

3-(2-(DIMETHYLAMINO)ETHYL)-1H-INDOL-4-YL DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/481,385, filed, January 24, 2023, and U.S. Provisional Application No. 63/457,469, filed April 6, 2023, the disclosure of each of which is incorporated by reference in its entirety for all purposes.

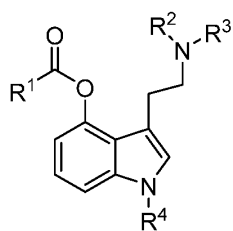
BACKGROUND

[0002] Over 50% of adults in the United States will be diagnosed with a psychiatric disorder at some point in their lifetime. Nearly 1 in 5 suffer from mental illness, and nearly 1 in 25 are afflicted with severe mental illness, such as major depression, schizophrenia, or bipolar disorder.

[0003] Psychedelics show promising activity in treating mental illness. New psychedelic compounds are needed for treating mental illness.

SUMMARY

[0004] In some embodiments, this disclosure provides a compound of Formula (I)



(I), or a pharmaceutically acceptable salt or deuterated form thereof,

wherein R¹, R², R³ and R⁴ are defined herein.

[0005] In some embodiments, this disclosure provides a compound selected from any of the compounds in Table 1, Table 2, Table 3, Table 4 or Table 5, or a pharmaceutical salt or deuterated form thereof.

DETAILED DESCRIPTION

[0006] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0007] “Cyano” refers to the -CN radical.

[0008] “Hydroxy” or “hydroxyl” refers to the -OH radical.

[0009] “Oxo” refers to the =O substituent.

[0010] “Alkyl” or “alkyl group” refers to a fully saturated, straight or branched hydrocarbon chain radical having from one to twelve carbon atoms, and which is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 12 are included. An alkyl comprising up to 12 carbon atoms is a C₁-C₁₂ alkyl, an alkyl comprising up to 10 carbon atoms is a C₁-C₁₀ alkyl, an alkyl comprising up to 6 carbon atoms is a C₁-C₆ alkyl and an alkyl comprising up to 5 carbon atoms is a C₁-C₅ alkyl. A C₁-C₅ alkyl includes C₅ alkyls, C₄ alkyls, C₃ alkyls, C₂ alkyls and C₁ alkyl (i.e., methyl). A C₁-C₆ alkyl includes all moieties described above for C₁-C₅ alkyls but also includes C₆ alkyls. A C₁-C₁₀ alkyl includes all moieties described above for C₁-C₅ alkyls and C₁-C₆ alkyls, but also includes C₇, C₈, C₉ and C₁₀ alkyls. Similarly, a C₁-C₁₂ alkyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkyls. Non-limiting examples of C₁-C₁₂ alkyl include methyl, ethyl, n-propyl, i-propyl, sec-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, t-amyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, and n-dodecyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0011] “Alkylene” or “alkylene chain” refers to a fully saturated, straight or branched divalent hydrocarbon chain radical, and having from one to twelve carbon atoms. Non-limiting examples of C₁-C₁₂ alkylene include methylene, ethylene, propylene, n-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain can be optionally substituted.

[0012] “Alkenyl” or “alkenyl group” refers to a straight or branched hydrocarbon chain radical having from two to twelve carbon atoms, and having one or more carbon-carbon double bonds. Each alkenyl group is attached to the rest of the molecule by a single bond. Alkenyl group comprising any number of carbon atoms from 2 to 12 are included. An alkenyl group comprising up to 12 carbon atoms is a C₂-C₁₂ alkenyl, an alkenyl comprising up to 10 carbon atoms is a C₂-C₁₀ alkenyl, an alkenyl group comprising up to 6 carbon atoms is a C₂-C₆ alkenyl and an alkenyl comprising up to 5 carbon atoms is a C₂-C₅ alkenyl. A C₂-C₅ alkenyl includes C₅ alkenyls, C₄ alkenyls, C₃ alkenyls, and C₂ alkenyls. A C₂-C₆ alkenyl includes all moieties described above for C₂-C₅ alkenyls but also includes C₆ alkenyls. A C₂-C₁₀ alkenyl includes all moieties described above for C₂-C₅ alkenyls and C₂-C₆ alkenyls, but also includes C₇, C₈, C₉ and C₁₀ alkenyls. Similarly, a C₂-C₁₂ alkenyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkenyls. Non-limiting examples of C₂-C₁₂

alkenyl include ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, 9-decenyl, 1-undecenyl, 2-undecenyl, 3-undecenyl, 4-undecenyl, 5-undecenyl, 6-undecenyl, 7-undecenyl, 8-undecenyl, 9-undecenyl, 10-undecenyl, 1-dodecenyl, 2-dodecenyl, 3-dodecenyl, 4-dodecenyl, 5-dodecenyl, 6-dodecenyl, 7-dodecenyl, 8-dodecenyl, 9-dodecenyl, 10-dodecenyl, and 11-dodecenyl. Unless stated otherwise specifically in the specification, an alkenyl group can be optionally substituted.

[0013] “Alkoxy” refers to a radical of the formula $-OR_a$ where R_a is an alkyl, alkenyl or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group can be optionally substituted.

[0014] “Alkylamino” refers to a radical of the formula $-NHR_a$ or $-NR_aR_a$ where each R_a is, independently, an alkyl, alkenyl or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkylamino group can be optionally substituted.

[0015] “Aryl” refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring. For purposes of this invention, the aryl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term “aryl” is meant to include aryl radicals that are optionally substituted.

[0016] “Aralkyl”, “arylalkyl” or “alkylene-aryl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene group as defined above and R_c is one or more aryl radicals as defined above, for example, benzyl, diphenylmethyl and the like. Unless stated otherwise specifically in the specification, an aralkyl group can be optionally substituted.

[0017] “Carbocyclyl,” “carbocyclic ring” or “carbocycle” refers to a non-aromatic ring structure, wherein the atoms which form the ring are each carbon. Carbocyclic rings can comprise from 3 to 20 carbon atoms in the ring. Carbocyclic rings include cycloalkyl,

cycloalkenyl and cycloalkynyl as defined herein. Unless stated otherwise specifically in the specification, a carbocyclyl group can be optionally substituted.

[0018] “Cycloalkyl” refers to a stable non-aromatic monocyclic or polycyclic fully saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, which can include fused or bridged ring systems, having from three to twenty carbon atoms, e.g., having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond.

Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl radicals include, for example, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group can be optionally substituted.

[0019] “Cycloalkenyl” refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon double bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, e.g., having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkenyl radicals include, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl, cycloctenyl, and the like. Polycyclic cycloalkenyl radicals include, for example, bicyclo[2.2.1]hept-2-enyl and the like. Unless otherwise stated specifically in the specification, a cycloalkenyl group can be optionally substituted.

[0020] “Cycloalkynyl” refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon triple bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, e.g., having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkynyl radicals include, for example, cycloheptynyl, cyclooctynyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkynyl group can be optionally substituted.

[0021] “Haloalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group can be optionally substituted.

[0022] “Haloalkenyl” refers to an alkenyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., 1-fluoropropenyl, 1,1-difluorobutenyl, and the

like. Unless stated otherwise specifically in the specification, a haloalkenyl group can be optionally substituted.

[0023] “Haloalkynyl” refers to an alkynyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., 1-fluoropropynyl, 1-fluorobutynyl, and the like. Unless stated otherwise specifically in the specification, a haloalkynyl group can be optionally substituted.

[0024] “Heterocyclyl” “heterocyclic ring” or “heterocycle” refers to a stable 3- to 20-membered non-aromatic radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen, sulfur, or silicon. Unless stated otherwise specifically in the specification, the heterocyclyl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical can be optionally oxidized; the nitrogen atom can be optionally quaternized; and the heterocyclyl radical can be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolynyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholynyl, octahydroindolyl, octahydroisindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholynyl, thiomorpholynyl, 1-oxo-thiomorpholynyl, and 1,1-dioxo-thiomorpholynyl. Unless stated otherwise specifically in the specification, a heterocyclyl group can be optionally substituted.

[0025] “Heterocyclalkyl” or “alkylene-heterocyclyl” refers to a radical of the formula $-R_b-R_e$ where R_b is an alkylene group as defined above and R_e is a heterocyclyl radical as defined above. Unless stated otherwise specifically in the specification, a heterocycloalkyl group can be optionally substituted.

[0026] “N-heterocyclyl” refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a nitrogen atom in the heterocyclyl radical. Unless stated otherwise specifically in the specification, a N-heterocyclyl group can be optionally substituted.

[0027] “Heteroaryl” refers to a 5- to 20-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from nitrogen, oxygen and sulfur, and at least one aromatic ring comprising at least one heteroatom selected from nitrogen, oxygen and sulfur. For purposes of this invention, the heteroaryl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged

ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical can be optionally oxidized; the nitrogen atom can be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophene), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolyl, dibenzofuranyl, dibenzothiophene, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolyl, isoindolyl, isoquinolyl, indolizyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolyl, quinoxalyl, quinolyl, quinuclidinyl, isoquinolyl, tetrahydroquinolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophene (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group can be optionally substituted.

[0028] “N-heteroaryl” refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. Unless stated otherwise specifically in the specification, an N-heteroaryl group can be optionally substituted.

[0029] “Heteroarylalkyl” or “alkylene-heteroaryl” refers to a radical of the formula -R_b-R_f where R_b is an alkylene chain as defined above and R_f is a heteroaryl radical as defined above. Unless stated otherwise specifically in the specification, a heteroarylalkyl group can be optionally substituted.

[0030] “Thioalkyl” refers to a radical of the formula -SR_a where R_a is an alkyl, alkenyl, or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, a thioalkyl group can be optionally substituted.

[0031] The term “substituted” used herein means any of the above groups (e.g., alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, carbocyclyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, heterocyclyl, N-heterocyclyl, heterocyclylalkyl, heteroaryl, N-heteroaryl and/or heteroarylalkyl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in

groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkylarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups.

[0032] “Substituted” also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, “substituted” includes any of the above groups in which one or more hydrogen atoms are replaced with $-\text{NR}_g\text{R}_h$, $-\text{NR}_g\text{C}(=\text{O})\text{R}_h$, $-\text{NR}_g\text{C}(=\text{O})\text{NR}_g\text{R}_h$, $-\text{NR}_g\text{C}(=\text{O})\text{OR}_h$, $-\text{NR}_g\text{SO}_2\text{R}_h$, $-\text{OC}(=\text{O})\text{NR}_g\text{R}_h$, $-\text{OR}_g$, $-\text{SR}_g$, $-\text{SOR}_g$, $-\text{SO}_2\text{R}_g$, $-\text{OSO}_2\text{R}_g$, $-\text{SO}_2\text{OR}_g$, $=\text{NSO}_2\text{R}_g$, and $-\text{SO}_2\text{NR}_g\text{R}_h$. “Substituted” also means any of the above groups in which one or more hydrogen atoms are replaced with $-\text{C}(=\text{O})\text{R}_g$, $-\text{C}(=\text{O})\text{OR}_g$, $-\text{C}(=\text{O})\text{NR}_g\text{R}_h$, $-\text{CH}_2\text{SO}_2\text{R}_g$, $-\text{CH}_2\text{SO}_2\text{NR}_g\text{R}_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, N-heterocyclyl, heterocyclylalkyl, heteroaryl, N-heteroaryl and/or heteroarylalkyl.

[0033] “Substituted” further includes any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, N-heterocyclyl, heterocyclylalkyl, heteroaryl, N-heteroaryl and/or heteroarylalkyl group.

[0034] In this specification, unless stated otherwise, the term “pharmaceutically acceptable” is used to characterize a moiety (e.g., a salt, dosage form, or excipient) as being appropriate for therapeutic use. In general, a pharmaceutically acceptable moiety has one or more benefits that outweigh any deleterious effect that the moiety may have. Deleterious effects may include, for example, excessive toxicity, irritation, allergic response, and other problems and complications.

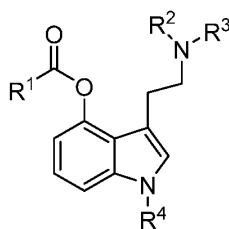
[0035] The term “pharmaceutically acceptable salt” includes both acid and base addition salts. Pharmaceutically acceptable salts include those obtained by reacting the active compound functioning as a base, with an inorganic or organic acid to form a salt, for

example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, camphorsulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, carbonic acid, etc. Those skilled in the art will further recognize that acid addition salts may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods.

[0036] The compounds of the disclosure, or their pharmaceutically acceptable salts can contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (*D*)- or (*L*)- for amino acids. The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms whether or not they are specifically depicted herein. Optically active (+) and (-), (*R*)- and (*S*)-, or (*D*)- and (*L*)- isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers. Likewise, all tautomeric forms are also intended to be included.

COMPOUNDS

[0037] In embodiments, the disclosure provides a compound of Formula (I)



(I), or a pharmaceutically acceptable salt thereof.

[0038] In embodiments, R^1 is NR^5R^6 , alkyl, haloalkyl, alkenyl, alkylene- NR^5R^6 , alkylene- $C(=O)O$ -alkyl, alkylene- $C(=O)O$ -heteroaryl wherein the heteroaryl is optionally substituted with alkyl or alkylene- NR^5R^6 , alkylene- O -alkyl, alkylene- $OC(=O)$ alkyl, alkylene- O -haloalkyl, alkylene- O -alkylene- O -alkyl, alkylene- $C(=O)NR^5R^6$, alkylene-aryl optionally substituted with 1, 2, 3, or 4 R^7 , alkylene-heteroaryl, alkylene-carbocyclyl, alkylene-heterocyclyl, aryl optionally substituted with 1, 2, 3, or 4 R^7 , heteroaryl optionally substituted with 1, 2, 3, or 4 R^7 , O -alkyl, O -alkylene-heterocyclyl, O -heterocyclyl, O -alkylene-carbocyclyl, O -aryl optionally substituted with 1, 2, 3, or 4 R^7 , O -alkylene-heteroaryl, or carbocyclyl optionally substituted with $Si(alkyl)_3$.

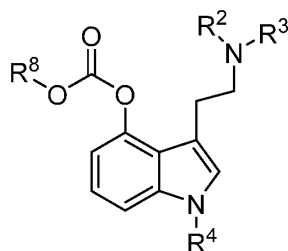
[0039] In embodiments, R^2 and R^3 are independently alkyl.

[0040] In embodiments, R^4 is H or $C(=O)O$ alkyl.

[0041] In embodiments, R^5 and R^6 are independently H , OH , alkyl, $C(=O)$ alkyl, or $C(=O)O$ alkyl.

[0042] In embodiments, R^7 is OH , halo, alky, NR^5R^6 , $OC(=O)$ alkyl, or O -alkyl.

[0043] In embodiments, the disclosure provides a compound of Formula (II)



(II), or a pharmaceutically acceptable salt thereof,

[0044] In embodiments, R^2 and R^3 are independently alkyl.

[0045] In embodiments, R^4 is H or $C(=O)O$ alkyl.

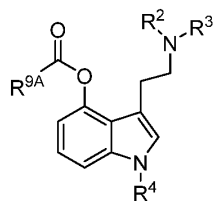
[0046] In embodiments, R^8 is alkylene-carbocyclyl, alkylene-heterocyclyl, alkylene-heterocyclyl substituted with 1, 2, 3, or 4 R^7 , alkylene- $C(=O)NR^5R^6$, alkylene- $C(=O)$ aryl, alkylene- $OC(=O)$ alkyl, alkylene- $N^+(C_{1-6} alkyl)_3$, alkylene- NR^5R^6 , alkylene- $S(O)_2(alkyl)$, alkylene- $S(O)_2(NR^5R^6)$, alkylene- $Si(alkyl)_3$, $(CH_2CH_2O)_m$ alkyl, heterocyclyl, or aryl substituted with 1, 2, 3, or 4 R^7 .

[0047] In embodiments, R^5 and R^6 are independently H , alkyl, $C(=O)$ alkyl, alkylene-aryl, or $S(O)_2$ alkyl.

[0048] In embodiments, R^7 is halo, alky, or O -alkyl.

[0049] In embodiments, m is 2, 3, 4, 5, 6, 7, or 8.

[0050] In some embodiments of compound of Formula (III)



(III), or a pharmaceutically acceptable salt thereof,

R^{9A} is branch C_{1-6} alkyl substituted with -O-aryl or -OC(=O) C_{1-6} alkyl, aryl optionally substituted with 1-4 R^7 , 5-10 membered heteroaryl optionally substituted with OH, 3-10 membered heterocyclyl optionally substituted with C(=O)Oalkyl or haloalkyl, 3-8 membered carbocyclyl, 3-8 membered carbocyclyl substituted with aryl or Si(alkyl)₃, -CH(R^A)- C_{1-6} alkyl, -CH(R^A) N^5R^6 , -CH(R^A)-O-aryl, -CH(R^A)-aryl, -CH(R^A)-5-10 membered heteroaryl, C(R^A)₂-Si(C_{1-3} alkyl)₃,

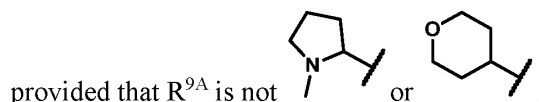
each R^A is independently H, OH, halo, unsubstituted C_{1-6} alkyl, or C_{1-6} alkylene-OH;

R^2 and R^3 are independently C_{1-4} alkyl;

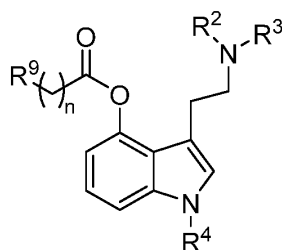
R^4 is H or C(=O)OC₁₋₄alkyl;

R^5 and R^6 are independently H, C_{1-6} alkyl, C(=O) C_{1-6} alkyl, C(=O)aryl, C(=O)O C_{1-6} alkyl, S(O)₂- C_{1-6} alkyl, C_{1-6} alkylene-3-10-membered heterocyclyl; and

R^7 is OH, halo, alky, O-alkyl, OC(=O) C_{1-6} alkyl, Si(C_{1-3} alkyl)₃, aryl, or 3-10 membered heterocycle;



[0051] In embodiments, the disclosure provides a compound of Formula (IV)



(IV), or a pharmaceutically acceptable salt thereof,

[0052] In embodiments, R^1 is branched alkyl, haloalkyl, alkylene-OH, NR^5R^6 , $S(O)_2NR^5R^6$, $S(O)_2alkyl$, alkylene- NR^5R^6 , $C(=O)O-alkyl$, $C(=O)NR^5R^6$, $C(=O)O-heteroaryl$ optionally substituted with alkyl or alkylene- NR^5R^6 , alkenylene- NR^5R^6 , alkenylene-aryl, alkenylene(OH)(aryl), alkylene- $OC(=O)alkyl$, alkylene-O-aryl optionally substituted with 1, 2, 3, or 4 R^7 , O-alkyl, O-haloalkyl, O-alkenylene- NR^5R^6 , O-alkylene-O-alkyl, O-aryl, $OC(=O)alkyl$, $OC(=O)haloalkyl$, $Si(alkyl)_3$, haloalkyl $Si(alkyl)_3$, aryl optionally substituted with 1, 2, 3, or 4 R^7 , heteroaryl, heterocyclyl optionally substituted with $C(=O)Oalkyl$, carbocyclyl, carbocyclyl substituted with aryl.

[0053] In embodiments, R^4 is H or $C(=O)Oalkyl$.

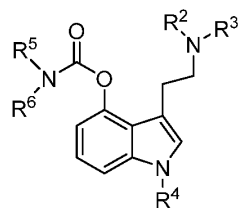
[0054] In embodiments, R^5 and R^6 are independently H, alkyl, $C(=O)alkyl$, $C(=O)aryl$, $C(=O)Oalkyl$, $S(O)_2alkyl$, alkylene-heterocyclyl.

[0055] In embodiments, R^7 is OH, halo, alky, O-alkyl, $OC(=O)alkyl$, or aryl.

[0056] In embodiments, n is 1, 2, 3, 4, 5, or 6.

[0057] In embodiments, when R^1 is NR^5R^6 , n is not 1 or R^5 and R^6 are both not H. In embodiments, when R^9 is aryl, n is not 1.

[0058] In embodiments, the disclosure provides a compound of Formula (V)



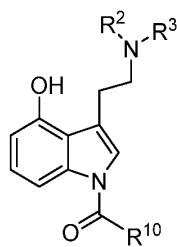
(V), or a pharmaceutically acceptable salt thereof,

[0059] In embodiments, R^2 and R^3 are independently alkyl.

[0060] In embodiments, R^4 is H or $C(=O)Oalkyl$.

[0061] In embodiments, R^5 and R^6 are independently H, OH, alkyl, haloalkyl, $C(=O)alkyl$, $C(=O)Oalkyl$, Oalkyl, or aryl optionally substituted with $C(=O)NH(alkyl)$. In embodiments, R^5 and R^6 together with the atoms to which they are attach form heterocyclyl.

[0062] In embodiments, the disclosure provides a compound of Formula (VI)



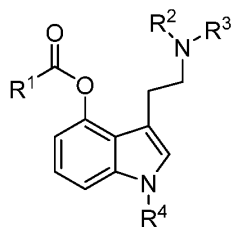
(VI), or a pharmaceutically acceptable salt thereof,

[0063] In embodiments, R^2 and R^3 are independently alkyl.

[0064] In embodiments, R^{10} is alkyl, alkylene-C(=O)Oalkyl, O-alkylene-aryl optionally substituted with 1, 2, 3, or 4 R^7 .

[0065] In embodiments, R^7 is OH, halo, alkyl, O-alkyl, OC(O)alkyl, alkylene-O-C(=O)alkyl.

[0066] In some embodiments, this disclosure provides a compound of Formula (I)



(I), or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are independently alkyl;

R^4 is H or C(=O)Oalkyl;

R^1 is defined according to **i**, **ii**, **iii**, or **iv**.

[0067] In embodiments of Formula (I) wherein R^1 is defined according to **i**, R^1 is -O- R^8 , wherein

R^8 is alkylene-carbocyclyl, alkylene-heterocyclyl wherein the heterocyclyl is substituted with 1-4 R^7 , alkylene-aryl wherein the aryl is substituted with 1-4 R^7 , alkylene-heteroaryl, alkylene-heteroaryl wherein the heteroaryl is substituted with 1-4 R^7 , alkylene-C(=O)NR⁵R⁶, alkylene-C(=O)aryl, alkylene-OC(=O)alkyl, alkylene-OH, alkylene-N⁺(C₁₋₆alkyl)₃, alkylene-NR⁵R⁶, alkylene-S(O)₂(alkyl), alkylene-S(O)₂(NR⁵R⁶), alkylene-Si(alkyl)₃, (CH₂CH₂O)_malkyl, -C(=O)alkyl, or aryl substituted with 1-4 R^7 ;

R^5 and R^6 are independently H, alkyl, C(=O)alkyl, alkylene-aryl, or S(O)₂alkyl;

R^7 is OH, halo, alkyl, haloalkyl, O-alkyl, OC(=O)alkyl, Si(alkyl)₃, aryl, -NH(C=O)alkyl, -N(alkyl)₂, or heterocyclyl;

m is 2, 3, 4, 5, 6, 7, or 8; or

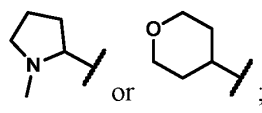
[0068] In embodiments of Formula (I) wherein R^1 is defined according to **ii**, R^1 is R^{9A} , wherein

R^{9A} is branch alkyl substituted with or -OC(=O)alkyl or -O-aryl optionally substituted with 1-4 R^7 , alkenyl substituted with aryl, aryl optionally substituted with 1-4 R^7 , heteroaryl optionally substituted with 1-4 R^7 , heterocyclyl optionally substituted with 1-4 R^7 , carbocyclyl optionally substituted with 1-4 R^7 , -C(R^A)₂-alkyl, -C(R^A)₂NR⁵R⁶, -C(R^A)₂-O-aryl, -C(R^A)₂-aryl, -C(R^A)₂-heteroaryl, or C(R^A)₂-Si(alkyl)₃,

each R^A is independently H, OH, halo, unsubstituted alkyl, or alkylene-OH, provided that at least one R^A is not H, and when R^{9A} is $-C(R^A)_2$ -alkyl then the two R^A cannot both be CH_3 ;

R^5 and R^6 are independently H, alkyl, $C(=O)$ alkyl, $C(=O)$ aryl, $C(=O)$ Oalkyl, $S(O)_2$ alkyl, alkylene-heterocyclyl;

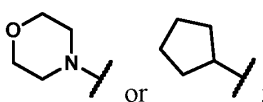
R^7 is OH, halo, alkyl, haloalkyl, O-alkyl, $OC(=O)$ alkyl, $Si(alkyl)_3$, aryl, -

$NH(C=O)$ alkyl, $-N(alkyl)_2$, or heterocyclyl; provided that R^{9A} is not  or
or

[0069] In embodiments of Formula (I) wherein R^1 is defined according to **iii**, R^1 is $-(CH_2)_n-$ R^{9B} , wherein

n is 1, 2, 3, 4, 5, or 6;

R^{9B} is haloalkyl, alkylene-OH, alkenyl, NR^5R^6 , $S(O)_2NR^5R^6$, $S(O)_2$ alkyl, $C(=O)$ Oalkyl, $C(=O)NR^5R^6$, $C(=O)O$ -heteroaryl optionally substituted with alkyl or alkylene- NR^5R^6 , O-alkyl, O-haloalkyl, O-alkenylene- NR^5R^6 , O-alkylene-O-alkyl, O-aryl, $OC(=O)$ alkyl, $OC(=O)$ haloalkyl, $Si(alkyl)_3$, aryl optionally substituted with 1-4 R^7 , heteroaryl, heterocyclyl optionally substituted with $C(=O)$ Oalkyl, carbocyclyl, carbocyclyl substituted with aryl; provided that when R^{9B} is $C(=O)$ Oalkyl, then n is less than 5; further provided that when R^{9B} is NR^5R^6 , n is not 1 or R^5 and R^6 are both not H, and when R^{9A} is aryl,

n is not 1; further provided that R^{9B} is not  ;

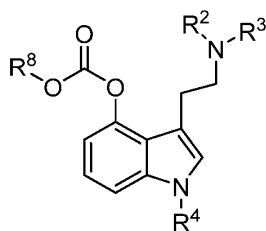
R^7 is OH, halo, alkyl, haloalkyl, O-alkyl, $OC(=O)$ alkyl, $Si(alkyl)_3$, aryl, -
 $NH(C=O)$ alkyl, $-N(alkyl)_2$, or heterocyclyl; or

[0070] In embodiments of Formula (I) wherein R^1 is defined according to **iv**, R^1 is $-NR^{5A}R^{6A}$, wherein

R^{5A} and R^{6A} are independently H, OH, unsubstituted C_{1-6} alkyl, haloalkyl, $C(=O)$ alkyl, $C(=O)$ Oalkyl, O-alkyl, or aryl substituted with $C(=O)NH(alkyl)$, provided that R^{5A} and R^{6A} cannot both be H, and further provided that when one of R^{5A} and R^{6A} is CH_3 , then the other cannot be H, CH_3 or CH_2CH_3 ;

or R^{5A} and R^{6A} together with the atoms to which they are attached form a heterocyclyl.

[0071] In some embodiments, this disclosure provides a compound of Formula (II)



(II), or a pharmaceutically acceptable salt thereof, wherein:

R⁸ is alkylene-heterocyclyl, alkylene-heterocyclyl wherein the heterocyclyl is substituted with 1-4 R⁷, alkylene-aryl wherein the aryl is substituted with 1-4 R⁷, alkylene-heteroaryl, alkylene-heteroaryl wherein the heteroaryl is substituted with 1-4 R⁷, alkylene-C(=O)NR⁵R⁶, alkylene-C(=O)aryl, alkylene-OC(=O)alkyl, alkylene-OH, alkylene-N⁺(C₁₋₆ alkyl)₃, alkylene-NR⁵R⁶, alkylene-S(O)₂(alkyl), alkylene-S(O)₂(NR⁵R⁶), alkylene-Si(alkyl)₃, (CH₂CH₂O)_malkyl, or aryl substituted with 1-4 R⁷;

R² and R³ are independently alkyl;

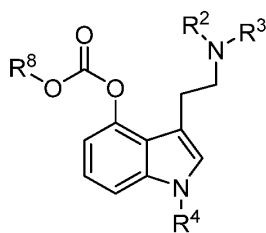
R⁴ is H or C(=O)Oalkyl;

R⁵ and R⁶ are independently H, alkyl, C(=O)alkyl, alkylene-aryl, or S(O)₂alkyl;

R⁷ is halo, alkyl, OH, or O-alkyl; and

m is 2, 3, 4, 5, 6, 7, or 8.

[0072] In some embodiments of compound of Formula (II)



(II), or a pharmaceutically acceptable salt thereof,

R⁸ is unsubstituted C₁₋₆ alkylene-C₃₋₁₀ carbocyclyl, C₁₋₆ alkylene-3-10 membered heterocyclyl wherein the heterocycle is substituted with 1-4 R⁷, C₁₋₆ alkylene-aryl wherein the aryl is substituted with 1-4 R⁷, C₁₋₆ alkylene-5-10 membered heteroaryl, C₁₋₆ alkylene-5-10 membered heteroaryl wherein the heteroaryl is substituted with 1-4 R⁷, C₁₋₆ alkylene-C(=O)NR⁵R⁶, C₁₋₆ alkylene-C(=O)aryl, C₁₋₆ alkylene-OC(=O)-C₁₋₆ alkyl, C₁₋₆ alkylene-OH, C₁₋₆ alkylene-N⁺(C₁₋₆ alkyl)₃, C₁₋₆ alkylene-NR⁵R⁶, C₁₋₆ alkylene-S(O)₂(C₁₋₆ alkyl), C₁₋₆

alkylene-S(O)₂(NR⁵R⁶), alkylene-Si(C₁₋₃ alkyl)₃, (CH₂CH₂O)_malkyl, -C(=O)-C₁₋₆ alkyl, or aryl substituted with 1-4 R⁷;

R² and R³ are independently C₁₋₃ alkyl;

R⁴ is H or C(=O)O C₁₋₆ alkyl;

R⁵ and R⁶ are independently H, C₁₋₆ alkyl, C(=O) C₁₋₆ alkyl, C₁₋₆ alkylene-aryl, or S(O)₂-C₁₋₆ alkyl;

R⁷ is halo, C₁₋₆ alky, OH, or O- C₁₋₆ alkyl; and

m is 2, 3, 4, 5, 6, 7, or 8.

[0073] In some embodiments of compound of formula (II),

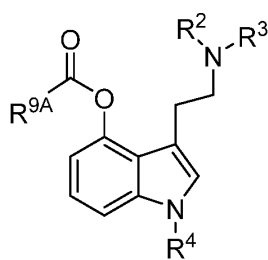
R² and R³ are independently C₁₋₃ alkyl;

R⁴ is H or C(=O)O-C₁₋₆alkyl;

R⁸ is C₁₋₆ alkylene-C₃₋₁₀ carbocyclyl, or aryl substituted with 1, 2, 3, or 4 R⁷; and

R⁷ is halo, C₁₋₆ alky, O-C₁₋₆ alkyl.

