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(54) Title: NOVEL PRODRUGS OF MDMA, MDA, AND DERIVATIVES THEREOF

(57) Abstract: The present disclosure provides prodrug compounds of MDMA, MDA, and derivatives thereof having an improved pharmacokinetic profile suitable for the treatment of various neurological diseases.

NOVEL PRODRUGS OF MDMA, MDA, AND DERIVATIVES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/251,430, filed October 1, 2021, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Field of the Invention

[0003] The present invention relates novel prodrugs of MDMA, MDA and derivatives thereof, as well as to methods employing such compounds for the treatment of post-traumatic stress disorder (PTSD), eating disorders, depression (including major depressive disorders (MDD) or treatment-resistant depression (TRD)), and anxiety disorders including generalized anxiety disorder.

[0004] Description of Related Art

[0005] 3,4-methylenedioxymethamphetamine (MDMA), also known as Ecstasy, is considered the prototype of a class of compounds called entactogens, which means "to touch within," their main characteristic being their ability to increase feelings of love, empathy, and closeness towards others. Structurally, MDMA is a ring-substituted phenethylamine with a chiral molecular center that gives rise to two stereoisomers: (*S*)(+)-MDMA and (*R*)(-)-MDMA. Typically, the effects of (*S*)-MDMA resemble those of psychostimulants and are primarily mediated by dopaminergic and noradrenergic pathways, including increases in motor activity and euphoria, whereas (*R*)-MDMA induces qualitative effects similar to classical psychedelics, such as ego-dissolution and perceptive alterations, mediated by serotonergic pathways, including direct 5-HT2A receptor agonism (Murnane et al., 2009). The molecular mechanisms for these differences are supported by preclinical evidence and point to a higher therapeutic index for the *R*-enantiomer.

[0006] To this point, harnessing the biological active of MDMA in an effective therapeutic treatment has been somewhat limited. This is due at least in part to a problematic pharmacokinetic profile related to non-proportional dose-dependency upon administration in humans. Studies have demonstrated that MDMA is metabolized to three main metabolites identified as MDA, HMMA and HMA, which are found in the plasma in different proportions, depending on the concentration of the drug administered. At doses around 50-100 mg, HMMA predominates, while at doses between 125-150 mg MDMA predominates, indicating a possible saturation of its own metabolic pathways. The main hepatic enzymes involved in MDMA

metabolism, as identified from *in vitro* experiments in human liver microsomes, are CYP1A2, CYP2D6 and CTP3A4. Furthermore, stereochemistry appears to play a role in the non-renal pharmacokinetics of MDMA, with the *S*-enantiomer having a shorter half-life, lower peak plasma concentrations and increased clearance (Green et al., 2003).

[0007] For two doses of racemic MDMA and MDA, the following PK measurements were observed in healthy human subjects:

- 125 mg MDMA: Cmax 236.4 ng/ml; Tmax at 2.4 hours; elimination half-life 8.6 hours; AUC_{0-24} 2623 ng/ml*h^{-1}
- 125 mg MDA: Cmax 13.7 ng/ml; Tmax at 7 hours; AUC_{0-24} 215 ng/ml*h^{-1}
- 75 mg MDMA: Cmax 130.9 ng/ml; Tmax 1.8 hours; elimination half-life 7.7 hours; AUC_{0-24} 1331 ng/ml*h^{-1}
- 75 mg MDA: Cmax 7.8 ng/ml; Tmax at 5 hours; AUC_{0-24} 122 ng/ml*h^{-1}

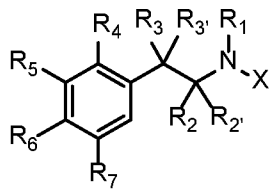
[0008] In reference to MDA pharmacokinetics, the MDA formation rate constant has been estimated for both MDMA doses of being about 0.75 h. Elimination half-life of MDA was in a range of 16 to 28 h (Mas, 1999).

[0009] Accordingly, novel approaches that improve the pharmacokinetics of MDMA and MDA are needed in order to take advantage of the wide ranging pharmacologic properties of these compounds in treating various diseases and conditions.

SUMMARY

[0001] MDA and MDMA prodrugs are herein disclosed that reduce C_{max} while maintaining AUC over an extended period after dosing. Several methodologies have been developed. Since primary and secondary amines have intrinsically different reactivities, MDA and MDMA require different pro-moieties. As set forth in the Detailed Description, two "enacarbil" analogues were initially synthesized as well as 3-5 amino acid analogues.

[0002] To address these and other issues, in one aspect, the present disclosure provides. a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof;

wherein,

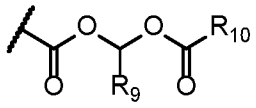
R_1 is H or alkyl;

R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl, or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

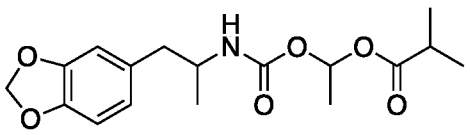
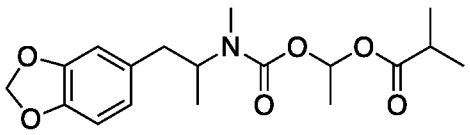
R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl;

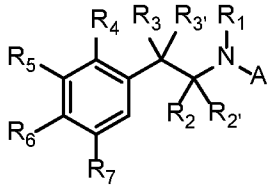
X is a cleavable promoiety having the structure  , wherein:

R_9 and R_{10} are each independently alkyl or phenyl. In some embodiments, R_9 and R_{10} are each alkyl, e.g., $C_{1\text{-}5}$ alkyl.

[0003] In some embodiments, the compound of the present disclosure has the following structure:

 or  .

