT
3	1.3615	4.09
6	1.16	3.33
7	0.85	NT
4	3.07	17.7
5a	74.53	NT
5	2.1836	NT
8a	>1225	NT
8	2.3775	NT
10	32.69	NT
11	0.69	NT
Int11	2.22	NT
Int8a	84.34	NT
Int8	1.0707	NT
Int14a	56.23	NT
Int14	0.47	NT
Int17a	41.3	NT
Int17	0.41	NT
12	5.61	NT
13	2.23	NT
16	2.18	NT
18	3.41	NT
19	5.58	NT
20	1.03	NT
21	1.93	NT
22	28.44	NT
23	26.57	NT

Example 31: Functional Activity at Serotonin Receptors

[00197] Disclosed compounds were tested for agonist activity at several serotonin receptor subtypes (5-HT2A, 2-HT2B, 5-HT2C, and 5-HT1A) using Ca^{2+} flux functional assays and the 5-HT1B receptor using a cAMP accumulation assay, with the results summarized in **Table 4**. Most compounds exhibited potent agonist activity at the 5-HT2A receptor, suggestive of potential hallucinogenic activity as well as possible therapeutic effects. Compounds having the R configuration at position 9 were much more potent at the 5-HT2A receptor than those having the S configuration at this position. Potent agonist activity was also observed at the other serotonin receptors tested, although the selectivity profile among the receptors varied across compounds. For example, compounds with longer alkyl chains on the amine nitrogen (e.g., 2, 3, 4, and 6) tended to exhibit greater selectivity for 5-HT2A over 5-HT1B compared to the N-methyl prototype LSD. Similarly, compounds with longer N-alkyl chains (e.g., the N-propyl compounds 3, 4, and 7), tended to be more selective for 5-HT2A over 5-HT2B than their closest N-methyl counterparts (e.g., Int8, Int11, and Int17, respectively). However, at the same time, the N-propyl compounds were more efficacious agonists at 5-HT2B than the corresponding N-methyl compounds. The selectivity of disclosed compounds for 5-HT2A over 5-HT2C and 5-HT1A was less predictable and varied widely across compounds, ranging from ~1:6 to ~20:1 (2C/2A) in the case of 5-HT2C and from ~1:4 to >100:1 (1A/2A) in the case of 5-HT1A. Compounds bearing an arylalkyl or heteroarylalkyl substituent on the amine nitrogen (position 7) tended to be much more selective for the 5-HT2A receptor in terms of agonist activity and did not exhibit substantial agonist activity at other serotonin receptors.

[00198] **Functional Assays at 5-HT2A, 5-HT2B, and 5-HT1A.** Agonist activity at 5-HT2A, 5-HT2B, and 5-HT1A receptors was determined using a FLIPR Ca^{2+} flux assay at WuXi AppTec (Hong Kong) Limited according to their standard protocols. Briefly, stably transfected cells expressing the receptor of interest (HEK293 for 5-HT2A and 5-HT2B; CHO cells for 5-HT1A) were grown and plated in a 384 well plate and incubated at 37°C and 5% CO_2 overnight. A solution of 250 mM probenecid in 1mL FLIPR assay buffer was prepared fresh. This was combined with a fluorescent dye (Fluo-4 DirectTM) to make a final assay concentration of 2.5 mM. Compounds were diluted 1:3.16 for 10 points and 750 nL was added to a 384 well compound plate using ECHO along with 30 µL assay buffer. The fluorescent dye was then added to the assay plate along with assay buffer to a final volume of 40 µL. The cell plate was incubated for 50 min at 37°C and 5% CO_2 and placed into the FLIPR Tetra along with the compound plate. 10µL of references and compounds were then transferred from the compound plate into the cell plate and the fluorescent signal was read.

[00199] **Functional Assay at 5-HT2C.** Agonist activity at 5-HT2C was determined using a FLIPR Ca^{2+} flux assay at Eurofins DiscoverX (Fremont, CA) according to their

standard protocols. Briefly, stably transfected cells expressing the human 5-HT2C receptor were grown and plated in a 384 well plate and incubated at 37 °C and 5% CO_2 overnight. Assays were performed in 1x Dye Loading Buffer consisting of 1x Dye, 1x Additive A, and 2.5 mM Probenecid in HBSS / 20 mM Hepes. Probenecid was prepared fresh. Cells were loaded with dye prior to testing and incubated at 37 °C for 30-60 minutes. After dye loading, cells were removed from the incubator and 10 µL HBSS / 20 mM Hepes was added. 3x vehicle was included in the assay buffer. Cells were incubated for 30 mins at room temperature in the dark to equilibrate plate temperature. Intermediate dilution of sample stocks was performed to generate 4x sample in assay buffer. Compound agonist activity was measured on a FLIPR Tetra (MDS). Calcium mobilization was monitored for 2 minutes and 10 µL 4X sample in HBSS / 20 mM Hepes was added to the cells 5 seconds into the assay.

[00200] **Functional Assay at 5-HT1B.** Agonist activity at 5-HT1B was determined using a cAMP accumulation protocol at WuXi AppTec (Hong Kong) Limited according to their standard protocols. Briefly, stably transfected cells were plated in an OptiPlate-384 well plate, incubated at RT for 60 mins, and cAMP standard solution (800 nM, 10 µL) was added to the blank well. Then, 10 µL detection reagent was added to each well, the plate incubated for 60 mins at RT, and the plate read using EnVision.

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Table 4. Agonist activity of compounds at select serotonin receptors in Ca^{2+} flux (5-HT2A, 2B, 2C, and 1A) and cAMP (5-HT1B) functional assays. NT = not tested

Compound	5-HT2A EC_{50} (nM)	5-HT2A %Act @ Max Dose	5-HT2B EC_{50} (nM)	5-HT2B %Act @ Max Dose	5-HT2C EC_{50} (nM)	5-HT2C %Act @ Max Dose	5-HT1A EC_{50} (nM)	5-HT1A %Act @ Max Dose	5-HT1B EC_{50} (nM)	5-HT1B %Act @ Max Dose
LSD	4.332	107.7	59.4	19.26	88.2551	92.119	25.13	91.39	2.065	98.03
1	18.49	96.96	104.3	103.75	11.8806	106.79	44.4	95.6	3.816	96.6
2a	168.6	90.29	2165	40.13	256.46	118.85	542.7	96.77	NT	NT
2	11.1	97.75	201.7	101.16	4.3513	105.48	25.36	92.42	193.5	89.97
3a	145.5	92.04	1825	52.81	131.758	108.705	155.2	108.14	NT	NT
3	1.568	102.64	61.98	94.11	0.82239	119.49	1.794	107.6	68.85	98.66
6	11.32	94.64	252.7	92.93	6.183	116.77	36.11	101.82	201	94.62
7	13.21	94.52	364	94.75	1.9931	114.78	12.83	107.16	NT	NT
4	21.28	97.6	511.3	87.46	5.60015	110.845	5.882	123.1	97.56	96
5a	118	89.59	2507	43.7	810.599	99.4405	130.7	111.65	NT	NT
5	0.7176	102.81	35.39	84.77	1.28585	114.5	0.9598	107.87	NT	NT
8a	395.6	87.45	3588	35.71	>10000	13.314	1559	90.34	NT	NT
8	0.6784	99.25	22.23	91.56	4.0451	108.26	2.533	116.41	NT	NT
10	642.6	49.44	>10000	2.005	>10000	13.417	30554	52.96	3192	87.29
11	216.1	63.46	>10000	2.5	74.502	107.89	29841	57.91	447.7	47.01
Int11	37	110.03	96.56	38.15	7.68228	93.265	8.879	89.9	NT	NT
Int8a	178.4	72.6	>10000	6.87	159.918	93.73	163.5	103.65	NT	NT
Int8	10.26	96.25	71.91	17.7	7.3198	98.245	9.694	90.25	NT	NT
Int14a	468	32.98	>10000	1.86	508.08	119.28	1550	70.27	NT	NT

Int14	15.9	93.33	>10000	9.84	3.6318	99.149	46.04	102.46	NT	NT
Int17a	425.3	63.31	>10000	5.63	962.16	112.06	265.6	88.52	NT	NT
Int17	9.67	91.47	70.76	25.49	2.5348	102.19	7.007	113.04	NT	NT
12	52.89	78.69	154.3	29.55	NT	NT	2138	71.42	193.8	95.51
13	25.95	92.60	182.5	91.75	NT	NT	15.33	83.08	98.61	90.43
16	546.9	62.05	>10000	26.497	NT	NT	>10000	22.29	682.2	90.1
18	226.9	61.09	>10000	4.69	NT	NT	>10000	28.93	1780	83.31
19	2964	70.54	>10000	2.44	NT	NT	>10000	-0.65	5850	71.08
20	264.8	77.19	>10000	3.60	NT	NT	>10000	3.85	>10000	34.59
21	619	51.23	>10000	1.73	NT	NT	>10000	8.2	2751	79.13
22	747.8	64.47	>10000	7.74	NT	NT	7839	57.33	846.7	89.15
23	511.9	85.397	>10000	12.50	NT	NT	>10000	46.19	449.8	83.68