[0074] In some embodiments, this disclosure provides a compound of Formula (III)



(III), or a pharmaceutically acceptable salt thereof, wherein

R^{9A} is branch alkyl substituted with or -OC(=O)alkyl or -O-aryl optionally substituted with 1-4 R⁷, aryl optionally substituted with 1-4 R⁷, heteroaryl optionally substituted with 1-4 R⁷, heterocyclyl optionally substituted with 1-4 R⁷, carbocyclyl optionally substituted with 1-4 R⁷, -C(R^A)₂-alkyl, -C(R^A)₂NR⁵R⁶; -C(R^A)₂-O-aryl, -C(R^A)₂-aryl, -C(R^A)₂-heteroaryl, or C(R^A)₂-Si(alkyl)₃,

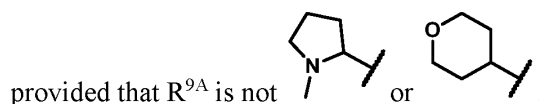
each R^A is independently H, OH, halo, unsubstituted alkyl, or alkylene-OH, provided that at least one R^A is not H, and when R^{9A} is -C(R^A)₂-alkyl then the two R^A cannot both be CH₃;

R² and R³ are independently alkyl;

R⁴ is H or C(=O)Oalkyl;

R^5 and R^6 are independently H, alkyl, $C(=O)$ alkyl, $C(=O)$ aryl, $C(=O)$ Oalkyl, $S(O)_2$ alkyl, alkylene-heterocyclyl;

R^7 is OH, halo, alkyl, haloalkyl, O-alkyl, $OC(=O)$ alkyl, $Si(alkyl)_3$, aryl, $-NH(C=O)$ alkyl, $-N(alkyl)_2$, or heterocyclyl;



[0075] In some embodiments of the compound of Formula (III)

R^{9A} is branch alkyl substituted with $-O$ -aryl or $-OC(=O)$ alkyl, aryl optionally substituted with 1-3 R^7 , heteroaryl optionally substituted with OH, heterocyclyl optionally substituted with $C(=O)$ Oalkyl, haloalkyl, carbocyclyl optionally substituted with aryl or $Si(alkyl)_3$, $-CH(R^A)$ -alkyl, $-CH(R^A)NR^5R^6$, $-CH(R^A)-O$ -aryl, $-CH(R^A)$ -aryl, $-CH(R^A)$ -heteroaryl, $C(R^A)_2-Si(alkyl)_3$;

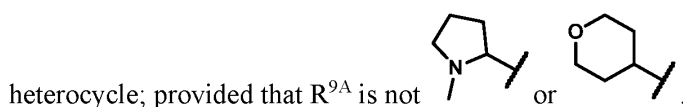
each one of R^A is independently H, OH, halo, unsubstituted alkyl, or alkylene-OH;

R^2 and R^3 are independently C_{1-4} alkyl;

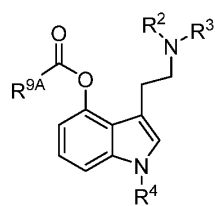
R^4 is H or $C(=O)OC_{1-4}$ alkyl;

R^5 and R^6 are independently H, alkyl, $C(=O)$ alkyl, $C(=O)$ aryl, $C(=O)$ Oalkyl, $S(O)_2$ alkyl, alkylene-heterocyclyl;

R^7 is OH, halo, alky, haloalkyl, O-alkyl, $OC(=O)$ alkyl, $Si(alkyl)_3$, aryl, $-N(alkyl)_2$ or



[0076] In some embodiments of compound of Formula (III)



(III), or a pharmaceutically acceptable salt thereof,

R^{9A} is branch C_{1-6} alkyl substituted with $-O$ -aryl or $-OC(=O)C_{1-6}$ alkyl, aryl optionally substituted with 1-4 R^7 , 5-10 membered heteroaryl optionally substituted with OH, 3-10 membered heterocyclyl optionally substituted with $C(=O)$ Oalkyl or haloalkyl, 3-8 membered carbocyclyl, 3-8 membered carbocyclyl substituted with aryl or $Si(alkyl)_3$, $-CH(R^A)-C_{1-6}$ alkyl,

$-\text{CH}(\text{R}^A)\text{NR}^5\text{R}^6$, $-\text{CH}(\text{R}^A)-\text{O}-\text{aryl}$, $-\text{CH}(\text{R}^A)-\text{aryl}$, $-\text{CH}(\text{R}^A)-5-10$ membered heteroaryl,
 $\text{C}(\text{R}^A)_2-\text{Si}(\text{C}_{1-3}\text{ alkyl})_3$,

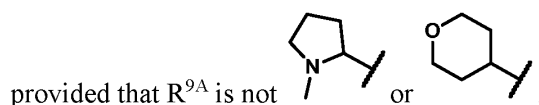
each R^A is independently H, OH, halo, unsubstituted C_{1-6} alkyl, or C_{1-6} alkylene-OH;

R^2 and R^3 are independently C_{1-4} alkyl;

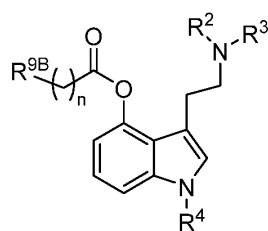
R^4 is H or $\text{C}(=\text{O})\text{OC}_{1-4}\text{alkyl}$;

R^5 and R^6 are independently H, C_{1-6} alkyl, $\text{C}(=\text{O})\text{C}_{1-6}$ alkyl, $\text{C}(=\text{O})\text{aryl}$, $\text{C}(=\text{O})\text{O C}_{1-6}\text{alkyl}$, $\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl, C_{1-6} alkylene-3-10-membered heterocyclyl; and

R^7 is OH, halo, alky, O-alkyl, $\text{OC}(=\text{O})\text{C}_{1-6}\text{alkyl}$, $\text{Si}(\text{C}_{1-3}\text{alkyl})_3$, aryl, or 3-10 membered heterocycle;



[0077] In some embodiments, this disclosure provides a compound of Formula (IV)



(IV), or a pharmaceutically acceptable salt thereof, wherein

n is 1, 2, 3, 4, 5, or 6;

R^{9B} is haloalkyl, alkylene-OH, NR^5R^6 , $\text{S}(\text{O})_2\text{NR}^5\text{R}^6$, $\text{S}(\text{O})_2\text{alkyl}$, $\text{C}(=\text{O})\text{Oalkyl}$, $\text{C}(=\text{O})\text{NR}^5\text{R}^6$, $\text{C}(=\text{O})\text{O}-\text{heteroaryl}$ optionally substituted with alkyl or alkylene- NR^5R^6 , O-alkyl, O-haloalkyl, O-alkenylene- NR^5R^6 , O-alkylene-O-alkyl, O-aryl, $\text{OC}(=\text{O})\text{alkyl}$, $\text{OC}(=\text{O})\text{haloalkyl}$, $\text{Si}(\text{alkyl})_3$, aryl optionally substituted with 1-4 R^7 , heteroaryl, heterocyclyl optionally substituted with $\text{C}(=\text{O})\text{Oalkyl}$, carbocyclyl, carbocyclyl substituted with aryl; provided that when R^{9B} is $\text{C}(=\text{O})\text{Oalkyl}$, then n is less than 5;

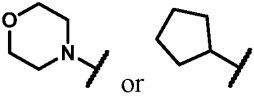
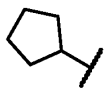
R^2 and R^3 are independently alkyl;

R^4 is H or $\text{C}(=\text{O})\text{Oalkyl}$;

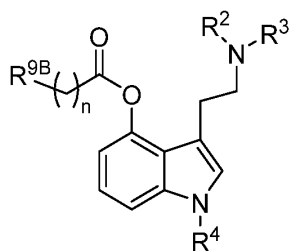
R^5 and R^6 are independently H, alkyl, $\text{C}(=\text{O})\text{alkyl}$, $\text{C}(=\text{O})\text{aryl}$, $\text{C}(=\text{O})\text{Oalkyl}$, $\text{S}(\text{O})_2\text{alkyl}$, alkylene-heterocyclyl;

R^7 is OH, halo, alkyl, O-alkyl, $\text{OC}(=\text{O})\text{alkyl}$, $\text{Si}(\text{alkyl})_3$, aryl, heterocyclyl; and

provided that when R^9 is NR^5R^6 , n is not 1 or R^5 and R^6 are both not H, and when R^9

is aryl, n is not 1; further provided that, and R^{9B} is not  or .

[0078] In some embodiments of the compound of Formula (IV)



(IV), or a pharmaceutically acceptable salt thereof,

n is 1, 2, 3, 4, 5, or 6,

R^{9B} is C_{1-6} haloalkyl, C_{1-6} alkylene-OH, NR^5R^6 , $S(O)_2NR^5R^6$, $S(O)_2-C_{1-6}$ alkyl, $C(=O)NR^5R^6$, $C(=O)O$ -5-10 membered heteroaryl optionally substituted with C_{1-6} alkyl or C_{1-6} alkylene- NR^5R^6 , $O-C_{1-6}$ alkyl, $O-C_{1-6}$ haloalkyl, $O-C_{1-6}$ alkenylene- NR^5R^6 , $O-C_{1-6}$ alkylene- $O-C_{1-6}$ alkyl, O -aryl, $OC(=O)-C_{1-6}$ alkyl, $OC(=O)$ C_{1-6} haloalkyl, $Si(C_{1-3}alkyl)_3$, aryl optionally substituted with 1-4 R^7 , 5-10 membered heteroaryl, 3-10 membered heterocyclyl optionally substituted with $C(=O)OC_{1-6}$ alkyl, 3-10 membered carbocyclyl, 3-10 membered carbocyclyl substituted with aryl;

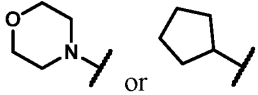
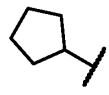
R^2 and R^3 are independently C_{1-3} alkyl;

R^4 is H or $C(=O)O$ C_{1-6} alkyl;

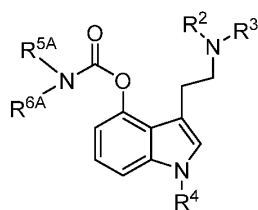
R^5 and R^6 are independently H, C_{1-6} alkyl, $C(=O)$ C_{1-6} alkyl, $C(=O)$ aryl, $C(=O)O$ C_{1-6} alkyl, $S(O)_2-C_{1-6}$ alkyl, C_{1-6} alkylene-3-10 membered heterocyclyl;

R^7 is OH, halo, C_{1-6} alky, O - C_{1-6} alkyl, $OC(=O)C_{1-6}$ alky, $Si(C_{1-3}alkyl)_3$, aryl, or heterocycle; and

provided that when R^9 is NR^5R^6 , n is not 1 or R^5 and R^6 are both not H; and when R^9

is aryl, n is not 1; further provided that R^{9B} is not  or .

[0079] In some embodiments, this disclosure provides a compound of Formula (V)



(V), or a pharmaceutically acceptable salt thereof, wherein:

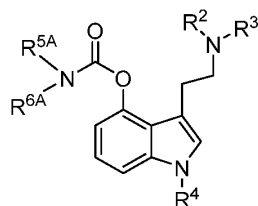
R^2 and R^3 are independently alkyl;

R^4 is H or $C(=O)$ Oalkyl;

R^{5A} and R^{6A} are independently H, OH, unsubstituted C_{1-6} alkyl, haloalkyl, $C(=O)$ alkyl, $C(=O)$ Oalkyl, O-alkyl, or aryl substituted with $C(=O)NH$ (alkyl), provided that R^{5A} and R^{6A} cannot both be H, and further provided that when one of R^{5A} and R^{6A} is CH_3 , the other cannot be H, CH_3 or CH_2CH_3 ;

or R^{5A} and R^{6A} together with the atoms to which they are attached form a heterocyclyl.

[0080] In some embodiments of compound of formula (V),



(V), or a pharmaceutically acceptable salt thereof,

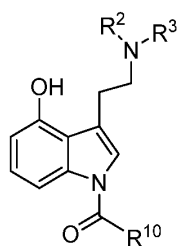
R^2 and R^3 are independently C_{1-3} alkyl;

R^4 is H or $C(=O)O-C_{1-6}$ alkyl;

R^{5A} and R^{6A} are independently H, OH, unsubstituted C_{3-6} alkyl, haloalkyl, $C(=O)$ C_{1-6} alkyl, $C(=O)OC_{1-6}$ alkyl, O- C_{1-6} alkyl, or aryl substituted with $C(=O)NH(C_{1-6}$ alkyl), provided that R^{5A} and R^{6A} cannot both be H, and further provided that when one of R^{5A} and R^{6A} is CH_3 , the other cannot be H, CH_3 or CH_2CH_3 ,

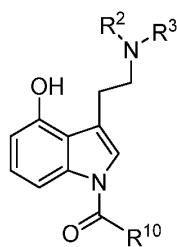
or R^{5A} and R^{6A} together with the atoms to which they are attached form a 3-10 membered heterocyclyl.

[0081] In some embodiments, this disclosure provides a compound of Formula (VI)



(VI), or a pharmaceutically acceptable salt thereof, wherein:
 R^2 and R^3 are independently alkyl;
 R^{10} is O-linear alkyl, alkylene-C(=O)Oalkyl, O-alkylene-aryl optionally substituted with 1, 2, 3, or 4 R^7 ; and
 R^7 is OH, halo, alkyl, O-alkyl, OC(=O)alkyl, alkylene-O-C(=O)alkyl.

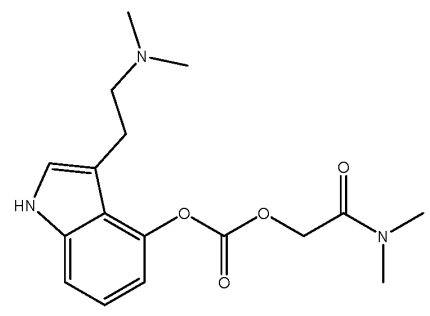
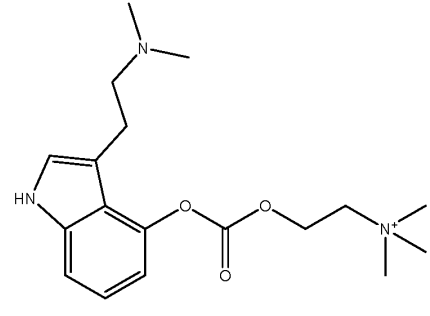
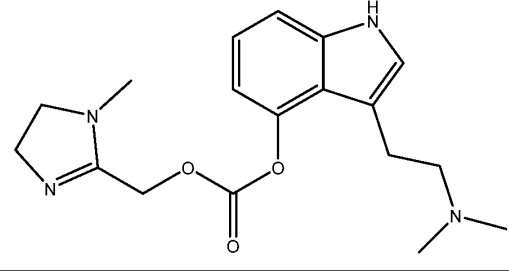
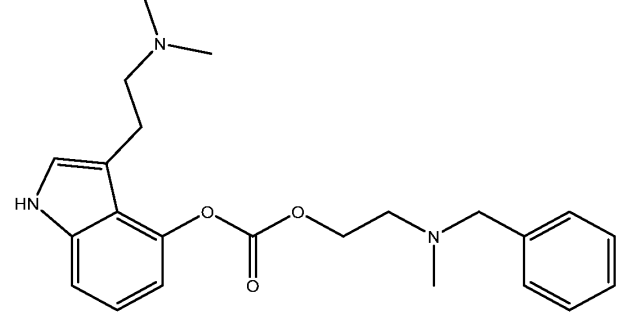
[0082] In some embodiment of compounds of Formula (VI)

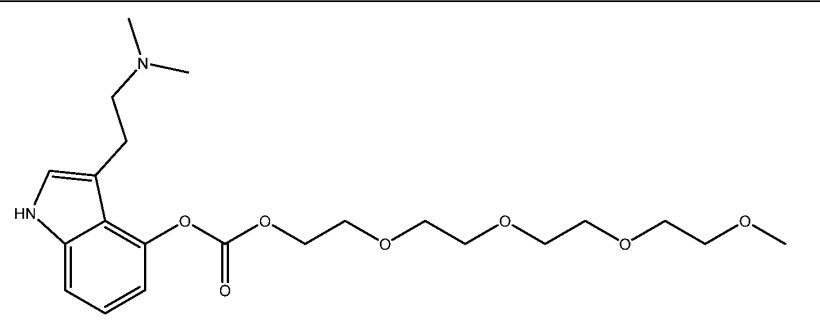
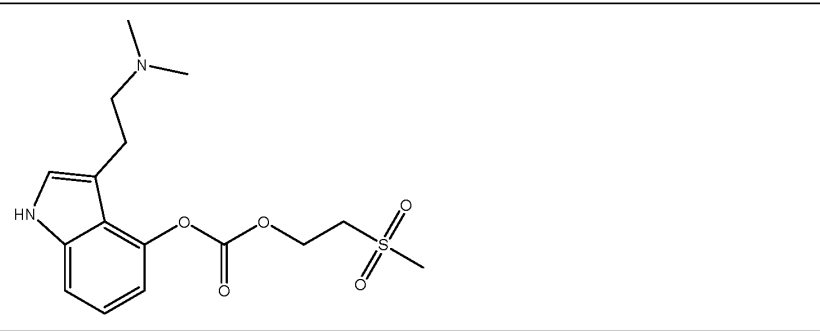
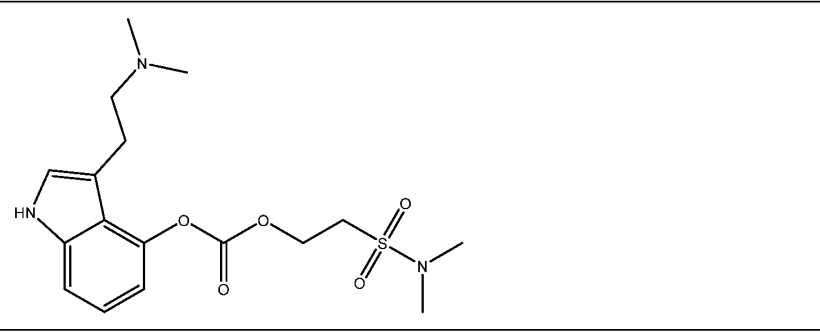
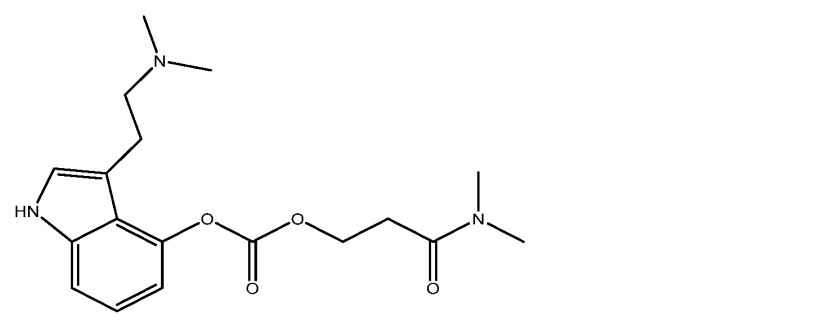


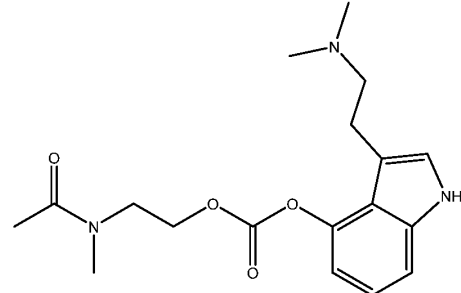
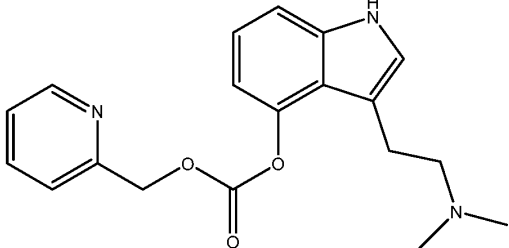
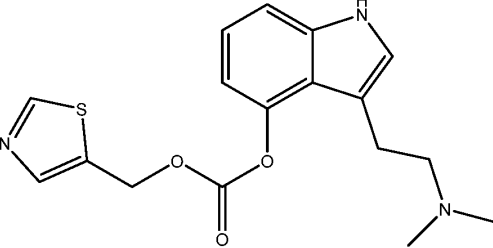
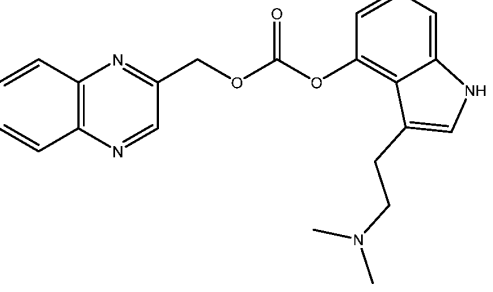
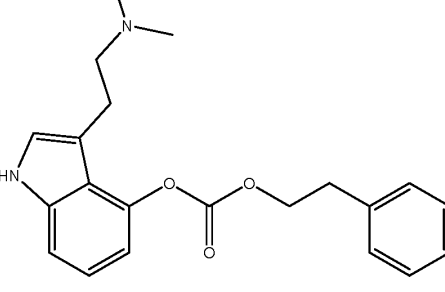
(VI), or a pharmaceutically acceptable salt thereof,
 R^2 and R^3 are independently C_{1-3} alkyl;
 R^{10} is O-linear C_{1-6} alkyl, C_{1-6} alkylene-C(=O)OC $_{1-6}$ alkyl, O- C_{1-6} alkylene-aryl optionally substituted with 1, 2, 3, or 4 R^7 ; and
 R^7 is OH, halo, C_{1-6} alkyl, O-alkyl, OC(=O)- C_{1-6} alkyl, alkylene-O-C(=O) C_{1-6} alkyl.

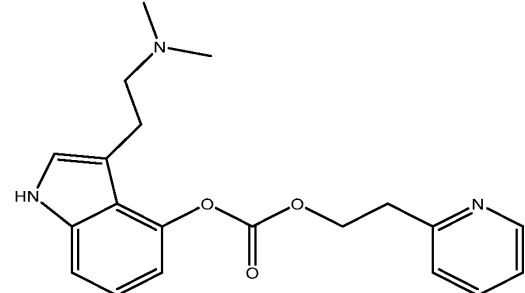
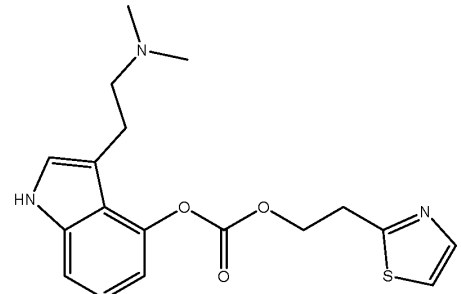
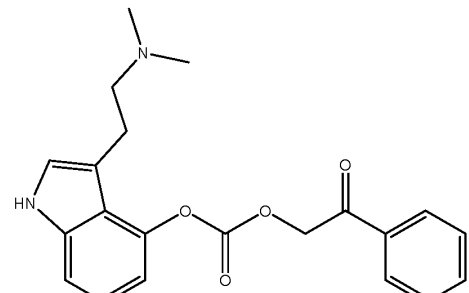
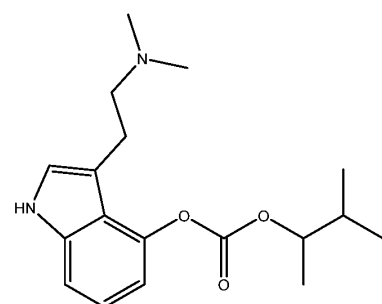
[0083] In some embodiments, this disclosure provides a compound selected from any of the compounds in Table 1, Table 2, Table 3, Table 4 or Table 5, or a pharmaceutical salt or deuterated form thereof. In some embodiments, this disclosure provides a compound selected from any of the compounds in Table 1, Table 2, Table 3, Table 4 or Table 5, or a pharmaceutically acceptable salt thereof.

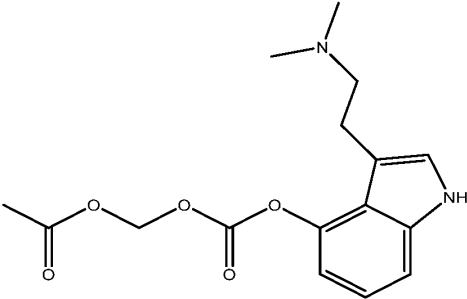
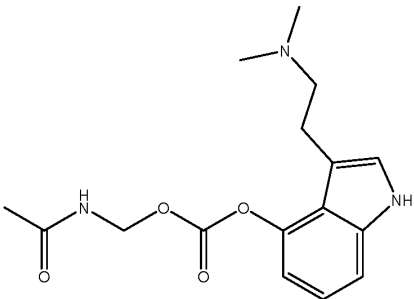
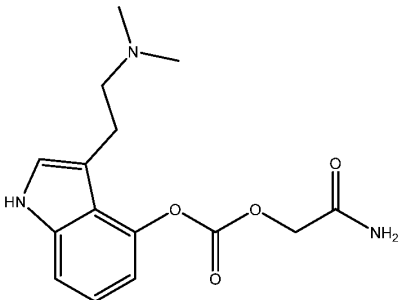
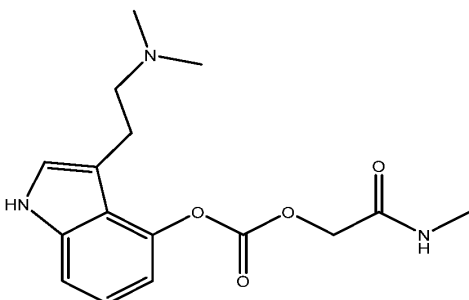
Table 1: Compounds of Formula (II)

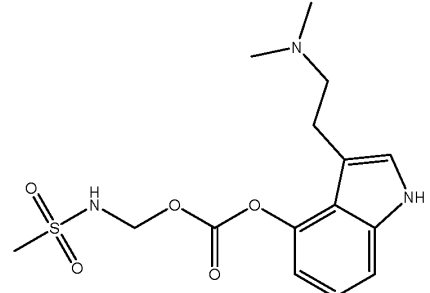
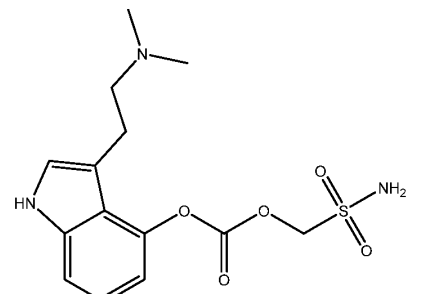
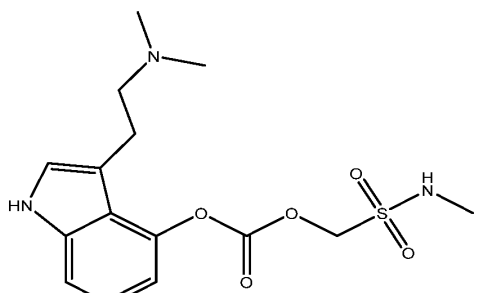
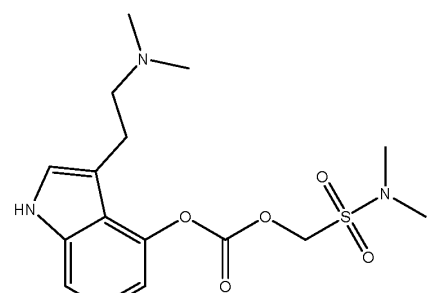
Compound	Structure
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80	
81	
82	

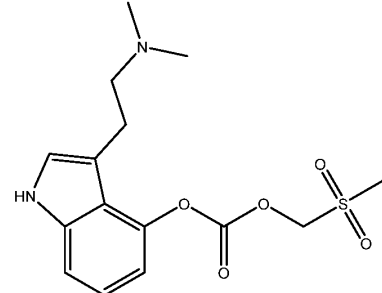
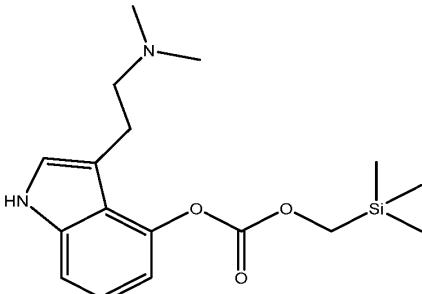
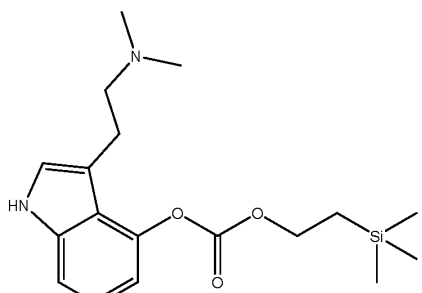
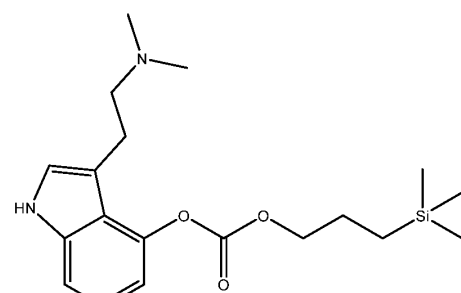
83	 <chem>CN(C)CCc1c[nH]c2ccccc12COC(=O)OCCOCCOCCOCCOCCOC</chem>
84	 <chem>CN(C)CCc1c[nH]c2ccccc12COC(=O)OCCS(=O)(=O)C</chem>
85	 <chem>CN(C)CCc1c[nH]c2ccccc12COC(=O)OCCS(=O)(=O)N(C)C</chem>
86	 <chem>CN(C)CCc1c[nH]c2ccccc12COC(=O)OCC(=O)N(C)C</chem>

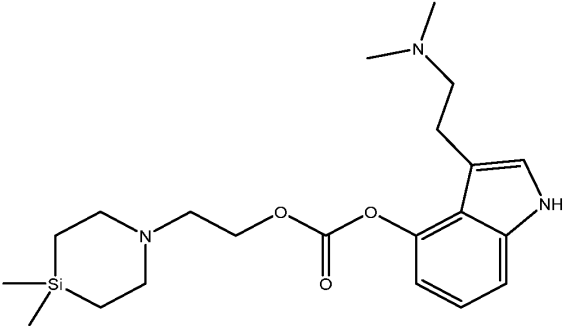
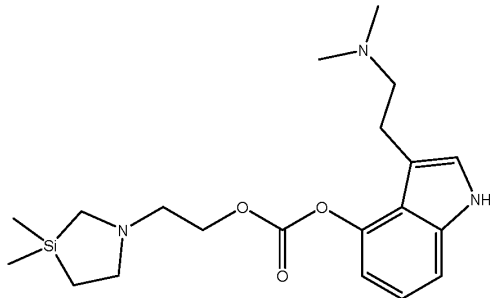
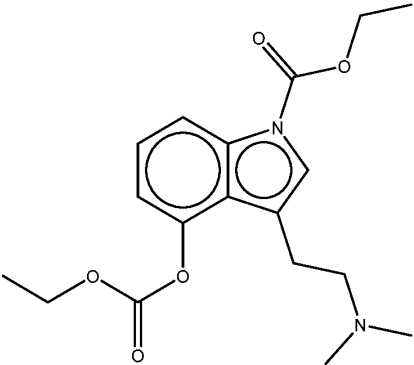
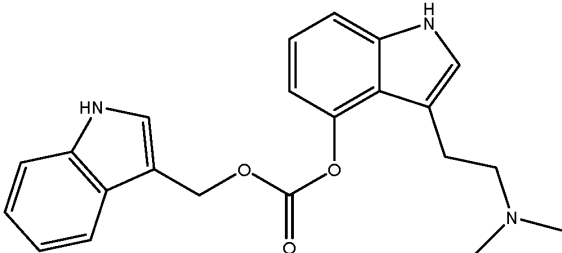
87	
106	
107	
108	
109	

110	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)OCCc1ccccn1</chem>
111	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)OCCc1cc[nH]s1</chem>
112	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)OCC(=O)c1ccccc1</chem>
136	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)OCC(C)C</chem>

141	
142	
144	
145	

147	
148	
149	
150	

151	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)OCS(=O)(=O)C(C)(C)C</chem>
189	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)OCSi(C)(C)C</chem>
190	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)OCC(C)(C)Si(C)(C)C</chem>
191	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)OCC(C)(C)Si(C)(C)C</chem>

206	
203	
52	
88	

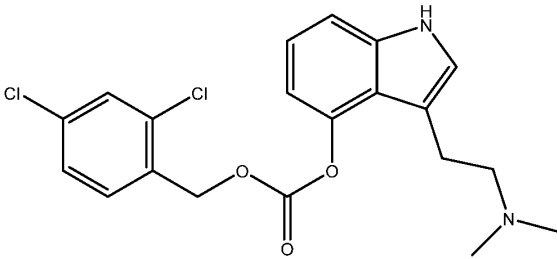
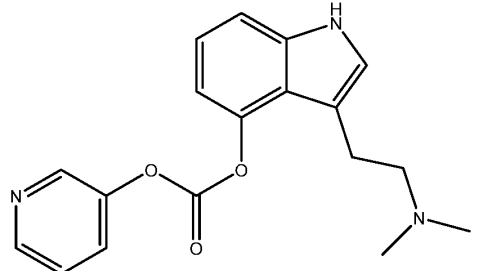
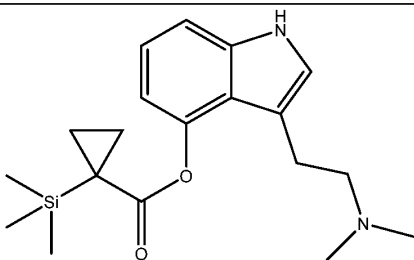
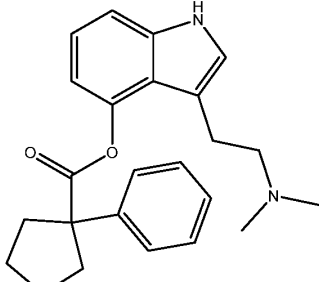
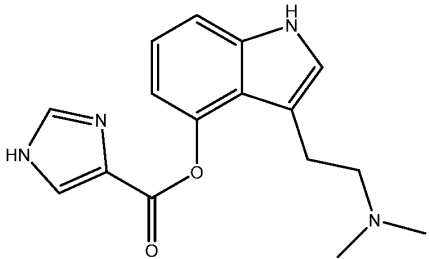
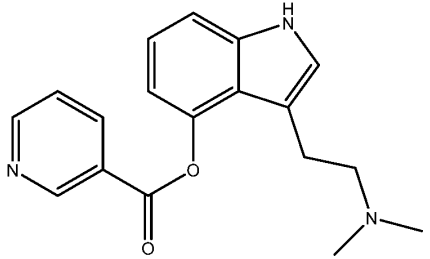
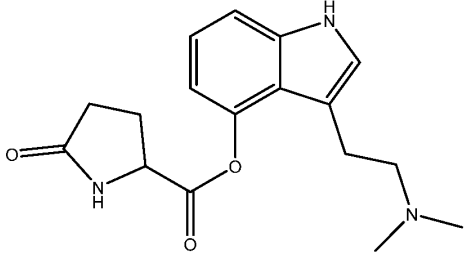
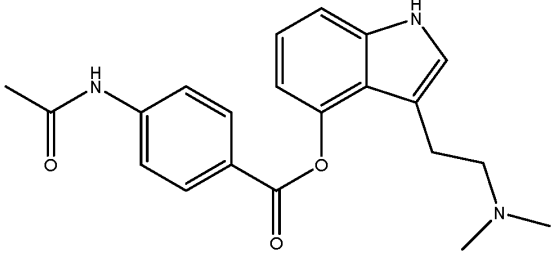
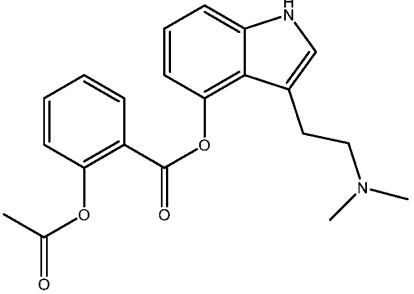
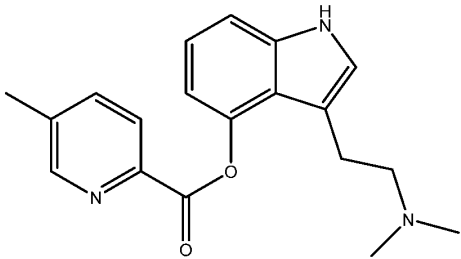
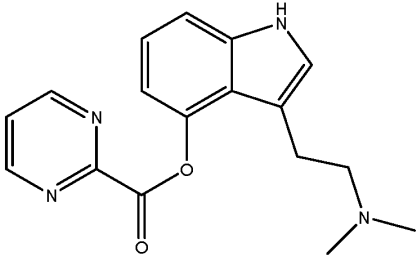
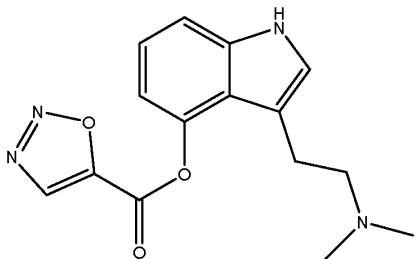
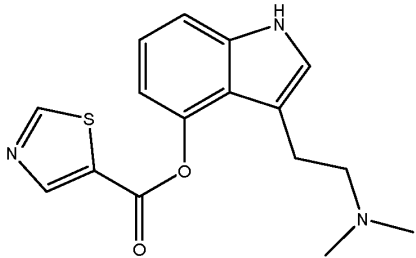
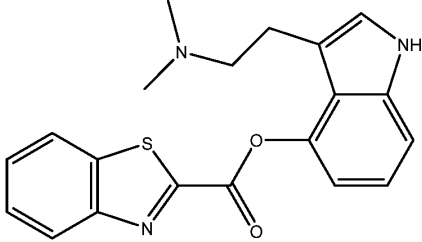
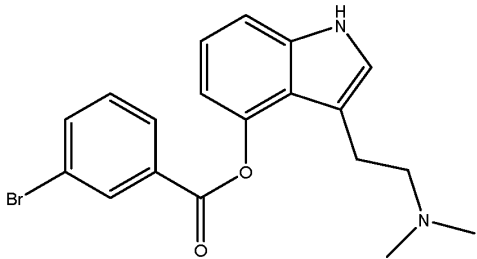
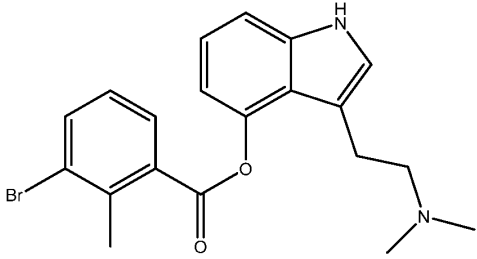
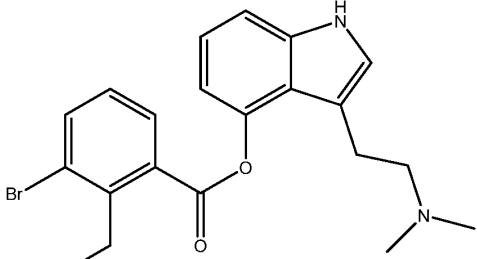
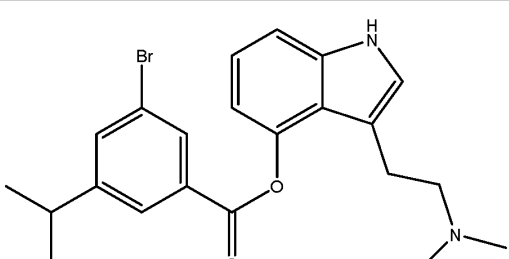
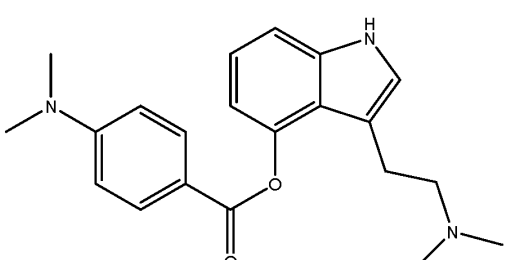
89	
104	