[0004] In another aspect, the present disclosure provides a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof;

wherein,

R_1 is H or alkyl;

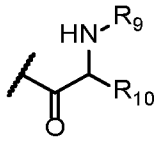
R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl , or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6

together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl; and

A is a cleavable promoiety having the structure  , wherein:

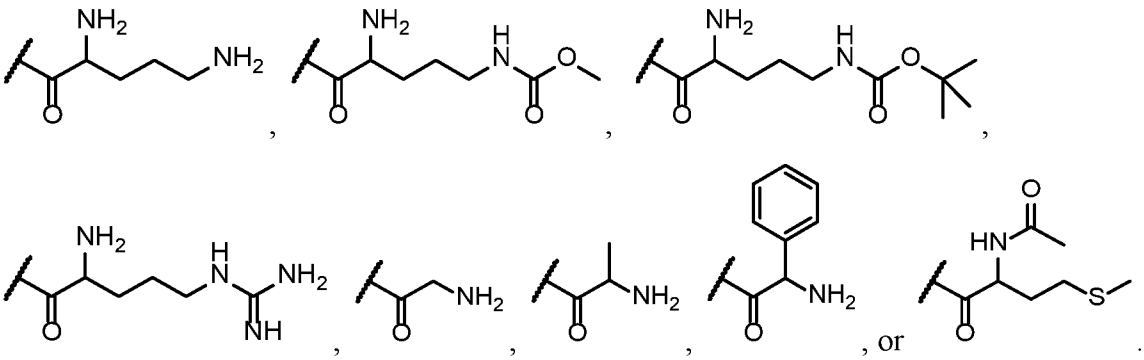
R_9 is H, alkyl or acyl; and

R_{10} is H, aryl, or $-(CH_2)_m-R_{11}$,

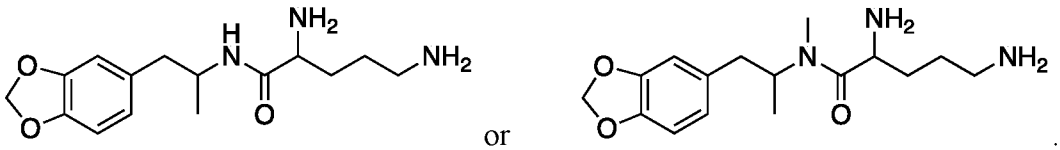
wherein m is an integer from 1-5; and

R_{11} is amino, guanidino, thioalkyl, or aryl.

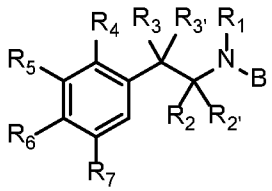
[0005] In some embodiments, A is :



[0006] In some embodiments, the compound of the present disclosure has the following structure:



[0007] In yet another aspect, the present disclosure provides a compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof;

wherein,

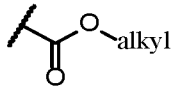
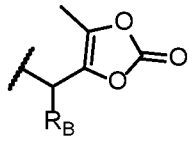
R_1 is H or alkyl;

R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

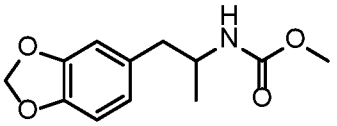
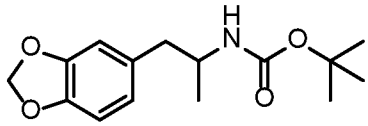
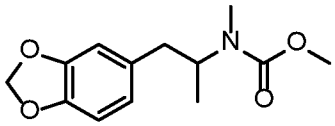
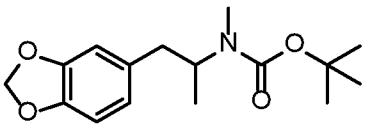
R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl , or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

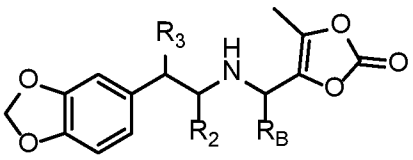
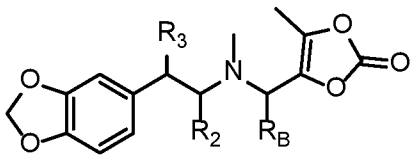
R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl; and

B is  or  , wherein R_B is H or alkyl. In some embodiments, each alkyl is independently a $C_{1\text{-}5}$ alkyl.

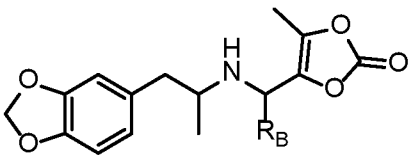
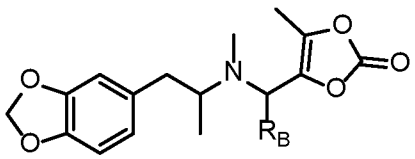
[0008] In some embodiments, the compound of Formula (III) has the following structure:

 ,  ,  , or  .

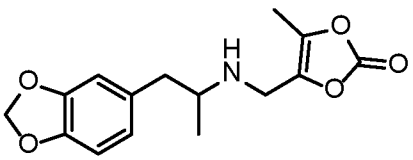
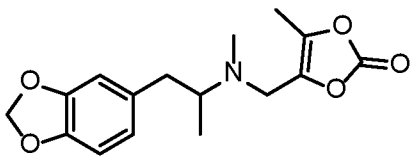
[0009] In some embodiments, the compound of Formula (III) has the following structure:

 or  .

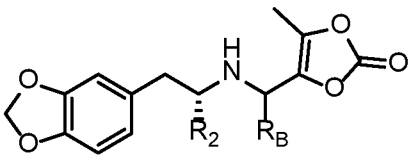
[0010] In some embodiments, the compound of Formula (III) has the following structure:

 or  .

[0011] In some embodiments, the compound of Formula (III) has the following structure:

 or  .