Example 32: Functional Activity at the 5-HT2A Receptor in a Beta-Arrestin Recruitment Assay

[00201] Disclosed compounds were tested for agonist activity at the 5-HT2A receptor using a beta-arrestin (arrestin) recruitment functional assay, with the results summarized in **Table 5**. All compounds tested were agonists in this assay and many were highly potent. Compounds having the R configuration at position 9 were much more potent at the 5-HT2A receptor than those having the S configuration at this position. It was found that the size and nature of the substituent on the amine nitrogen (position 7) was an important determinant of maximal efficacy in this assay. Compounds with longer alkyl chains at this position (e.g., 1, 2, 3, 4, 5, 6, 7, and 8) were all full agonists, whereas compounds with a methyl substituent on the amine (e.g., LSD, Int11, Int8, Int14, and Int17) were all partial agonists with an E_{max} <60%. Interestingly, compounds 10 and 11, with much larger aryl substituents at this position, were also partial agonists. These compounds (10 and 11) were also unique in that they exhibited substantial arrestin bias in signaling, as they were much more potent (>50-fold) in this assay compared to the G protein-dependent Ca^{2+} signaling assay (see **Table 4**). The degree of arrestin bias varied substantially across the other compounds tested as well.

[00202] **Arrestin Functional Assay at 5-HT2A.** Recruitment of beta-arrestin was determined using a PathHunter assay at Eurofins DiscoverX (Fremont, CA) according to their standard protocols. PathHunter GPCR beta-arrestin assays take advantage of DiscoverX's proprietary Enzyme Fragment Complementation technology. The GPCR is fused in frame with a small enzyme donor fragment ProLink™ (PK) and co-expressed in cells stably expressing a fusion protein of beta-arrestin and the larger, N-terminal deletion mutant of beta-galactosidase. Activation of the GPCR (5-HT2A receptor in this case) stimulates binding of beta-arrestin to the PK-tagged GPCR and forces complementation of the two enzyme fragments, resulting in the formation of an active beta-galactosidase enzyme. This interaction leads to an increase in enzyme activity that can be measured using chemiluminescent PathHunter Detection Reagents. Briefly, PathHunter cells expressing 5-HT2A receptors were seeded in a volume of 20 µL into 384-well plates and incubated at 37 °C for the appropriate time prior to testing. For agonist activity determination, cells were incubated with 5 µL of 5x sample in assay buffer and incubated at 37 °C for 90-180 min with a vehicle concentration of 1%. Plates were then imaged on a microplate reader and the agonist activity was calculated using the following formula: % Activity = 100% x (mean RLU of test sample - mean RLU of vehicle control) / (mean MAX control ligand - mean RLU of vehicle control), where RLU = relative light units.

Table 5. Agonist activity of compounds at the 5-HT2A receptor in an arrestin recruitment assay.

Compound	5-HT2A Arrestin EC_{50} (nM)	5-HT2A Arrestin %Act @ Max Dose
LSD	2.1839	52.646
1	2.0083	128.71
2a	50.62	83.328
2	2.2682	114.55
3a	53.9995	112.91
3	<0.509	109.57
6	1.9128	102.75
7	1.5951	110.2
4	1.44168	116.8
5a	66.7575	62.444
5	1.91871	105.72
8a	1184.02	81.117
8	1.70581	112.42
10	8.47423	47.06
11	1.2686	54.255
Int11	1.56921	49.269
Int8a	19.3215	35.52
Int8	4.04977	46.06
Int14a	35.713	44.321
Int14	1.475	44.377
Int17a	75.772	43.729
Int17	1.187	38.809

Example 33: Functional Activity at Other Monoamine Receptors

[00203] Disclosed compounds were tested for agonist activity at several adrenergic (Alpha1A and Alpha2A) and dopamine (D1 and D2) receptor subtypes using Ca^{2+} flux functional assays, with the results summarized in **Table 6**. Selectivity for the 5-HT2A receptor over these other targets varied depending on the specific target and compound. In many cases, the disclosed compounds were more selective than LSD for the 5-HT2A receptor over the tested adrenergic and dopamine receptors. In particular, compound 3 showed exceptional selectivity. It was also found that the size and nature of the substituent on the amine nitrogen (position 7) was an important determinant of maximal efficacy at these receptors. Compounds with longer alkyl chains at this position (e.g., 1, 2, 3, 4, and 6) showed substantially higher maximal efficacy at Alpha1A, Alpha2A, and D2 compared to the N-methyl compound LSD.

Interestingly, compounds 10 and 11, with much larger aryl substituents at this position, were very low efficacy agonists at Alpha1A and Alpha2A.

[00204] **Functional Assays at Adrenergic and Dopamine Receptors.** Agonist activity at Alpha1A, Alpha2A, D1, and D2 receptors was determined using a FLIPR Ca^{2+} flux assay at WuXi AppTec (Hong Kong) Limited according to their standard protocols. Briefly, stably transfected cells expressing the receptor of interest were grown and plated in a 384 well plate and incubated at 37°C and 5% CO_2 overnight. A solution of 250 mM probenecid in 1mL FLIPR assay buffer was prepared fresh. This was combined with a fluorescent dye (Fluo-4 DirectTM) to make a final assay concentration of 2.5 mM. Compounds were diluted 1:3.16 for 10 points and 750 nL was added to a 384 well compound plate using ECHO along with 30 µL assay buffer. The fluorescent dye was then added to the assay plate along with assay buffer to a final volume of 40 µL. The cell plate was incubated for 50 min at 37°C and 5% CO_2 and placed into the FLIPR Tetra along with the compound plate. 10µL of references and compounds were then transferred from the compound plate into the cell plate and the fluorescent signal was read.

Table 6. Agonist activity of compounds at other monoamine receptors in Ca^{2+} flux functional assays. NT = not tested.

Compound	Alpha1A EC_{50} (nM)	Alpha 1A %Act @ Max Dose	Alpha 2A EC_{50} (nM)	Alpha 2A %Act @ Max Dose	D1 EC_{50} (nM)	D1 %Act @ Max Dose	D2 EC_{50} (nM)	D2 %Act @ Max Dose
LSD	91.06	60.3	201.2	21.3	4.866	94.9	4.928	78.33
1	8.818	80.6	42.23	58.3	4.641	108.68	2.168	94.51
2	237.1	109.68	1003	64.96	86.39	113.6	27.67	91.2
3	42.27	124.7	3639	96.82	47.86	121.3	27.18	116.9
6	NT	NT	NT	NT	18.1	93.13	7.009	91.67
4	115.8	118.64	1078	102.86	81.75	113.6	21.04	116.6
10	>31600	26.56	>31600	36.52	2778	114.19	983.3	86.87
11	>31600	28.23	>31600	14.18	1592	90.9	853.8	98.49
12	>3160	2.08	NT	NT	NT	NT	NT	NT
13	44.59	80.79	NT	NT	NT	NT	NT	NT

Example 34: Effects of Compound 1 on the Head Twitch Response (HTR) in Mice

[00205] Compound 1 was tested for its ability to induce a head twitch response (HTR) in mice, with the results summarized in **FIG. 1**. Agonists of the 5-HT2A receptor are well known to induce this effect in rodents and the potency of this HTR is correlated with hallucinogenic potency in humans. Compound 1 induced a robust and dose-dependent HTR.

Methods:

[00206] **Animals**. Adult male C57BL/6 mice, aged 6-8 weeks (body weight 20-25g) were used in this experiment. Animals were housed under controlled temperatures and 12-hour light/dark cycles (lights on between 07:00–19:00 h), with *ad libitum* food and water. This study was carried out in strict accordance with the requirements of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. All efforts were made to minimize suffering.

[00207] **Drugs and Drug Administration.** Compound 1 was synthesized as described above. It was administered subcutaneously (SC) dissolved in saline vehicle at a volume of 10 mL/kg. Five doses were tested, with n=6 animals/group. Doses were calculated on the basis of the freebase.

[00208] **Procedure.** Mice were administered one dose of the drug and immediately placed into a small open field for behavioral observation. Animals were observed continuously for 20 mins and the number of head twitches (HTs) were counted by an observer blind to the treatment condition.

[00209] **Statistical Analysis**. The data points shown are the mean ± standard error of the mean (SEM). Analysis was performed using GraphPad Prism 6. Curves were fit using a non-linear gaussian distribution to calculate ED_{50} and E_{max} values.