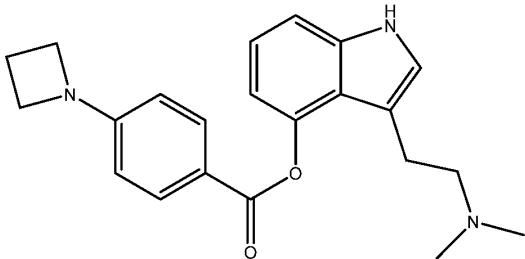
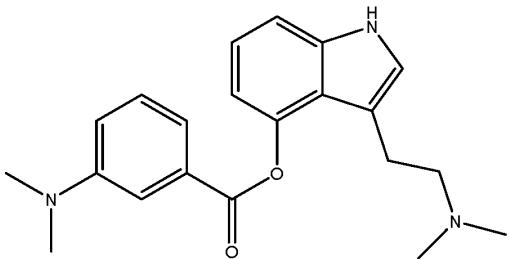
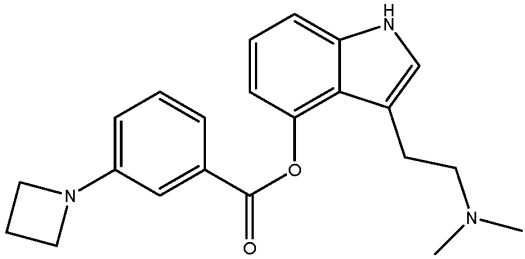
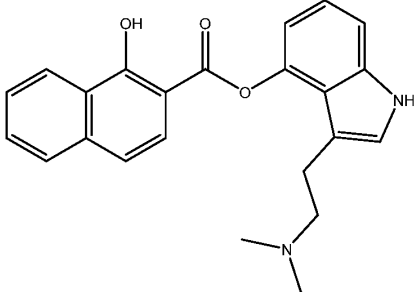
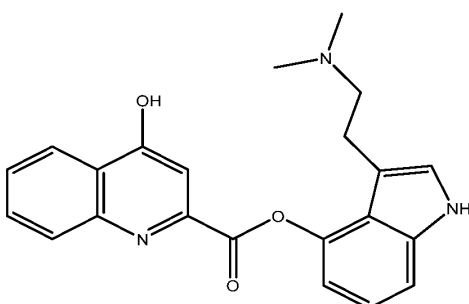
Table 2. Compounds of Formula (III)

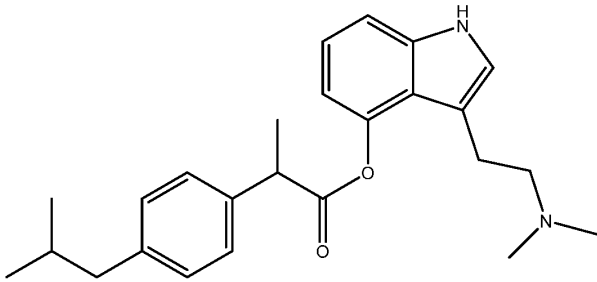
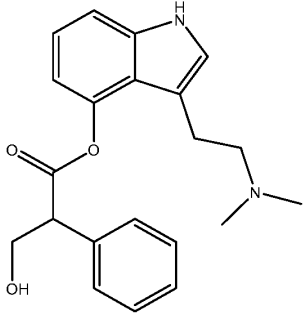
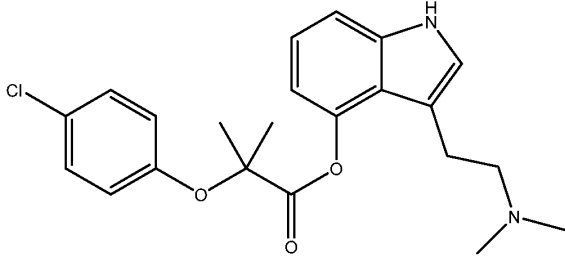
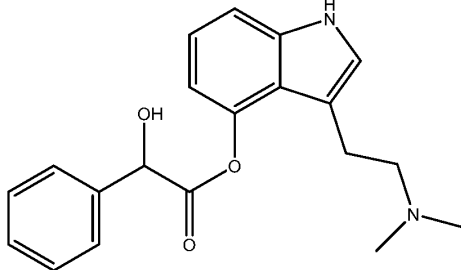
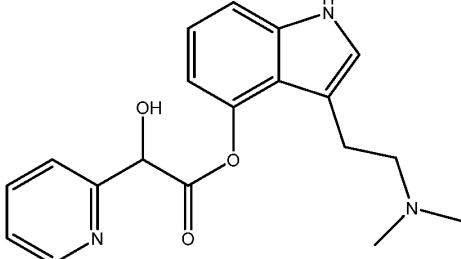
Compound	Structure
194	
77	

90	 <chem>CN(C)CCc1c[nH]c2ccccc12C(=O)Oc3cc[nH]n3</chem>
91	 <chem>CN(C)CCc1c[nH]c2ccccc12C(=O)Oc3ccncc3</chem>
92	 <chem>CN(C)CCc1c[nH]c2ccccc12C(=O)Oc3cc[nH]c3=O</chem>
97	 <chem>CN(C)CCc1c[nH]c2ccccc12C(=O)Oc3ccc(NC(=O)C)cc3</chem>
99	 <chem>CC(=O)Oc1ccc(cc1)C(=O)Oc2c[nH]c3ccccc23CN(C)CC</chem>

113	 <chem>CC1=CC=C(C=C1C2=CC=CC=C2N2)C(CCN(C)C)OC(=O)C3=CC=CC=C3N</chem>
115	 <chem>CC1=CC=C(C=C1C2=CC=CC=C2N2)C(CCN(C)C)OC(=O)C3=CC=NC(=N)N=C3</chem>
116	 <chem>CC1=CC=C(C=C1C2=CC=CC=C2N2)C(CCN(C)C)OC(=O)C3=CC=NN=C3O</chem>
117	 <chem>CC1=CC=C(C=C1C2=CC=CC=C2N2)C(CCN(C)C)OC(=O)C3=CC=NC=C3S</chem>
118	 <chem>CC1=CC=C(C=C1C2=CC=CC=C2N2)C(CCN(C)C)OC(=O)C3=CC4=CC=CC=C4S4=N3</chem>

168	 <chem>CN(C)CCc1c[nH]c2cc(OC(=O)c3ccc(Br)cc3)ccc12</chem>
169	 <chem>Cc1cc(Br)ccc1C(=O)Oc2c[nH]c3ccccc23CN(C)CC</chem>
170	 <chem>CCc1cc(Br)ccc1C(=O)Oc2c[nH]c3ccccc23CN(C)CC</chem>
171	 <chem>CC(C)c1cc(Br)ccc1C(=O)Oc2c[nH]c3ccccc23CN(C)CC</chem>
172	 <chem>CN(C)CCc1c[nH]c2cc(OC(=O)c3ccc(N(C)C)cc3)ccc12</chem>

173	
174	
175	
101	
102	

188	
76	
78	
93	
94	

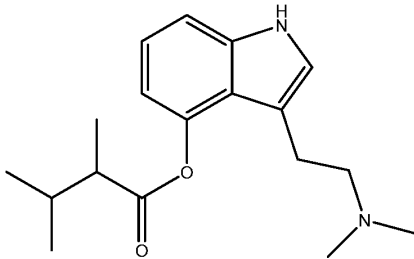
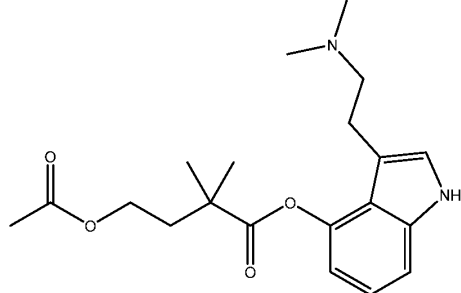
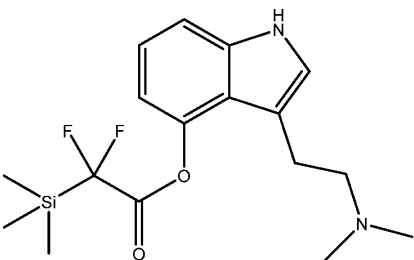
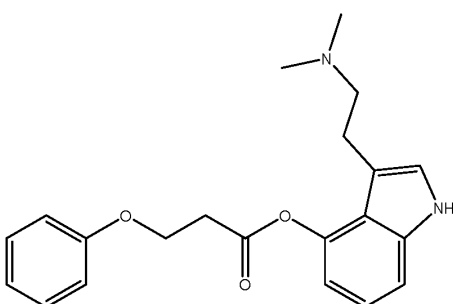
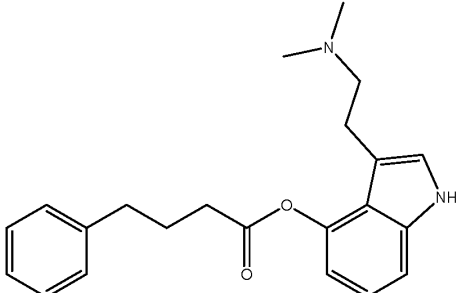
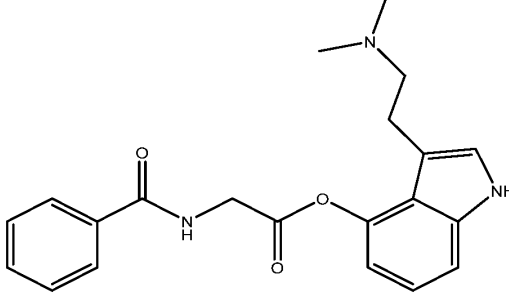
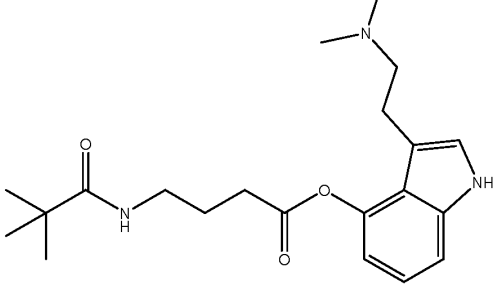
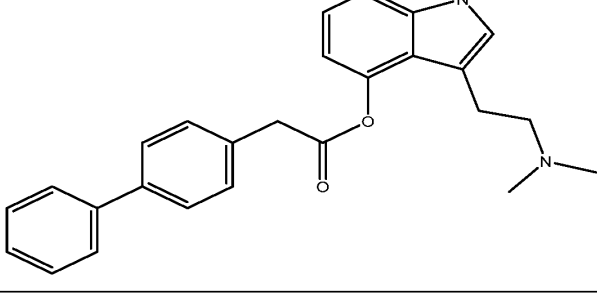
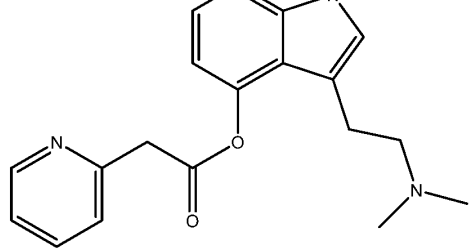
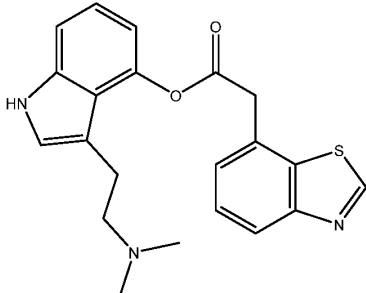
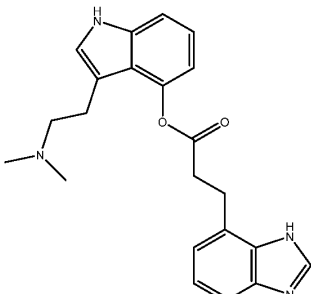
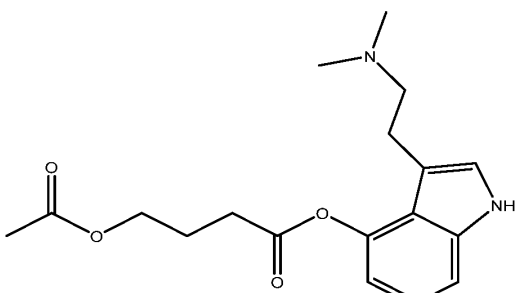
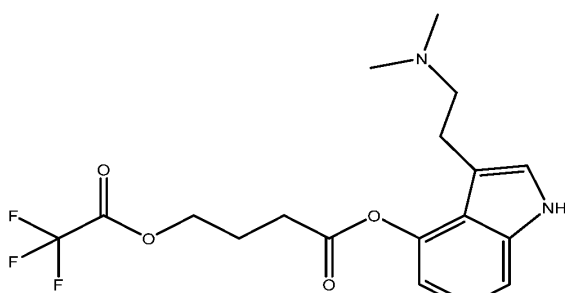
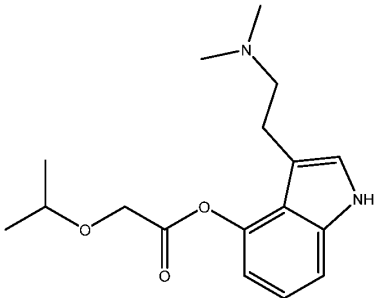
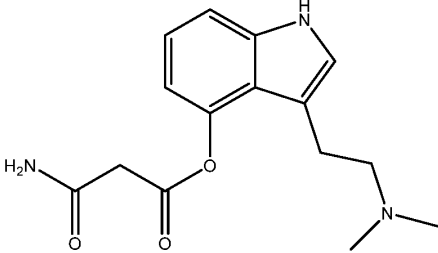
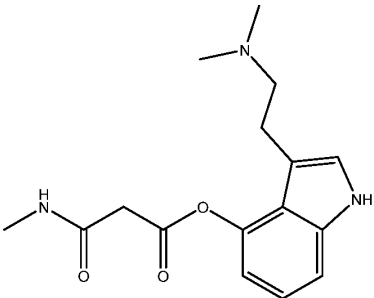
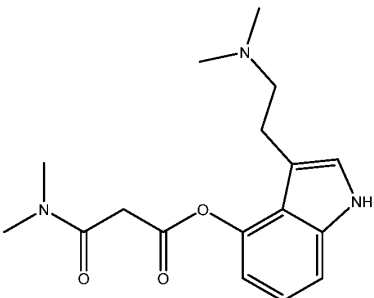
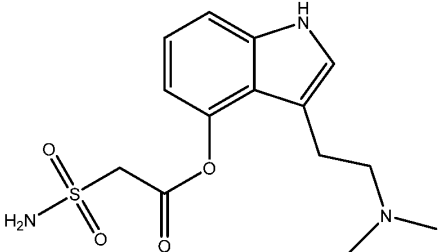
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182	
193	

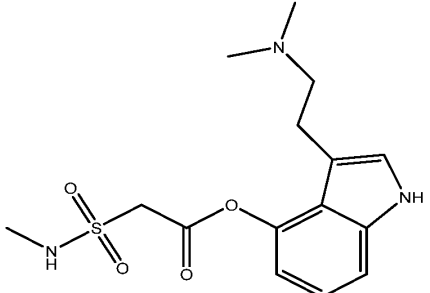
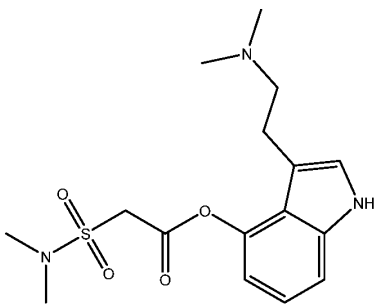
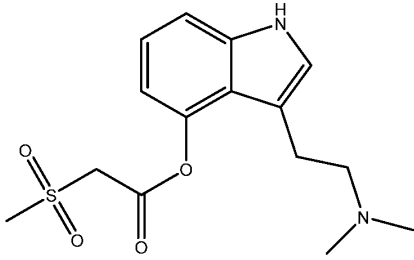
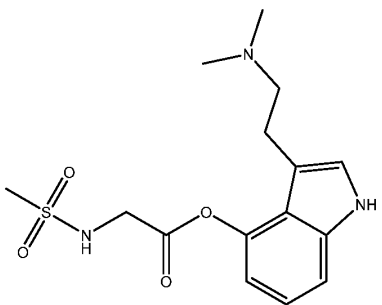
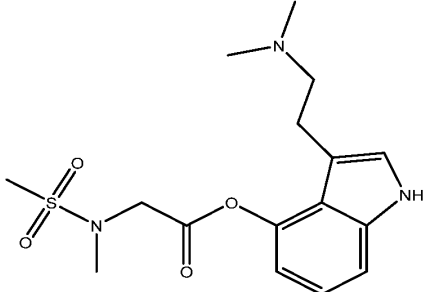
Table 3. Compounds of Formula (IV)

Compound	Structure
95	

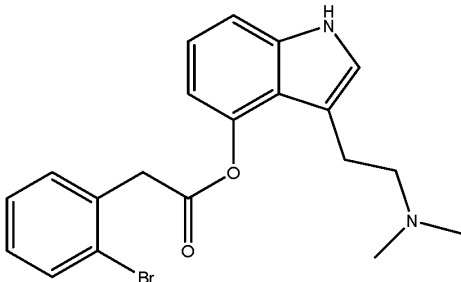
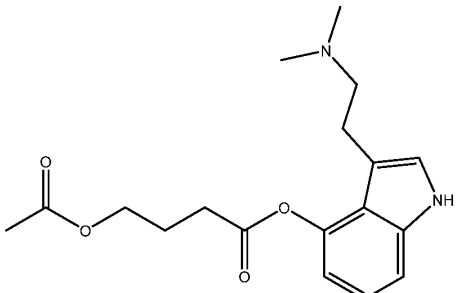
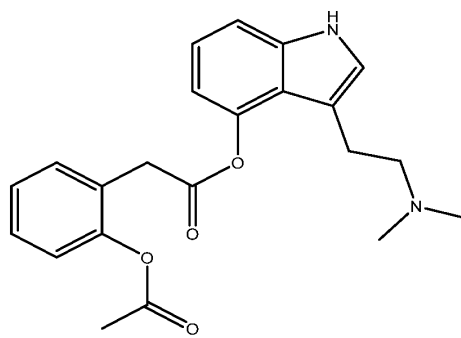
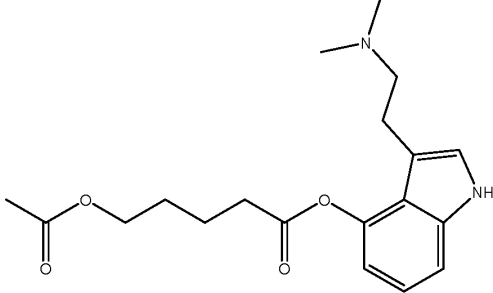
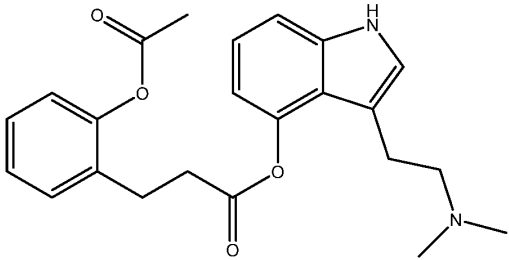
96	 <chem>CN(C)CCc1c[nH]c2cc(OC(=O)CCCCc3ccccc3)ccc12</chem>
98	 <chem>CN(C)CCc1c[nH]c2cc(OC(=O)CCNC(=O)c3ccccc3)ccc12</chem>
100	 <chem>CC(C)(C)C(=O)NCCCCOC(=O)c1c[nH]c2ccccc12</chem>
103	 <chem>CN(C)CCc1c[nH]c2cc(OC(=O)CCc3ccc(cc3)C4=CC=CC=C4)ccc12</chem>
105	 <chem>CN(C)CCc1c[nH]c2cc(OC(=O)CCc3ccncc3)ccc12</chem>

119	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)CCc3ccc4[nH]cnc4c3</chem>
120	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)CCc3c[nH]c4ccccc34</chem>
121	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)CCCC(=O)OCC(=O)C</chem>
122	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)CCCC(=O)OCC(=O)C(F)(F)F</chem>

139	 <chem>CC(C)OCC(=O)Oc1ccc2c(c1)c(c[nH]2)CCN(C)C</chem>
153	 <chem>NC(=O)CC(=O)Oc1ccc2c(c1)c(c[nH]2)CCN(C)C</chem>
154	 <chem>CNC(=O)CC(=O)Oc1ccc2c(c1)c(c[nH]2)CCN(C)C</chem>
155	 <chem>CN(C)CC(=O)CC(=O)Oc1ccc2c(c1)c(c[nH]2)CCN(C)C</chem>
156	 <chem>NC(=O)CC(=O)Oc1ccc2c(c1)c(c[nH]2)CCN(C)C</chem>

157	
158	
159	
163	
164	

161	
162	
176	
177	
178	

179	 <chem>CN(C)CCc1c[nH]c2ccccc12OC(=O)Cc1ccccc1Br</chem>
180	 <chem>CC(=O)OCCCCCOC(=O)c1c[nH]c2ccccc12CCN(C)C</chem>
181	 <chem>CC(=O)Oc1ccccc1OC(=O)Cc2c[nH]c3ccccc23CCN(C)C</chem>
183	 <chem>CC(=O)OCCCCCCOC(=O)c1c[nH]c2ccccc12CCN(C)C</chem>
184	 <chem>CC(=O)Oc1ccccc1OC(=O)Cc2c[nH]c3ccccc23CCN(C)C</chem>

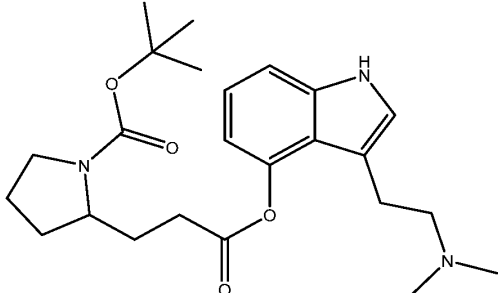
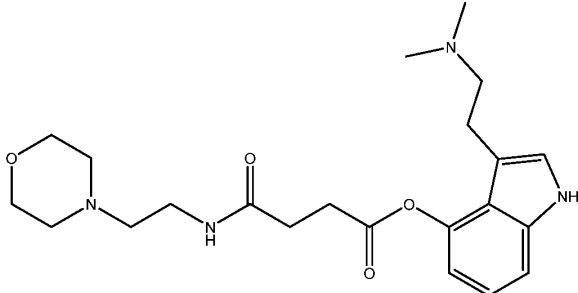
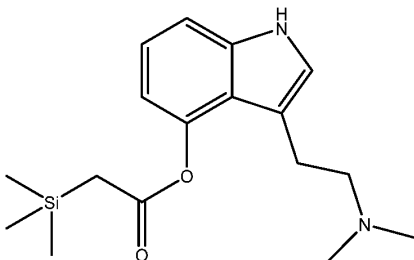
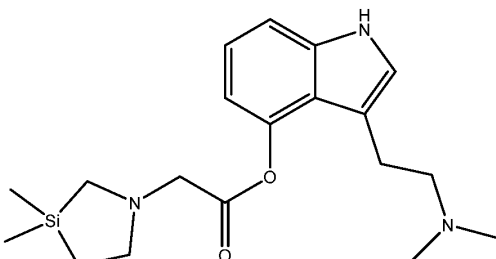
185	
187	
192	
201	

Table 4. Compounds of Formula (V)

Compound	Structure
137	 <chem>CC(C)CNC(=O)Oc1ccc2c(c1)c(c[nH]2)CCN(C)C</chem>
165	 <chem>CN(C)CCCc1c[nH]c2ccccc12C(=O)ONC=O</chem>
166	 <chem>CN(C)CCCc1c[nH]c2ccccc12C(=O)OCN(C)C</chem>
167	 <chem>CN(C)CCc1c[nH]c2ccccc12C(=O)OCC(F)(F)F</chem>
135	 <chem>CC(C)CNC(=O)Oc1ccc2c(c1)c(c[nH]2)CCN(C)C</chem>

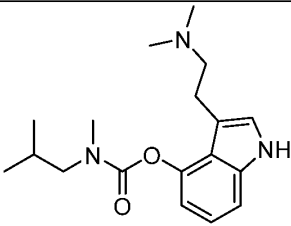
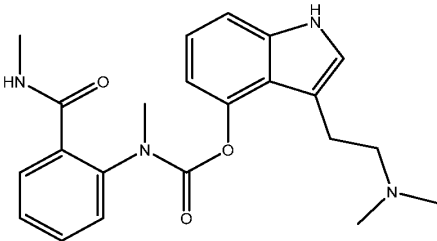
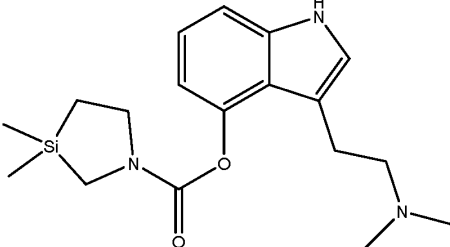
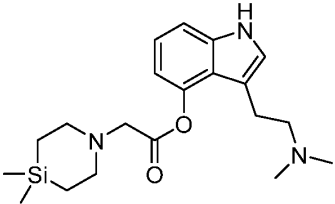
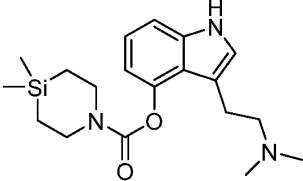
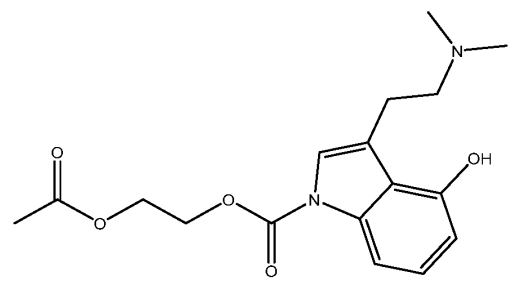
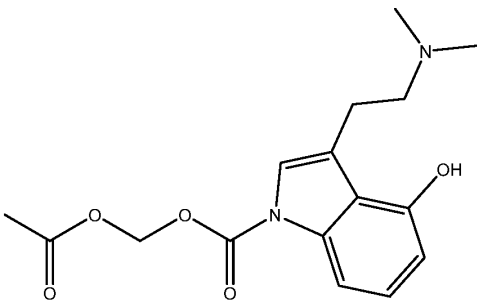
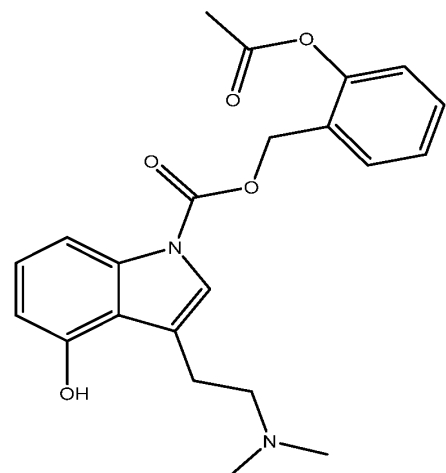
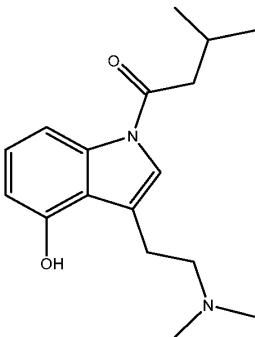
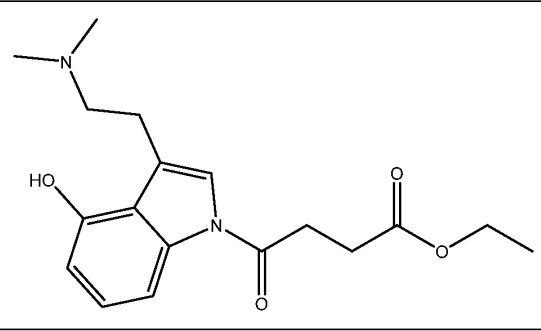
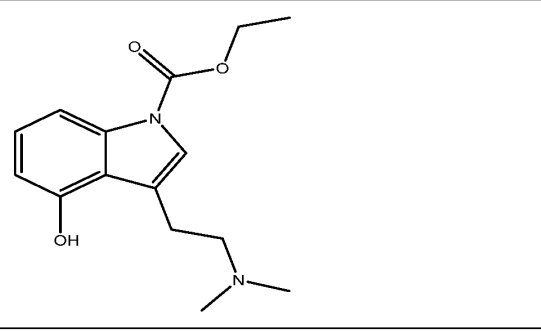
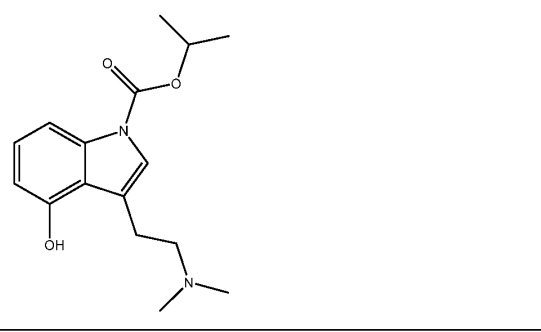
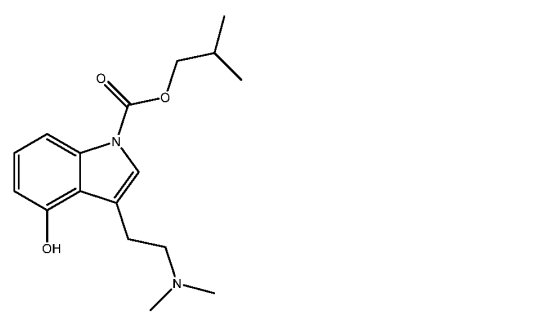
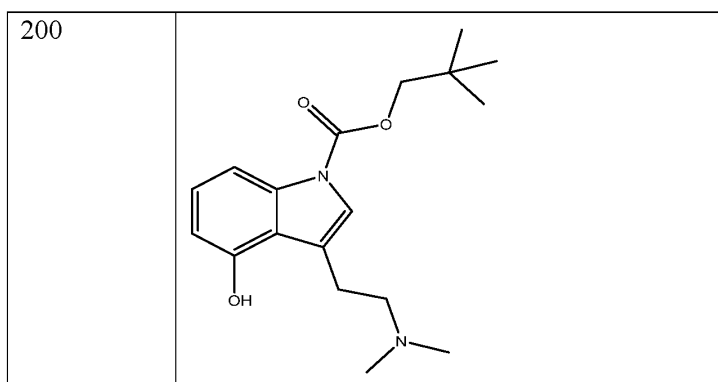
138	
186	
202	
204	
205	

Table 5: Compounds of Formula (VI)

Compound	Structure
126	
127	
128	
195	

196	 <chem>CCOC(=O)CCC(=O)N1C=C(CCN(C)C)c2cc(O)ccc21</chem>
197	 <chem>CCOC(=O)N1C=C(CCN(C)C)c2cc(O)ccc21</chem>
198	 <chem>CC(C)OC(=O)N1C=C(CCN(C)C)c2cc(O)ccc21</chem>
199	 <chem>CC(C)COC(=O)N1C=C(CCN(C)C)c2cc(O)ccc21</chem>



Pharmaceutical Composition

[0084] The present disclosure provides pharmaceutical compositions comprising at least one compound disclosed herein and one or more pharmaceutically acceptable excipients.

[0085] The compounds provided herein may be administered as compounds per se or may be formulated as pharmaceutical compositions. The pharmaceutical compositions may comprise one or more pharmaceutically acceptable excipients, such as carriers, diluents, fillers, disintegrants, lubricating agents, binders, colorants, pigments, stabilizers, preservatives, and/or antioxidants.