[0012] In some embodiments, the compound of Formula (III) has the following structure: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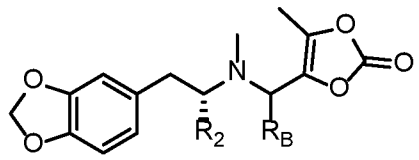
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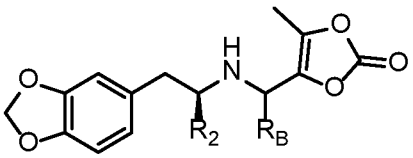
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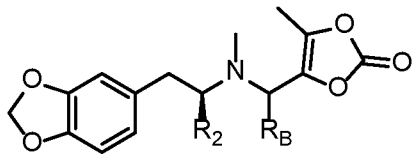
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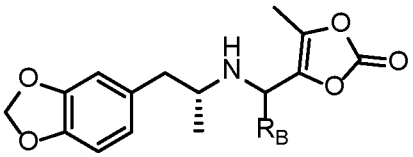
[0013] In some embodiments, the compound of Formula (III) has the following structure: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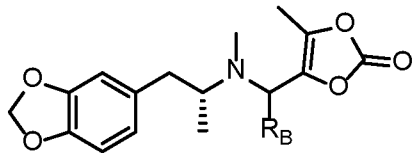
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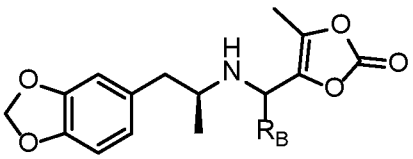
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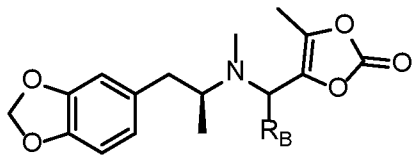
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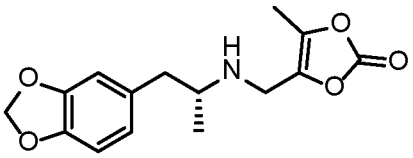
[0014] In some embodiments, the compound of Formula (III) has the following structure: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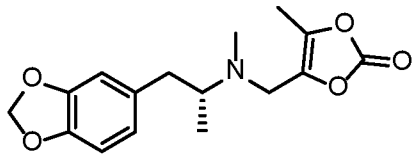
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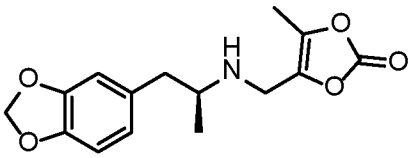
[0015] In some embodiments, the compound of Formula (III) has the following structure: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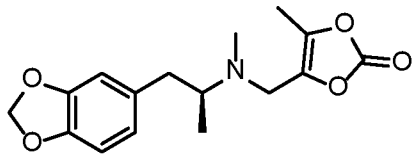
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[0016] In some embodiments, the pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by a Cmax of free amine of about 100 ng/mL to about 500 ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

[0017] In some embodiments, the pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by an $AUC_{(0-24)}$ of free amine of about 1000 h*ng/mL to about 6000 h*ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

[0018] In some embodiments, the pharmaceutical composition of the present disclosure provides an *in vivo* $T_{1/2}$ of free amine of about 5 h to about 15 h, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

[0019] In some embodiments, a pharmaceutical composition is provided that comprises a compound of the present disclosure (e.g., a compound of Formula I, II, or III) and one or more pharmaceutically acceptable excipients.

[0020] In some embodiments, the present disclosure provides a method of treating a neurological disease or condition in a subject in need thereof, the method comprising, administering to the subject a therapeutically effective amount of a compound or pharmaceutical composition disclosed herein.

DEFINITIONS

[0021] While the following terms are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter.

[0022] The term "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.

[0023] "Alkyl" or "alkyl group" refers to a fully saturated, straight or branched hydrocarbon chain 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 C_1-C_{12} alkyl, an alkyl comprising up to 10 carbon atoms is a C_1-C_{10} alkyl, an alkyl comprising up to 6 carbon atoms is a C_1-C_6 alkyl and an alkyl comprising up to 5 carbon atoms is a C_1-C_5 alkyl. A C_1-C_5 alkyl includes C_5 alkyls, C_4 alkyls, C_3 alkyls, C_2 alkyls and C_1 alkyl (*i.e.*, methyl). A C_1-C_6 alkyl includes all moieties described above for C_1-C_5 alkyls but also includes C_6 alkyls. A C_1-C_{10} alkyl includes all moieties described above for C_1-C_5 alkyls and C_1-C_6 alkyls, but also includes C_7, C_8, C_9 and C_{10} alkyls. Similarly, a C_1-C_{12} alkyl includes all the foregoing moieties, but also includes C_{11}

and C_{12} alkyls. Non-limiting examples of C_1-C_{12} 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.

[0024] "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 C_1-C_{12} 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 a radical group (e.g., those described herein) 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.

[0025] "Alkoxy" refers to a group of the formula $-OR_a$ where R_a is an alkyl, alkenyl or alknyl as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group can be optionally substituted.

[0026] "Aryl" refers to a hydrocarbon ring system comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring, and which is attached to the rest of the molecule by a single bond. For purposes of this disclosure, the aryl can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems. Aryls include, but are not limited to, aryls 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 "aryl" can be optionally substituted.

[0027] "Carbocyclyl," "carbocyclic ring" or "carbocycle" refers to a rings structure, wherein the atoms which form the ring are each carbon, and which is attached to the rest of the molecule by a single bond. Carbocyclic rings can comprise from 3 to 20 carbon atoms in the ring. Carbocyclic rings include aryls and cycloalkyl, cycloalkenyl, and cycloalkynyl as defined herein. Unless stated otherwise specifically in the specification, a carbocyclyl group can be optionally substituted.

[0028] "Carbocyclylalkyl" refers to a radical of the formula $-R_b$-R_d where R_b is an alkylene, alkenylene, or alkynylene group as defined above and R_d is a carbocyclyl radical as defined above. Unless stated otherwise specifically in the specification, a carbocyclylalkyl group can be optionally substituted.

[0029] "Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic fully saturated hydrocarbon 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 cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls 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.

[0030] "Heterocyclyl," "heterocyclic ring" or "heterocycle" refers to a stable saturated, unsaturated, or aromatic 3- to 20-membered ring which includes two to nineteen carbon atoms and from one to six heteroatoms including nitrogen, oxygen or sulfur, and which is attached to the rest of the molecule by a single bond. Heterocyclycl or heterocyclic rings include heteroaryls, heterocyclylalkyls, heterocyclylalkenyls, and hetercyclylalkynyls. Unless stated otherwise specifically in the specification, the heterocyclyl 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 can be optionally oxidized; the nitrogen atom can be optionally quaternized; and the heterocyclyl can be partially or fully saturated. Examples of such heterocyclyl include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocyclyl group can be optionally substituted.