Example 35: Effects of Compound 1 in the Forced Swim Test in Rats

[00210] Compound 1 induced antidepressant-like effects in the forced swim test (FST) in rats with a 23.5-h pre-treatment time (**FIG. 2**). Specifically, the compound at the highest dose reduced immobility time relative to vehicle control, indicative of an antidepressant-like effect. This effect on immobility was observed 23.5 hours after a single compound administration, a time point at which most or all of the drug has been cleared from the systemic circulation.

Methods:

[00211] **Animals.** Male Sprague Dawley rats, aged 9-10 weeks, were used in this experiment. Animals were housed in groups of 2 under controlled temperature (22 ± 3°C) and relative humidity (30-70%) conditions, with 12-hour light/dark cycles, and with *ad libitum* food and water. This study was carried out in strict accordance with the requirements of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. All efforts were made to minimize suffering.

[00212] **Drugs and Drug Administration.** Compound 1 was synthesized as described above. Desipramine HCl was commercially obtained. The test compound, saline vehicle, and

the positive control desipramine were administered subcutaneously (SC), with doses calculated based on the freebase. Normal saline was used as the vehicle. All compounds were administered at a volume of 5 mL/kg. The test compound and vehicle were administered 0.5 h after the start of the training swim (Swim 1) and 23.5 h before the test swim (Swim 2). Desipramine was administered 3 times, at 23.5 h, 5 h, and 1 h before the test swim (Swim 2), each time at a dose of 20 mg/kg. Group size was n=10 per treatment.

[00213] **Forced Swim Test (FST).** Animals were randomized based on body weight, and it was ensured that inter-group variations were minimal and did not exceed ± 20% of the mean body weight across the groups. Rats were handled for about 2 min daily for the 5 days prior to the beginning of the experimental procedure. On the first day of the experiment (i.e., Day 0), post randomization, training swim sessions (Swim 1) were conducted between 12:00 and 18:00 h with all animals by placing rats in individual glass cylinders (46 cm tall x 20 cm in diameter) containing 23 – 25 °C water 30 cm deep for 15 minutes. At the conclusion of Swim 1, animals were dried with paper towels, placed in heated drying cages for 15 minutes, and then returned to their home cages. Animals were then administered the appropriate drug or vehicle treatment(s), as described above. For clarity, a compound administration time of 23.5 h before Swim 2 means 0.5 h after the start of Swim 1 and 0.25 h after the completion of Swim 1 (i.e., immediately after return to the home cage). On Day 1 (i.e., 24 h after start of Swim 1), animals performed the test swim (Swim 2) for a period of 5 min but otherwise under the same conditions as Swim 1. During all swim sessions, the water was changed between each animal.

[00214] Behavioral scoring was conducted by observers who were blind to the treatment groups. Animals were continuously observed during Swim 2 and the total time spent engaging in the following behaviors was recorded: immobile, swimming, and climbing. A rat was judged to be immobile when it remained floating in the water without struggling and was making only those movements necessary to keep its head above water. A rat was judged to be swimming when it made active swimming motions, more than necessary to merely maintain its head above water (e.g., moving around in the cylinder). A rat was judged to be climbing when it made active movements with its forepaws in and out of the water, usually directed against the walls.

[00215] **Statistical Analysis.** The data points shown represent the mean ± standard error of the mean (SEM). Analysis was performed using GraphPad Prism 6. Comparisons between groups were performed using the one-way analysis of variance (ANOVA), followed by Dunnett's test for comparisons to vehicle.

Example 36: Effects of Compound 1 on Marble Burying in Mice

[00216] Compound 1 produced an anxiolytic-like effect in the marble burying test (MBT) in C57BL/6 mice (**FIG. 3**). Specifically, Compound 1 reduced the number of marbles buried in a 30-minute period compared to vehicle.

Methods:

[00217] **Animals**. Adult male C57BL/6 mice, aged 8-10 weeks (body weight 20-25g) were used in these experiments. Animals were housed under controlled temperatures and 12-hour light/dark cycles (lights on between 07:00–19:00 h), with *ad libitum* food and water. This study was carried out in strict accordance with the requirements of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. All efforts were made to minimize suffering.

[00218] **Drugs and Drug Administration.** Compound 1 was synthesized as described above. Desipramine HCl was commercially obtained. The test compound, vehicle, and the positive control desipramine were administered subcutaneously (SC), with doses calculated based on the freebase. Normal saline was used as the vehicle. All compounds were administered at a volume of 10 mL/kg. All treatments were administered 30 minutes prior to the start of behavioral testing. Group size was n = 9-10 per treatment.

[00219] **Marble Burying Test (MBT).** Animals were randomized based on body weight, and it was ensured that inter-group variations were minimal and did not exceed ± 20% of the mean body weight across the groups. Mice were handled for about 2 min daily for the 3 days prior to the beginning of the experimental procedure. Twenty glass marbles (16 mm diameter) were placed with equal distances in a 5 x 4 pattern on a 5-cm layer of corn-cob bedding, with marbles at least 2 cm from the borders of the cage. The total number of marbles buried were counted in three 10-minute time bins (total 30 minutes). A marble was considered buried when it was >2/3 covered by bedding material.

[00220] **Statistical Analysis.** The data points shown are the mean ± standard error of the mean (SEM). Analysis was performed using GraphPad Prism 6. Comparisons between groups were performed using the one-way analysis of variance (ANOVA), followed by Dunnett's test for comparisons to vehicle.

Example 37. Effects of Additional Compounds in the Mouse Head Twitch Assay

[00221] Additional disclosed compounds were tested in the mouse head twitch response (HTR) assay according to the procedure described in Example 34. The compounds induced a HTR, with the results summarized in **Table 7**. Interestingly, the compounds varied

substantially in the maximal effect (E_{max}) induced in this assay, and the size and nature of the substituent on the amine nitrogen (position 7) and of the amide substituent(s) were found to be important determinants of efficacy in this assay as quantified by the number of HTR elicited at the most efficacious dose. For example, compounds with larger alkyl substituents on the amine (e.g., 1, 2, 3, 5, 6, 7, and 8; all >15 HTR at most efficacious dose) tended to be more efficacious in inducing a HTR compared to compounds with a methyl group at this position (e.g., Int8, Int14, and Int17; all <15 HTR at most efficacious dose). However, some compounds showed the opposite trend. For example, *N*-propyl derivative 4 was less efficacious than its *N*-methyl counterpart compound Int11. Further, both of these azetidinyl amide compounds (4 and Int11) were lower efficacy than analogous compounds bearing other amide substituents, suggesting that they may have a decreased propensity to induce hallucinogenic effects. Lastly, compounds with much larger benzyl and phenethyl substituents on the amine nitrogen (e.g., 10 and 11) were low efficacy in this assay, consistent with their lower maximal efficacy in the arrestin functional assay (see Example 32).

Table 7. Effects of disclosed compounds in the mouse HTR assay.

Compound	**ED_{50} (95% CI)***	**E_{max} (95% CI)***	**# HTR at Most Efficacious Dose (Most Efficacious Dose)**
1	0.09456 (0.04319 – 0.2157)	21.63 (18.45 – 25.78)	19.5 (1 mg/kg)
2	0.07031 (0.05272 – 0.09029)	20.47 (18.43 – 22.6)	21.833 (0.32 mg/kg)
3	0.04009 (0.02296 – 0.06228)	25.56 (22.08 – 29.36)	27.0 (0.32 mg/kg)
6	0.1387 (0.072 – 0.2822)	23.06 (19.86 – 27.47)	20.5 (1 mg/kg)
7	58.85 (0.5552 - ???)	720.4 (??? - ???)	16.667 (1 mg/kg)
4	0.3757 (0.1774 – 1.543)	4.034 (2.965 – 5.217)	4.667 (0.1 mg/kg)
5	0.03057 (0.01093 – 0.06217)	15.22 (11.77 – 19.03)	17.667 (0.32 mg/kg)
8	0.0282 (0.002515 – 0.1076)	12.03 (9.571 – 14.68)	15.75 (1 mg/kg)
10	1.257 (??? – ???)	7.749 (4.126 – ???)	6.5 (3.2 mg/kg)
11	2.205 (0.7678 – 19.75)	19.79 (12.66 – 80.7)	12.0 (3.2 mg/kg)
Int11	0.0154 (0.006325 – 0.02682)	10.93 (9.181 – 12.76)	10.667 (0.1 mg/kg)
Int8	0.1063 (0.004925 – 2.219)	14.34 (10.41 – 31.47)	13.5 (1 mg/kg)

Int14	1.473 (0.22 – ???)	21.63 (10.59 – ???)	10.5 (1 mg/kg)
Int17	0.004054 (4.78E-07 – 0.01872)	4.96 (3.764 – 6.286)	6.0 (0.32 mg/kg)

*In some cases, curve fitting was poor due to low maximal response and/or incomplete dose range tested.