[0086] The pharmaceutical compositions can be formulated by techniques known to the person skilled in the art, such as the techniques published in "Remington: The Science and Practice of Pharmacy", Pharmaceutical Press, 22nd edition. The pharmaceutical compositions can be formulated as dosage forms for oral, parenteral, such as intramuscular, intravenous, subcutaneous, intradermal, intraarterial, intracardial, rectal, nasal, topical, aerosol or vaginal administration. Dosage forms for oral administration include coated and uncoated tablets, soft gelatin capsules, hard gelatin capsules, lozenges, troches, solutions, emulsions, suspensions, syrups, elixirs, powders and granules for reconstitution, dispersible powders and granules, medicated gums, chewing tablets and effervescent tablets. Dosage forms for parenteral administration include solutions, emulsions, suspensions, dispersions and powders and granules for reconstitution. Emulsions are a preferred dosage form for parenteral administration. Dosage forms for rectal and vaginal administration include suppositories and ovula. Dosage forms for nasal administration can be administered via inhalation and insufflation, for example by a metered inhaler. Dosage forms for topical administration include creams, gels, ointments, salves, patches and transdermal delivery systems.

Method of Treatment

[0087] The disclosure further relates to compounds disclosed herein, or a pharmaceutical composition comprising at least one compound disclosed here, for use in the treatment of a serotonin 5-HT_{2A} receptor associated disease/disorder. In embodiments, the compounds may be used in the treatment of an anxiety disorder, attention deficit hyperactivity disorder (ADHD), depression (including treatment resistant depression), cluster headache, diminished drive, burn-out, bore-out, migraine, Parkinson's disease, schizophrenia, an eating disorder (including anorexia nervosa), psychotic disorder, schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar I disorder, bipolar II disorder, major depressive disorder, psychotic depression, delusional disorders, shared psychotic disorder, Shared paranoia disorder, brief psychotic disorder, paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder, social anxiety disorder, substance-induced anxiety disorder, selective mutism, panic disorder, panic attacks, agoraphobia, posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), and premenstrual syndrome (PMS).

[0088] In embodiments, the 5-HT_{2A} receptor associated disease or disorder is depression. In embodiments, the depression is treatment resistant depression.

[0089] In embodiments, the 5-HT_{2A} receptor associated disease or disorder is an eating disorder. In embodiments, the eating disorder is anorexia nervosa.

[0090] In embodiments, the 5-HT_{2A} receptor associated disease or disorder is an anxiety disorder.

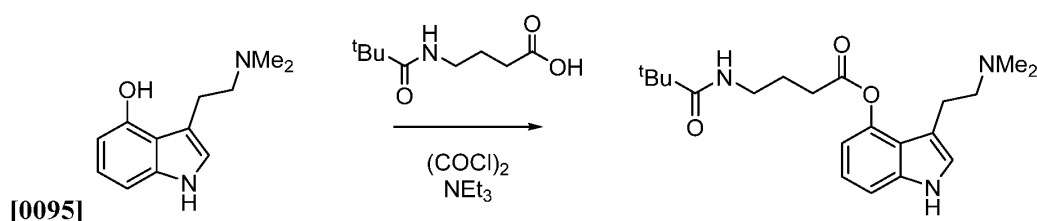
[0091] In embodiments, the 5-HT_{2A} receptor associated disease or disorder is bipolar I disorder.

[0092] In embodiments, the 5-HT_{2A} receptor associated disease or disorder is bipolar II disorder.

[0093] In embodiments, the 5-HT_{2A} receptor associated disease or disorder is major depressive disorder.

[0094] In embodiments, the 5-HT_{2A} receptor associated disease or disorder is posttraumatic stress disorder (PTSD).

EXAMPLES

Example 1. Synthesis of compound 100: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 4-pivalamidobutanoate, Formic Acid

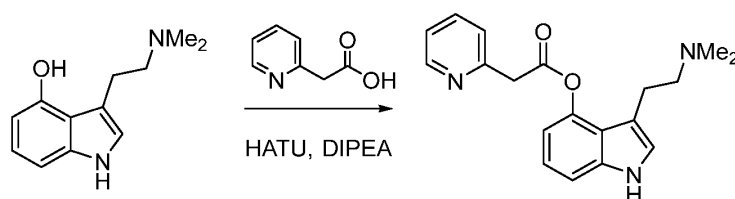
[0096] To a stirred solution of 4-[(2,2-Dimethylpropionyl)amino]butyric acid (187 mg, 1.1 Eq, 999 μmol) in dry DCM (4 mL) under a nitrogen atmosphere at r.t. was added oxalyl chloride (173 mg, 120 μL , 1.5 Eq, 1.37 mmol) and a drop of DMF. The reaction mixture was stirred at r.t. for 3 h. The volatiles were removed *in vacuo*. The residue was redissolved in DCM (2 mL) and added to a solution of psilocin (204.6 mg, 1 Eq, 942 μmol) and triethylamine (363 mg, 500 μL , 3.8 Eq, 3.59 mmol) in DCM (2 mL) at 0 °C. The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with water (10 mL), extracted with DCM (3 x 10 mL). The combined organic layers were collected, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (24 g cartridge, 0-20% MeOH/DCM) to afford partially purified product. The material was dissolved in DMSO (1.94 mL), filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130 Å, 5 μm , 30 mm X 100 mm, flow rate 40 mLmin⁻¹ eluting with a 0.1% formic acid in water-MeCN gradient over 8.5 min using UV across all wavelengths with PDA as well as a QDA and ELS detector. At column dilution pump gives 2 mLmin⁻¹ MeCN over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 10% MeCN; 0.5-5.5 min, ramped from 10% MeCN to 40% MeCN; 5.5-5.6 min, ramped from 40% MeCN to 100% MeCN; 5.6-8.5 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac to afford the title compound (25.7 mg, 52 μmol , 6%) was afforded as a yellow oil.

m/z 374.3 ($\text{M}+\text{H}$)⁺ (ES^+)

[0097] ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.02 (s, 1H), 8.17 (s, 1H), 7.55 (t, J = 5.7 Hz, 1H), 7.22 (dd, J = 8.1, 0.8 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 7.03 (t, J = 7.9 Hz, 1H), 6.67 (dd, J = 7.6, 0.8 Hz, 1H), 3.16 (q, J = 6.5 Hz, 2H), 2.79 – 2.71 (m, 2H), 2.64 (t, J = 7.6 Hz, 2H), 2.23

(s, 6H), 1.85 – 1.77 (m, 2H), 1.10 (s, 9H). 2H not observed - signal overlaps with DMSO solvent peak. 1 x exchangeable H not observed.

Example 2. Synthesis of compound 105: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-(pyridin-2-yl)acetate, Formic Acid



[0098]

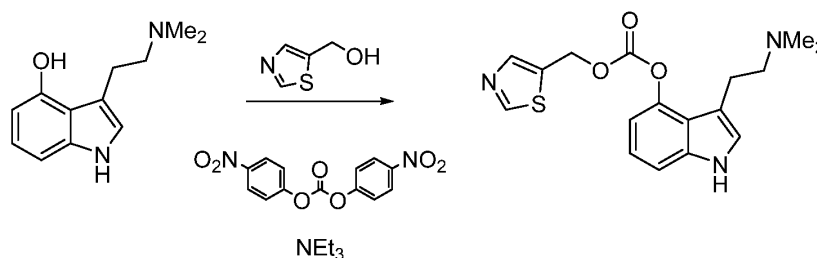
[0099] A mixture of psilocin (200.0 mg, 1 Eq, 960 μmol), 2-(pyridin-2-yl)acetic acid, HCl (168 mg, 1 Eq, 960 μmol), HATU (525 mg, 1.4 Eq, 1.38 mmol) and DIPEA (417 mg, 557 μL , 3.4 Eq, 3.22 mmol) in dry DMF (2.5 mL) was stirred at r.t. for 16 h. The reaction mixture was diluted with sat. NaHCO_3 (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (3 x 20 mL) and brine (25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was loaded onto celite and purified by chromatography on RP Flash C18 (12 g cartridge, 0-100% (0.1% formic acid in MeCN)/(0.1% formic acid in water)). The partially purified sample was dissolved in DMSO (1.8 mL), filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130 $\text{\AA}$, 5 μm , 30 mm X 100 mm, flow rate 40 mLmin^{-1} eluting with a 0.1% formic acid in water-MeCN gradient over 12.5 min using UV across all wavelengths with PDA as well as a QDA and ELS detector. At column dilution pump gives 2 mLmin^{-1} MeCN over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 5% MeCN; 0.5-10.5 min, ramped from 5% MeCN to 22.5% MeCN; 10.5-10.6 min, ramped from 22.5% MeCN to 100% MeCN; 10.6-12.5 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac to afford the title compound (7.0 mg, 17 μmol , 2%) as a brown solid.

[0100] m/z 324.1 ($\text{M}+\text{H}^+$) (ES+)

[0101] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.08 (s, 1H), 8.56 (dd, $J = 5.1, 1.8$ Hz, 1H), 8.24 (s, 1H), 7.85 – 7.78 (m, 1H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.33 (dd, $J = 7.6, 4.9$ Hz, 1H), 7.24 (d, $J = 8.1$ Hz, 1H), 7.17 (d, $J = 2.3$ Hz, 1H), 7.07 – 7.01 (m, 1H), 6.69 (d, $J = 7.6$ Hz, 1H), 4.23

(s, 2H), 2.87 – 2.81 (m, 2H), 2.68 – 2.62 (m, 2H), 2.35 (s, 6H). (1x exchangeable H not observed).

Example 3. Synthesis of compound 107: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (thiazol-5-ylmethyl) carbonate, 0.5Fumaric acid



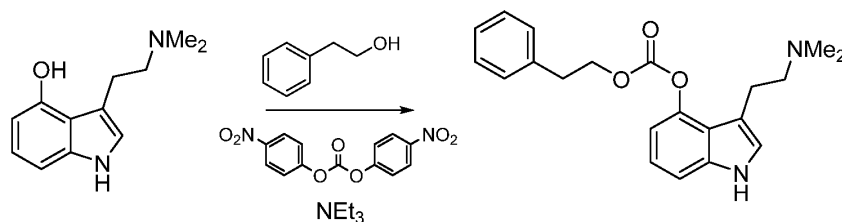
[0102]

[0103] To a stirred solution of thiazol-5-ylmethanol (114 mg, 1 Eq, 990 μ mol) and bis(4-nitrophenyl) carbonate (361 mg, 1.2 Eq, 1.19 mmol) in dry DCM (8 mL) under a nitrogen atmosphere at 20 °C was added triethylamine (220 mg, 304 μ L, 2.2 Eq, 2.18 mmol). The reaction mixture was stirred for 1 h at r.t. To the reaction mixture under a nitrogen atmosphere at 20 °C was added a solution of psilocin (202.2 mg, 1 Eq, 990 μ mol) in DMF (2 mL). The reaction mixture was stirred for 1 h at rt. The reaction mixture was then heated at 38 °C overnight. The reaction mixture was diluted with DCM (10 mL), poured into ice/water (20 mL) and transferred into a separating funnel. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (24 g cartridge, 5-50 % (0.1 % formic acid in MeCN)/(0.1% formic acid in water)) to afford 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (thiazol-5-ylmethyl) carbonate, Formic Acid (94.7 mg, 242 μ mol, 24%) as a light yellow oil. The material was dissolved in acetone (5 mL) and a solution of fumaric acid (28 mg, 0.24 Eq, 242 μ mol) in acetone (5 mL) was added. The resulting solid was filtered, washed with acetone and dried *in vacuo* for 24 h to afford the title compound (48.7 mg, 0.12 mmol, 12%) as an off-white solid.

[0104] m/z 346.1 (M+H)⁺ (ES⁺)

[0105] ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.13 (s, 1H), 9.18 (s, 1H), 8.05 (s, 1H), 7.30 – 7.25 (m, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.09 – 7.02 (m, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.54 (s, 1H), 5.56 (s, 2H), 2.75 – 2.69 (m, 2H), 2.56 – 2.51 (m, 2H), 2.20 (s, 6H). 1 x exchangeable H not observed.

Example 4. Synthesis of compound 109: 3-(2-(Dimethylamino)ethyl)-1H-indol-4-yl phenethyl carbonate, Fumaric acid



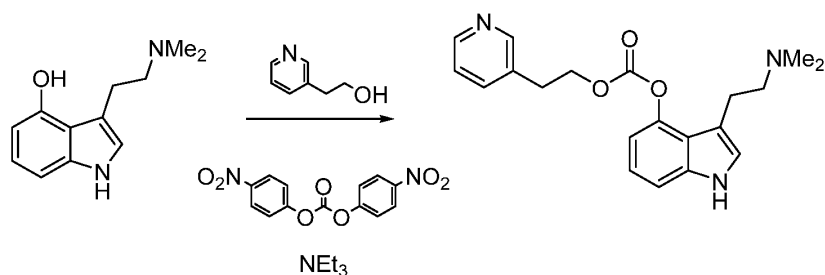
[0106]

[0107] To a stirred solution of 2-phenylethan-1-ol (121.8 mg, 1 Eq, 996.7 μ mol) and bis(4-nitrophenyl) carbonate (363.9 mg, 1.2 Eq, 1.196 mmol) in dry DCM (8.00 mL) under a nitrogen atmosphere at 20 °C was added Et₃N (221.9 mg, 306 μ L, 2.2 Eq, 2.193 mmol). The reaction mixture was stirred for 1 h at rt. To the reaction mixture, under a nitrogen atmosphere at 20 °C, was added a solution of psilocin (203.6 mg, 1 Eq, 996.7 μ mol) in DMF (2.00 mL). The reaction mixture was stirred for 1 h at rt. The reaction mixture was then heated at 38 °C for 17 h. The reaction mixture was cooled to rt, diluted with DCM (10 mL), poured into ice/water (30 mL) and transferred into a separating funnel. The aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were washed with water (3 x 20 mL) and brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (12 g cartridge, 5-35 % (0.1 % formic acid in MeCN) / (0.1% formic acid in water)) to afford a formic acid salt (173.1 mg, 0.35 mmol, 35 %, 80% Purity) as a brown oil. The material was dissolved in acetone (8 mL) and a solution of fumaric acid (50.42 mg, 0.4358 Eq, 434.4 μ mol) in acetone (6 mL) was added. The resulting solid was filtered, washed with acetone and dried in a vacuum desiccator over weekend to afford the title compound (111.5 mg, 0.23 mmol, 23 %, 95% Purity) as a brown solid.

[0108] m/z 353.15 (M+H)⁺ (ES⁺); 307.80 (M-NMe₂-H)⁻ (ES⁻)

[0109] ¹H NMR (500 MHz, DMSO) δ 11.17 (d, J = 2.7 Hz, 1H), 7.36 – 7.22 (m, 6H), 7.20 (d, J = 2.4 Hz, 1H), 7.05 (t, J = 7.9 Hz, 1H), 6.75 (dd, J = 7.7, 0.9 Hz, 1H), 6.54 (d, J = 1.4 Hz, 2H), 4.46 (t, J = 6.8 Hz, 2H), 3.01 (t, J = 6.8 Hz, 2H), 2.84 (dd, J = 10.0, 5.6 Hz, 2H), 2.74 (dd, J = 9.2, 6.1 Hz, 2H), 2.38 (s, 6H). 2H are absent (exchangeable protons of fumaric acid).

Example 5. Synthesis of compound 110: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (2-(pyridin-2-yl)ethyl) carbonate, 2Formic Acid



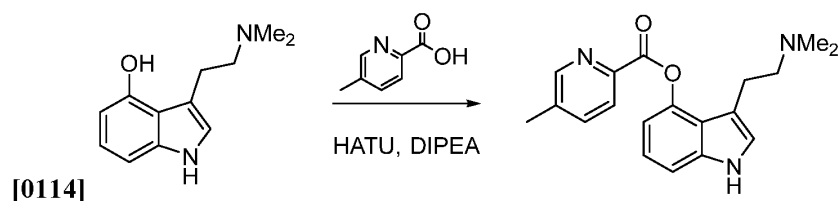
[0110]

[0111] To a solution of 2-(pyridin-2-yl)ethan-1-ol (116 mg, 1 Eq, 920 μ mol) and bis(4-nitrophenyl) carbonate (297 mg, 1.1 Eq, 966 μ mol) in dry DMF (2 mL) under a nitrogen atmosphere at r.t. was added DIPEA (742 mg, 1.0 mL, 6.2 Eq, 5.74 mmol). The reaction mixture was stirred at r.t. for 2 h. To the reaction mixture was added a solution of psilocin (200 mg, 1 Eq, 920 μ mol) in DMF (2 mL). The reaction mixture was stirred at 40 °C for 48 h. The reaction mixture was diluted with distilled water (25 mL). The layer was extracted with DCM (3 x 20 mL). The combined organic layers were collected, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was loaded onto celite and purified by chromatography on RP Flash C18 (12 g cartridge, 5-20% (0.1 % formic acid in MeCN)/(0.1% formic acid in water)) to afford the title compound (196 mg, 0.38 mmol, 42%) as a dark brown oil.

[0112] m/z 354.2 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0113] ¹H NMR (500 MHz, DMSO- d_6) δ 11.13 (s, 1H), 8.53 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 8.21 (s, 2H), 7.75 (td, J = 7.6, 1.9 Hz, 1H), 7.35 (dt, J = 7.8, 1.1 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.19 (d, J = 2.3 Hz, 1H), 7.07 – 7.01 (m, 1H), 6.74 (dd, J = 7.7, 0.8 Hz, 1H), 4.63 (t, J = 6.6 Hz, 2H), 3.17 (d, J = 13.1 Hz, 2H), 2.78 (dd, J = 9.2, 6.5 Hz, 2H), 2.63 (dd, J = 9.2, 6.5 Hz, 2H), 2.30 (s, 6H). 2 x exchangeable H not observed.

Example 6. Synthesis of compound 113: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 5-methylpicolinate, 0.5Fumaric acid



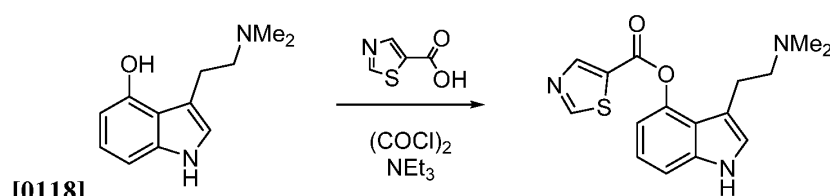
[0114]

[0115] A mixture of psilocin (202.0 mg, 1 Eq, 930 μ mol), 5-methylpicolinic acid (130 mg, 1 Eq, 930 μ mol), HATU (509 mg, 1.4 Eq, 1.34 mmol) and DIPEA (284 mg, 379 μ L, 2.4 Eq, 2.19 mmol) in dry DMF (2.5 mL) was stirred at r.t. for 7 days. The reaction mixture was diluted with sat. NaHCO_3 (25 mL), and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (3 x 20 mL) and brine (25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was loaded onto celite and purified by chromatography on RP Flash C18 (12 g cartridge, 5-30% (0.1% formic acid in MeCN)/(0.1% formic acid in water)) to afford 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 5-methylpicolinate, formic acid salt (42 mg) a glassy oil. To a solution the material (40.0 mg, 1 Eq, 103 μ mol) in acetone (2 mL) was added a solution of fumaric acid (13 mg, 1.05 Eq, 108 μ mol) in acetone (2 mL). The stored at -20 °C for 64 h. The resulting solid was isolated by filtration and dried *in vacuo* at 45 °C for 2 h to afford the title compound (35.2 mg, 90 μ mol, 10%) as an off-white solid.

[0116] m/z 324.6 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0117] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.19 – 11.05 (m, 1H), 8.70 – 8.65 (m, 1H), 8.20 (d, $J = 7.9$ Hz, 1H), 7.93 – 7.88 (m, 1H), 7.29 (dd, 1H), 7.18 (d, $J = 2.3$ Hz, 1H), 7.12 – 7.08 (m, 1H), 6.81 (dd, 1H), 6.52 (s, 1H), 2.77 – 2.71 (m, 2H), 2.56 – 2.52 (m, 2H), 2.45 (s, 3H), 2.04 (s, 6H). (1x exchangeable H not observed).

Example 7. Synthesis of compound 117: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl thiazole-5-carboxylate, Formic Acid



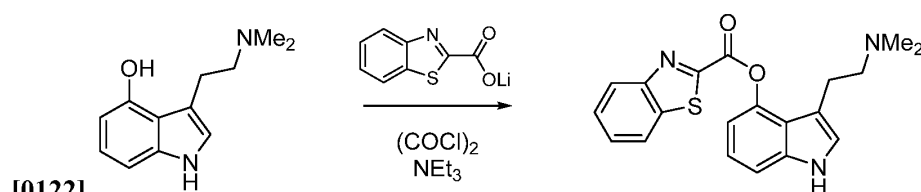
[0119] To a stirred solution of thiazole-5-carboxylic acid (135 mg, 1.1 Eq, 1.04 mmol) in dry DCM (4 mL) under a nitrogen atmosphere at r.t. was added oxalyl chloride (173 mg, 120 μ L, 1.5 Eq, 1.37 mmol) and a drop of DMF. The reaction mixture was stirred at r.t. for 3 h. The resulting mixture was stirred at r.t. for 3 h. The volatiles were removed *in vacuo*. The residue was redissolved in DCM (2 mL) and added to a solution of psilocin (200.1 mg, 1 Eq, 921 μ mol) and triethylamine (363 mg, 500 μ L, 3.9 Eq, 3.59 mmol) in DCM (2 mL) at 0 °C. The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with water (10 mL), extracted with DCM (3 x 10 mL). The combined organic layers were collected, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by

chromatography on RP Flash C18 (24 g cartridge, 5-40% (0.1 % formic acid in MeCN)/(0.1% formic acid in water)) to afford partially purified title compound (224.1 mg) as a brown oil. 101.9 mg of the material was triturated with diethyl ether and dried in a vacuum desiccator at 40 °C for 72 h to afford the title compound (66.4 mg, 0.18 mmol, 20%) as a light brown solid.

[0120] m/z 316.1 (M+H)⁺ (ES⁺)

[0121] ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.15 (s, 1H), 9.51 (d, J = 0.8 Hz, 1H), 8.83 (d, J = 0.8 Hz, 1H), 8.17 (s, 1H), 7.31 (dd, J = 8.2, 0.8 Hz, 1H), 7.20 (d, J = 2.3 Hz, 1H), 7.10 (t, J = 7.9 Hz, 1H), 6.85 (dd, J = 7.7, 0.8 Hz, 1H), 2.79 – 2.72 (m, 2H), 2.07 (s, 6H). Two protons from CH₂ not observed. Signal overlaps with DMSO solvent peak. 1 x exchangeable H not observed.

Example 8. Synthesis of compound 118: 3-(2-(Dimethylamino)ethyl)-1H-indol-4-yl benzo[d]thiazole-2-carboxylate, Fumaric acid

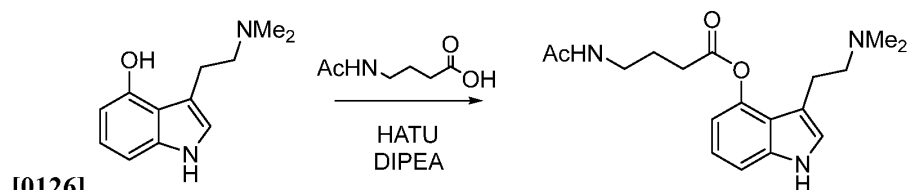


[0123] To a stirred solution of lithium benzo[d]thiazole-2-carboxylate (184.2 mg, 1 Eq, 994.8 μmol) in dry DCM (4.00 mL) under an atmosphere of N₂ at rt was added oxalyl chloride (265.1 mg, 182.9 μL, 2.1 Eq, 2.089 mmol) and a drop of DMF (72.72 mg, 77.0 μL, 1 Eq, 994.8 μmol). The reaction mixture was stirred at rt for 2 h. The volatiles were removed *in vacuo*. The residue was dissolved in DCM (2.00 mL) and added to a solution of psilocin (203.2 mg, 1 Eq, 994.8 μmol) and Et₃N (362.4 mg, 499 μL, 3.6 Eq, 3.581 mmol) in DCM (2.00 mL) at 0 °C. The reaction mixture was stirred at room temp for 1 h. The reaction mixture was concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (24 g cartridge, 5-40 % (0.1 % formic acid in MeCN) / (0.1% formic acid in water)) to afford 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl benzo[d]thiazole-2-carboxylate, Formic Acid (199.4 mg, 0.35 mmol, 35 %, 72% Purity) as a dark yellow oil. The material was dissolved in acetone (8 mL) and a solution of fumaric acid (46 mg, 0.40 Eq, 0.40 mmol) in acetone (6 mL) was added. The resulting solid was filtered, washed with acetone and dried in a vacuum desiccator overnight to afford the title compound (92.2 mg, 0.17 mmol, 17 %, 88% Purity) as a light brown solid.

[0124] m/z 366.14 (M+H)⁺ (ES⁺); 319.88 (M-NMe₂-H)⁻ (ES⁻)

[0125] ^1H NMR (500 MHz, DMSO) δ 11.24 (s, 1H), 8.37 – 8.29 (m, 2H), 7.77 – 7.67 (m, 2H), 7.36 (d, J = 8.1 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 7.18 – 7.11 (m, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.56 (s, 2H), 2.90 – 2.84 (m, 2H), 2.73 (s, 2H), 2.17 (s, 6H). 2H not observed (exchangeable protons of fumaric acid).

Example 9. Synthesis of compound 123: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 4-acetamidobutanoate, 0.2 HPF6, 0.8 Formic acid

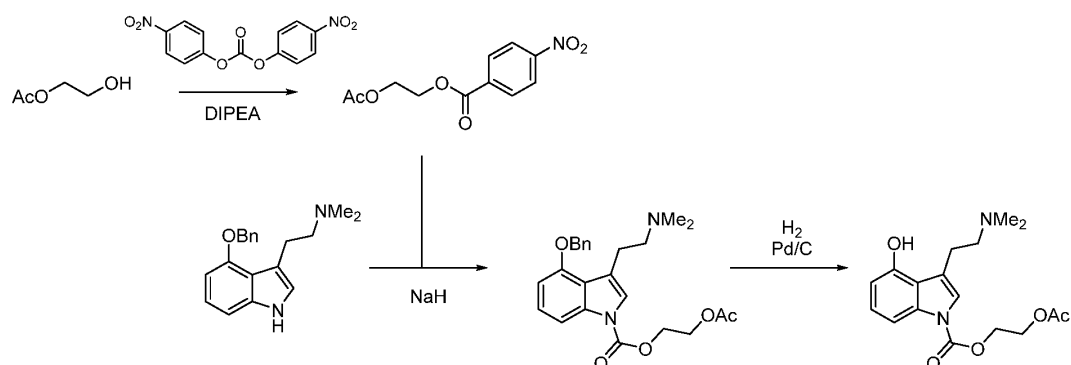


[0127] A mixture of 4-acetamidobutanoic acid (141 mg, 1 Eq, 969 μmol), HATU (516 mg, 1.4 Eq, 1.36 mmol), DIPEA (301 mg, 405 μL , 2.4 Eq, 2.33 mmol) and psilocin (200 mg, 1 Eq, 969 μmol) in DMF (4 mL) was stirred at r.t overnight. The reaction mixture was directly loaded on to a 80 g C18 reverse column and purified (80 g cartridge, 0-100% (0.1% formic acid in MeCN)/(0.1% formic acid in water)) to afford the desired product as an amber glass with a DMF impurity. Upon standing the desired product crystallized out of the amber glass. The amber glass/crystalline product was triturated in diethyl ether to afford the title compound (25.0 mg, 63.1 μmol , 7%) as a beige solid.

[0128] m/z 332.2 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0129] ^1H NMR (500 MHz, DMSO- d_6) δ 11.23 (d, J = 2.5 Hz, 1H), 9.26 (s, 1H), 7.96 (s, 1H), 7.28 – 7.26 (m, 2H), 7.08 (dd, J = 7.9 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 3.16 (q, J = 6.6 Hz, 2H), 3.02 (t, J = 7.9 Hz, 2H), 2.84 (s, 6H), 2.74 – 2.67 (m, 2H), 1.83 (s, 3H), 1.82 – 1.78 (m, 2H). 2H obscured by water peak. 1x exchangeable H not observed.

Example 10. Synthesis of compound 126: 2-Acetoxyethyl 3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indole-1-carboxylate, Formic Acid



[0130] Step 1: 2-(((4-Nitrophenoxy)carbonyl)oxy)ethyl acetate

[0131] To a solution of ethylene glycol monoacetate (100 mg, 90.0 μ L, 1 Eq, 961 μ mol) and carbonic acid, bis(4-nitrophenyl)ester (315.5 mg, 1.08 Eq, 1.037 mmol) in dry DMF (3.0 mL) at rt was added DIPEA (742 mg, 1.00 mL, 5.98 Eq, 5.74 mmol). The reaction mixture was stirred for 3 h at rt. The reaction mixture was diluted with distilled water (5 mL), extracted with DCM (3 x 5 mL). The combined organic layers were collected, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-50% EtOAc/isohexane) to afford the sub-title compound (351.7 mg, 0.61 mmol, 64 %, 47% Purity) as a yellow oil.

[0132] ^1H NMR (500 MHz, DMSO) δ 8.35 – 8.29 (m, 2H), 7.60 – 7.53 (m, 2H), 4.48 – 4.41 (m, 2H), 4.34 – 4.29 (m, 2H), 2.06 (s, 3H).

[0133] Step 2: 2-Acetoxyethyl-4-(benzyloxy)-3-(2-(dimethylamino)ethyl)-1H-indole-1-carboxylate

[0134] To a solution of 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethylethan-1-amine (145.5 mg, 95% Wt, 1 Eq, 469.5 μ mol) in DMF (5.00 mL) at 0 $^\circ\text{C}$ was added NaH (21.8 mg, 60% Wt, 1.16 Eq, 545 μ mol) and the reaction was stirred for 10 min at 0 $^\circ\text{C}$. The product from step 1, above (351.7 mg, 47% Wt, 1.308 Eq, 614.0 μ mol) was added at 0 $^\circ\text{C}$ then stirred at rt for 3 h. The reaction mixture was diluted with distilled water (5 mL), extracted with DCM (3 x 5 mL). The combined organic layers were collected, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (24 g cartridge, 0-10% MeOH/DCM) to afford the sub-title compound (142.6 mg, 0.29 mmol, 62 %, 86% Purity) as a light-yellow oil.

[0135] m/z 425.2 ($\text{M}+\text{H}$) $^+$ (ES $^+$)

[0136] ^1H NMR (500 MHz, DMSO) δ 7.69 (d, J = 8.3 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.43 – 7.39 (m, 2H), 7.38 – 7.31 (m, 2H), 7.24 (t, J = 8.2 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.22 (s, 2H), 4.58 – 4.54 (m, 2H), 4.42 – 4.37 (m, 2H), 2.92 – 2.86 (m, 2H), 2.06 (s, 6H), 2.05 (s, 3H). Two protons from CH_2 not observed. Signal overlaps with DMSO solvent peak.

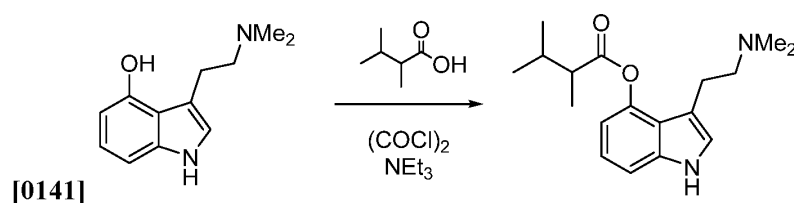
[0137] Step 3: 2-Acetoxyethyl 3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indole-1-carboxylate, Formic Acid

[0138] A solution of the product from step 2, above (142.6 mg, 86% Wt, 1 Eq, 288.9 μmol) in EtOH (20 mL) was hydrogenated in the H-Cube (Pd/C cat cart) at 5 bar at 60 °C, 1 mL/min for 30 min (recirculation). The mixture was concentrated *in vacuo* to afford impure product. The crude material was dissolved in DMSO (1.91 mL), filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130Å, 5 μm , 30 mm X 100 mm, flow rate 40 mL min⁻¹ eluting with a 0.1% formic acid in water-MeCN gradient over 17.5 mins using UV across all wavelengths with PDA as well as a QDA and ELS detector. At-column dilution pump gives 2 mL min⁻¹ MeOH over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 5% MeCN; 0.5-15.5 min, ramped from 5% MeCN to 22.5% MeCN; 15.5-15.6 min, ramped from 22.5% MeCN to 100% MeCN; 15.6-17.5 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac, affording the title compound (35.4 mg, 92 μmol , 32 %, 99% Purity) as a light brown oil.

[0139] m/z 335.2 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0140] ^1H NMR (500 MHz, DMSO) δ 8.18 (s, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.32 (s, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.60 (dd, J = 7.9, 0.8 Hz, 1H), 4.57 – 4.52 (m, 2H), 4.40 – 4.36 (m, 2H), 2.94 – 2.89 (m, 2H), 2.66 – 2.60 (m, 2H), 2.26 (s, 6H), 2.05 (s, 3H). 2 x exchangeable protons not observed.

Example 11. Synthesis of compound 129: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2,3-dimethylbutanoate, Fumaric acid

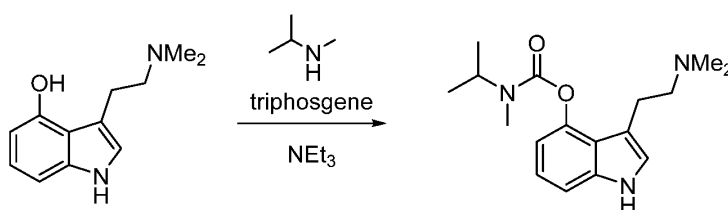


[0142] To a stirred solution of 2,3-dimethylbutanoic acid (123 mg, 1.1 Eq, 1.06 mmol) in dry DCM (4 mL) under a nitrogen atmosphere at r.t. was added oxalyl chloride (146 mg, 101 μ L, 1.2 Eq, 1.15 mmol) and a drop of DMF. The reaction mixture was stirred at r.t. for 3 h. The volatiles were removed *in vacuo*. The residue was redissolved in DCM (2 mL) and added to a solution of psilocin (200 mg, 1 Eq, 960 μ mol) and triethylamine (485 mg, 669 μ L, 5 Eq, 4.80 mmol) in DCM (2 mL) at 0 °C. The resulting mixture was stirred at r.t. for 16 h. The reaction mixture was diluted with water (25 mL) and extracted with DCM (3 x 25 mL). The combined organic layers were collected, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was loaded onto celite and purified by chromatography on RP Flash C18 (24 g cartridge, 0-30% (0.1% formic acid in MeCN)/(0.1% formic acid in water)) to afford 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2,3-dimethylbutanoate, formic acid (110 mg, 364 μ mol, 38%). The material was dissolved in acetone (6 mL) and a solution of fumaric acid (43 mg, 1.02 Eq, 370 μ mol) in acetone (6 mL) was added. The mixture was cooled at -20 °C for 60 h. The resulting solid was isolated by filtration and washed with MeCN (2x 2 mL) to afford the title compound (52.3 mg, 0.12 mmol, 13%) as a tan solid.