[0031] "Heteroaryl" refers to a 5- to 20-membered ring system comprising hydrogen atoms, one to nineteen carbon atoms, one to six heteroatoms including nitrogen, oxygen or sulfur, at least one aromatic ring, and which is attached to the rest of the molecule by a single bond. For purposes of this disclosure, the heteroaryl 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 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 (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group can be optionally substituted.

[0032] "Heterocyclylalkyl" refers to a radical of the formula $-R_b-R_e$ where R_b is an alkylene, alkenylene, or alkynylene group as defined above and R_e is a heterocyclyl radical as defined above. Unless stated otherwise specifically in the specification, a heterocycloalkylalkyl group can be optionally substituted.

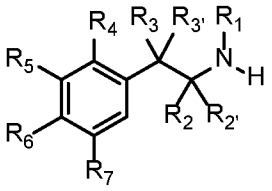
[0033] The term "substituted" used herein means any of the groups described herein (*e.g.*, alkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, carbocyclyl, cycloalkyl, cycloalkenyl, cycloalkynyl, haloalkyl, heterocyclyl, and/or heteroaryl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen 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, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. "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 $-NR_gR_h$, $-NR_gC(=O)R_h$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. "Substituted" also means any of the above groups in which one or more hydrogen atoms are

replaced with $-C(=O)R_g$, $-C(=O)OR_g$, $-C(=O)NR_gR_h$, $-CH_2SO_2R_g$, $-CH_2SO_2NR_gR_h$. 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. "Substituted" further means 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. In addition, each of the foregoing substituents can also be optionally substituted with one or more of the above substituents.

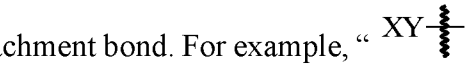
[0034] As used herein, reference to prodrugs of MDMA, MDA, and derivatives thereof includes their (R) and (S) stereoisomers and mixtures thereof, including the racemic mixture. Compounds related to prodrugs of MDMA, as one aspect of the present disclosure, may include compounds which are structurally related to MDMA, but which have modified properties, for example, where the entactogenic effects of MDMA are retained without some of its known adverse effects. Similarly, compounds related to prodrugs, MDA, as one aspect of the present disclosure, may include compounds which are structurally related to MDA, but which have modified properties, for example, where the entactogenic effects of MDA are retained without some of its known adverse effects.

[0035] As used herein, the term "promoiety" refers to a functional group used to modify the structure of a pharmacologically active agent (e.g., MDMA, MDA or derivative thereof) to improve physicochemical, biopharmaceutical or pharmacokinetic properties. The promoiety is generally a covalently bonded group that is chemically and/or enzymatically labile *in vitro* or *in vivo*. In some embodiments, the active agent-promoiety is pharmacologically inactive or significantly less active than the active agent. Upon cleavage of the promoiety, e.g., by an enzymatic and/or chemical transformation, the active agent is released and able to provide the intended pharmacologic response.

[0036] As used herein, the term "free amine" refers to a compound where the promoiety group ("X" is Formula I, "A" in Formula II, and "B" is Formula III) has been cleaved *in vitro* or *in vivo* (e.g., by an enzyme in a metabolic reaction) to release the parent amine compound from a prodrug compound of Formula I, II, or III. Accordingly, the free amine compound provided after release of promoiety X, A, or B from a compound of Formula I, II, or III, respectively, can have the structure:



, wherein R_1, R_2, $R_{2'}$, R_3, $R_{3'}$, R_4, R_5, R_6, and R_7 are as defined herein.

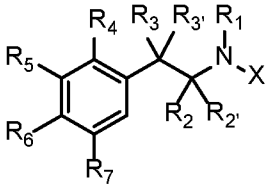
[0037] As used herein, the symbol " " (hereinafter can be referred to as "a point of attachment bond") denotes a bond that is a point of attachment between two chemical entities, one of which is depicted as being attached to the point of attachment bond and the other of which is not depicted as being attached to the point of attachment bond. For example, "  " indicates that the chemical entity "XY" is bonded to another chemical entity via the point of attachment bond. Furthermore, the specific point of attachment to the non-depicted chemical entity can be specified by inference. For example, the compound CH_3-R^3, wherein R^3 is H or " " infers that when R^3 is "XY", the point of attachment bond is the same bond as the bond by which R^3 is depicted as being bonded to CH_3.

DETAILED DESCRIPTION

Compounds of the Disclosure

[0038] The present disclosure provides compounds that are prodrugs of MDMA, MDA, and derivatives thereof, as well as pharmaceutical compositions thereof.

[0039] In some embodiments, the present disclosure provides a compound of Formula (I):



(I),

or a pharmaceutically accept able salt thereof;

wherein:

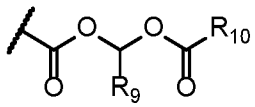
R_1 is H or alkyl;

R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl , or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl;

X is a cleavable promoiety having the structure  , wherein:

R_9 and R_{10} are each independently alkyl or aryl.

[0040] In some embodiments of Formula (I), R_1 is H, alkyl, or cycloalkyl. In some embodiments, R_1 is H, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl. In some embodiments, R_1 is H or C_1-C_6 alkyl. In some embodiments, R_1 is H. In some embodiments, R_1 is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl. In some embodiments, R_1 is methyl, ethyl, or isopropyl. In some embodiments, R_1 is methyl or ethyl. In some embodiments R_1 is methyl. In some embodiments, R_1 is ethyl. In some embodiments, R_1 is isopropyl. In some embodiments, R_1 is cyclopropyl.

[0041] In some embodiments of Formula (I), R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl. In some embodiments, R_2 and $R_{2'}$ are each independently H, halogen, C_1-C_6 alkyl, –OH, or –O–C_1-C_6 alkyl. In some embodiments, R_2 and $R_{2'}$ are each independently H or alkyl. In some embodiments, R_2 and $R_{2'}$ are each independently H or C_1-C_6 alkyl. In some embodiments, the halogen is F. In some embodiments, the alkyl is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl.