Example 38. Effects of Additional Compounds in the Forced Swim Test in Rats

[00222] Additional disclosed compounds were tested in the forced swim test (FST) in rats according to the procedure described in Example 35. The compounds decreased time immobile in a dose-dependent manner, indicative of an antidepressant-like effect, with the results summarized in **Table 8**. All compounds tested reduced immobility time in a dose-dependent manner 23.5 hours after a single dose, suggesting that the compounds rapidly induce durable antidepressant-like effects. Compounds 2 and 4 were the most potent tested in this assay, being as efficacious as the positive control desipramine at a dose of 0.032 mg/kg, SC.

Table 8. Effects of disclosed compounds in the rat FST 23.5 hours after a single dose. Significant values compared to vehicle ($p < 0.05$) are in bold.

Compound (dose, mg/kg, SC)	**Time Immobile (s)**
Vehicle*	140.6
Desipramine (20)*	60.93
1 (0.032)	161.6
1 (0.32)	**68.2**
2 (0.032)	**76.44**
2 (0.32)	**41.33**
3 (0.032)	137.5
3 (0.32)	**50.4**
6 (0.032)	**93.6**
6 (0.32)	**76.6**
4 (0.01)	110.4
4 (0.032)	**68.89**
4 (0.32)	117.9

*Values are the average of 3 independent experiments.

Example 39. Effects of Additional Compounds in the Mouse Marble Burying Assay

[00223] Additional compounds of the present invention are tested in the marble burying test (MBT) in mice according to the procedure described in Example 36. The compounds decrease the number of marbles buried in a dose-dependent manner, indicative of an anxiolytic-like effect.

Example 40: Metabolic Stability in Human Liver Microsomes

[00224] Disclosed compounds were tested for stability in human liver microsomes (HLM), with the results summarized in **Table 9**. The compounds varied in stability in this assay. It was found that the size and nature of the substituent on the amine nitrogen (position 7) was an important determinant of stability in this assay. Among compounds having the R configuration at position 9, those with longer alkyl chains or bulky substituents on the amine (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 10, and 11) exhibited much lower stability (higher clearance) than compounds with a methyl substituent at this position (e.g., LSD, Int11, Int8, Int14, and Int17), suggesting that the former might exhibit shorter half-lives *in vivo*.

Methods:

[00225] **HLM Stability.** Pooled HLM from adult male and female donors (Corning 452117) were used. Microsomal incubations were carried out in multi-well plates. Liver microsomal incubation medium consisted of PBS (100 mM, pH 7.4), $MgCl_2$ (1 mM), and NADPH (1 mM), with 0.50 mg of liver microsomal protein per mL. Control incubations were performed by replacing the NADPH-cofactor system with PBS. Test compounds (1 μM, final solvent concentration 1.0%) were incubated with microsomes at 37 °C with constant shaking. Six time points over 60 minutes were analyzed, with 60 μL aliquots of the reaction mixture being drawn at each time point. The reaction aliquots were stopped by adding 180 μL of cold (4 °C) acetonitrile containing 200 ng/mL tolbutamide and 200 ng/mL labetalol as internal standards (IS), followed by shaking for 10 minutes, and then protein sedimentation by centrifugation at 4,000 rpm for 20 minutes at 4 °C. Supernatant samples (80 μL) were diluted with water (240 μL) and analyzed for parent compound remaining using a fit-for-purpose liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

[00226] **Data Analysis.** The elimination constant (k_{el}), half-life ($t_{1/2}$), and intrinsic clearance (Cl_{int}) were determined in a plot of ln(AUC) versus time, using linear regression analysis.

[00227] **Table 9.** Intrinsic clearance (Cl_{int}) and half-life ($t_{1/2}$) of compounds in the presence of HLM.

Compound	Cl_{int} (μL/min/mg)	$t_{1/2}$ (min)

Compound	Cl_{int} (µL/min/mg)	$t_{1/2}$ (min)
LSD	19.4	71.6
1	91.6	15.1
2a	81.445	17.018
2	72.715	19.061
3a	63.4	2.2
3	330.9	4.2
6	862.385	1.607
7	839.957	1.65
4	130.2	10.6
5a	250.9	5.5
5	62.3	22.2
8a	408.9	3.4
8	174.4	7.9
10	190.3	7.3
11	584.336	2.372
Int11	53.9	25.7
Int8a	124.6	11.1
Int8	21.3	64.9
Int14a	413.701	3.35
Int14	78.783	17.593
Int17a	302.78	4.578
Int17	87.363	15.865
12	103.0	13.5
13	65.7	21.1
16	285.8	4.9
18	101.7	13.6
19	82.7	16.8
20	649.2	2.1
21	367.7	3.8
22	58.2	23.8
23	193.3	7.2

Example 41: Metabolic Stability in Mouse Liver Microsomes

[00228] Disclosed compounds were tested for stability in mouse liver microsomes (MLM), with the results summarized in **Table 10**. The compounds varied in stability in this assay. It was found that the size and nature of the substituent on the amine nitrogen (position 7) was an important determinant of stability in this assay. Among compounds having the R configuration at position 9, those with longer alkyl chains or bulky substituents on the amine (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 10, and 11) exhibited much lower stability (higher clearance) than compounds with a methyl substituent at this position (e.g., LSD, Int11, Int8, Int14, and Int17), suggesting that the former might exhibit shorter half-lives *in vivo*.

Methods:

[00229] **MLM Stability** Pooled MLM from CD-1 mice (BIOIVT M00501) were used. Microsomal incubations were carried out in multi-well plates. Liver microsomal incubation medium consisted of PBS (100 mM, pH 7.4), $MgCl_2$ (1 mM), and NADPH (1 mM), with 0.50 mg of liver microsomal protein per mL. Control incubations were performed by replacing the NADPH-cofactor system with PBS. Test compounds (1 μM, final solvent concentration 1.0%) were incubated with microsomes at 37 °C with constant shaking. Six time points over 60 minutes were analyzed, with 60 μL aliquots of the reaction mixture being drawn at each time point. The reaction aliquots were stopped by adding 180 μL of cold (4 °C) acetonitrile containing 200 ng/mL tolbutamide and 200 ng/mL labetalol as internal standards (IS), followed by shaking for 10 minutes, and then protein sedimentation by centrifugation at 4,000 rpm for 20 minutes at 4 °C. Supernatant samples (80 μL) were diluted with water (240 μL) and analyzed for parent compound remaining using a fit-for-purpose liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

[00230] **Data Analysis.** The elimination constant (k_{el}), half-life ($t_{1/2}$) and intrinsic clearance (Cl_{int}) were determined in a plot of ln(AUC) versus time, using linear regression analysis.

[00231] **Table 10.** Intrinsic clearance (Cl_{int}) and half-life ($t_{1/2}$) of compounds in the presence of MLM.

Compound Number	Cl_{int} (μL/min/mg)	$t_{1/2}$ (min)
LSD	44.2	31.3
1	615.3	2.3
2a	780.349	1.776
2	519.811	2.666
3a	2487.8	0.6
3	893.8	1.6

Compound Number	Cl_{int} (µL/min/mg)	$t_{1/2}$ (min)
6	2419.6	0.6
7	2560.375	0.541
4	1672.5	0.8
5a	834	1.7
5	170.4	8.1
8a	1663.2	0.8
8	377.2	3.7
10	1396.8	1
11	1512.047	0.917
Int11	100	13.9
Int8a	842.8	1.6
Int8	34.7	39.9
Int14a	815.747	1.699
Int14	228.32	6.07
Int17a	879.576	1.576
Int17	167.954	8.252
12	654.8	2.1
13	375.7	3.7
16	1053.2	1.3
18	523.7	2.6
19	192.7	7.2
20	1548.2	0.9
21	717.4	1.9
22	150.0	9.2
23	768.7	1.8

Example 42: Metabolic Stability in Rat Liver Microsomes

[00232] Disclosed compounds were tested for stability in rat liver microsomes (RLM), with the results summarized in **Table 11**. The compounds varied in stability in this assay. It was found that the size and nature of the substituent on the amine nitrogen (position 7) was an important determinant of stability in this assay. Among compounds having the R configuration at position 9, those with longer alkyl chains or bulky substituents on the amine (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 10, and 11) exhibited much lower stability (higher clearance) than compounds with a

methyl substituent at this position (e.g., LSD, Int11, Int8, Int14, and Int17), suggesting that the former might exhibit shorter half-lives *in vivo*.