[0143] m/z 303.5 (M+H)⁺ (ES⁺)

[0144] ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.85 (s, 2H), 11.07 (s, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.04 (dd, J = 7.9, 7.9 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 6.56 (s, 2H), 2.89 – 2.76 (m, 2H), 2.73 – 2.60 (m, 4H), 2.32 (s, 6H), 2.14 – 2.04 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 1.02 (dd, J = 21.7, 6.8 Hz, 6H).

Example 12. Synthesis of compound 135: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl isopropyl(methyl)carbamate, 0.63Formic Acid, 0.37HCl



[0145]

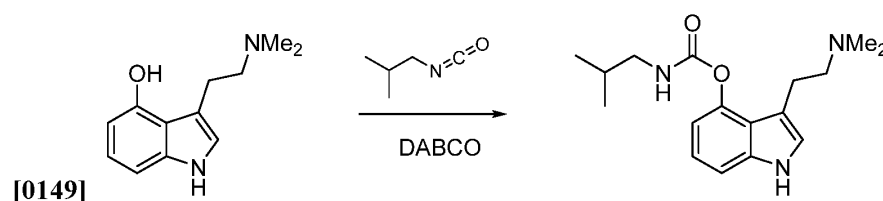
[0146] To a solution of N-methylpropan-2-amine (59 mg, 84 μ L, 1.1 Eq, 808 μ mol) and triethylamine (149 mg, 205 μ L, 2 Eq, 1.47 mmol) in THF (4 mL) at 0 °C was added triphosgene (113 mg, 0.5 Eq, 367 μ mol). The reaction was stirred at 0 °C for 20 min. A suspension of psilocin (150 mg, 1 Eq, 734 μ mol) in THF (3 mL) was added at 0 °C. The mixture was stirred at r.t. for 48 h. The reaction was stirred for a further 4 days at 40 °C. The

reaction was quenched with ice-cold water (10 mL) and diluted with ethyl acetate (10 mL). The phases were separated, and the aqueous phase was further extracted with ethyl acetate (10 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude material (211 mg) was dissolved in DMSO (2.7 mL), filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130 Å, 5 μm , 30 mm x 100 mm, flow rate 40 mLmin^{-1} eluting with a 0.1% formic acid in water-MeCN gradient over 8.5 min using UV across all wavelengths with PDA as well as a QDA and ELS detector. At column dilution pump gives 2 mLmin^{-1} MeCN over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 7.5% MeCN; 0.5-5.5 min, ramped from 7.5% MeCN to 37.5% MeCN; 5.5-5.6 min, ramped from 37.5% MeCN to 100% MeCN; 5.6-8.5 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac to afford the title compound (50.0 mg, 145 μmol , 20%) as a light brown solid.

[0147] m/z 304.2 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0148] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.03 (s, 1H), 8.15 (s, 0.63 H), 7.20 (dd, $J = 8.1, 0.8$ Hz, 1H), 7.15 (d, $J = 2.3$ Hz, 1H), 7.04 – 6.98 (m, 1H), 6.65 – 6.58 (m, 1H), 4.57 – 4.48 (m, 0.33H), 4.31 (p, $J = 6.6$ Hz, 0.67H), 2.97 (s, 2H), 2.90 – 2.82 (m, 2H), 2.80 (s, 1H), 2.79 – 2.71 (m, 2H), 2.38 (s, 6H), 1.24 (d, $J = 6.7$ Hz, 2H), 1.15 (d, $J = 6.8$ Hz, 4H). 1x exchangeable H not observed.

Example 13. Synthesis of compound 137: 3-(2-(Dimethylamino)ethyl)-1H-indol-4-yl isobutylcarbamate, HCl



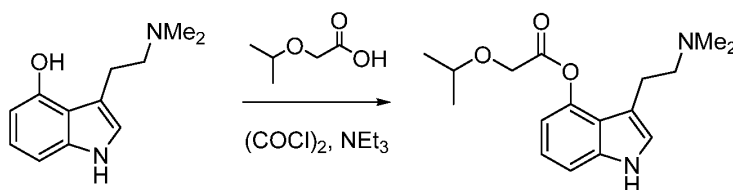
[0150] To a suspension of psilocin (205.0 mg, 88% Wt, 1 Eq, 883.1 μmol) in MeCN (5.00 mL) was added DABCO (118.9 mg, 1.2 Eq, 1.060 mmol) and 1-isocyanato-2-methylpropane, 1M in DCM (131.3 mg, 1.325 mL, 1.00 molar, 1.5 Eq, 1.325 mmol). The reaction was stirred at rt for 16 h. The volatiles were removed *in vacuo*. The crude product was loaded onto celite and purified by chromatography on RP Flash C18 (24 g cartridge, 0-20% (0.1 % formic acid

in MeCN) / (0.1% formic acid in water)) to afford an oil. The sample was triturated with acetone to afford the title compound (9.20 mg, 26 μ mol, 2.3 %, 95% Purity) as a dark brown solid.

[0151] m/z 304.2 (M+H)⁺ (ES⁺)

[0152] ¹H NMR (500 MHz, DMSO) δ 11.21 – 11.10 (m, 1H), 10.98-10.10 (br s, 1H), 7.94 (m, 1H), 7.25 – 7.18 (m, 2H), 7.06 – 7.00 (m, 1H), 6.71 (d, J = 7.6 Hz, 1H), 3.24 – 3.17 (m, 2H), 3.11 – 3.04 (m, 2H), 2.93 (t, J = 6.4 Hz, 2H), 2.75 (s, 6H), 1.78 (hept, J = 6.7 Hz, 1H), 0.91 (d, J = 6.7 Hz, 6H).

Example 14. Synthesis of compound 139: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-isopropoxyacetate, Fumaric acid



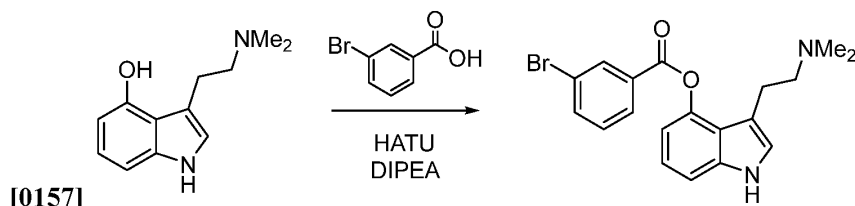
[0153]

[0154] To a stirred solution of 2-(1-methylethoxy)-acetic acid (143 mg, 1.4 Eq, 1.21 mmol) in dry DCM (4 mL) under an atmosphere of nitrogen at room temp. was added oxalyl chloride (233mg, 161 μ L, 2.1 Eq, 1.84 mmol) and a drop of DMF. The reaction mixture was stirred at room temp for 2 h. The volatiles were removed *in vacuo* and the residue was dissolved in DCM (2 mL) and added to a solution of psilocin (179.0 mg, 1 Eq, 876 μ mol) and triethylamine (323 mg, 445 μ L, 3.6 Eq, 3.19 mmol) in DCM (2 mL) at 0 °C. The reaction mixture was stirred at room temp for 1 h. The reaction mixture was diluted with water (5 mL). The aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were collected, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (24 g cartridge, 5-50% (0.1% formic acid in MeCN)/(0.1% formic acid in water)) to afford 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-isopropoxyacetate (187 mg, 614 μ mol) as a brown oil. The material was dissolved in acetone (10 mL) and a solution of fumaric acid (71 mg, 0.7 Eq, 614 μ mol) in acetone (10 mL) was added. The resulting solid was isolated by filtration, washed with acetone and dried *in vacuo* to afford the title compound (130 mg, 309 μ mol, 35%) as an off-white solid.

[0155] m/z 305.2 (M+H)⁺ (ES⁺)

[0156] ^1H NMR (500 MHz, DMSO- d_6) δ 11.10 (s, 1H), 7.25 (dd, J = 8.1, 0.8 Hz, 1H), 7.18 (d, J = 2.3 Hz, 1H), 7.09 – 7.02 (m, 1H), 6.72 (dd, J = 7.6, 0.8 Hz, 1H), 6.56 (s, 2H), 4.48 (s, 2H), 3.75 (hept, J = 6.0 Hz, 1H), 2.86 – 2.78 (m, 2H), 2.70 – 2.60 (m, 2H), 2.35 (s, 6H), 1.17 (d, J = 6.1 Hz, 6H). (2x exchangeable H not observed).

Example 15. Synthesis of compound 168: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 3-bromobenzoate, Formic Acid

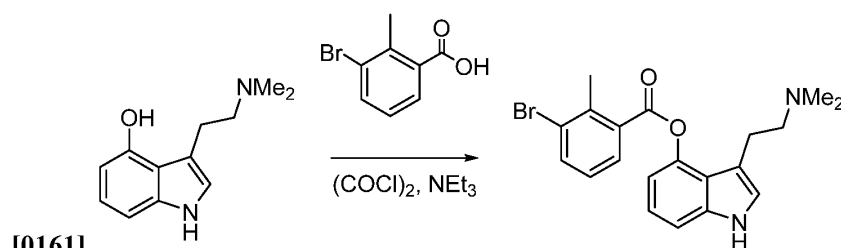


[0158] A mixture of psilocin (200.0 mg, 1 Eq, 881 μmol), 3-bromobenzoic acid (181 mg, 1 Eq, 881 μmol), HATU (483 mg, 1.4 Eq, 1.27 mmol) and diisopropylethylamine (269 mg, 359 μL , 2.4 Eq, 2.08 mmol) in dry DMF (2.5 mL) was stirred at r.t. for 16 h. The reaction mixture was diluted with sat. aq. NaHCO_3 (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (3 x 20 mL) and brine (25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was loaded onto silica and purified by chromatography on silica gel (12 g cartridge, 2-10% (0.7 M ammonia/MeOH)/DCM) to afford partially purified title compound. The material was loaded onto celite and purified by chromatography on RP Flash C18 (24 g cartridge, 5-50% (0.1% formic acid in MeCN)/(0.1% formic Acid in Water)) to afford the title compound (29.2 mg, 67 μmol , 8%) as a light brown solid.

[0159] m/z 387.1/389.0 ($\text{M}+\text{H}$) $^+$ (ES $^+$)

[0160] ^1H NMR (500 MHz, DMSO- d_6) δ 11.21 – 11.10 (m, 1H), 8.36 – 8.29 (m, 1H), 8.26 – 8.17 (m, 2H), 8.03 – 7.95 (m, 1H), 7.63 – 7.57 (m, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 2.3 Hz, 1H), 7.14 – 7.08 (m, 1H), 6.83 (d, J = 7.6 Hz, 1H), 2.78 – 2.70 (m, 2H), 2.61 – 2.55 (m, 2H), 2.10 (s, 6H). 1x exchangeable H not observed.

Example 16. Synthesis of compound 169: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 3-bromo-2-methylbenzoate, Fumaric acid

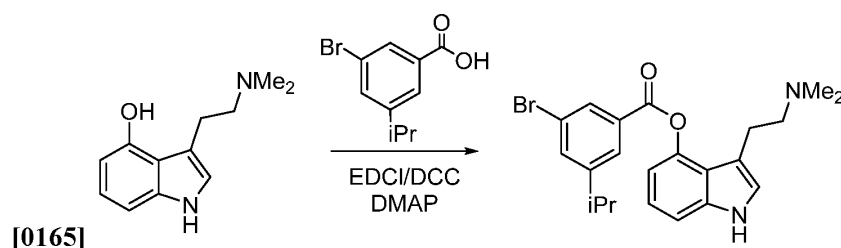


[0162] To a stirred solution of 3-bromo-2-methylbenzoic acid (249 mg, 1.2 Eq, 1.16 mmol) in dry DCM (4 mL) under a nitrogen atmosphere at r.t. was added oxalyl dichloride (260 mg, 180 μ L, 2.1 Eq, 2.05 mmol) and a drop of DMF. The reaction mixture was stirred at r.t. for 2 h. The volatiles were *removed in vacuo*. The residue was redissolved in DCM (2 mL) and added to a solution of psilocin (200.9 mg, 1 Eq, 964 μ mol) and triethylamine (290 mg, 400 μ L, 3 Eq, 2.87 mmol) in DCM (2 mL) at 0 °C. The resulting mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with water (5 mL), extracted with DCM (3 x 5 mL). The combined organic layers were collected, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (24 g cartridge, 0-20% MeOH/DCM). The purified product was dissolved in acetone (15 mL). Fumaric acid (88 mg, 756 μ mol) in acetone (20 mL) was added. The precipitate formed was collected by filtration to afford the title compound (283.2 mg, 0.54 mmol, 56%) as a white solid.

[0163] m/z 401.1/403.4 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0164] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.15 (s, 1H), 8.16 (dd, J = 7.8, 1.3 Hz, 1H), 7.95 (dd, J = 8.0, 1.3 Hz, 1H), 7.38 (dd, J = 7.9 Hz, 1H), 7.31 (dd, J = 8.1, 0.8 Hz, 1H), 7.20 (d, J = 2.3 Hz, 1H), 7.11 (dd, J = 7.9 Hz, 1H), 6.87 (dd, J = 7.6, 0.8 Hz, 1H), 6.56 (s, 2H), 2.80 – 2.73 (m, 2H), 2.67 (s, 3H), 2.60 (t, J = 8.1 Hz, 2H), 2.11 (s, 6H). 2 x exchangeable protons not observed.

Example 17. Synthesis of compound 171: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 3-bromo-5-isopropylbenzoate, Fumaric acid



[0166] To a stirred solution of psilocin (79.4 mg, 1.1 Eq, 338 μmol), 3-bromo-5-isopropylbenzoic acid (76 mg, 1 Eq, 311 μmol) in dry DMF (2 mL) at r.t. was added DMAP (121 mg, 3.2 Eq, 990 μmol) and EDCI (91 mg, 1.5 Eq, 472 μmol). The reaction mixture was stirred at r.t. for 72 h. The reaction mixture was diluted with EtOAc (5 mL), washed with 5% citric acid solution (5 mL), water (5 mL) and sat. aq. NaHCO_3 (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-10% MeOH/DCM) to afford a light brown oil.

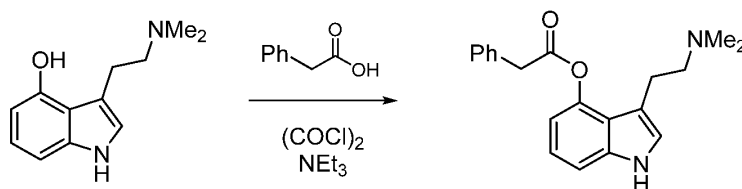
[0167] Separately, to a stirred solution of psilocin (124.2 mg, 1.1 Eq, 529 μmol) and 3-bromo-5-isopropylbenzoic acid (120 mg, 1 Eq, 494 μmol) in dry DMF (2.5 mL) at r.t. was added DMAP (102 mg, 1.7 Eq, 837 μmol) and DCC (181 mg, 157 μL , 1.8 Eq, 867 μmol). The reaction mixture was stirred at r.t. for 72 h. The reaction mixture was diluted with EtOAc (5 mL), washed with 5% citric acid solution (5 mL), water (5 mL) and sat. aq. NaHCO_3 (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-10% MeOH/DCM) to afford a light brown oil.

[0168] The two oils were dissolved in acetone (1 mL) and combined. A solution of fumaric acid (7 mg, 0.20 Eq, 64 μmol) in acetone (1 mL) was added. The precipitate formed was collected by filtration to afford the title compound (12.2 mg, 22 μmol , 3%) as a beige solid.

[0169] m/z 429.5/431.6 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0170] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.16 (s, 1H), 8.14 (dd, J = 1.7 Hz, 1H), 8.05 (dd, J = 1.6 Hz, 1H), 7.87 (dd, J = 1.8 Hz, 1H), 7.31 (dd, J = 8.1, 0.8 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 7.10 (dd, J = 7.9 Hz, 1H), 6.83 (dd, J = 7.7, 0.8 Hz, 1H), 6.55 (s, 2H), 3.11 – 3.02 (m, 1H), 2.79 – 2.72 (m, 2H), 2.66 – 2.59 (m, 2H), 2.12 (s, 6H), 1.26 (d, J = 6.9 Hz, 6H). 2 x exchangeable protons not observed.

Example 18. Synthesis of compound 176: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-phenylacetate, 0.8Fumaric acid, 0.2HCl



[0171]

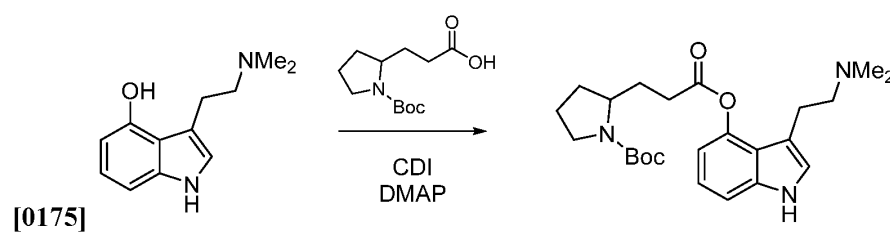
[0172] To a stirred solution of 2-phenylacetic acid (117 mg, 1 Eq, 857 μmol) in dry DCM (4 mL) under an atmosphere of nitrogen at r.t. was added oxalyl chloride (228 mg, 158 μL , 2.1

Eq, 1.80 mmol) and a drop of DMF. The reaction mixture was stirred at r.t. for 2 h. The volatiles were removed *in vacuo*. The residue was dissolved in DCM (2 mL) and added to a solution of psilocin (198.9 mg, 1 Eq, 857 μ mol) and triethylamine (312 mg, 430 μ L, 3.6 Eq, 3.09 mmol) in DCM (2 mL) at 0 °C. The reaction mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with water (5 mL) and transferred into a separating funnel. The aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were collected, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (24 g cartridge, 5-40 % (0.1% formic acid in MeCN)/(0.1% formic acid in water)) to afford 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-phenylacetate, Formic Acid (84.6 mg, 0.18 mmol, 21%) as a brown oil. The partially purified material was dissolved in acetone (3 mL) and a solution of fumaric acid (21 mg, 0.21 Eq, 0.18 mmol) in acetone (4 mL) was added. The resulting solid was filtered, washed with acetone (2 mL) and dried in a vacuum desiccator for 24 h to afford the title compound (32.8 mg, 70 μ mol, 8%) as a brown solid.

[0173] m/z 323.1 (M+H)⁺ (ES⁺)

[0174] ¹H NMR (500 MHz, DMSO) δ 11.07 (s, 1H), 7.43 – 7.35 (m, 4H), 7.33 – 7.26 (m, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H), 7.06 – 6.99 (m, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.52 (s, 1.6H), 4.06 (s, 2H), 2.80 (t, J = 7.8 Hz, 2H), 2.66 – 2.59 (m, 2H), 2.32 (s, 6H). (2x exchangeable H not observed)

Example 19. Synthesis of compound 185: tert-Butyl 2-(3-((3-(2-(dimethylamino)ethyl)-1H-indol-4-yl)oxy)-3-oxopropyl)pyrrolidine-1-carboxylate, Fumaric acid



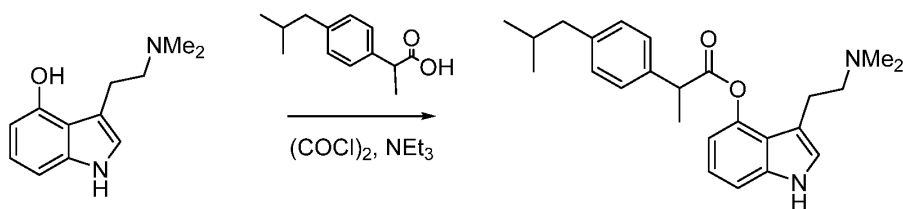
[0176] A solution of 3-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)propanoic acid (155 mg, 1.3 Eq, 636 μ mol), DMAP (12.0 mg, 0.2 Eq, 97.9 μ mol) and CDI (159 mg, 2 Eq, 979 μ mol) was stirred at rt for 1 h. Psilocin (100 mg, 1 Eq, 490 μ mol) was then added and the mixture was stirred at rt overnight. Another solution of 3-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)propanoic acid (119 mg, 1 Eq, 490 μ mol), CDI (87.3 mg, 1.1 Eq, 539 μ mol) and DMAP (5.98 mg, 0.1 Eq, 49.0 μ mol) in THF (2.00 mL), previously stirred at rt for 1h, was added to the mixture. The reaction mixture was left stirring at rt for 24 h. The mixture was heated at 40

°C for 24 h. The mixture was then heated at 55 °C over the weekend. The reaction mixture was cooled to rt, diluted with distilled water (10 mL) and transferred into a separating funnel. The organic layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (1 x 15 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (12 g cartridge, 5-50% (0.1 % formic acid in MeCN) / (0.1% formic acid in water)) to afford the desired product (89.4 mg, 0.16 mmol, 33 %, 85% Purity) as a brown oil. The material was dissolved in acetone (5 mL) and a solution of fumaric acid (19 mg, 0.33 Eq, 0.16 mmol) in acetone (5 mL) was added. The resulting solid was filtered, washed with acetone and dried in a vacuum desiccator over the weekend to afford the title compound (29.9 mg, 49.6 µmol, 10.1 %, 90.6% Purity) as a brown solid.

[0177] m/z 430.36 (M+H)⁺ (ES⁺)

[0178] ¹H NMR (500 MHz, DMSO) δ 11.10 (s, 1H), 7.23 (dd, J = 8.1, 0.8 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.08 – 7.01 (m, 1H), 6.73 – 6.66 (m, 1H), 6.57 (s, 2H), 3.81 (s, 1H, rotamer), 3.32 – 3.19 (m, 2H, rotamer), 2.86 (s, 1H, rotamer), 2.78 (s, 2H, rotamer), 2.70 – 2.65 (m, 1H, rotamer), 2.45 (s, 3H, rotamer), 2.42 (s, 3H, rotamer), 1.97 – 1.65 (m, 9H, rotamer), 1.40 (s, 9H). 2H are absent (exchangeable protons of fumaric acid).

Example 20. Synthesis of compound 188: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-(4-isobutylphenyl)propanoate, 0.75Fumaric acid



[0179]

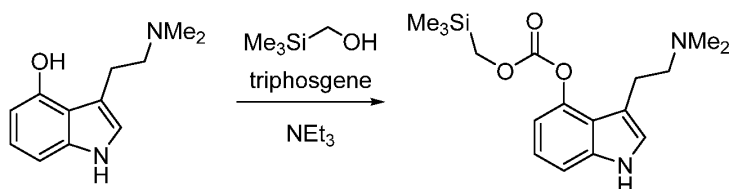
[0180] To a stirred solution of 2-(4-isobutylphenyl) propionic acid (124 mg, 1.2 Eq, 593 µmol) in dry DCM (4 mL) under a nitrogen atmosphere at r.t. was added oxalyl chloride (130 mg, 90 µL, 2.1 Eq, 1.02 mmol) and a drop of DMF. The reaction mixture was stirred at r.t. for 2 h. The volatiles were removed *in vacuo*. The residue was redissolved in DCM (2 mL) and added to a solution of psilocin (102.6 mg, 1 Eq, 492 µmol) and triethylamine (182 mg, 250 µL, 3.6 Eq, 1.79 mmol) in DCM (2 mL) at 0 °C. The resulting mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with water (5 mL), extracted with DCM (3 x 5 mL). The combined organic layers were collected, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-

20% MeOH/DCM) to afford a light brown oil. The product was dissolved in acetone (2 mL). fumaric acid (34 mg, 293 μ mol) in acetone (2 mL) was added. The precipitate formed was collected by filtration to afford the title compound (51.4 mg, 0.11 mmol, 22%) as a beige solid.

[0181] m/z 393.3 (M+H)⁺ (ES⁺)

[0182] ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.04 (s, 1H), 7.36 – 7.32 (m, 2H), 7.23 – 7.16 (m, 3H), 7.14 (d, *J* = 2.3 Hz, 1H), 7.00 (t, *J* = 7.9 Hz, 1H), 6.55 (s, 1.5H), 6.50 (dd, *J* = 7.6, 0.8 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 1H), 2.72 – 2.65 (m, 2H), 2.61 – 2.52 (m, 2H), 2.45 (d, *J* = 7.1 Hz, 2H), 2.28 (s, 6H), 1.83 (dq, *J* = 13.5, 6.7 Hz, 1H), 1.55 (d, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 6H). 1.5 x exchangeable protons not observed.

Example 21. Synthesis of compound 189: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl ((trimethylsilyl)methyl) carbonate, Formic Acid

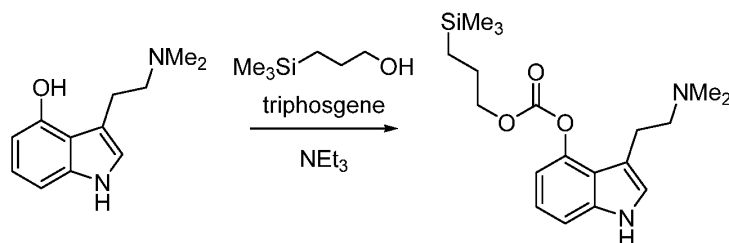


[0183] To a solution of (trimethylsilyl)methanol (148 mg, 1.3 Eq, 1.42 mmol) and triethylamine (174 mg, 240 μ L, 1.6 Eq, 1.72 mmol) in THF (6 mL) at 0 °C was added triphosgene (160 mg, 0.5 Eq, 518 μ mol). The reaction was stirred for 3 h at 0 °C. A suspension of psilocin (227.2 mg, 1 Eq, 1.11 mmol) and triethylamine (145 mg, 200 μ L, 1.3 Eq, 1.43 mmol) in THF (5 mL) was added at 0 °C. The mixture was stirred at 0 °C. for 30 min then at r.t. for 40 h. The reaction was quenched with ice-cold water (10 mL) and diluted with ethyl acetate (10 mL). The phases were separated and the aqueous phase was further extracted with ethyl acetate (10 mL). The combined organics were washed with brine (20 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (4 g cartridge, 5-50% (0.1% formic acid in MeCN)/0.1% formic acid in water)) (eluting ~25%) to afford the title compound (12.4 mg, 31 μ mol, 3%) as a sticky brown gum after trituration with diethyl ether (3x 5 mL).

[0184] m/z 335.2 (M+H)⁺ (ES⁺)

[0185] ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.07 (s, 1H), 8.19 (s, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 2.3 Hz, 1H), 7.04 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 3.95 (s, 2H), 2.81 – 2.72 (m, 2H), 2.48 (s, 2H), 2.21 (s, 6H), 0.10 (s, 9H). 1x exchangeable H not observed

Example 22. Synthesis of compound 191: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (3-(trimethylsilyl)propyl) carbonate, Formic Acid



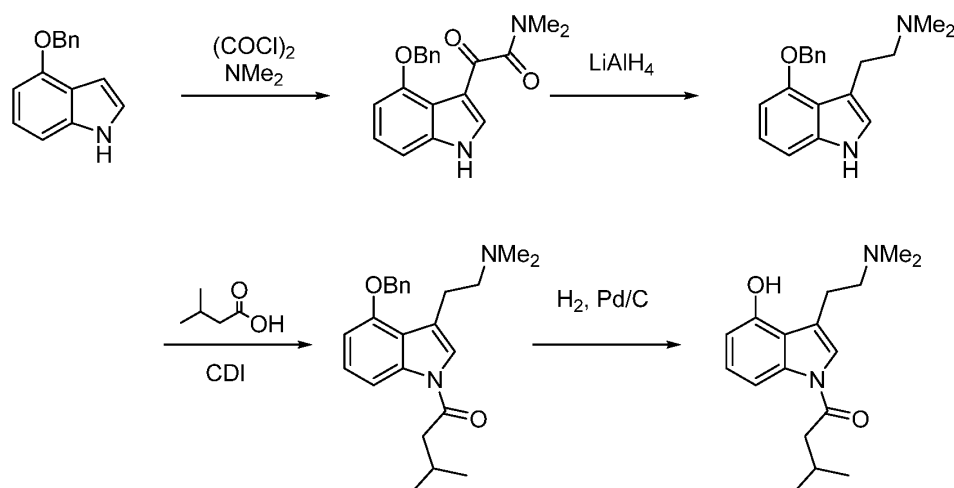
[0186]

[0187] To a solution of 3-(trimethylsilyl)propan-1-ol (179 mg, 1.1 Eq, 1.35 mmol) and triethylamine (174 mg, 240 μ L, 1.4 Eq, 1.72 mmol) in THF (6 mL) at 0 °C was added triphosgene (189 mg, 0.5 Eq, 612 μ mol). The reaction was stirred for 20 min at 0 °C. A suspension of psilocin (250.8 mg, 1 Eq, 1.23 mmol) in THF (5 mL) was added at 0 °C. The mixture was stirred at r.t. for 16 h. The reaction was quenched with ice-cold water (10 mL) and diluted with ethyl acetate (10 mL). The phases were separated, and the aqueous phase was further extracted with ethyl acetate (10 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was partially purified by chromatography on silica gel (4 g cartridge, 0-10% (0.7 M Ammonia/MeOH)/DCM) (eluting ~2%). The partially purified crude product was purified by chromatography on RP Flash C18 (4 g cartridge, 10-100% (0.1% Formic acid in MeCN)/(0.1% Formic Acid in Water)) (eluting ~25%) to afford the title compound (92.0 mg, 0.22 mmol, 18%) as an off-white solid after trituration with diethyl ether (2x 5 mL).

[0188] m/z 363.2 ($\text{M}+\text{H}^+$) (ES+)

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.09 (s, 1H), 8.17 (s, 1H), 7.26 (d, $J = 8.1$ Hz, 1H), 7.18 (d, $J = 2.3$ Hz, 1H), 7.04 (dd, $J = 7.9, 7.9$ Hz, 1H), 6.75 (d, $J = 7.6$ Hz, 1H), 4.17 (t, $J = 6.8$ Hz, 2H), 2.83 – 2.73 (m, 2H), 2.55 – 2.51 (m, 2H), 2.23 (s, 6H), 1.72 – 1.60 (m, 2H), 0.61 – 0.48 (m, 2H), 0.01 (s, 9H). 1x exchangeable H not observed.

Example 23. Synthesis of compound 195: 1-(3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indol-1-yl)-3-methylbutan-1-one, Formic Acid



[0189]

[0190] **Step 1: 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethyl-2-oxoacetamide**

[0191] Oxalyl chloride (3.13 g, 2.2 mL, 1.1 Eq, 24.6 mmol) was added portion-wise to a stirred solution of 4-(benzyloxy)-1H-indole (5.00 g, 1 Eq, 22.4 mmol) in MTBE (100 mL) and stirred at r.t. for 90 min. The reaction mixture was then cooled to 0 °C and dimethylamine in THF (5.55 g, 61.6 mL, 2.0 M, 5.5 Eq, 123 mmol) added portion-wise over 5 min. The reaction mixture was left in the ice-bath which was allowed to warm slowly to r.t. over the course of another 90 min. The resultant suspension was filtered and the filtered solid partitioned between EtOAc (300 ml) and water (200 mL). The organic layer was separated, washed with sat. aq. NaHCO₃ (200 ml) and concentrated *in vacuo* to afford 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethyl-2-oxoacetamide (4.76 g, 14.8 mmol, 66%) as a beige foam.

[0192] *m/z* 323.5 (M+H)⁺ (ES⁺)

[0193] ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.26 (s, 1H), 8.06 (s, 1H), 7.64 – 7.58 (m, 2H), 7.37 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.14 – 7.06 (m, 2H), 6.69 (dd, *J* = 7.2, 1.5 Hz, 1H), 5.26 (s, 2H), 2.90 (d, *J* = 16.8 Hz, 6H).

[0194] **Step 2: 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethylethan-1-amine**

[0195] Lithium Aluminium hydride in THF (1.96 g, 21.5 mL, 2.4 molar, 3.5 Eq, 51.7 mmol) was added portion-wise to stirred suspension of the product from step 1 above (4.76 g, 1 Eq, 14.8 mmol) in 2-MeTHF (100 mL) at 0 °C and under nitrogen. The mixture was left to stir as the ice-bath warmed to r.t. for 30 min before being stirred at 80 °C for 4 h. The reaction mixture was allowed to cool to r.t. before sodium sulfate decahydrate was added portionwise until the resultant effervescence subsided. The reaction mixture was filtered, the solid plug washed with MeOH (30 mL) and the clear filtrate collected allowed to stand at r.t. overnight. The resulting dark green solution was concentrated under reduced pressure to afford a dark

green oil which solidified on standing. The solid was partitioned between EtOAc (200 mL) and water (100 mL). The organic layer was separated and concentrated under vacuum to afford the sub-title compound (4.16 g, 13 mmol, 90%) as a brown solid which solidified on standing.

[0196] m/z 295.2 (M+H)⁺ (ES⁺)

[0197] ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.75 (s, 1H), 7.56 – 7.50 (m, 2H), 7.39 (dd, J = 8.3, 6.8 Hz, 2H), 7.36 – 7.29 (m, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.53 (dd, J = 6.0, 2.5 Hz, 1H), 5.16 (s, 2H), 2.94 – 2.87 (m, 2H), 2.50 – 2.42 (m, 2H), 2.05 (s, 6H).

[0198] Step 3: 1-(4-(benzyloxy)-3-(2-(dimethylamino)ethyl)-1H-indol-1-yl)-3-methylbutan-1-one

[0199] CDI (214 mg, 1.7 Eq, 1.32 mmol) was added to solution of 3-methylbutanoic acid (122 mg, 1.5 Eq, 1.20 mmol) in DCM (3.00 mL) and stirred at for 2 h. Separately, potassium tert-butoxide (148 mg, 1.7 Eq, 1.32 mmol) was added to a solution of the product from step 2 above (250 mg, 1 Eq, 798 μ mol) in DMF (5 mL) and stirred at r.t. for 90 min. The DCM solution was added to the DMF solution and left to stir at r.t. for 20 h. The reaction mixture was a partitioned between EtOAc (20 mL) and brine (20 mL). The organic layer was separated and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (12 g cartridge, 0-100% (0.1 % formic acid in MeCN)/(0.1% formic acid in water)) to afford the sub-title compound (102 mg, 269 μ mol, 34%) as a colourless gum.