[0042] In some embodiments, R_2 and $R_{2'}$ together with the atom to which they are attached form an oxo or a cycloalkyl ring. In some embodiments, R_2 and $R_{2'}$ together with the atom to which they are attached form an oxo. In some embodiments, R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring. In some embodiments, the cycloalkyl ring is a C_{3-6} cycloalkyl ring. In some embodiments, the cycloalkyl ring is a cyclopropyl. In some

embodiments, R_2 is alkyl and $R_{2'}$ is H. In some embodiments, R_2 is alkyl and $R_{2'}$ is absent. In some embodiments, R_2 is H and $R_{2'}$ is alkyl. In some embodiments, R_2 is H and $R_{2'}$ is F. In some embodiments, R_2 is H and $R_{2'}$ is –OH. In some embodiments, R_2 is H and $R_{2'}$ is $–OCH_3$. In some embodiments, R_2 is F and $R_{2'}$ is F. In some embodiments, R_2 is alkyl and $R_{2'}$ is alkyl. In some embodiments, the alkyl is methyl.

[0043] In some embodiments of Formula (I), R_3 and $R_{3'}$ are each independently H, halogen, alkyl, –OH, –O–alkyl or –O–cycloalkyl. In some embodiments, R_3 and $R_{3'}$ are each independently H, halogen, C_1-C_6 alkyl, –OH,–O–C_1-C_6 alkyl, or –O–$C_{3\text{-}6}$ cycloalkyl. In some embodiments, R_3 and $R_{3'}$ are each independently H or alkyl. In some embodiments, R_3 and $R_{3'}$ are each H. In some embodiments, R_3 and $R_{3'}$ are each independently H or C_1-C_6 alkyl. In some embodiments, the halogen is F. In some embodiments, the alkyl is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl.

[0044] In some embodiments, R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo or a cycloalkyl ring. In some embodiments, R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo. In some embodiments, R_3 and $R_{3'}$ together with the atom to which they are attached form a cycloalkyl ring. In some embodiments, the cycloalkyl ring is a $C_{3\text{-}6}$ cycloalkyl ring. In some embodiments, the cycloalkyl ring is a cyclopropyl. In some embodiments, R_3 is H and $R_{3'}$ is alkyl. In some embodiments, R_3 is H and $R_{3'}$ is F. In some embodiments, R_3 is H and $R_{3'}$ is –OH. In some embodiments, R_3 is H and $R_{3'}$ is $–OCH_3$. In some embodiments, R_3 is F and $R_{3'}$ is F. In some embodiments, R_3 is alkyl and $R_{3'}$ is alkyl. In some embodiments, the alkyl is methyl. In some embodiments, R_3 is H and $R_{3'}$ is absent.

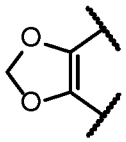
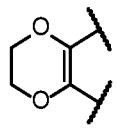
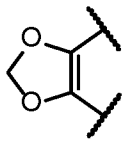
[0045] In some embodiments of Formula (I), R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, alkyl, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–C_1-C_6 alkyl, –O–C_3-C_6 cycloalkyl, alkylene–OR_8, –SH, –S–C_1-C_6 alkyl, –S–C_3-C_6 cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, or alkylene–OR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–C_1-C_6 alkyl, –O–C_3-C_6 cycloalkyl, or alkylene–OR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently H, halogen, alkyl, –OH, –O–alkyl or –O–cycloalkyl. In some

embodiments, R_4, R_5, R_6 and R_7 are each independently H, halogen, C_1-C_6 alkyl, –OH,–O–C_1-C_6 alkyl, or –O–C_{3-6} cycloalkyl. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, or –O–alkyl. In some embodiments, R_4, R_5, R_6 and R_7 are each independently alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently H or –O–alkyl. In some embodiments, R_4, R_5, R_6 and R_7 are each independently H or –O–C_1-C_6 alkyl. In some embodiments, the halogen is F. In some embodiments, the alkyl is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl. In some embodiments, the alkyl is –O–C_1-C_6 alkyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–methyl, –O–ethyl, or –O–isopropyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–methyl or –O–ethyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–methyl. In some embodiments, the –O–C_1-C_6 alkyl is ethyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–isopropyl. In some embodiments, alkylene is a C_{1-6} alkylene. In some embodiments, alkylene is a C_{1-3} alkylene. In some embodiments, alkylene is a methylene or ethylene. In some embodiments, alkylene is methylene.

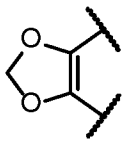
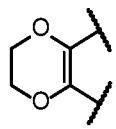
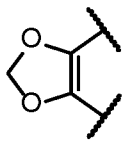
[0046] In some embodiments of Formula (I), R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl. In some embodiments, R_8 is H, alkyl, or alkylenecycloalkyl. In some embodiments, R_8 is H or alkyl. In some embodiments, the alkyl is a C_{1-6} alkyl. In some embodiments, the alkylenecycloalkyl is a C_{1-3}alkylene-C_{3-6}cycloalkyl.

[0047] In some embodiments of Formula (I), at least one of R_4, R_5, R_6 and R_7 is not H. In some embodiments, at least two of R_4, R_5, R_6 and R_7 are not H. In some embodiments, two of R_4, R_5, R_6 and R_7 are not H. In some embodiments, R_5 and R_6 are not H.

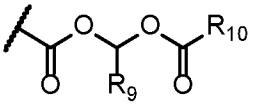
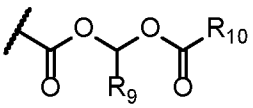
[0048] In some embodiments of Formula (I), R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring. In some embodiments of Formula (I), R_5 and R_6 together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring. In some embodiments of Formula (I), R_5 and R_6 together with the atoms to which they are attached form a 5-membered heterocyclyl ring. In some embodiments of Formula (I), R_5 and R_6 together with the atoms to which they are attached form a 5-membered heterocyclyl ring. In some embodiments, the heterocyclyl ring has one or two oxygen atoms. In some embodiments, the heterocyclyl ring has two oxygen atoms. In some embodiments, the

heterocyclic ring is  or  . In some embodiments, the heterocyclic ring is  .

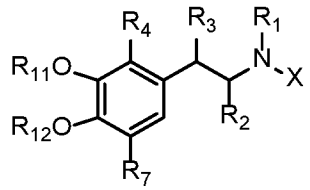
[0049] In some embodiments of Formula (I), R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 are each independently –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 are each independently –OH, –O–alkyl, –O–cycloalkyl, or alkylene–OR_8. In some embodiments, R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 are each independently –OH, –O–C_1-C_6 alkyl, –O–C_3-C_6 cycloalkyl, or alkylene–OR_8. In some embodiments, R_4 and R_7 are each H.