Methods:

[00233] **RLM Stability** Pooled RLM from adult male and female donors (Xenotech R1000) were used. Microsomal incubations were carried out in multi-well plates. Liver microsomal incubation medium consisted of PBS (100 mM, pH 7.4), $MgCl_2$ (1 mM), and NADPH (1 mM), with 0.50 mg of liver microsomal protein per mL. Control incubations were performed by replacing the NADPH-cofactor system with PBS. Test compounds (1 µM, final solvent concentration 1.0%) were incubated with microsomes at 37 °C with constant shaking. Six time points over 60 minutes were analyzed, with 60 µL aliquots of the reaction mixture being drawn at each time point. The reaction aliquots were stopped by adding 180 µL of cold (4 °C) acetonitrile containing 200 ng/mL tolbutamide and 200 ng/mL labetalol as internal standards (IS), followed by shaking for 10 minutes, and then protein sedimentation by centrifugation at 4,000 rpm for 20 minutes at 4 °C. Supernatant samples (80 µL) were diluted with water (240 µL) and analyzed for parent compound remaining using a fit-for-purpose liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

[00234] **Data Analysis.** The elimination constant (k_{el}), half-life ($t_{1/2}$) and intrinsic clearance (Cl_{int}) were determined in a plot of ln(AUC) versus time, using linear regression analysis.

[00235] **Table 11.** Intrinsic clearance (Cl_{int}) and half-life ($t_{1/2}$) of compounds in the presence of RLM.

Compound	Cl_{int} (µL/min/mg)	$t_{1/2}$ (min)
LSD	23.0	60.2
1	85.4	16.2
2a	143.287	9.673
2	115.768	11.972
3a	960.1	1.4
3	317.5	4.4
6	837.443	1.655
7	859.914	1.612
4	108	12.8
5a	453.2	3.1
5	72.0	19.3
8a	835.1	1.7

Compound	Cl_{int} (μL/min/mg)	$t_{1/2}$ (min)
8	180.1	7.7
10	407.4	3.4
11	1195.423	1.159
Int11	25.3	54.9
Int8a	394	3.5
Int8	13.9	99.5
Int14a	770.023	1.8
Int14	36.486	37.988
Int17a	706.862	1.961
Int17	49.688	27.894
12	236.2	5.9
13	50.0	27.7
16	616.3	2.2
18	262.8	5.3
19	139.0	10.0
20	1147.6	1.2
21	323.2	4.3
22	104.8	13.2
23	331.7	4.2

INCORPORATION BY REFERENCE

[00236] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety for all purposes as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

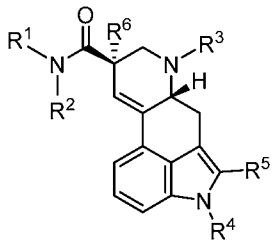
[00237] While specific embodiments of the present disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the present disclosure will become apparent to those skilled in the art upon review of this specification. The full scope of the present disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[00238] Unless otherwise indicated, all numbers expressing quantities of ingredients, 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 this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present disclosure.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein

R^1 is C_1-C_6 alkyl or 3-7 membered carbocyclyl, wherein R^1 is optionally substituted with one or more halogen or C_1-C_6 alkyl;

R^2 is hydrogen or C_1-C_6 alkyl, wherein R^2 is optionally substituted with one or more halogen or C_1-C_6 alkyl; or

wherein R^1 and R^2 can be taken together with the atom on which they are attached to form an optionally substituted 3-7 membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O, and S, wherein the heterocyclyl is optionally substituted with one or more fluoro or C_1-C_6 alkyl;

R^3 is selected from the group consisting of C_2-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, --CH_2-(cyclopropyl), and 3-7 membered cycloalkyl,

wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, and -OMe;

or

R^3 is selected from the group consisting of -(C_1-C_2 alkyl)-phenyl and -(C_1-C_2 alkyl)-(6-membered heteroaryl),

wherein C_1-C_2 alkyl is optionally substituted with one or more fluoro, hydroxyl, and -OMe, and wherein phenyl and 6-membered heteroaryl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, -NO_2, -NH_2, -C(O)NH_2, C_1-C_4 alkyl, C_3-C_5 cycloalkyl, and C_1-C_4 alkoxy;

R^4 is hydrogen or -C(O)(C_1-C_8 alkyl);

R^5 is hydrogen or halogen;

R^6 is hydrogen or deuterium;

wherein when R^1 and R^2 are both ethyl, and R^4 and R^5 are both hydrogen, R^3 is not unsubstituted linear C_2-C_6 alkyl, isopropyl, $-CH_2CH=CH_2$, $-CH_2CH_2F$, or $-CH_2CH_2Ph$;

wherein when R^1 and R^2 are both ethyl, R^4 is $-C(O)(C_2$ alkyl), and R^5 is hydrogen, R^3 is not unsubstituted ethyl;

wherein when R^1 is ethyl and R^2 is H, R^3 is not unsubstituted ethyl, unsubstituted n-propyl, or $-CH_2CH=CH_2$.

2. The compound of claim 1, wherein

R^1 is C_1-C_6 alkyl or 3-5 membered carbocyclyl, wherein R^1 is optionally substituted with one or more fluoro or C_1-C_4 alkyl;

R^2 is hydrogen or C_1-C_3 alkyl, wherein R^2 is optionally substituted with one or more fluoro or C_1-C_4 alkyl; or

wherein R^1 and R^2 can be taken together with the atom on which they are attached to form an optionally substituted 3-6 membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O, and S, wherein the heterocyclyl is optionally substituted with one or more fluoro or C_1-C_3 alkyl;

R^3 is selected from the group consisting of C_2-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, $-CH_2$-(cyclopropyl), and 3-5 membered cycloalkyl,

wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, and -OMe;

or R^3 is selected from the group consisting of $-(C_1$-C_2 alkyl)-phenyl and $-(C_1$-C_2 alkyl)-(6-membered heteroaryl),

wherein C_1-C_2 alkyl is optionally substituted with one or more fluoro, and wherein phenyl and 6-membered heteroaryl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, $-OC(O)(C_1$-C_8 alkyl), -CN, $-NO_2$, $-NH_2$, $-C(O)NH_2$, C_1-C_3 alkyl, cyclopropyl, and C_1-C_3 alkoxy;

R^4 is hydrogen or $-C(O)(C_1$-C_8 alkyl);

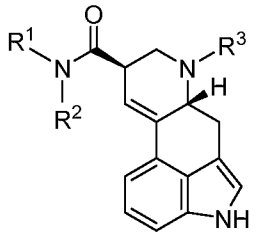
R^5 is hydrogen or halogen;

R^6 is hydrogen or deuterium;

3. The compound of any of claims 1-2, wherein R^4 is hydrogen.

4. The compound of any of claims 1-2, wherein R^5 is hydrogen.

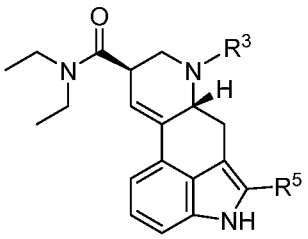
5. The compound of any of claims 1-2, wherein the compound is a compound of formula (Ia):



(Ia),

or a pharmaceutically acceptable salt thereof.

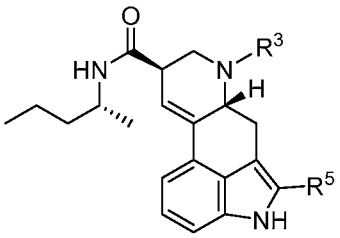
6. The compound of any of claims 1-2, wherein the compound is a compound of formula (Ib):



(Ib),

or a pharmaceutically acceptable salt thereof.

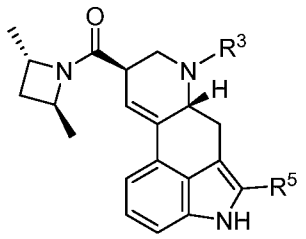
7. The compound of any of claims 1-2, wherein the compound is a compound of formula (Ic):



(Ic),

or a pharmaceutically acceptable salt thereof.

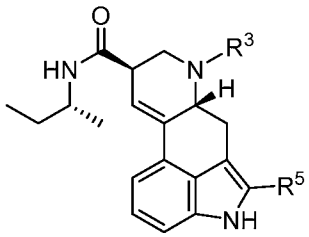
8. The compound of any of claims 1-2, wherein the compound is a compound of formula (Id):



(Id),

or a pharmaceutically acceptable salt thereof.

9. The compound of any of claims 1-2, wherein the compound is a compound of formula (Ie):



(Ie),

or a pharmaceutically acceptable salt thereof.

10. The compound of any of claims 6-9, wherein R^5 is hydrogen.

11. The compound of any of claims 1-10, wherein R^3 is selected from the group consisting of ethyl, *n*-propyl, $-CH_2CH=CH_2$, cyclopropyl, and $-CH_2$-(cyclopropyl),
wherein R^3 may be substituted with one to three instances of fluoro.