[0200] m/z 379.2 (M+H)⁺ (ES⁺)

[0201] Step 4: 1-(3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indol-1-yl)-3-methylbutan-1-one, Formic Acid

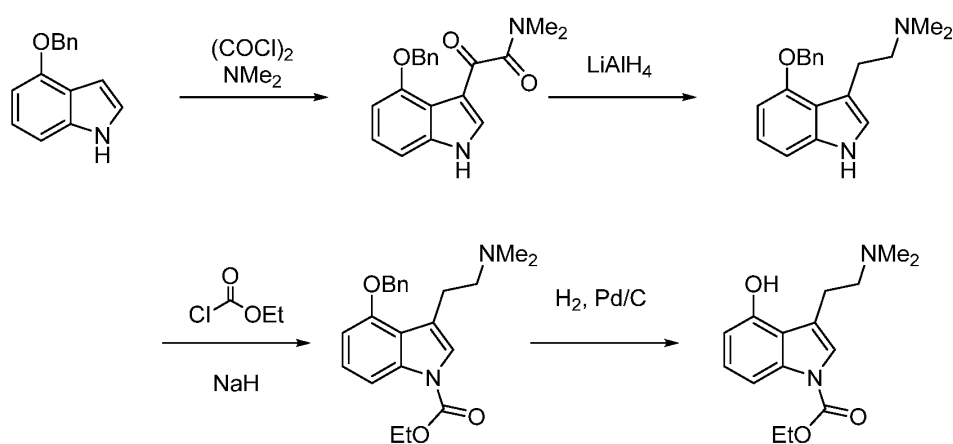
[0202] The product from step 3 above (102 mg, 1 Eq, 256 μ mol) in methanol (10 mL) was passed through a 10% Pd/C CatCart (H-cube, recirculation) at 1mL/min, 60 °C and at 1 bar for 90 min. The bulk solvent was removed *in vacuo*. The crude product was dissolved in DMSO (2 mL), filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130 Å, 5 μ m, 30 mm X 100 mm, flow rate 40 mLmin⁻¹ eluting with a 0.1% formic acid in water-MeCN gradient over 8.5 min using UV across all wavelengths with PDA as well as a QDA and ELS detector. At column dilution pump gives 2 mLmin⁻¹ MeCN over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 12.5% MeCN; 0.5-5.5 min, ramped from 12.5% MeCN to 42.5% MeCN; 5.5-5.6 min, ramped from 42.5% MeCN to

100% MeCN; 5.6-8.5 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac to afford the title compound (37.0 mg, 0.11 mmol, 43%) as colourless flakes.

[0203] m/z 289.2 (M+H)⁺ (ES⁺)

[0204] ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.19 (s, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.53 (s, 1H), 7.08 – 7.05 (m, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 2.92 (t, *J* = 7.1 Hz, 2H), 2.82 (d, *J* = 7.0 Hz, 2H), 2.69 (t, *J* = 7.1 Hz, 2H), 2.30 (s, 6H), 2.18 (dq, *J* = 13.4, 6.7 Hz, 1H), 0.99 (d, *J* = 6.7 Hz, 6H). (2x exchangeable H not observed).

Example 24. Synthesis of compound 197: ethyl 3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indole-1-carboxylate, Formic Acid



[0205]

[0206] **Step 1: 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethyl-2-oxoacetamide**

[0207] Oxalyl chloride (3.13 g, 2.2 mL, 1.1 Eq, 24.6 mmol) was added portion-wise to a stirred solution of 4-(benzyloxy)-1H-indole (5.00 g, 1 Eq, 22.4 mmol) in MTBE (100 mL) and stirred at r.t. for 90 min. The reaction mixture was then cooled to 0 °C and dimethylamine in THF (5.55 g, 61.6 mL, 2.0 M, 5.5 Eq, 123 mmol) added portion-wise over 5 min. The reaction mixture was left in the ice-bath which was allowed to warm slowly to r.t. over the course of another 90 min. The resultant suspension was filtered and the filtered solid partitioned between EtOAc (300 ml) and water (200 mL). The organic layer was separated, washed with sat. aq. NaHCO₃ (200 ml) and concentrated *in vacuo* to afford 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethyl-2-oxoacetamide (4.76 g, 14.8 mmol, 66%) as a beige foam.

[0208] m/z 323.5 (M+H)⁺ (ES⁺)

[0209] ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.26 (s, 1H), 8.06 (s, 1H), 7.64 – 7.58 (m, 2H), 7.37 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.14 – 7.06 (m, 2H), 6.69 (dd, *J* = 7.2, 1.5 Hz, 1H), 5.26 (s, 2H), 2.90 (d, *J* = 16.8 Hz, 6H).

[0210] **Step 2: 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethylethan-1-amine**

[0211] Lithium Aluminium hydride in THF (1.96 g, 21.5 mL, 2.4 molar, 3.5 Eq, 51.7 mmol) was added portion-wise to stirred suspension of the product from step 1 above (4.76 g, 1 Eq, 14.8 mmol) in 2-MeTHF (100 mL) at 0 °C and under nitrogen. The mixture was left to stir as the ice-bath warmed to r.t. for 30 min before being stirred at 80 °C for 4 h. The reaction mixture was allowed to cool to r.t. before sodium sulfate decahydrate was added portionwise until the resultant effervescence subsided. The reaction mixture was filtered, the solid plug washed with MeOH (30 mL) and the clear filtrate collected allowed to stand at r.t. overnight. The resulting dark green solution was concentrated under reduced pressure to afford a dark green oil which solidified on standing. The solid was partitioned between EtOAc (200 mL) and water (100 mL). The organic layer was separated and concentrated under vacuum to afford the sub-title compound (4.16 g, 13 mmol, 90%) as a brown solid which solidified on standing.

[0212] m/z 295.2 (M+H)⁺ (ES+)

[0213] ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.75 (s, 1H), 7.56 – 7.50 (m, 2H), 7.39 (dd, J = 8.3, 6.8 Hz, 2H), 7.36 – 7.29 (m, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.53 (dd, J = 6.0, 2.5 Hz, 1H), 5.16 (s, 2H), 2.94 – 2.87 (m, 2H), 2.50 – 2.42 (m, 2H), 2.05 (s, 6H).

[0214] Step 3: ethyl 3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indole-1-carboxylate, Formic Acid

[0215] To a solution of the product from step 2 above (53.9 mg, 1 Eq, 183 μmol) in DMF (1 mL) at 0 °C was added sodium hydride (9 mg, 60% Wt, 1.2 Eq, 220 μmol) and the reaction was stirred for 10 min at 0 °C. Ethyl chloroformate (34 mg, 30 μL, 1.7 Eq, 312 μmol) was added at 0 °C then stirred at r.t. for 22 h.

[0216] In a separate vial, to a solution of the product from step 1 above (252.9 mg, 1 Eq, 859 μmol) in DMF (5 mL) at 0 °C was added sodium hydride (48.0 mg, 1.4 Eq, 1.20 mmol) and the reaction was stirred for 10 min at 0 °C. Ethyl chloroformate (170 mg, 150 μL, 1.8 Eq, 1.56 mmol) was added at 0 °C then stirred at r.t. for 18 h. The mixture was combined with the mixture above, diluted with ethyl acetate (15 mL), and poured into water/brine (4:1, 50 mL). The phases were separated and the aqueous was further extracted with ethyl acetate (20 mL). The combined organics were washed with brine (50 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (12 g cartridge, 5-50% (0.1% formic acid in MeCN)/(0.1% formic acid in water)) (eluting 20%) to afford the sub-title compound (163 mg, 0.34 mmol, 32%) as a clear yellow oil.

[0217] m/z 367.3 (M+H)⁺ (ES+)

[0218] ^1H NMR (500 MHz, DMSO- d_6) δ 8.20 (s, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.45 – 7.31 (m, 4H), 7.25 (dd, J = 8.2, 8.2 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 5.22 (s, 2H), 4.42 (q, J = 7.1 Hz, 2H), 2.99 – 2.89 (m, 2H), 2.69 (q, J = 5.5 Hz, 2H), 2.19 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H) (1x exchangeable H not observed).

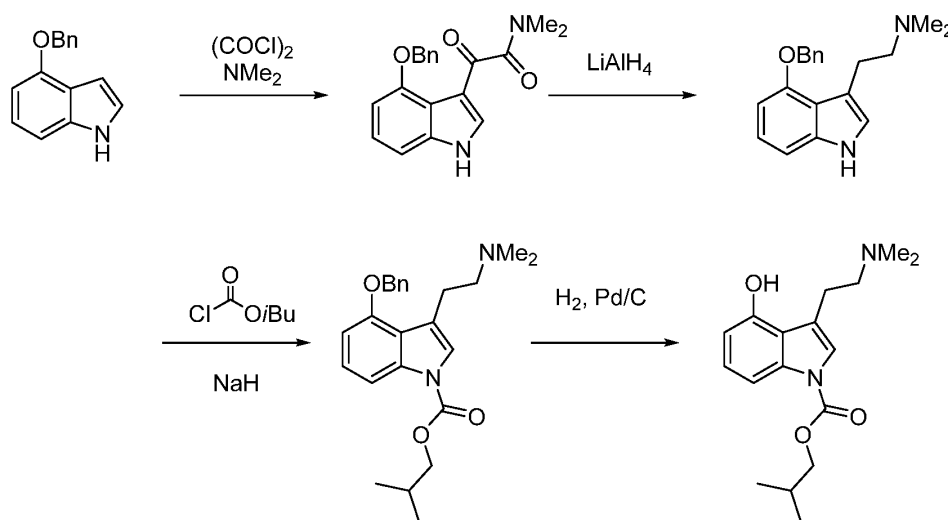
[0219] Step 4: ethyl 3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indole-1-carboxylate, Formic Acid

[0220] A solution of the product from step 3 above (163 mg, 1 Eq, 395 μmol) in Ethanol (5 mL) was hydrogenated in the H-Cube (10% Pd/C cat cart, Batch: N0755, ID, THS-01131) at 5 bar, 1 mL/min for 1 h (recirculation). The solution was then hydrogenated at 15 bar, 1 mL/min for 1 h (recirculation). The collected mixture was concentrated *in vacuo*. The resulting material was triturated with acetonitrile (5 mL) and diethyl ether (5 mL) to afford the title compound (78.0 mg, 0.24 mmol, 60%) as a white solid.

[0221] m/z 277.2 ($\text{M}+\text{H}$) $^+$ (ES $^+$)

[0222] ^1H NMR (500 MHz, DMSO- d_6) δ 11.95 (br, 1H), 8.19 (s, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.34 (s, 1H), 7.08 (dd, J = 8.1, 8.1 Hz, 1H), 6.59 (d, J = 7.9 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 2.92 (t, J = 7.0 Hz, 2H), 2.66 (t, J = 7.0 Hz, 2H), 2.28 (d, J = 1.5 Hz, 6H), 1.37 (t, J = 7.1 Hz, 3H) (1x exchangeable H not observed).

Example 25. Synthesis of compound 199: isobutyl 3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indole-1-carboxylate, 0.5Fumaric acid.



[0223]

[0224] Step 1: 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethyl-2-oxoacetamide

[0225] Oxalyl chloride (3.13 g, 2.2 mL, 1.1 Eq, 24.6 mmol) was added portion-wise to a stirred solution of 4-(benzyloxy)-1H-indole (5.00 g, 1 Eq, 22.4 mmol) in MTBE (100 mL)

and stirred at r.t. for 90 min. The reaction mixture was then cooled to 0 °C and dimethylamine in THF (5.55 g, 61.6 mL, 2.0 M, 5.5 Eq, 123 mmol) added portion-wise over 5 min. The reaction mixture was left in the ice-bath which was allowed to warm slowly to r.t. over the course of another 90 min. The resultant suspension was filtered and the filtered solid partitioned between EtOAc (300 ml) and water (200 mL). The organic layer was separated, washed with sat. aq. NaHCO₃ (200 ml) and concentrated *in vacuo* to afford 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethyl-2-oxoacetamide (4.76 g, 14.8 mmol, 66%) as a beige foam.

[0226] *m/z* 323.5 (M+H)⁺ (ES⁺)

[0227] ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.26 (s, 1H), 8.06 (s, 1H), 7.64 – 7.58 (m, 2H), 7.37 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.14 – 7.06 (m, 2H), 6.69 (dd, *J* = 7.2, 1.5 Hz, 1H), 5.26 (s, 2H), 2.90 (d, *J* = 16.8 Hz, 6H).

[0228] Step 2: 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethylethan-1-amine

[0229] Lithium Aluminium hydride in THF (1.96 g, 21.5 mL, 2.4 molar, 3.5 Eq, 51.7 mmol) was added portion-wise to stirred suspension of the product from step 1 above (4.76 g, 1 Eq, 14.8 mmol) in 2-MeTHF (100 mL) at 0 °C and under nitrogen. The mixture was left to stir as the ice-bath warmed to r.t. for 30 min before being stirred at 80 °C for 4 h. The reaction mixture was allowed to cool to r.t. before sodium sulfate decahydrate was added portionwise until the resultant effervescence subsided. The reaction mixture was filtered, the solid plug washed with MeOH (30 mL) and the clear filtrate collected allowed to stand at r.t. overnight. The resulting dark green solution was concentrated under reduced pressure to afford a dark green oil which solidified on standing. The solid was partitioned between EtOAc (200 mL) and water (100 mL). The organic layer was separated and concentrated under vacuum to afford the sub-title compound (4.16 g, 13 mmol, 90%) as a brown solid which solidified on standing.

[0230] *m/z* 295.2 (M+H)⁺ (ES⁺)

[0231] ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.75 (s, 1H), 7.56 – 7.50 (m, 2H), 7.39 (dd, *J* = 8.3, 6.8 Hz, 2H), 7.36 – 7.29 (m, 1H), 6.97 (d, *J* = 2.3 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.53 (dd, *J* = 6.0, 2.5 Hz, 1H), 5.16 (s, 2H), 2.94 – 2.87 (m, 2H), 2.50 – 2.42 (m, 2H), 2.05 (s, 6H).

[0232] Step 3: isobutyl 4-(benzyloxy)-3-(2-(dimethylamino)ethyl)-1H-indole-1-carboxylate, Formic Acid

[0233] To a solution of 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethylethan-1-amine (257.5 mg, 1 Eq, 875 μmol) in DMF (5 mL) at 0 °C was added sodium hydride (45 mg, 60% Wt, 1.3 Eq, 1.13 mmol) and the reaction was stirred for 10 min at 0 °C. isobutyl carbonochloridate (263 mg, 250 μL, 2.2 Eq, 1.93 mmol) was added at 0 °C then stirred at r.t. for 2 h. The

mixture was diluted with ethyl acetate (20 mL). Water/brine (1:1, 50 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (20 mL). The combined organics were washed sequentially with water/brine (1:1, 50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (24 g cartridge, 5-50% (0.1% formic acid in MeCN) / (0.1% formic acid in water)) to afford the sub-title compound (161 mg, 0.30 mmol, 35%) as a thick brown oil.

[0234] m/z 395.3 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0235] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.19 (s, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.46 – 7.39 (m, 3H), 7.38 – 7.32 (m, 1H), 7.25 (dd, J = 8.2, 8.2 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 5.23 (s, 2H), 4.18 (d, J = 6.5 Hz, 2H), 3.01 – 2.93 (m, 2H), 2.73 – 2.64 (m, 2H), 2.19 (s, 6H), 2.12 – 2.03 (m, 1H), 1.00 (d, J = 6.7 Hz, 6H). (1x exchangeable H not observed).

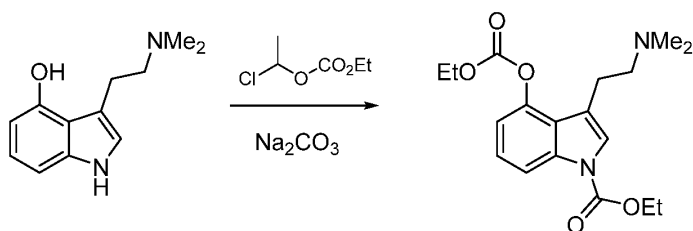
[0236] Step 4: isobutyl 3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indole-1-carboxylate, 0.5Fumaric acid

[0237] A solution of the product from step 3 above (161 mg, 1 Eq, 303 μmol) in ethanol (5 mL) was hydrogenated in the H-Cube (Pd/C cat cart) at 1 bar at 60 °C, 1 mL/min for 90 min (recirculation). The mixture was concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (12 g cartridge, 5-50% (0.1 % formic acid in MeCN)/(0.1% formic acid in water)) to afford isobutyl 3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indole-1-carboxylate, formic acid (47.0 mg, 134 μmol , 44%) as a pale brown oil. To a solution of the oil in acetone (2 mL) was added a solution of fumaric acid (17 mg, 1.1 Eq, 146 μmol) in acetone (3 mL). The mixture was chilled at -20 °C for 1 h. The resulting solid was isolated by filtration and dried *in vacuo* to afford the title compound (30.1 mg, 81 μmol , 61%) as a white solid.

[0238] m/z 305.2 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0239] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.62 (1H, br), 7.53 (d, J = 8.2 Hz, 1H), 7.37 (s, 1H), 7.09 (dd, J = 8.1, 8.1 Hz, 1H), 6.60 (d, J = 7.8 Hz, 1H), 6.53 (s, 1H), 4.16 (d, J = 6.5 Hz, 2H), 2.94 (t, J = 7.0 Hz, 2H), 2.74 – 2.68 (m, 2H), 2.32 (s, 6H), 2.12 – 2.02 (m, 1H), 1.00 (d, J = 6.7 Hz, 6H). (1x exchangeable H not observed).

Example 26. Synthesis of compound 52: Ethyl 3-(2-(dimethylamino)ethyl)-4-((ethoxycarbonyl)oxy)-1H-indole-1-carboxylate



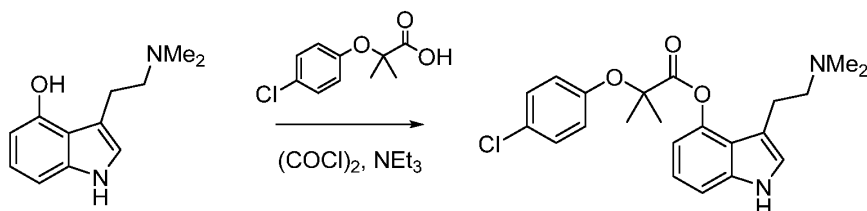
[0240]

[0241] To a suspension of 3-(2-(dimethylamino)ethyl)-1H-indol-4-ol (25.0 mg, 99% Wt, 1 Eq, 121 μ mol) and Na_2CO_3 (128 mg, 10 Eq, 1.21 mmol) in dry MeCN (1.00 mL) at 0 °C was added 1-chloroethyl ethyl carbonate (21.3 mg, 18.7 μ L, 1.15 Eq, 139 μ mol). The reaction mixture was allowed to warm to rt, and then stirred at 50 °C for 72 h. The reaction mixture was poured into water (20 mL) and diluted with EtOAc (20 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined extracted layers were collected, dried (MgSO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-10% EtOAc/isohexane) to afford the title compound (20.5 mg, 51 μ mol, 42 %, 87% Purity) as a yellow oil.

[0242] m/z 349.07 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0243] ^1H NMR (500 MHz, CDCl_3) δ 8.08 (d, J = 8.3 Hz, 1H), 7.40 (s, 1H), 7.30 (t, J = 8.2 Hz, 1H), 7.06 (dd, J = 8.0, 0.8 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 2.93 – 2.86 (m, 2H), 2.65 – 2.59 (m, 2H), 2.32 (s, 6H), 1.46 (t, J = 7.1 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H).

Example 27. Synthesis of compound 78: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-(4-chlorophenoxy)-2-methylpropanoate, Fumaric acid



[0244]

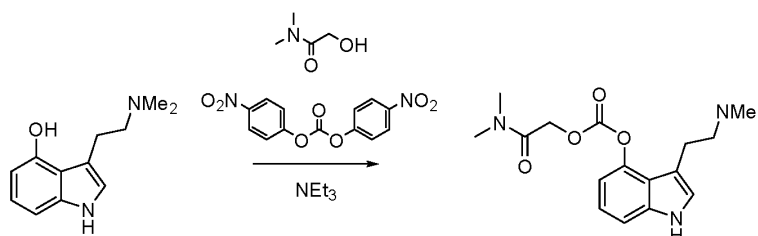
[0245] To a stirred solution of Clofibric acid (381 mg, 1.4 Eq, 1.78 mmol) in dry DCM (5 mL) under an atmosphere of nitrogen at room temp. was added oxalyl chloride (338 mg, 233 μ L, 2.1 Eq, 2.67 mmol) and a drop of DMF. The reaction mixture was stirred at room temp

for 2 h. The volatiles were removed *in vacuo*. The residue was dissolved in DCM (3 mL) and added to a solution of psilocin (259.3 mg, 1 Eq, 1.27 mmol) and triethylamine (462 mg, 637 μ L, 3.6 Eq, 4.57 mmol) in DCM (3 mL) at 0 °C. The reaction mixture was stirred r.t. for 1 h. The reaction mixture was diluted with water (5 mL) and transferred into a separating funnel. The aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were collected, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (24 g cartridge, 5-50% (0.1% formic acid in MeCN)/(0.1% formic acid in water)) to afford 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-(4-chlorophenoxy)-2-methylpropanoate, Formic Acid (322 mg, 720 μ mol, 57%) as a brown oil. The material was dissolved in acetone (10 mL) and a solution of fumaric acid (84 mg, 0.720 mmol) in acetone (10 mL) was added. The resulting solid was filtered, washed with acetone and dried *in vacuo* to afford the title compound (85.0 mg, 0.16 mmol, 13%) as a beige solid.

[0246] m/z 401.2/403.5 (M+H)⁺ (ES⁺)

[0247] ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.13 (s, 1H), 7.43 – 7.36 (m, 2H), 7.26 (dd, J = 8.2, 0.8 Hz, 1H), 7.18 (d, J = 2.3 Hz, 1H), 7.08 – 7.00 (m, 3H), 6.64 (dd, J = 7.7, 0.8 Hz, 1H), 6.56 (s, 2H), 2.86 – 2.79 (m, 2H), 2.70 – 2.64 (m, 2H), 2.29 (s, 6H), 1.76 (s, 6H). (2x exchangeable H not observed).

Example 28. Synthesis of compound 79: 2-(dimethylamino)-2-oxoethyl (3-(2-(dimethylamino)ethyl)-1H-indol-4-yl) carbonate, Formic Acid



[0248]

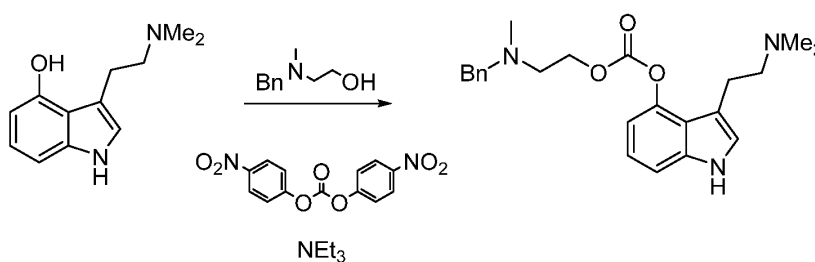
[0249] To a stirred solution of 2-hydroxy-N,N-dimethylacetamide (103 mg, 1.04 Eq, 997 μ mol) and bis(4-nitrophenyl) carbonate (357 mg, 1.22 Eq, 1.18 mmol) in dry DMF (3 mL) under a nitrogen atmosphere at r.t. was added triethylamine (218 mg, 300 μ L, 2.23 Eq, 2.15 mmol). The reaction mixture was stirred at r.t. for 2 h. A solution of psilocin (200.8 mg, 1 Eq, 963 μ mol) in DMF (1 mL) was added. The reaction mixture was heated at 40 °C o.n. The reaction mixture was cooled to r.t., diluted with DCM (10 mL) and water (10 mL) was added. The aqueous layer was extracted with DCM (3 x 25 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product

was purified by chromatography on RP Flash C18 (24 g cartridge, 0-30% (0.1% formic acid in MeCN)/(0.1% formic acid in water)) to afford partially purified title compound (96.6 mg, 0.22 mmol, 22%) as a brown oil. The product was dissolved in acetone (5 mL). fumaric acid (34 mg, 0.306 Eq, 295 μmol) in acetone (5 mL) was added. The mixture was left in the freezer for 1 week and no solid was formed. The volatiles were removed in vacuo and the residue was dissolved in DMSO (1.93 mL), filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130 Å, 5 μm , 30 mm X 100 mm, flow rate 40 mLmin⁻¹ eluting with a 0.1% formic acid in water-MeCN gradient over 12.5 min using UV across all wavelengths with PDA as well as a QDA and ELS detector. At column dilution pump gives 2 mLmin⁻¹ MeCN over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 5% MeCN; 0.5-10.5 min, ramped from 5% MeCN to 22.5% MeCN; 10.5-10.6 min, ramped from 22.5% MeCN to 100% MeCN; 10.6-12.5 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac to afford the title compound (61.7 mg, 0.15 mmol, 15%) as a brown oil.

[0250] m/z 334.2 (M+H)⁺ (ES⁺)

[0251] ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.11 (s, 1H), 8.22 (s, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.19 (s, 1H), 7.06 (dd, J = 7.9, 7.9 Hz, 1H), 6.76 (d, J = 7.8 Hz, 1H), 4.95 (s, 2H), 2.94 – 2.90 (m, 5H), 2.85 (s, 3H), 2.70 – 2.59 (m, 2H), 2.34 (s, 6H). 1x exchangeable H not observed.

Example 29. Synthesis of compound 82: 2-(benzyl(methyl)amino)ethyl (3-(2-(dimethylamino)ethyl)-1H-indol-4-yl) carbonate, Formic Acid



[0252]

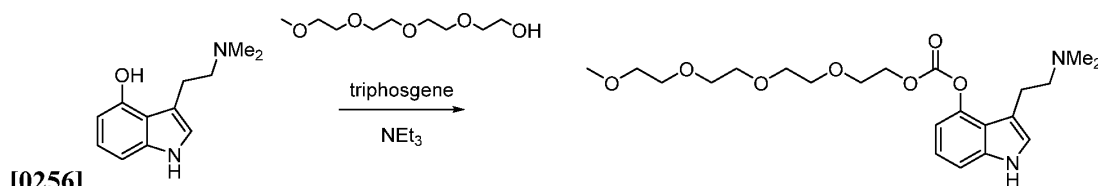
[0253] To a solution of 2-(benzyl(methyl)amino)ethan-1-ol (125 mg, 0.8 Eq, 755 μmol) and bis(4-nitrophenyl) carbonate (301 mg, 1.1 Eq, 990 μmol) in dry DMF (2 mL) under a nitrogen atmosphere at r.t. was added DIPEA (742 mg, 1.0 mL, 6.1 Eq, 5.74 mmol). The

reaction mixture was stirred for 1.5 h at r.t. To the reaction mixture was added a solution of psilocin (202.8 mg, 1 Eq, 943 μmol) in DMF (2 mL), followed by DMAP (12 mg, 0.1 Eq, 98.2 μmol). The reaction mixture was stirred at r.t. and monitored over a period of 5 days. The reaction mixture was diluted with water (25 mL). The layer was extracted with DCM (3 x 20 mL). The combined organic layers were collected, dried (Na_2SO_4) filtered and concentrated *in vacuo*. The crude product was loaded onto celite and purified by chromatography on RP Flash C18 (12 g cartridge, 5-30% (0.1 % formic acid in MeCN)/(0.1% formic acid in water)) to afford partially purified target compound (307 mg). The sample was dissolved in DMSO (3.32 mL), filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130 Å, 5 μm , 30 mm x 100 mm, flow rate 40 mLmin⁻¹ eluting with a 0.1% formic acid in water-MeCN gradient over 12.5 min using UV across all wavelengths with PDA as well as a QDA and ELS detector. At column dilution pump gives 2 mLmin⁻¹ MeCN over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 5% MeCN; 0.5-10.5 min, ramped from 5% MeCN to 20% MeCN; 10.5-10.6 min, ramped from 20% MeCN to 100% MeCN; 10.6-12.5 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac. The partially purified sample was dissolved in DMSO (2 mL), filtered and purified by reversed phase preparative HPLC (Gilson) using a Phenomenex Gemini NC-C18 prep column, 110 Å, 5 μm , 30 mm x 150 mm, flow rate 42 mLmin⁻¹ eluting with a 0.1% formic acid in water-MeCN gradient over 15 min. At column dilution pump gives 5 mLmin⁻¹ 10 % MeCN in water for 1.2 min. Gradient information: 0.0-0.5 min, 1% MeCN; 0.5-15.0min, ramped from 1% MeCN to 14.9% MeCN; 15.0-15.1 min, ramped from 14.9% MeCN to 100% MeCN; 15.1-17.0 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac to afford the title compound (16.0 mg, 31 μmol , 3%) as a sticky brown gum.

[0254] m/z 396.5 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0255] ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.18 – 11.05 (m, 1H), 8.25 (s, 1H), 7.32 – 7.30 (m, 4H), 7.29 – 7.22 (m, 2H), 7.19 (d, J = 2.3 Hz, 1H), 7.05 (dd, J = 7.9 Hz, 1H), 6.76 (dd, J = 7.7, 0.8 Hz, 1H), 4.34 (t, J = 5.7 Hz, 2H), 3.54 (s, 2H), 2.82 (dd, J = 9.2, 6.7 Hz, 2H), 2.70 (t, J = 5.7 Hz, 2H), 2.60 – 2.55 (m, 2H), 2.26 (s, 6H), 2.19 (s, 3H). 1x exchangeable H not observed.

Example 30. Synthesis of compound 83: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (2,5,8,11-tetraoxatridecan-13-yl) carbonate, 0.9Formic Acid, 0.1Fumaric acid

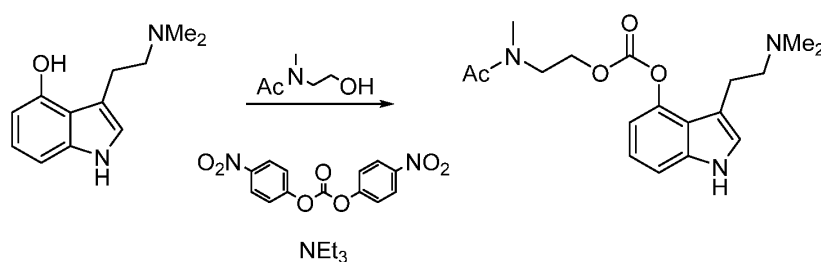


[0257] To a solution of 2,5,8,11-tetraoxatridecan-13-ol (310 mg, 1.5 Eq, 1.49 mmol) and triethylamine (0.7 g, 1 mL, 7 Eq, 7 mmol) in THF (3 mL) at 0 °C was added triphosgene (160 mg, 0.5 Eq, 518 µmol). The reaction was stirred for 2 h at 0 °C. A suspension of psilocin (202.5 mg, 1 Eq, 991 µmol) in THF (3 mL) was added at 0 °C. The mixture was stirred for 2 h at 0 °C then a further 16 h at r.t. The mixture was diluted with EtOAc (10 mL) and water (10 mL). The phases were separated and the aqueous was further extracted with EtOAc (10 mL). The combined organics were washed with brine (20 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (24 g cartridge, 5-10% (0.1 % formic acid in MeCN)/(0.1% formic acid in water)) (eluting 10%) to afford 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (2,5,8,11-tetraoxatridecan-13-yl) carbonate, formic acid (55.0 mg, 103 µmol, 10%) as a thick brown oil. The material was dissolved in acetone (3 mL) and a solution of fumaric acid (16 mg, 1.2 Eq, 138 µmol) in acetone (3 mL). The mixture was cooled at -20 °C for 100 h. The mixture was concentrated *in vacuo*. The crude material was dissolved in DMSO (2.1 mL), filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130 Å, 5 µm, 30 mm X 100 mm, flow rate 40 mLmin⁻¹ eluting with a 0.1% formic acid in water-MeCN gradient over 8.5 min using UV across all wavelengths with PDA as well as a QDA and ELS detector. At column dilution pump gives 2 mLmin⁻¹ MeCN over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 7.5% MeCN; 0.5-5.5 min, ramped from 7.5% MeCN to 37.5% MeCN; 5.5-5.6 min, ramped from 37.5% MeCN to 100% MeCN; 5.6-8.5 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac to afford the title compound (33.0 mg, 66 µmol, 7%) as a brown oil.

[0258] *m/z* 439.2 (M+H)⁺ (ES⁺)

[0259] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.10 (s, 1H), 8.18 (s, 0.9H), 7.26 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 2.3 Hz, 1H), 7.05 (dd, J = 7.9, 7.9 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.50 (s, 0.2H), 4.34 (dd, J = 5.7, 3.4 Hz, 2H), 3.73 – 3.65 (m, 2H), 3.60 – 3.48 (m, 10H), 3.42 (dd, J = 5.9, 3.7 Hz, 2H), 3.23 (s, 3H), 2.82 – 2.76 (m, 2H), 2.57 – 2.52 (m, 2H), 2.26 (s, 6H). 2x exchangeable H not observed.

Example 31. Synthesis of compound 87: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (2-(N-methylacetamido)ethyl) carbonate, Formic Acid



[0260]

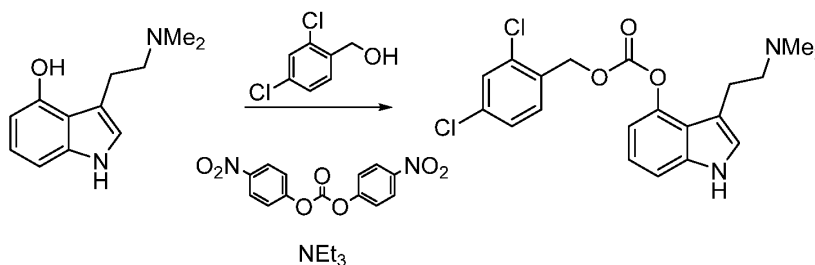
[0261] To a stirred solution of N-(2-hydroxyethyl)-N-methylacetamide (136 mg, 1.2 Eq, 1.16 mmol) and bis(4-nitrophenyl) carbonate (411 mg, 1.4 Eq, 1.35 mmol) in dry DCM (8 mL) under a nitrogen atmosphere at 20 °C was added triethylamine (234 mg, 323 μL , 2.4 Eq, 2.31 mmol). The reaction mixture was stirred for 1 h at r.t. To the reaction mixture under a nitrogen atmosphere at 20 °C was added a solution of psilocin (197 mg, 1 Eq, 964 μmol) in DMF (2 mL). The reaction mixture was stirred for 18 h at rt. The reaction mixture was then heated at 40 °C for 24 h. The reaction mixture was cooled to r.t. and was diluted with DCM (10 mL), poured into ice/water (20 mL) and transferred into a separating funnel. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The material was dissolved in DMSO (5.1 mL), filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130 Å, 5 μm , 30 mm X 100 mm, flow rate 40 mLmin^{-1} eluting with a 0.1% formic acid in water-MeCN gradient over 17.5 min using UV across all wavelengths with PDA as well as a QDA and ELS detector. At column dilution pump gives 2 mLmin^{-1} MeCN over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 5% MeCN; 0.5-15.5 min, ramped from 5% MeCN to 17.5% MeCN; 15.5-15.6 min, ramped from 17.5% MeCN to 100% MeCN; 15.6-17.5 min, held at 100% MeCN. The clean

fractions were evaporated in a Genevac to afford the title compound (74.0 mg, 0.18 mmol, 19%) as a brown oil.