[0050] In some embodiments of Formula (I), R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 together with the atoms to which they are attached form heterocyclyl ring. In some embodiments of Formula (I), R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring. In some embodiments, the heterocyclyl ring has one or two oxygen atoms. In some embodiments, the heterocyclyl ring has two oxygen atoms. In some embodiments, the heterocyclic ring is  or  . In some embodiments, the heterocyclic ring is  . In some embodiments, R_4 and R_7 are each H.

[0051] In some embodiments, X is a cleavable promoiety that is cleaved at a pH of from about 1 to about 5. In some embodiments, X is a cleavable promoiety that is cleaved at a pH of from about 2 to about 4. In some embodiments, X is a cleaved at pH 2. In some embodiments, X is a cleaved at pH 3. In some embodiments, X is a cleaved at pH 4.

[0052] In some embodiments of Formula (I), X is a cleavable promoiety having the structure  , wherein R_9 and R_{10} are each independently alkyl or phenyl. In some embodiments of Formula (I), X is a cleavable promoiety having the structure  , wherein R_9 and R_{10} are each independently alkyl. In some embodiments, the alkyl is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl. In some embodiments, R_9 and R_{10} are each independently methyl or isopropyl. In some embodiments, R_9 and R_{10} are each methyl. In some embodiments, R_9 and R_{10} are each ethyl. In some embodiments, R_9 and R_{10} are each isopropyl.

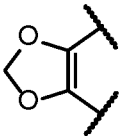
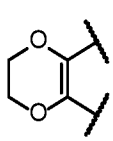
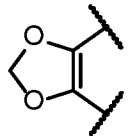
[0053] In some embodiments, the present disclosure provides a compound of Formula (Ia):

 (Ia),

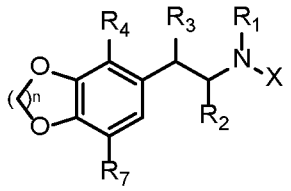
wherein R_1, R_2, R_3, R_4, R_7, and X are as defined above in Formula (I); and

R_{11} and R_{12} are each independently H, alkyl, cycloalkyl, or R_{11} and R_{12} together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring.

[0054] In some embodiments of Formula (Ia), R_{11} and R_{12} are each independently H, alkyl, alkylenecycloalkyl, or cycloalkyl. In some embodiments, R_{11} and R_{12} are each independently H, C_{1-5} alkyl, C_{1-3}alkylene-C_{3-6}cycloalkyl, or C_{3-6} cycloalkyl. In some embodiments, R_{11} and R_{12} are each independently H or C_{1-5} alkyl.

[0055] In some embodiments of Formula (Ia), R_{11} and R_{12} together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring. In some embodiments, R_{11} and R_{12} together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring. In some embodiments, R_{11} and R_{12} together with the atoms to which they are attached form a 5-membered heterocyclyl ring. In some embodiments, the heterocyclic ring is  or  . In some embodiments, the heterocyclic ring is  .

[0056] In some embodiments, the compound of the present disclosure is a compound of Formula (Ib):

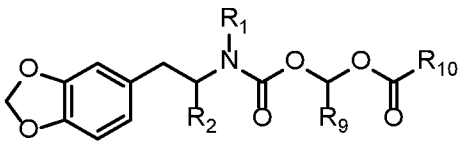


(Ib),

wherein R_1, R_2, R_3, R_4, R_7, and X are as defined above in Formula (I); and n is 1 or 2.

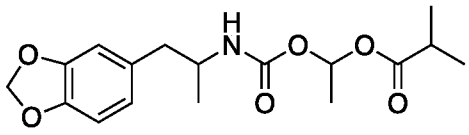
[0057] In some embodiments of Formula (I), n is 1. In some embodiments, n is 2.

[0058] In some embodiments, the compound of the present disclosure is a compound of Formula (Ic):

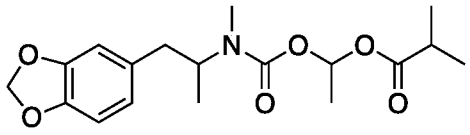


(Ic), wherein R_1, R_2, R_9 and R_{10} are as defined above in Formula (I). In some embodiments, R_1 is H or alkyl; and R_2, R_9, and R_{10} are each independently Me or *i*Pr.

[0059] In some embodiments, the compound of the present disclosure is :

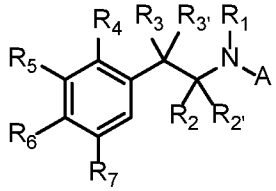


or



.

[0060] In some embodiments, the present disclosure provides a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof;

wherein:

R_1 is H or alkyl;

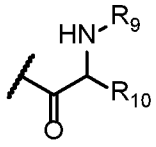
R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl, or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6

together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl; and

A is a cleavable promoiety having the structure  , wherein:

R_9 is H, alkyl or acyl; and

R_{10} is H, aryl, or $–(CH_2)_m–R_{11}$, wherein:

m is an integer from 1-5; and

R_{11} is amino, guanidino, thioalkyl, or aryl.

[0061] In some embodiments of Formula (II), R_1 is H, alkyl, or cycloalkyl. In some embodiments, R_1 is H, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl. In some embodiments, R_1 is H or C_1-C_6 alkyl. In some embodiments, R_1 is H. In some embodiments, R_1 is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl. In some embodiments, R_1 is methyl, ethyl, or isopropyl. In some embodiments, R_1 is methyl or ethyl. In some embodiments R_1 is methyl. In some embodiments, R_1 is ethyl. In some embodiments, R_1 is isopropyl. In some embodiments, R_1 is cyclopropyl.

[0062] In some embodiments of Formula (II), R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl. In some embodiments, R_2 and $R_{2'}$ are each independently H, halogen, C_1-C_6 alkyl, –OH, or –O–C_1-C_6 alkyl. In some embodiments, R_2 and $R_{2'}$ are each independently H or alkyl. In some embodiments, R_2 and $R_{2'}$ are each independently H or C_1-C_6 alkyl. In some embodiments, the halogen is F. In some embodiments, the alkyl is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl.