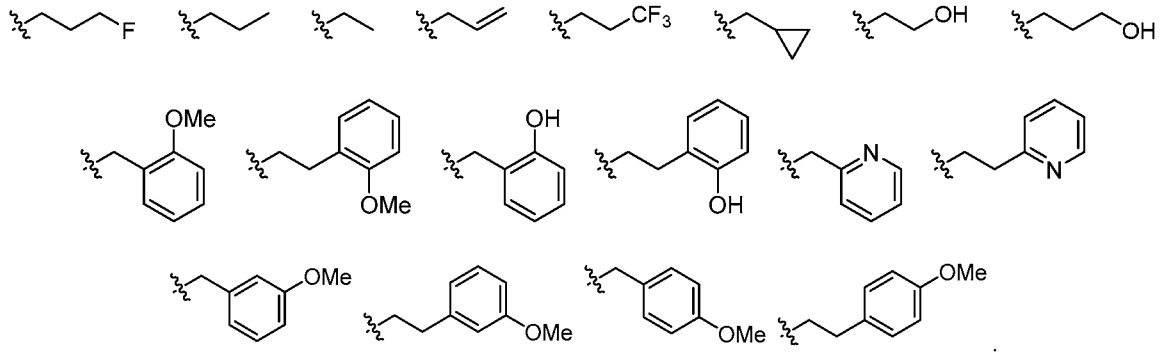
12. The compound of any of claims 1-10, wherein R^3 is selected from the group consisting of ethyl, *n*-propyl, $-CH_2CH=CH_2$, cyclopropyl, $-CH_2$-(cyclopropyl), $-CH_2CH_2CH_2F$, and $-CH_2CH_2CF_3$.

13. The compound of any of claims 1-10, wherein R^3 is selected from the group consisting of -(C_1-C_2 alkyl)-phenyl and -(C_1-C_2 alkyl)-(6-membered heteroaryl),
wherein C_1-C_2 alkyl is optionally substituted with one or more fluoro, and wherein phenyl and 6-membered heteroaryl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, $-NO_2$, $-NH_2$, $-C(O)NH_2$, C_1-C_3 alkyl, cyclopropyl, and C_1-C_3 alkoxy.

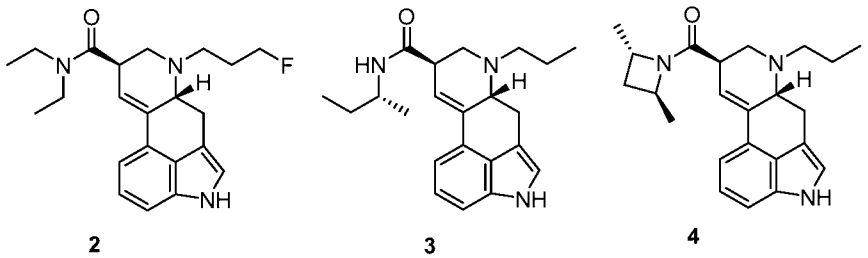
14. The compound of any of claims 1-10, wherein R^3 is selected from the group consisting of -(C_1-C_2 alkyl)-phenyl and -(C_1-C_2 alkyl)-pyridinyl,

wherein phenyl and pyridinyl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, -NO_2, -NH_2, -C(O)NH_2, C_1-C_3 alkyl, cyclopropyl, and C_1-C_3 alkoxy.

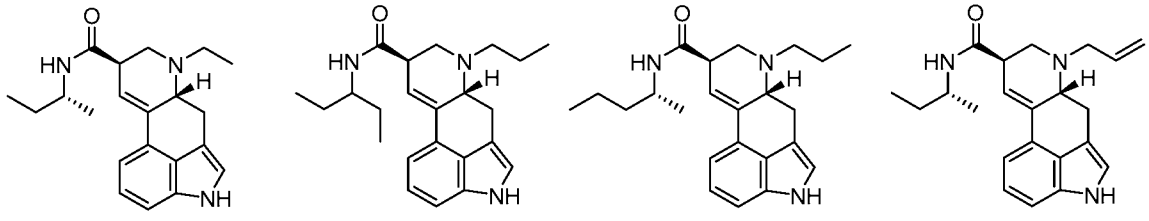
15. The compound of any of claims 1-10, wherein R^3 is selected from the group consisting of



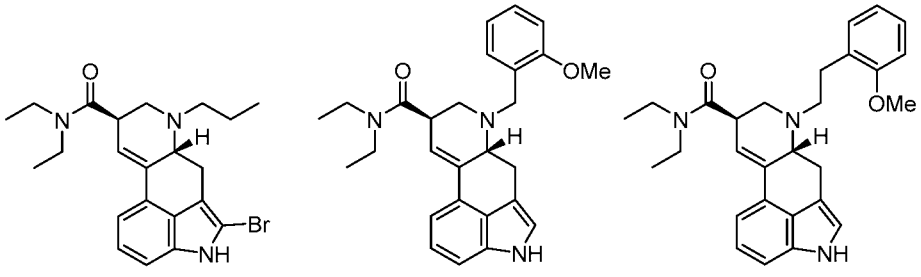
16. A compound selected from the group consisting of:



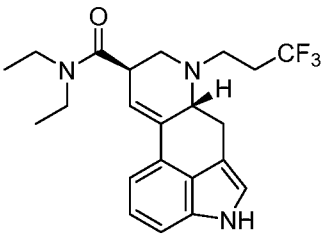
2 3 4



5 6 7 8



9 10 11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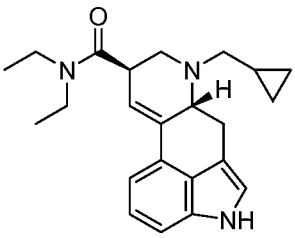
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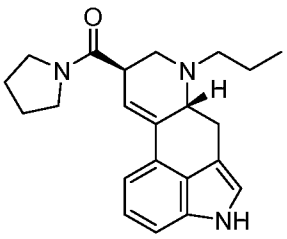
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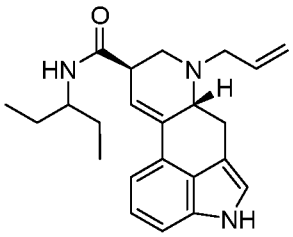
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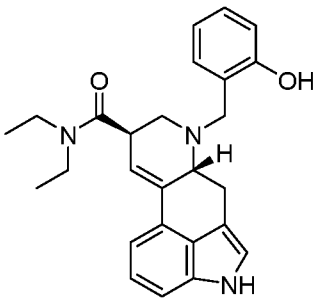
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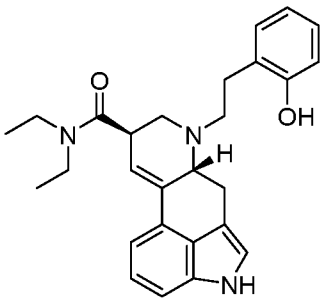
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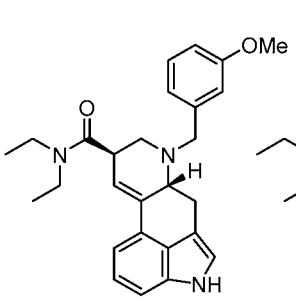
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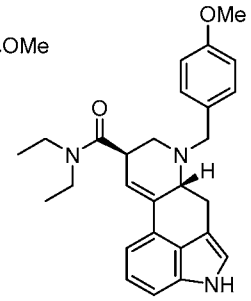
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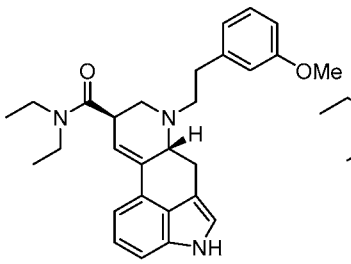
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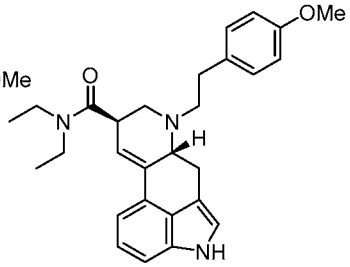
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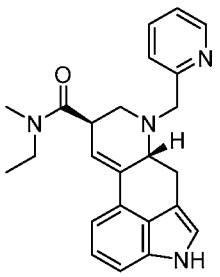
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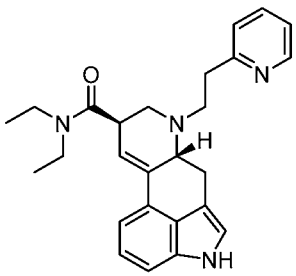
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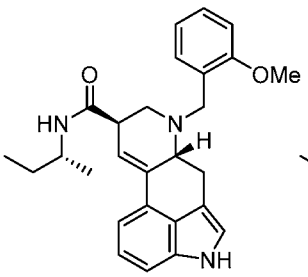
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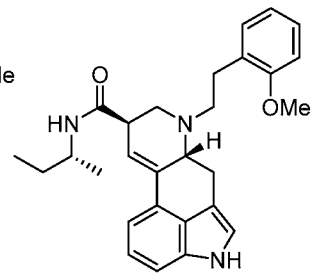
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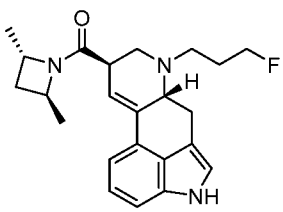
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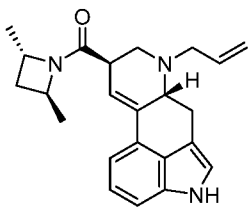
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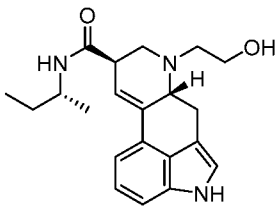
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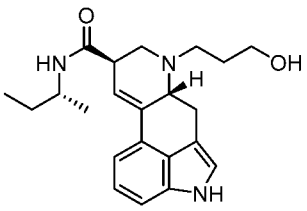
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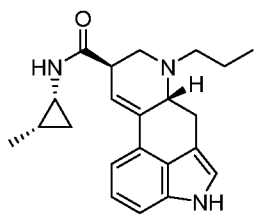
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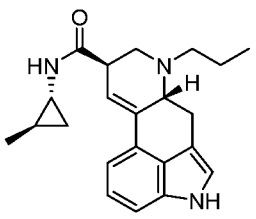
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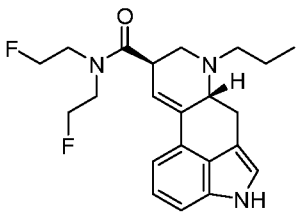
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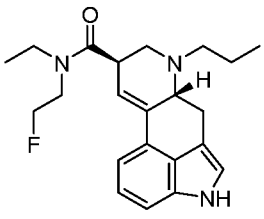
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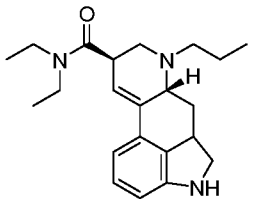
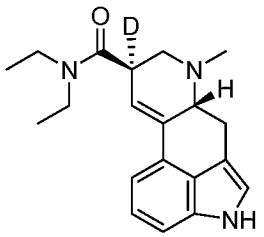