[0262] m/z 348.1 (M+H)⁺ (ES+)

[0263] ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.10 (s, 1H), 8.20 (s, 1H), 7.26 (dd, *J* = 7.9, 2.5 Hz, 1H), 7.18 (d, *J* = 2.1 Hz, 1H), 7.08 – 7.01 (m, 1H), 6.80 – 6.73 (m, 1H), 4.38 (t, *J* = 5.3 Hz, 1H), 4.29 (t, *J* = 5.5 Hz, 1H), 3.60 (t, *J* = 5.5 Hz, 1H), 3.65 (t, *J* = 5.3 Hz, 1H), 3.00 (s, 2H), 2.83 (s, 1H), 2.81 – 2.76 (m, 2H), 2.55 – 2.51 (m, 2H), 2.24 (s, 3H), 2.22 (s, 3H), 2.00 (d, *J* = 3.3 Hz, 3H). 1x exchangeable H not observed.

Example 32. Synthesis of compound 89: 2,4-dichlorobenzyl (3-(2-(dimethylamino)ethyl)-1H-indol-4-yl) carbonate, Formic Acid



[0264]

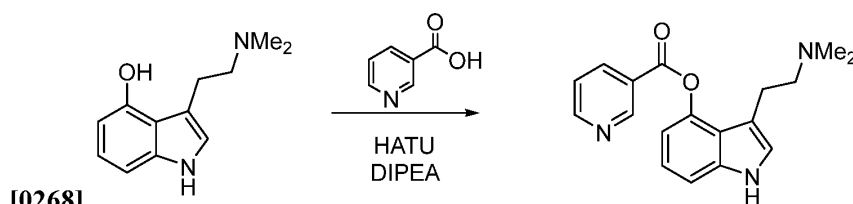
[0265] To a stirred solution of (2,4-dichlorophenyl)methanol (200 mg, 1.1 Eq, 1.13 mmol) and bis(4-nitrophenyl) carbonate (376 mg, 1.2 Eq, 1.23 mmol) in dry DCM (8 mL) under a nitrogen atmosphere at 20 °C was added triethylamine (229 mg, 316 μ L, 2.2 Eq, 2.26 mmol). The reaction mixture was stirred for 1 h at r.t. To the reaction mixture under a nitrogen atmosphere at 20 °C was added a solution of psilocin (210.2 mg, 1 Eq, 1.03 mmol) in DMF (2 mL). The reaction mixture was stirred for 1 h at rt. The reaction mixture was then heated at 38 °C for 18 h. The reaction mixture was diluted with DCM (10 mL), poured into ice/water (20 mL) and transferred into a separating funnel. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-20% MeOH/DCM) to afford a brown oil. The partially purified material was purified by chromatography on RP Flash C18 (12 g cartridge, 0-50 % (0.1 % formic acid in MeCN)/(0.1% formic acid in water)) to afford the title compound (69.1 mg, 156 μ mol, 15%) as a brown oil.

[0266] m/z 407.2/409.2 (M+H)⁺ (ES+)

[0267] ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.12 (s, 1H), 8.19 (s, 1H), 7.74 (d, *J* = 2.1 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.52 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.27 (dd, *J* = 8.1, 0.8 Hz, 1H),

7.18 (d, $J = 2.3$ Hz, 1H), 7.09 – 7.02 (m, 1H), 6.80 (dd, $J = 7.7, 0.8$ Hz, 1H), 5.36 (s, 2H), 2.78 – 2.71 (m, 2H), 2.56 – 2.51 (m, 2H), 2.19 (s, 6H). 1x exchangeable H not observed.

Example 33. Synthesis of compound 91: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl nicotinate, Formic Acid

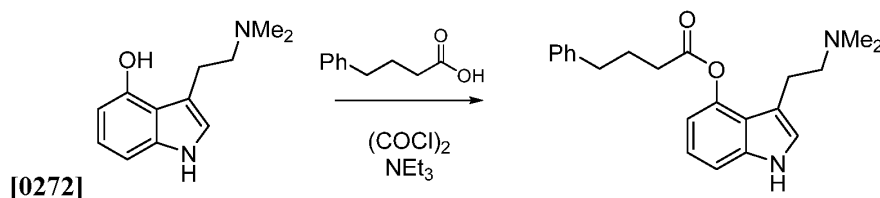


[0269] A mixture of psilocin (200.0 mg, 1 Eq, 852 μ mol), nicotinic acid (106 mg, 1 Eq, 852 μ mol), HATU (466 mg, 1.4 Eq, 1.23 mmol) and diisopropylethylamine (260 mg, 347 μ L, 2.4 Eq, 2.01 mmol) in dry DMF (2.5 mL) was stirred at r.t. for 16 h. The reaction mixture was diluted with sat. aq. NaHCO_3 (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (3 x 20 mL) and brine (25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was loaded onto celite and purified by chromatography on RP Flash C18 (12 g cartridge, 0-100% (0.1% formic acid in MeCN)/(0.1% formic Acid in Water)) to afford the title compound (150.6 mg, 0.41 mmol, 48%) as a light brown solid.

[0270] m/z 310.1 ($\text{M}+\text{H}$)⁺ (ES⁺)

[0271] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.16 (s, 1H), 9.35 (d, $J = 2.2$ Hz, 1H), 8.92 (dd, $J = 4.8, 1.7$ Hz, 1H), 8.62 – 8.51 (m, 1H), 8.21 (s, 1H), 7.68 (dd, $J = 8.0, 4.8$ Hz, 1H), 7.32 (d, $J = 8.1$ Hz, 1H), 7.20 (d, $J = 2.3$ Hz, 1H), 7.16 – 7.08 (m, 1H), 6.86 (d, $J = 7.6$ Hz, 1H), 2.79 – 2.72 (m, 2H), 2.60 – 2.53 (m, 2H), 2.06 (s, 6H). 1x exchangeable H not observed.

Example 34. Synthesis of compound 96: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 4-phenylbutanoate, 0.5Fumaric acid



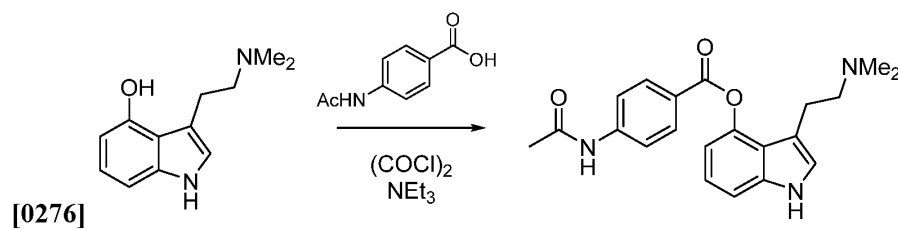
[0273] To a stirred solution of 4-phenylbutanoic acid (141 mg, 1 Eq, 860 μ mol) in dry DCM (4 mL) under an atmosphere of nitrogen at r.t. was added oxalyl chloride (229 mg, 158 μ L,

2.1 Eq, 1.81 mmol) and a drop of DMF. The reaction mixture was stirred at room temp for 2 h. The volatiles were removed *in vacuo*. The residue was dissolved in DCM (2 mL) and added to a solution of psilocin (199.6 mg, 1 Eq, 860 μ mol) and triethylamine (313 mg, 431 μ L, 3.6 Eq, 3.10 mmol) in DCM (2 mL) at 0 °C. The reaction mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with water (5 mL) and transferred into a separating funnel. The aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were collected, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (24 g cartridge, 5-50 % (0.1% formic acid in MeCN)/(0.1% formic acid in water)) to afford 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 4-phenylbutanoate, formic acid (144 mg, 0.30 mmol, 35%) as a brown oil. The material was dissolved in acetone (2 mL) and a solution of fumaric acid (35 mg, 0.35 Eq, 0.30 mmol) in acetone (4 mL) was added. The resulting solid was filtered, washed with acetone (2 mL) and dried in a vacuum desiccator overnight to afford the title compound (56.8 mg, 137 μ mol, 16%) as a light brown solid.

[0274] m/z 351.0 (M+H)⁺ (ES⁺)

[0275] ¹H NMR (500 MHz, DMSO) δ 11.08 (d, J = 2.5 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.26 – 7.18 (m, 4H), 7.16 (d, J = 2.3 Hz, 1H), 7.04 (dd, J = 7.9 Hz, 1H), 6.66 (dd, J = 7.6, 0.8 Hz, 1H), 6.53 (s, 1H), 2.81 (dd, J = 9.4, 6.6 Hz, 2H), 2.73 – 2.67 (m, 4H), 2.64 (dd, J = 9.6, 6.3 Hz, 2H), 2.31 (s, 6H), 1.99 (app. p, J = 7.6 Hz, 2H). (2x 0.5 exchangeable H not observed)

Example 35. Synthesis of compound 97: 3-(2-(Dimethylamino)ethyl)-1H-indol-4-yl 4-acetamidobenzoate, 0.5 Fumaric acid



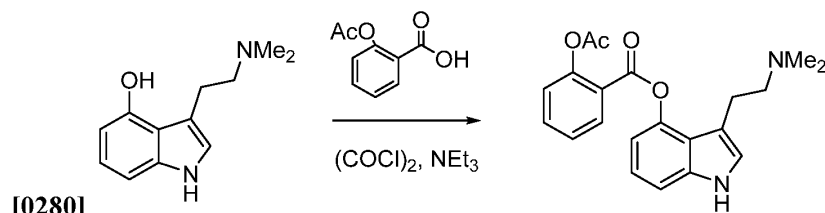
[0277] To a stirred solution of 4-acetamidobenzoic acid (182.6 mg, 1 Eq, 1.019 mmol) in dry DCM (4.00 mL) under an atmosphere of N₂ at rt was added oxalyl chloride (271.7 mg, 187.4 μ L, 2.1 Eq, 2.140 mmol) and a drop of DMF (74.51 mg, 78.9 μ L, 1 Eq, 1.019 mmol). The reaction mixture was stirred at rt for 2 h. The volatiles were removed *in vacuo*. The residue was dissolved in DCM (2.00 mL) and added to a solution of psilocin (208.2 mg, 1 Eq, 1.019 mmol) and Et₃N (371.3 mg, 511 μ L, 3.6 Eq, 3.669 mmol) in DCM (2.00 mL) at 0 °C. The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated *in vacuo*.

The crude product (diluted in 1.5 mL of DMF) was purified by chromatography on RP Flash C18 (12 g cartridge, 5-50% (0.1 % formic acid in MeCN) / (0.1% formic acid in water)) to afford impure material (220 mg, 0.40 mmol, 39 %, 75% Purity) as a brown oil. The material was subjected to a second purification on RP Flash C18 (12 g cartridge, 5-50% (0.1 % formic acid in MeCN) / (0.1% formic acid in water)) to afford the desired material as the formate salt (76.0 mg, 0.15 mmol, 14 %, 80% Purity (20% acetonitrile)) as a brown oil. The material was dissolved in acetone (5 mL) and a solution of fumaric acid (17 mg, 0.15 Eq, 0.15 mmol) in acetone (5 mL) was added. The resulting solid was filtered, washed with acetone and dried in a vacuum desiccator over the weekend to afford the title compound (44.7 mg, 97.6 μ mol, 9.58 %, 92.5% Purity) as a yellow solid.

[0278] m/z 366.19 (M+H)⁺ (ES+); 364.19 (M-H)⁻ (ES-)

[0279] ¹H NMR (500 MHz, DMSO) δ 11.11 (s, 1H), 10.38 (s, 1H), 8.16 – 8.12 (m, 2H), 7.84 – 7.78 (m, 2H), 7.28 (dd, J = 8.1, 0.8 Hz, 1H), 7.17 (d, J = 2.3 Hz, 1H), 7.12 – 7.05 (m, 1H), 6.77 (dd, J = 7.6, 0.8 Hz, 1H), 6.53 (s, 1H), 2.77 – 2.70 (m, 2H), 2.58 – 2.51 (m, 2H), 2.11 (s, 3H), 2.06 (s, 6H). 1H not observed (exchangeable proton of fumaric acid)

Example 36. Synthesis of compound 99: 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-acetoxybenzoate, Fumaric acid



[0281] To a stirred solution of 2-acetoxybenzoic acid (210 mg, 1.2 Eq, 1.17 mmol) in dry DCM (2 mL) under a nitrogen atmosphere at r.t. was added oxalyl chloride (149 mg, 103 μ L, 1.2 Eq, 1.17 mmol) and a drop of DMF. The reaction mixture was stirred at r.t. for 2 h. The volatiles were removed *in vacuo*. The residue was redissolved in DCM (2 mL) and added to a solution of psilocin (202.9 mg, 1 Eq, 973 μ mol) and triethylamine (218 mg, 300 μ L, 2.2 Eq, 2.15 mmol) in DCM (2 mL) at 0 °C. The resulting mixture was stirred at r.t. for 18 h. The mixture was diluted with DCM (10 mL) poured into ice/water (20 mL). The phases were separated and the aqueous extracted with further DCM (10 mL). The combined organics were washed with brine (20 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by chromatography on RP Flash C18 (12 g cartridge, 5-50% (0.1% formic acid in MeCN)/(0.1% formic acid in water)) (eluting ~20%) to afford 3-(2-(dimethylamino)ethyl)-

1H-indol-4-yl 2-acetoxybenzoate, Formic Acid (244 mg, 592 μ mol, 61%) as a sticky orange oil. To a solution of the resultant oil in acetone (2 mL) was added a solution of fumaric acid (240 mg, 2.12 Eq, 2.1 mmol) in acetone (12 mL). The mixture was stored at -20 °C for 16 h. The resulting crystalline solid was isolated by filtration and washed with cold acetone (2x 5 mL) to afford the title compound (164.9 mg, 0.32 mmol, 33%) as a white crystalline solid.

[0282] m/z 367.4 (M+H)⁺ (ES⁺)

[0283] ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.84 (s, 2H), 11.14 (s, 1H), 8.29 (dd, J = 7.8, 1.7 Hz, 1H), 7.80 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.52 (dd, J = 7.6, 7.6 Hz, 1H), 7.32 (dd, J = 24.2, 8.1 Hz, 2H), 7.19 (d, J = 2.4 Hz, 1H), 7.10 (dd, J = 7.9, 7.9 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.56 (s, 2H), 2.78 – 2.69 (m, 2H), 2.58 (t, J = 8.0 Hz, 2H), 2.21 (s, 3H), 2.09 (s, 6H).

Example 37. Human Hepatocyte Clearance and Human Plasma Stability

[0284] Human Plasma Stability Summary

[0285] The plasma stability of compounds was assessed by monitoring the disappearance of parent compounds for up to 2 hours at 37°C in plasma in duplicate, using positive (Propantheline), negative (Pepstatin) and solvent controls (DMSO) to confirm suitability of the assay. Psilocin was also run as a control to monitor psilocin formation in a semi-quantitative manner.

[0286] Samples were analysed by UHPLC-MS/MS - Sciex™ MS500 Triple Quad QTRAP UHPLC system with a HESI-II electrospray source on a Waters™ Acquity UPLC® HSS T3 column (1.8 μ m, 2.1 mm X 50 mm), mobile were phases water + 0.1% formic acid and methanol + 0.1% formic acid.

[0287] The elimination rate constant and half-life ($t_{1/2}$) were determined using Ln(MS response) vs time plots. In addition, the appearance of psilocin from test compounds was monitored and assessed (as a percentage) against control psilocin peaks (at Time 0) to provide a semi-quantitative measure of psilocin release. The human plasma stability data are included in table A.

[0288] Human Hepatocyte Clearance

[0289] The metabolic stability of compounds was assessed by monitoring the disappearance of parent compounds for up to 1 hour at 37°C in cryopreserved hepatocytes, using established controls (Diltazem and Naloxone), to confirm suitability of the assay. Psilocin was also run as an additional control to monitor psilocin formation in a semi-quantitative manner.

[0290] Samples were analysed by UHPLC-MS/MS - Waters™ Acquity UPLC system, Waters™ Xevo TQ-XS on a Waters™ Acquity UPLC® HSS T3 column (1.8 µm, 2.1 mm X 30 mm), mobile phases were water + 0.1% formic acid and methanol + 0.1% formic acid.

[0291] The elimination rate constant, half-life ($t_{1/2}$) and intrinsic clearance (CL_{int} , µL/min/ 10^6 cells) were determined using Ln(MS response) vs time plots. In addition, the appearance of psilocin from test compounds was monitored and assessed (as a percentage) against control psilocin peaks (at Time 0) to provide a semi-quantitative measure of psilocin release. The human hepatocyte clearance plasma data are included in table A.

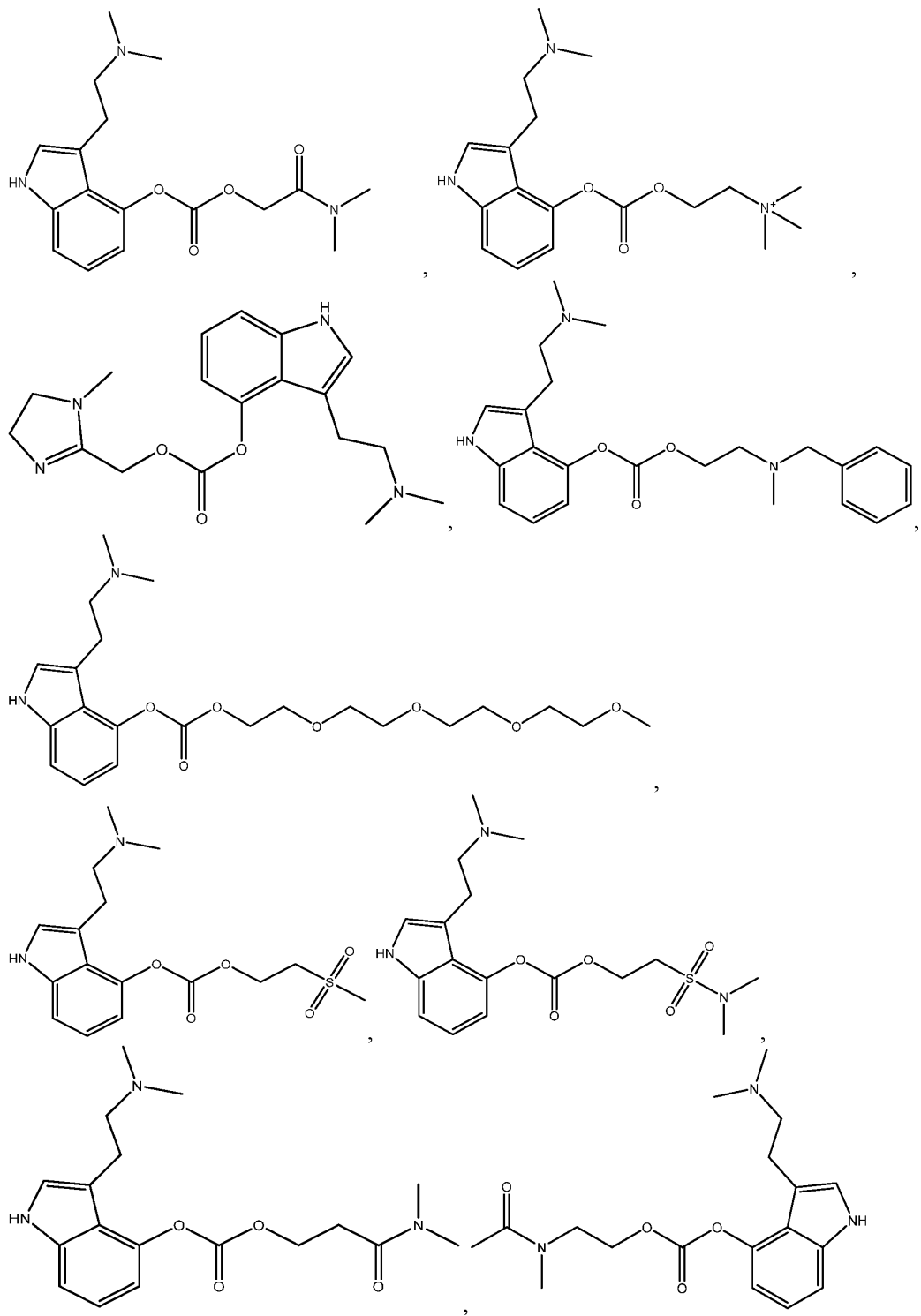
Table A. Human plasma stability data and human hepatocyte clearance plasma data of selected compounds

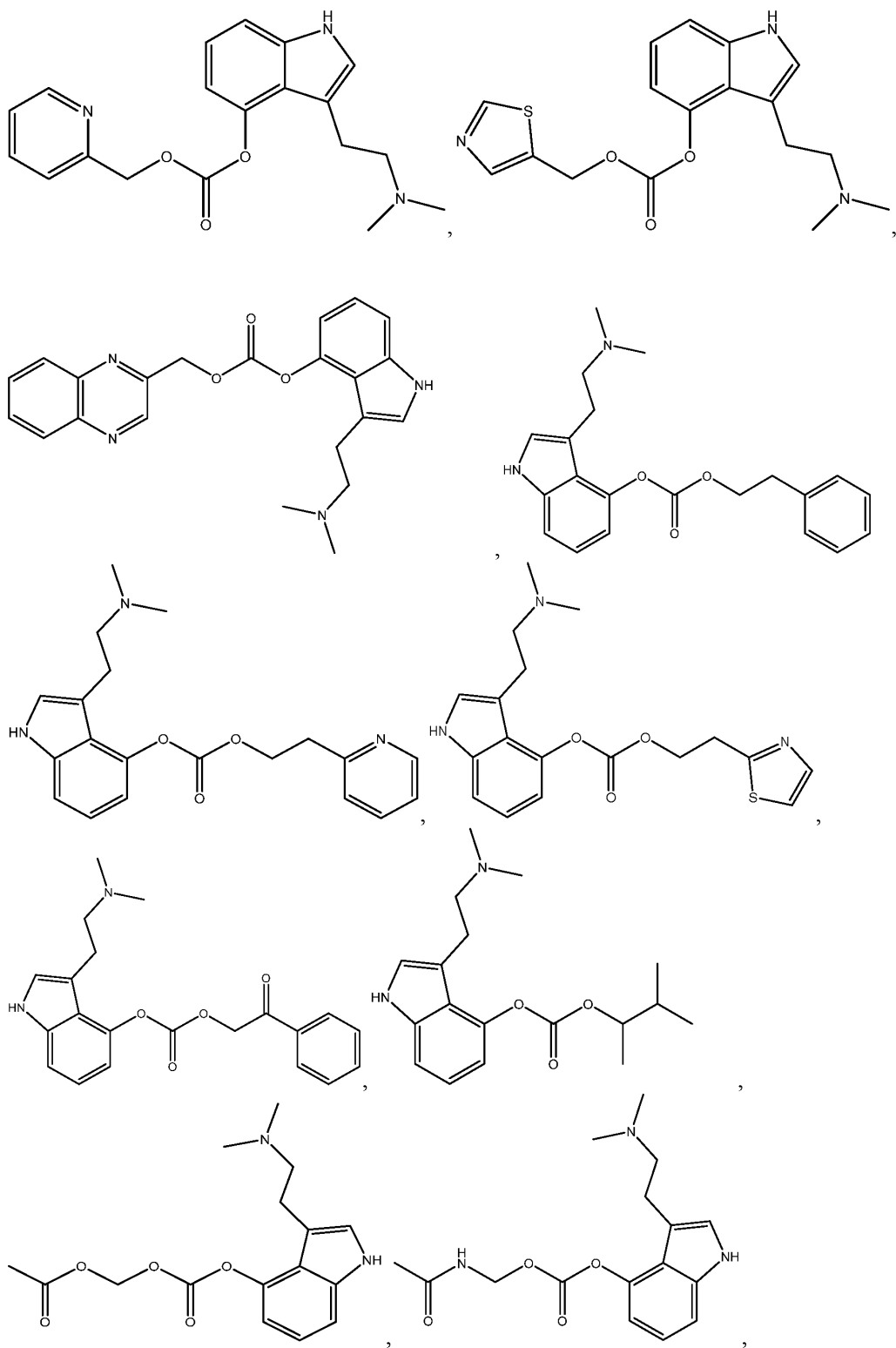
Compound_Number	Human Plasma Maximum % Psilocin	Human Hepatocytes Maximum % Psilocin
52	100	54
189	100	100
191	100	82
168	100	100
169	8	21
171	26	67
188	18	34
82	85	
87	91	100
89	100	100
91	100	200
99	100	100
105	82	65
107	81	
110	100	
135	2	1
139	100	
195	2	25
197		57
123	100	
78	100	100
97	100	
113	100	100
117	100	200
126	12	
137	11	
79	100	
185	100	

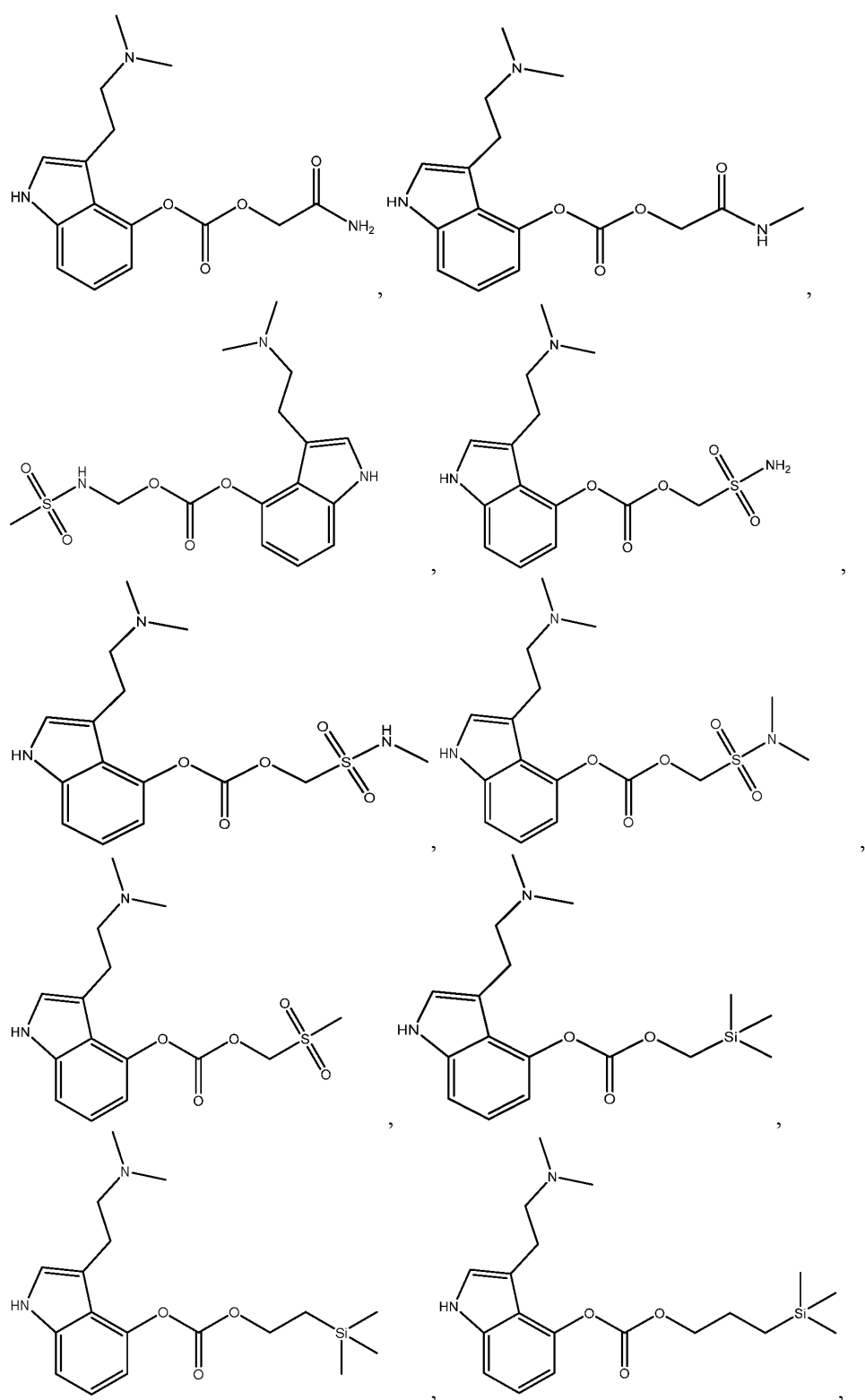
100	100	
118	100	
109	100	
129	31	
176	100	
96	75	
83	100	59

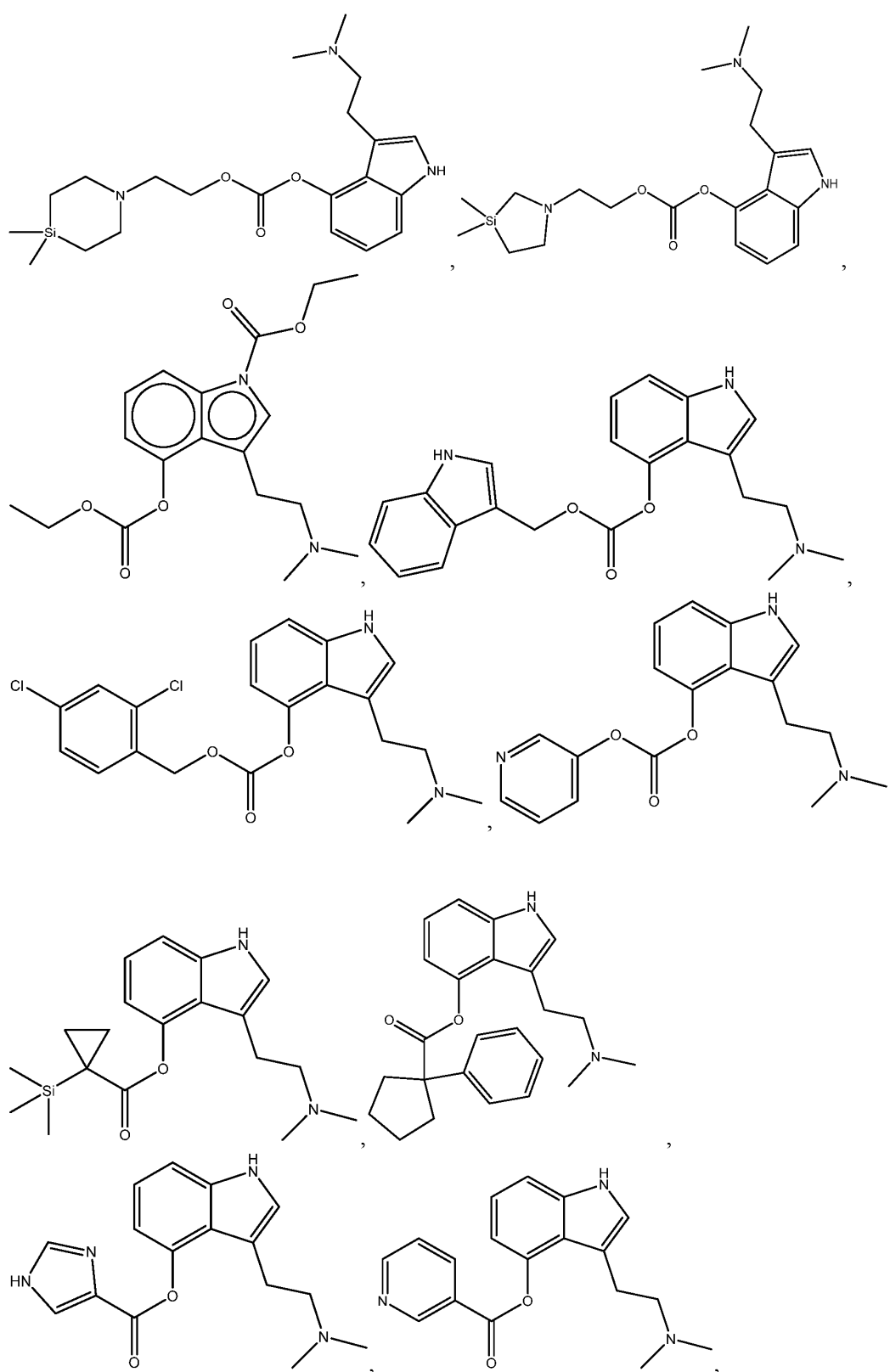
CLAIMS

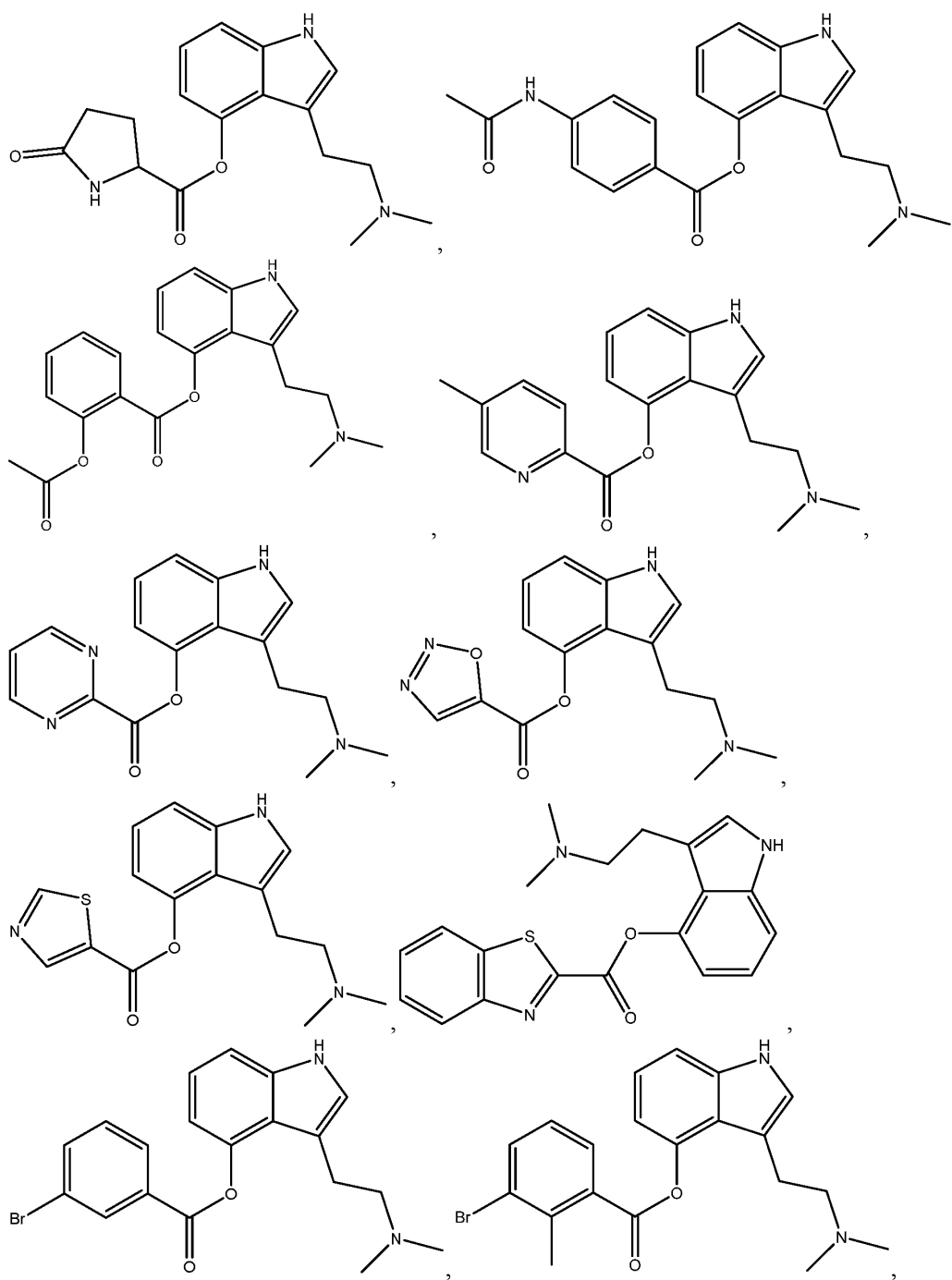
1. A compound selected from any one of the following structures, or a pharmaceutically acceptable salt or a deuterated form thereof:

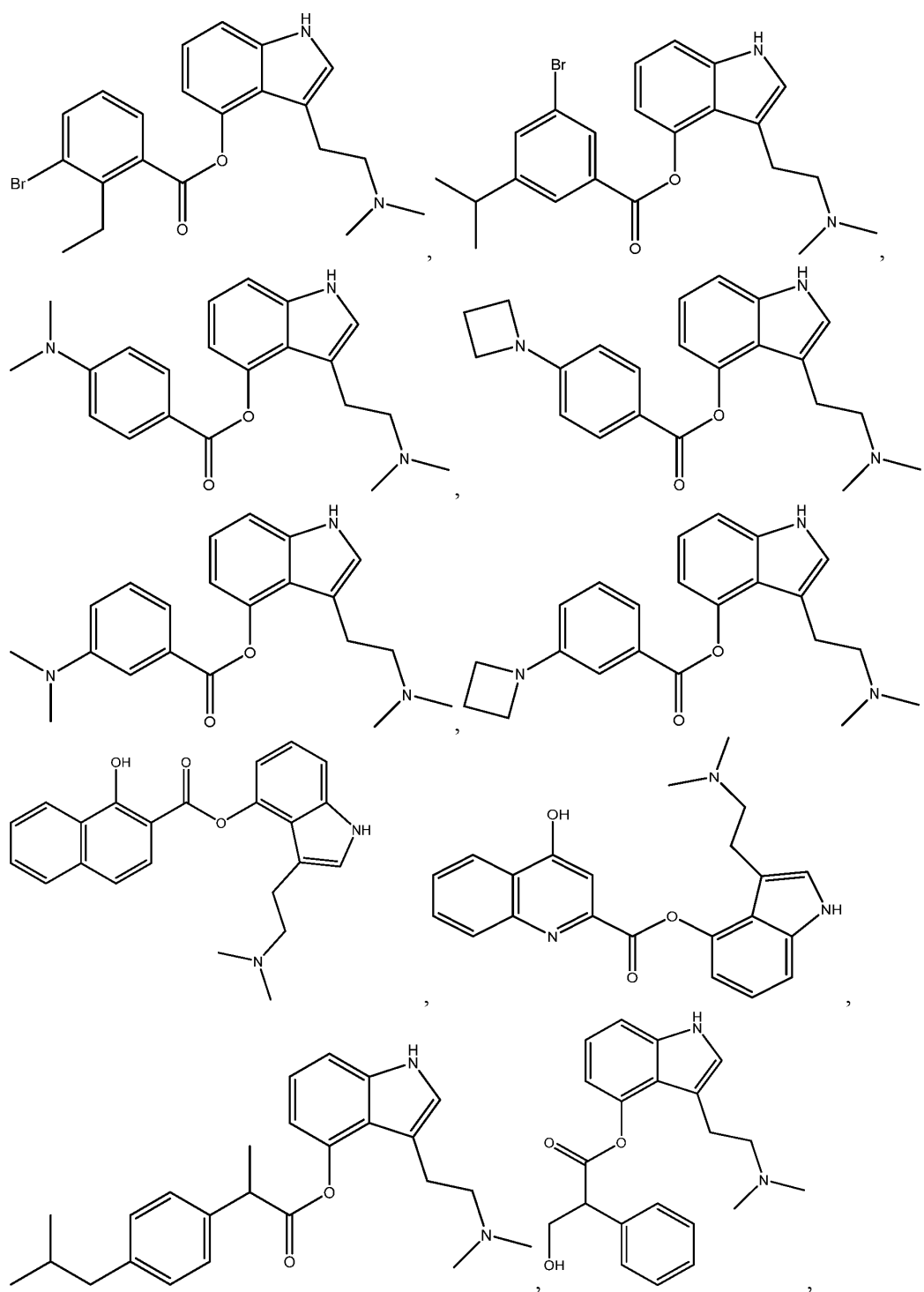


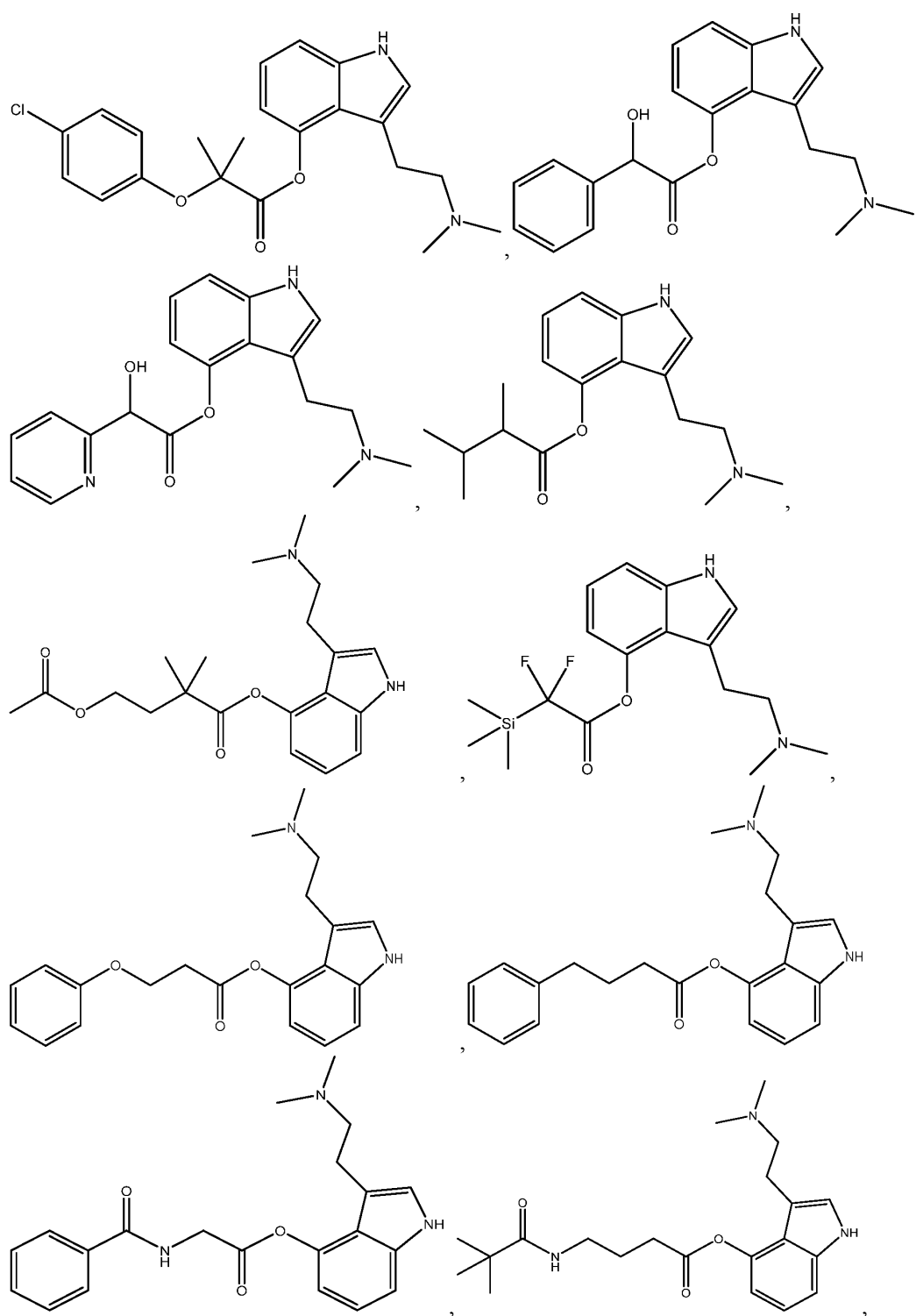


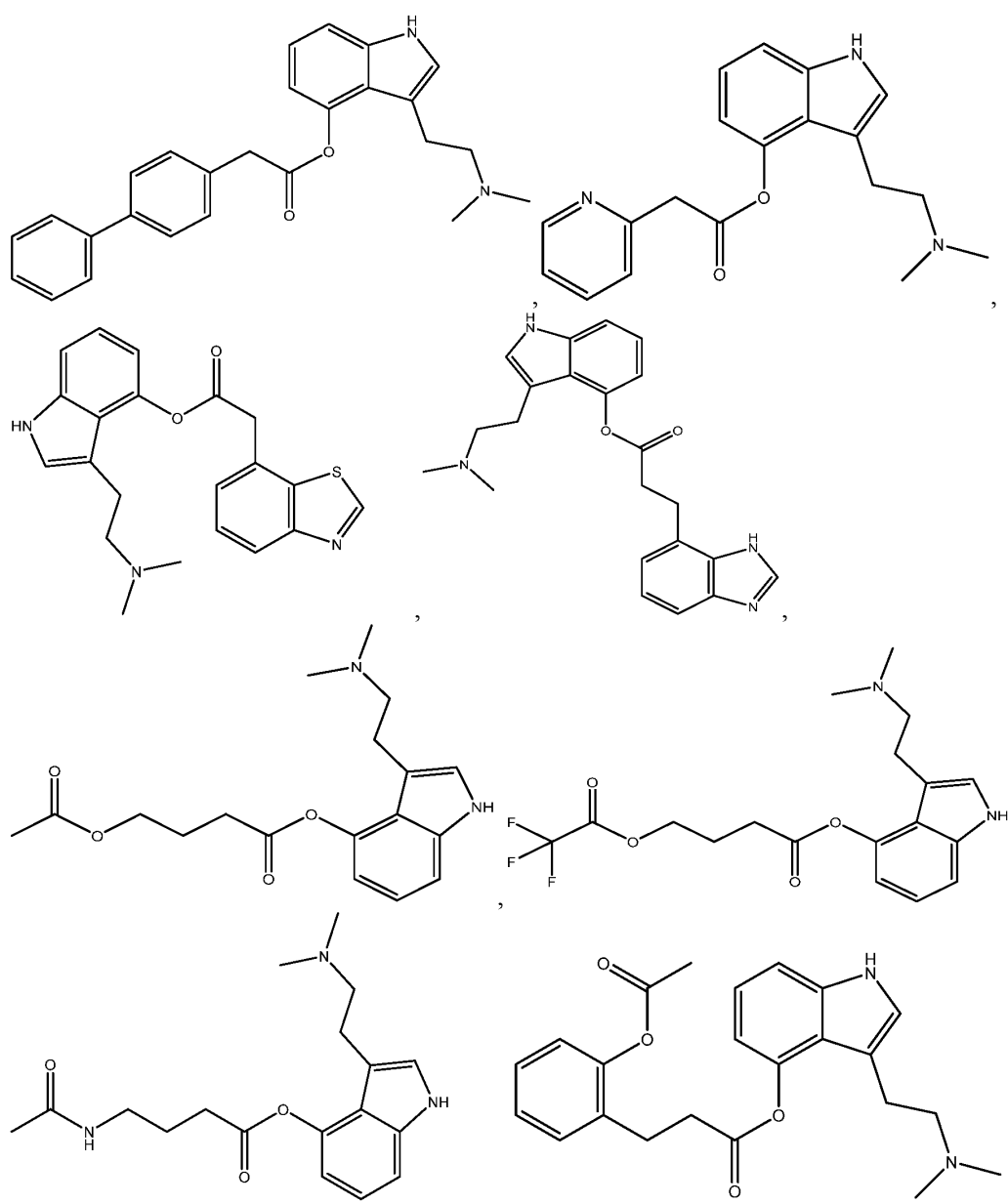


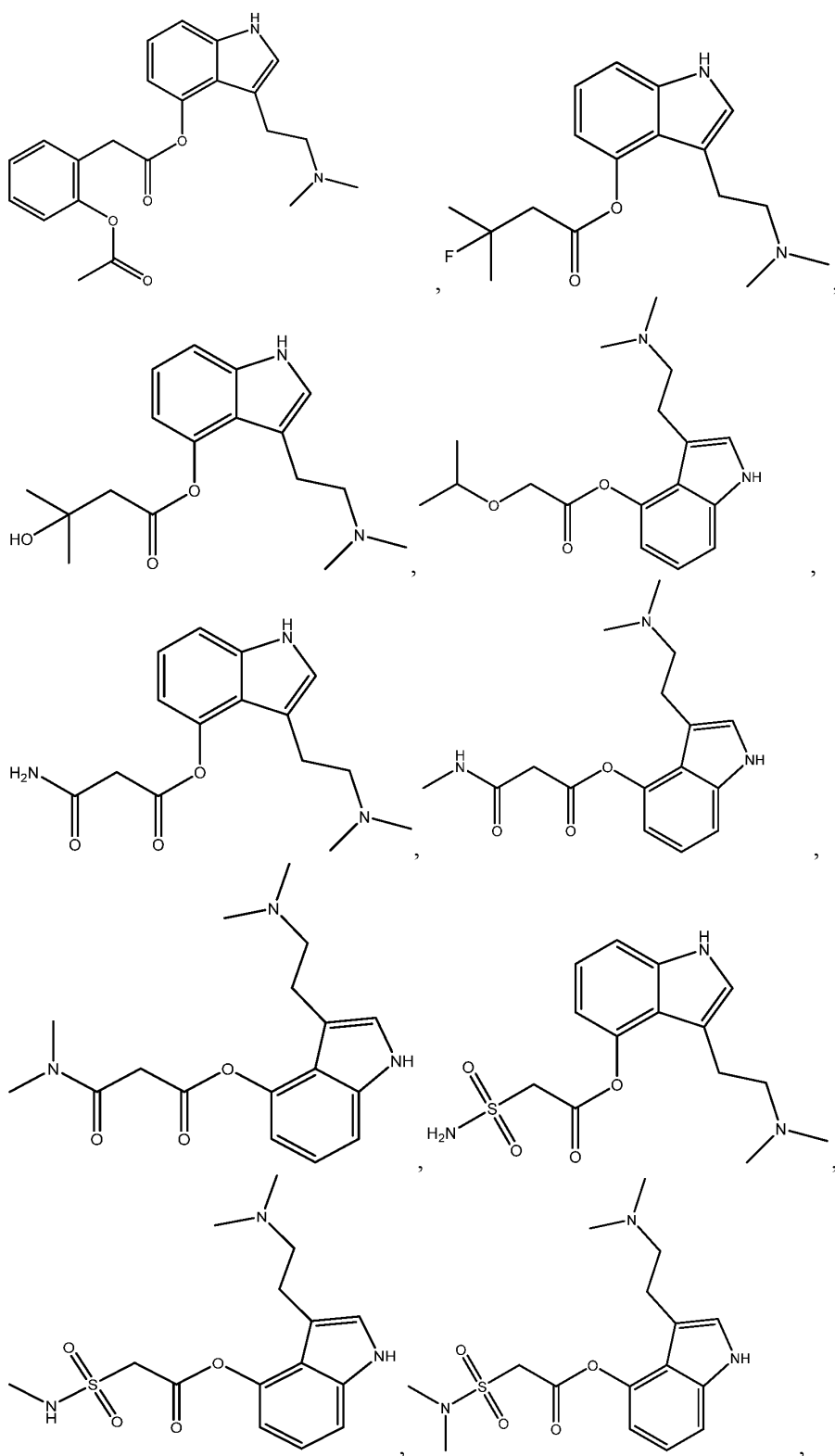


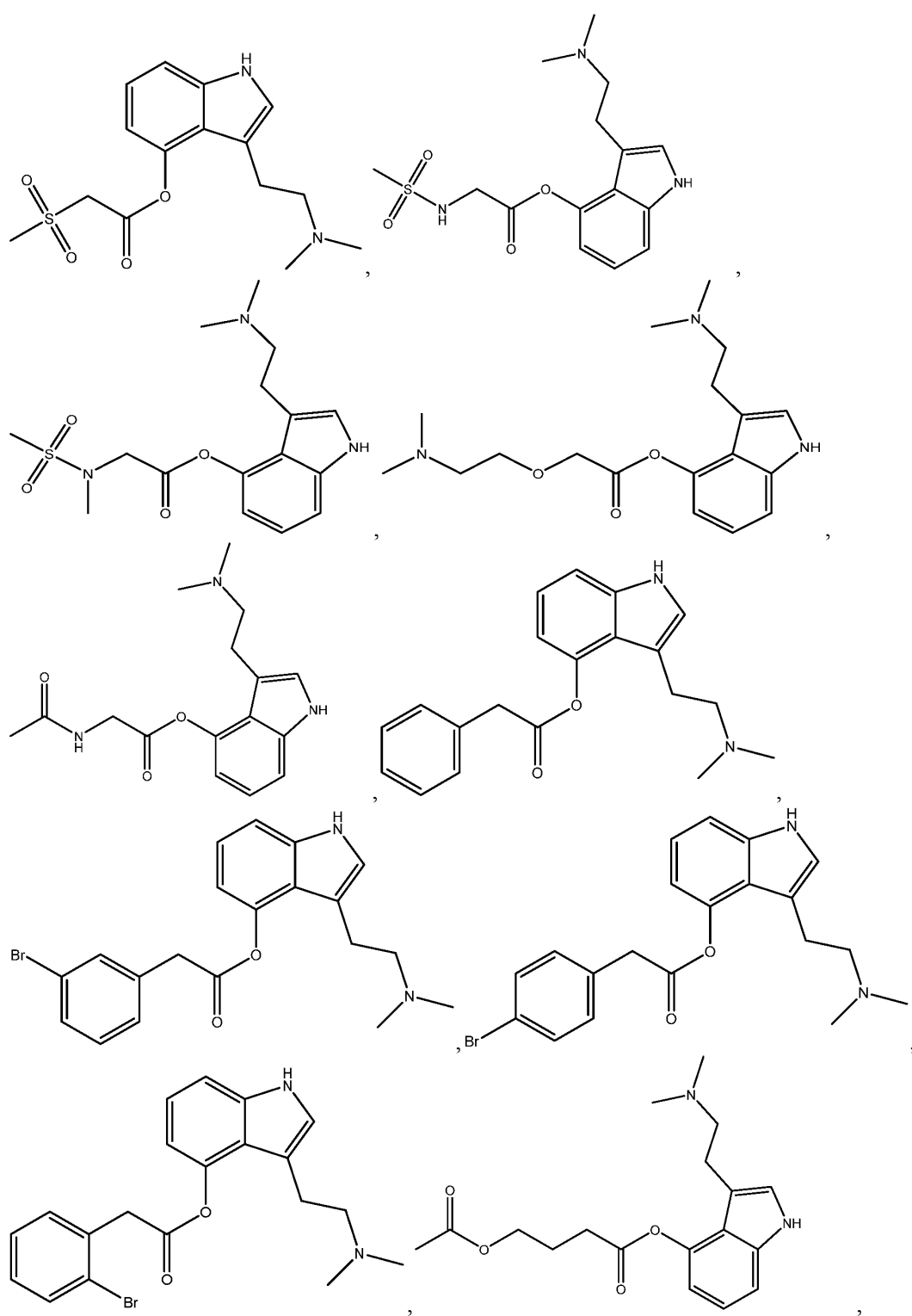


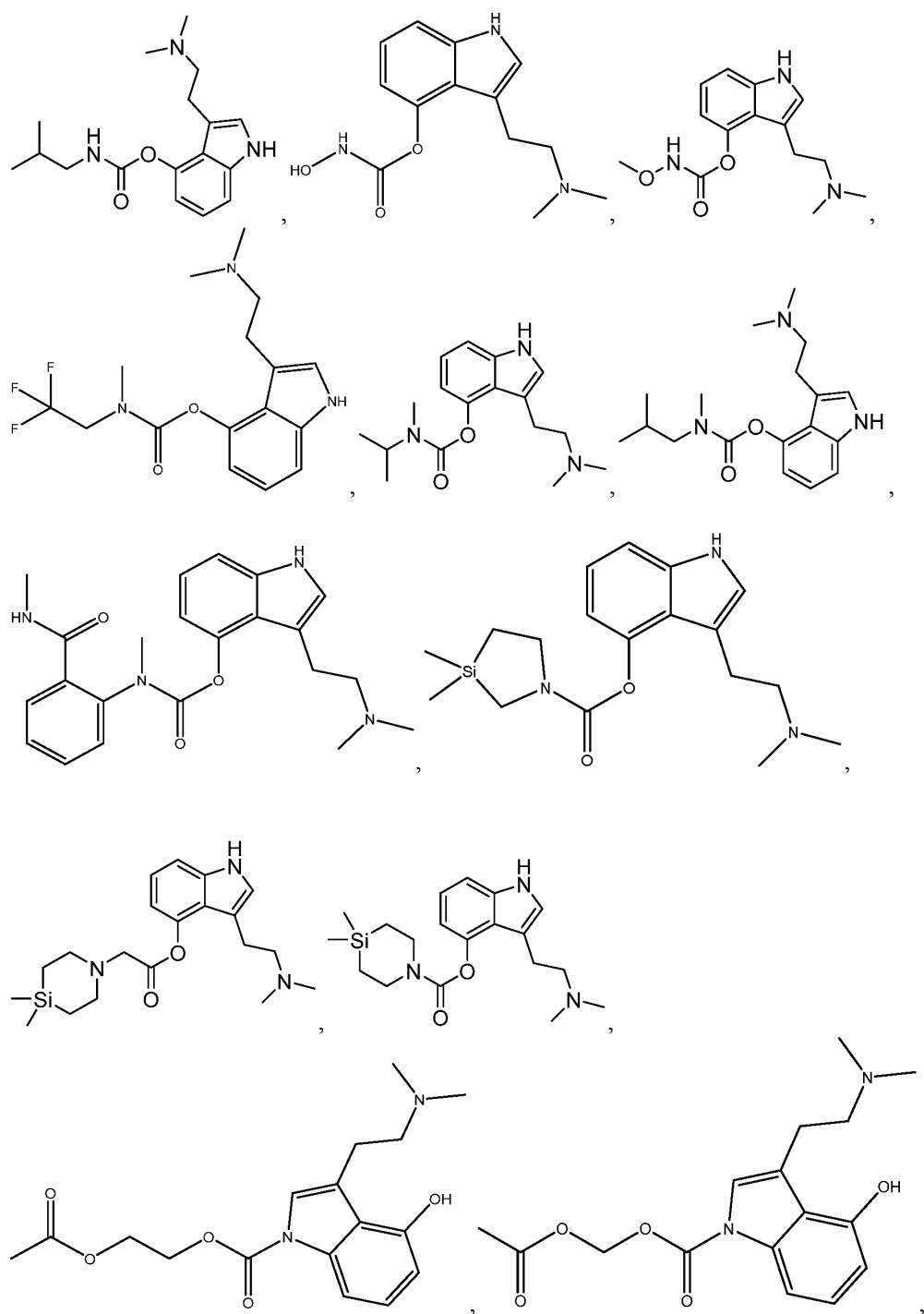


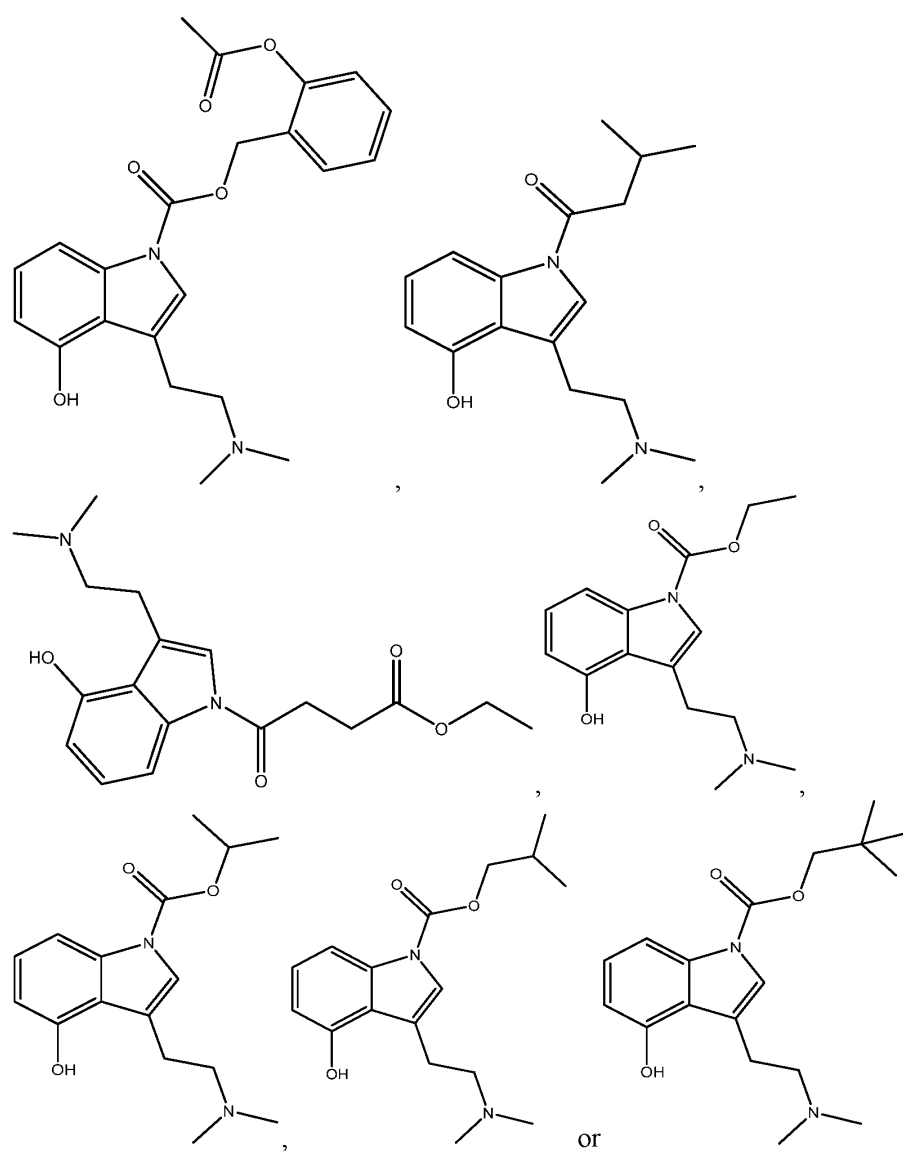




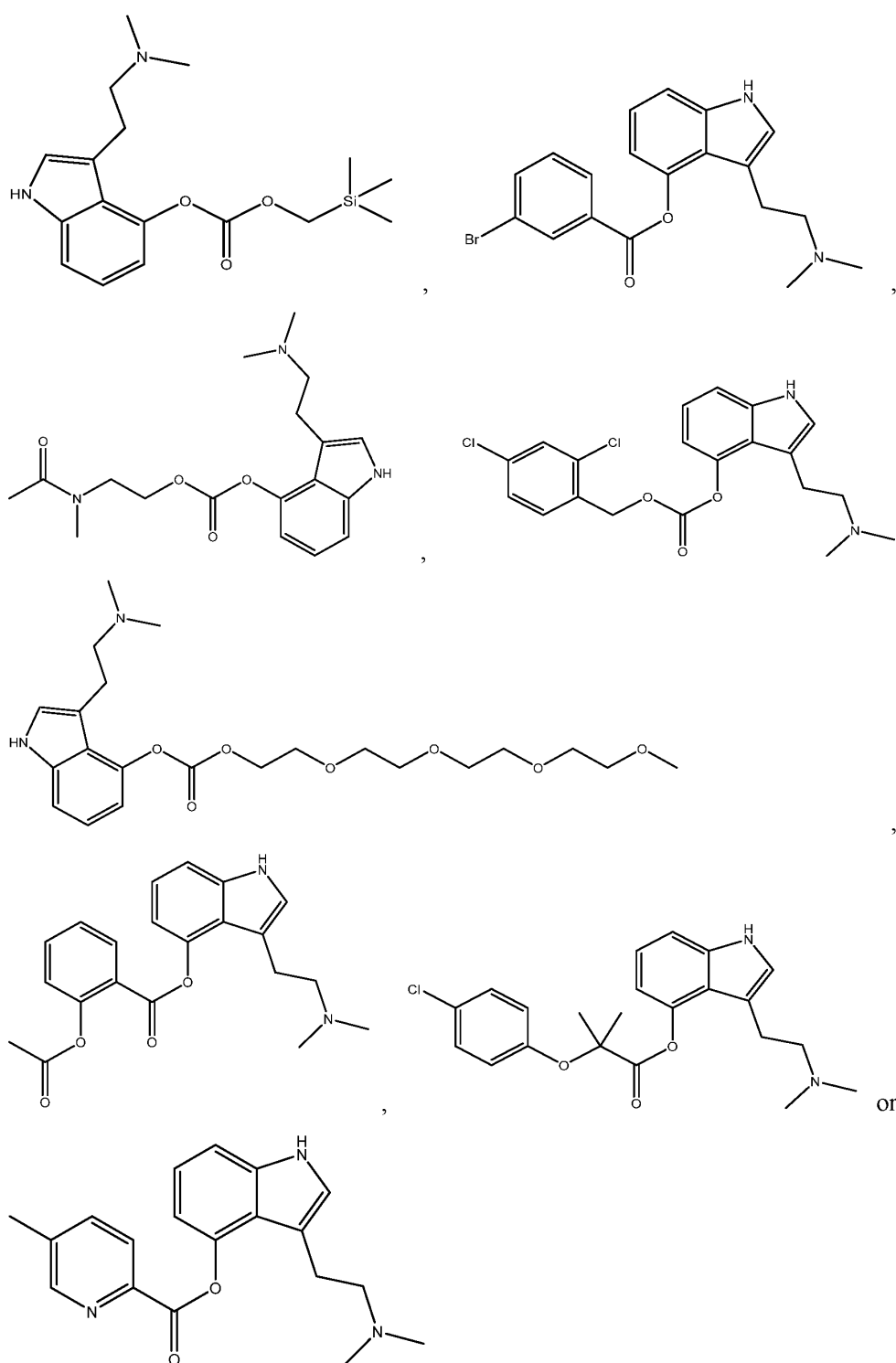








2. The compound of claim 1, having the following structure:



or a pharmaceutically acceptable salt or deuterated form thereof.

3. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt or deuterated form thereof.
4. A method of treating 5-HT_{2A} receptor associated disease or disorder, comprising administering a compound of claim 1 or 2, or a pharmaceutically acceptable salt or deuterated form thereof.
5. The method of claim 4, wherein the 5-HT_{2A} receptor associated disease or disorder is an anxiety disorder, attention deficit hyperactivity disorder (ADHD), depression, cluster headache, diminished drive, burn-out, bore-out, migraine, Parkinson's disease, schizophrenia, an eating disorder, psychotic disorder, schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar I disorder, bipolar II disorder, major depressive disorder, psychotic depression, delusional disorders, shared psychotic disorder, Shared paranoia disorder, brief psychotic disorder, paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder, social anxiety disorder, substance-induced anxiety disorder, selective mutism, panic disorder, panic attacks, agoraphobia, posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), and premenstrual syndrome (PMS).
6. The method of claim 5, wherein the 5-HT_{2A} receptor associated disease or disorder is depression
7. The method of claim 6, wherein the depression is treatment resistant depression.
8. The method of claim 5, wherein the 5-HT_{2A} receptor associated disease or disorder is an eating disorder.
9. The method of claim 8, wherein the eating disorder is anorexia nervosa.
10. The method of claim 5, wherein the 5-HT_{2A} receptor associated disease or disorder is an anxiety disorder.
11. The method of claim 5, wherein the 5-HT_{2A} receptor associated disease or disorder is bipolar I disorder.
12. The method of claim 5, wherein the 5-HT_{2A} receptor associated disease or disorder is bipolar II disorder.
13. The method of claim 5, wherein the 5-HT_{2A} receptor associated disease or disorder is major depressive disorder.

14. The method of claim 5, wherein the 5-HT_{2A} receptor associated disease or disorder is posttraumatic stress disorder (PTSD).