[0063] In some embodiments, R_2 and $R_{2'}$ together with the atom to which they are attached form an oxo or a cycloalkyl ring. In some embodiments, R_2 and $R_{2'}$ together with the atom to which they are attached form an oxo. In some embodiments, R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring. In some embodiments, the cycloalkyl ring is a C_{3-6} cycloalkyl ring. In some embodiments, the cycloalkyl ring is a cyclopropyl. In some

embodiments, R_2 is alkyl and $R_{2'}$ is H. In some embodiments, R_2 is alkyl and $R_{2'}$ is absent. In some embodiments, R_2 is H and $R_{2'}$ is alkyl. In some embodiments, R_2 is H and $R_{2'}$ is F. In some embodiments, R_2 is H and $R_{2'}$ is –OH. In some embodiments, R_2 is H and $R_{2'}$ is $–OCH_3$. In some embodiments, R_2 is F and $R_{2'}$ is F. In some embodiments, R_2 is alkyl and $R_{2'}$ is alkyl. In some embodiments, the alkyl is methyl.

[0064] In some embodiments of Formula (II), R_3 and $R_{3'}$ are each independently H, halogen, alkyl, –OH, –O–alkyl or –O–cycloalkyl. In some embodiments, R_3 and $R_{3'}$ are each independently H, halogen, C_1-C_6 alkyl, –OH,–O–C_1-C_6 alkyl, or –O–C_{3-6} cycloalkyl. In some embodiments, R_3 and $R_{3'}$ are each independently H or alkyl. In some embodiments, R_3 and $R_{3'}$ are each H. In some embodiments, R_3 and $R_{3'}$ are each independently H or C_1-C_6 alkyl. In some embodiments, the halogen is F. In some embodiments, the alkyl is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl.

[0065] In some embodiments, R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo or a cycloalkyl ring. In some embodiments, R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo. In some embodiments, R_3 and $R_{3'}$ together with the atom to which they are attached form a cycloalkyl ring. In some embodiments, the cycloalkyl ring is a C_{3-6} cycloalkyl ring. In some embodiments, the cycloalkyl ring is a cyclopropyl. In some embodiments, R_3 is H and $R_{3'}$ is alkyl. In some embodiments, R_3 is H and $R_{3'}$ is F. In some embodiments, R_3 is H and $R_{3'}$ is –OH. In some embodiments, R_3 is H and $R_{3'}$ is $–OCH_3$. In some embodiments, R_3 is F and $R_{3'}$ is F. In some embodiments, R_3 is alkyl and $R_{3'}$ is alkyl. In some embodiments, the alkyl is methyl. In some embodiments, R_3 is H and $R_{3'}$ is absent.

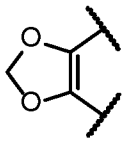
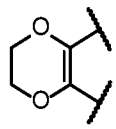
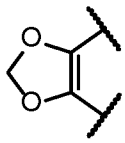
[0066] In some embodiments of Formula (II), R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, alkyl, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–C_1-C_6 alkyl, –O–C_3-C_6 cycloalkyl, alkylene–OR_8, –SH, –S–C_1-C_6 alkyl, –S–C_3-C_6 cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, or alkylene–OR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–C_1-C_6 alkyl, –O–C_3-C_6 cycloalkyl, or alkylene–OR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently H, halogen, alkyl, –OH, –O–alkyl or –O–cycloalkyl. In some

embodiments, R_4, R_5, R_6 and R_7 are each independently H, halogen, C_1-C_6 alkyl, –OH,–O–C_1-C_6 alkyl, or –O–C_{3-6} cycloalkyl. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, or –O–alkyl. In some embodiments, R_4, R_5, R_6 and R_7 are each independently alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently H or –O–alkyl. In some embodiments, R_4, R_5, R_6 and R_7 are each independently H or –O–C_1-C_6 alkyl. In some embodiments, the halogen is F. In some embodiments, the alkyl is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl. In some embodiments, the alkyl is –O–C_1-C_6 alkyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–methyl, –O–ethyl, or –O–isopropyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–methyl or –O–ethyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–methyl. In some embodiments, the –O–C_1-C_6 alkyl is ethyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–isopropyl. In some embodiments, alkylene is a C_{1-6} alkylene. In some embodiments, alkylene is a C_{1-3} alkylene. In some embodiments, alkylene is a methylene or ethylene. In some embodiments, alkylene is methylene.

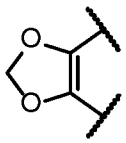
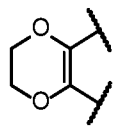
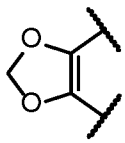
[0067] In some embodiments of Formula (II), R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl. In some embodiments, R_8 is H, alkyl, or alkylenecycloalkyl. In some embodiments, R_8 is H or alkyl. In some embodiments, the alkyl is a C_{1-6} alkyl. In some embodiments, the alkylenecycloalkyl is a C_{1-3}alkylene-C_{3-6}cycloalkyl.

[0068] In some embodiments of Formula (II), at least one of R_4, R_5, R_6 and R_7 is not H. In some embodiments, at least two of R_4, R_5, R_6 and R_7 are not H. In some embodiments, two of R_4, R_5, R_6 and R_7 are not H. In some embodiments, R_5 and R_6 are not H.

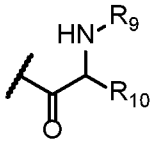
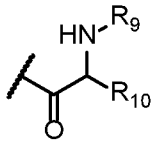
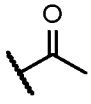
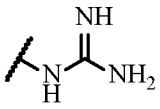
[0069] In some embodiments of Formula (II), R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring. In some embodiments of Formula (II), R_5 and R_6 together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring. In some embodiments of Formula (II), R_5 and R_6 together with the atoms to which they are attached form a 5-membered heterocyclyl ring. In some embodiments of Formula (II), R_5 and R_6 together with the atoms to which they are attached form a 5-membered heterocyclyl ring. In some embodiments, the heterocyclyl ring has one or two oxygen atoms. In some embodiments, the heterocyclyl ring has two oxygen atoms. In some embodiments, the

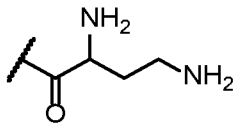
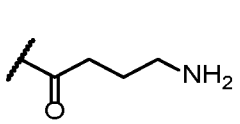
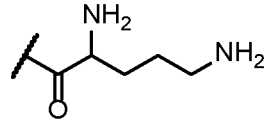
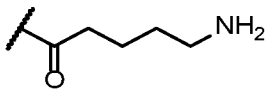
heterocyclic ring is  or  . In some embodiments, the heterocyclic ring is  .