36

or a pharmaceutically acceptable salt thereof.

17. A compound having the structure:


34

or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a compound of any of claims 1-17 and a pharmaceutically acceptable adjuvant or carrier.

19. A method of treating a mood disorder comprising administering to a patient in need thereof a pharmaceutical composition comprising an effective amount of a compound of any of claims 1-17.

20. The method of claim 19, wherein the mood disorder is selected from the group consisting of depressive disorders and bipolar disorders.

21. The method of claim 19, wherein the mood disorder is a depressive disorder.

22. The method of claim 19, wherein the mood disorder is a treatment-resistant depressive disorder.

23. The method of claim 19, wherein the mood disorder is selected from the group consisting of major depressive disorder, persistent depressive disorder, postpartum depression, premenstrual dysphoric disorder, seasonal affective disorder, psychotic depression, disruptive mood dysregulation disorder, substance/medication-induced depressive disorder, and depressive disorder due to another medical condition.

24. The method of claim 19, wherein the mood disorder is selected from the group consisting of bipolar disorder I, bipolar disorder II, cyclothymic disorder, substance/medication-induced bipolar and related disorder, and bipolar and related disorder due to another medical condition.

25. The method of claim 19, wherein the mood disorder is a substance-related disorder.

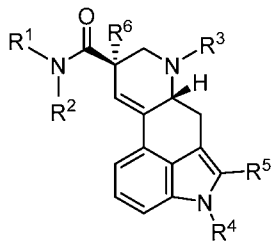
26. The method of claim 19, wherein the mood disorder is a substance-use disorder.

27. The method of claim 19, wherein the mood disorder is an anxiety disorder.

28. The method of claim 19, wherein the mood disorder is selected from the group consisting of obsessive-compulsive and related disorders, trauma- and stressor-related disorders, feeding and eating disorders, borderline personality disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder.

29. The method of claim 19, wherein the mood disorder is a neurocognitive disorder.

30. A method of treating a mood disorder comprising administering to a patient in need thereof a pharmaceutical composition comprising an effective amount of a compound according to Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein

R^1 is C_1-C_6 alkyl or 3-7 membered carbocyclyl, wherein R^1 is optionally substituted with one or more halogen or C_1-C_6 alkyl;

R^2 is hydrogen or C_1-C_6 alkyl, wherein R^2 is optionally substituted with one or more halogen or C_1-C_6 alkyl; or

wherein R^1 and R^2 can be taken together with the atom on which they are attached to form an optionally substituted 3-7 membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O, and S, wherein the heterocyclyl is optionally substituted with one or more fluoro or C_1-C_6 alkyl;

R^3 is selected from the group consisting of C_2-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, --CH_2-(cyclopropyl), and 3-7 membered cycloalkyl,

wherein R^3 may be substituted with one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, and -OMe;

or

R^3 is selected from the group consisting of –(C_1-C_2 alkyl)-phenyl and –(C_1-C_2 alkyl)-(6-membered heteroaryl),

wherein C_1-C_2 alkyl is optionally substituted with one or more fluoro, hydroxyl, and -Ome, and wherein phenyl and 6-membered heteroaryl are optionally substituted with one or more substitutents each independently selected from the group consisting of halogen, hydroxyl, -OC(O)(C_1-C_8 alkyl), -CN, -NO_2, -NH_2, -C(O)NH_2, C_1-C_4 alkyl, C_3-C_5 cycloalkyl, and C_1-C_4 alkoxy;

R^4 is hydrogen or -C(O)(C_1-C_8 alkyl);

R^5 is hydrogen or halogen;

R^6 is hydrogen or deuterium.

31. The method of claim 30, wherein the mood disorder is selected from the group consisting of depressive disorders and bipolar disorders.

32. The method of claim 30, wherein the mood disorder is a depressive disorder.

33. The method of claim 30, wherein the mood disorder is a treatment-resistant depressive disorder.

34. The method of claim 30, wherein the mood disorder is selected from the group consisting of major depressive disorder, persistent depressive disorder, postpartum depression, premenstrual dysphoric disorder, seasonal affective disorder, psychotic depression, disruptive mood dysregulation disorder, substance/medication-induced depressive disorder, and depressive disorder due to another medical condition.

35. The method of claim 30, wherein the mood disorder is selected from the group consisting of bipolar disorder I, bipolar disorder II, cyclothymic disorder, substance/medication-induced bipolar and related disorder, and bipolar and related disorder due to another medical condition.

36. The method of claim 30, wherein the mood disorder is a substance-related disorder.

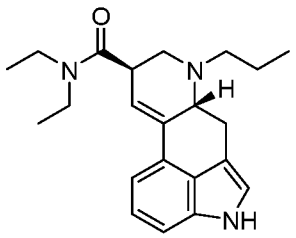
37. The method of claim 30, wherein the mood disorder is a substance-use disorder.

38. The method of claim 30, wherein the mood disorder is an anxiety disorder.

39. The method of claim 30, wherein the mood disorder is selected from the group consisting of obsessive-compulsive and related disorders, trauma- and stressor-related disorders, feeding and eating disorders, borderline personality disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder.

40. The method of claim 30, wherein the mood disorder is a neurocognitive disorder.

41. The method of any one of claims 30-40, wherein the compound has the structure:



1

or a pharmaceutically acceptable salt thereof.

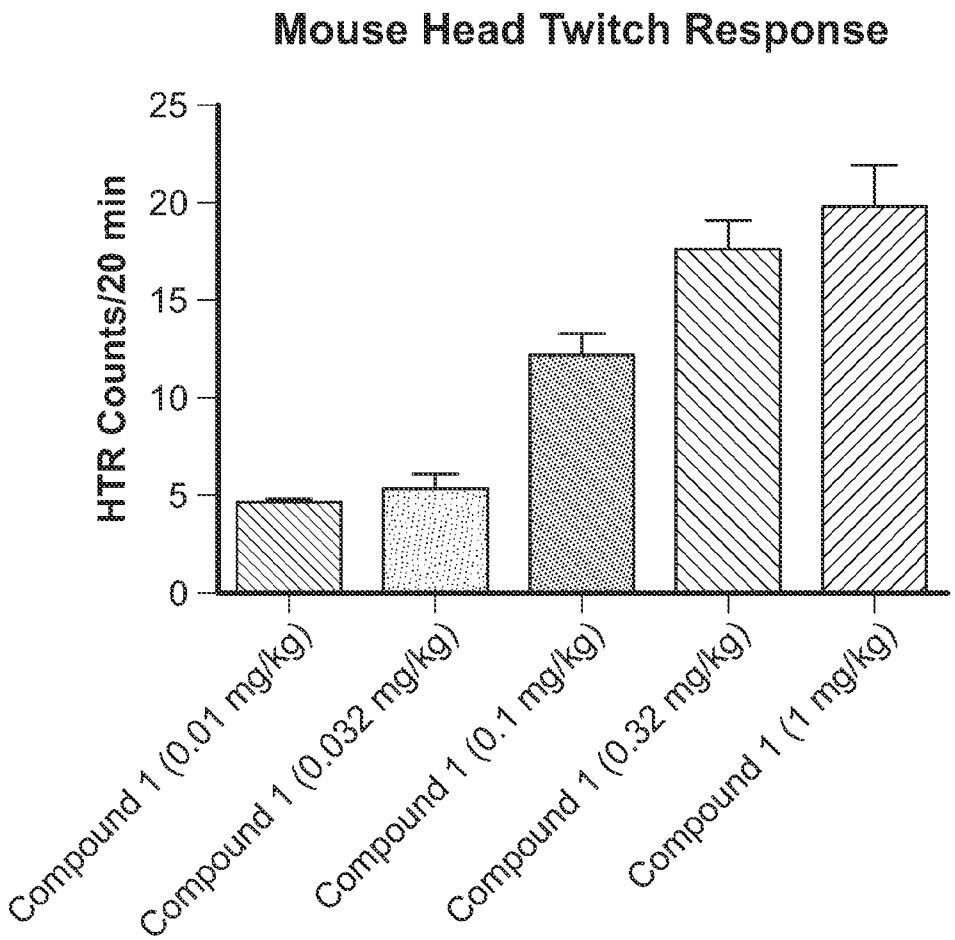

Mouse Head Twitch Response
HTR Counts/20 min
25
20
15
10
5
0
Compound 1 (0.01 mg/kg)
Compound 1 (0.032 mg/kg)
Compound 1 (0.1 mg/kg)
Compound 1 (0.32 mg/kg)
Compound 1 (1 mg/kg)

FIG. 1

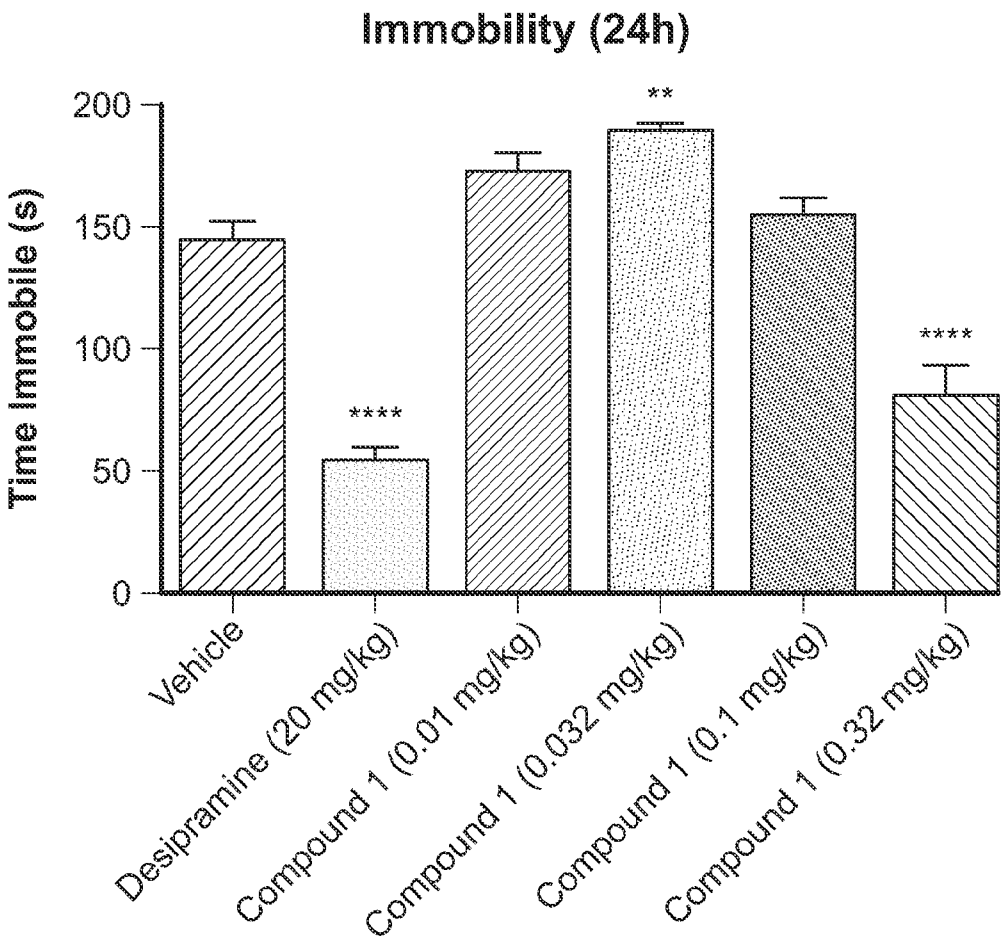

Immobility (24h)
Time Immobile (s)
200
150
100
50
0
**
****
****
Vehicle
Desipramine (20 mg/kg)
Compound 1 (0.01 mg/kg)
Compound 1 (0.032 mg/kg)
Compound 1 (0.1 mg/kg)
Compound 1 (0.32 mg/kg)

FIG. 2

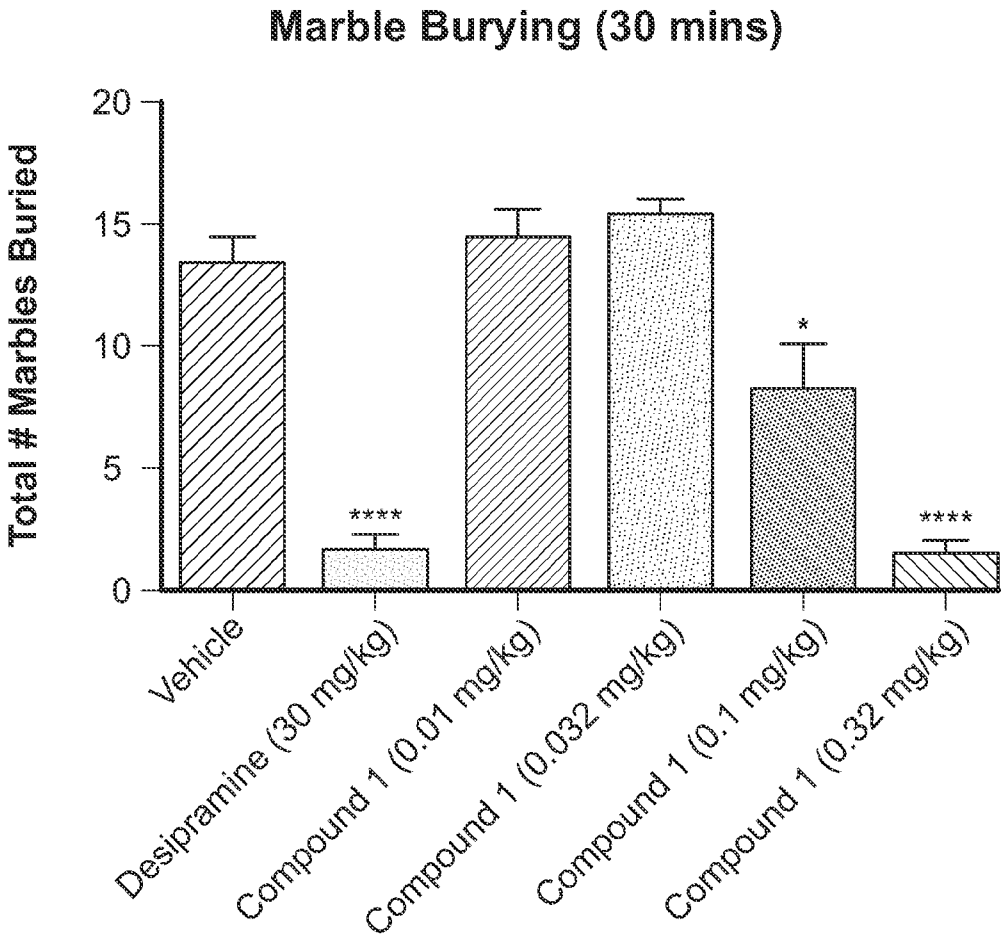

Marble Burying (30 mins)
Total # Marbles Buried
20
15
10
5
0
****
*
****
Vehicle
Desipramine (30 mg/kg)
Compound 1 (0.01 mg/kg)
Compound 1 (0.032 mg/kg)
Compound 1 (0.1 mg/kg)
Compound 1 (0.32 mg/kg)

FIG. 3