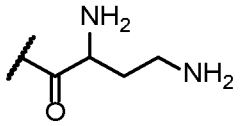
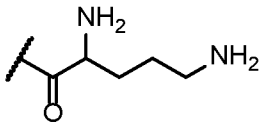
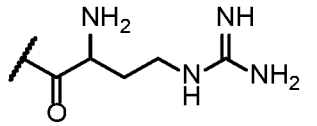
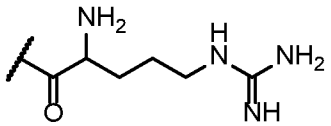
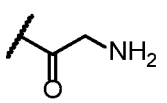
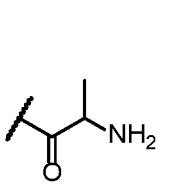
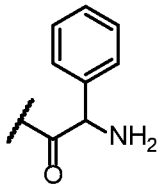
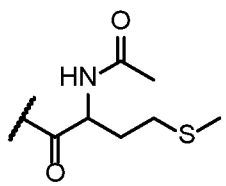
[0070] In some embodiments of Formula (II), R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 are each independently –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 are each independently –OH, –O–alkyl, –O–cycloalkyl, or alkylene–OR_8. In some embodiments, R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 are each independently –OH, –O–C_1-C_6 alkyl, –O–C_3-C_6 cycloalkyl, or alkylene–OR_8. In some embodiments, R_4 and R_7 are each H.

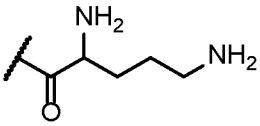
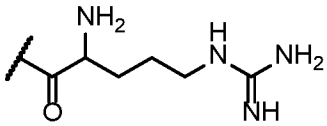
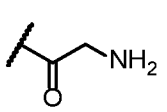
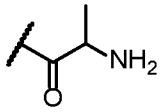
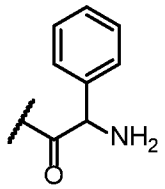
[0071] In some embodiments of Formula (II), R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 together with the atoms to which they are attached form heterocyclyl ring. In some embodiments of Formula (II), R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring. In some embodiments, the heterocyclyl ring has one or two oxygen atoms. In some embodiments, the heterocyclyl ring has two oxygen atoms. In some embodiments, the heterocyclic ring is  or  . In some embodiments, the heterocyclic ring is  . In some embodiments, R_4 and R_7 are each H.

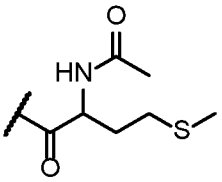
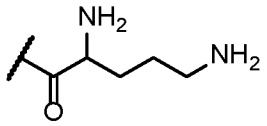
[0072] In some embodiments, A is a cleavable promoiety that is cleaved at a pH of from about 7 to about 11. In some embodiments, A is a cleavable promoiety that is cleaved at a pH of from about 8 to about 10. In some embodiments, A is a cleavable promoiety that is cleaved at a pH of from about 8 to about 9. In some embodiments, A is a cleaved at pH 8. In some embodiments, A is a cleaved at pH 9.

[0073] In some embodiments of Formula (II), A is a cleavable promoiety having the structure  , wherein R_9 is H or acyl and R_{10} is as defined herein. In some embodiments of Formula (II), A is a cleavable promoiety having the structure  , wherein R_9 is H or  and R_{10} is as defined herein. In some embodiments, R_{10} is H, Ph or $-(CH_2)_m-R_{11}$, wherein R_{11} is $-NH_2$,  or $-SCH_3$ and m is an integer from 1-5. In some embodiments, m is an integer from 2-4.

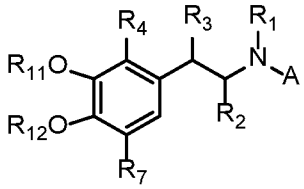
[0074] In some embodiments, the promoiety A is a group capable of internal release. A specific example of an internally released protecting group utilizes ornithine. The prodrug in such a case can be stabilized to prevent cyclization and release by dosing a salt of the amine or by utilizing a slow release of a secondary protecting group such as a carbamate. Accordingly, in some embodiments, a promoiety A capable of internal release is:  ,  ,  ,  , or a pharmaceutically acceptable salt or carbamate thereof.

[0075] In some embodiments of Formula (II), promoiety A is :  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, promoiety A is :






, or


. In some embodiments, promoiety A is  .

[0076] In some embodiments, the present disclosure provides a compound of Formula (IIa):

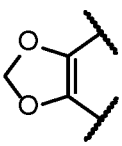
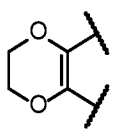
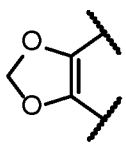

(IIa),

wherein R_1, R_2, R_3, R_4, R_7, and A are as defined above in Formula (II); and

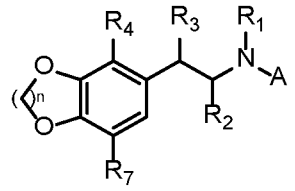
R_{11} and R_{12} are each independently H, alkyl, cycloalkyl, or R_{11} and R_{12} together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring.

[0077] In some embodiments of Formula (IIa), R_{11} and R_{12} are each independently H, alkyl, alkylenecycloalkyl, or cycloalkyl. In some embodiments, R_{11} and R_{12} are each independently H, C_{1-5} alkyl, C_{1-3}alkylene-C_{3-6}cycloalkyl, or C_{3-6} cycloalkyl. In some embodiments, R_{11} and R_{12} are each independently H or C_{1-5} alkyl.

[0078] In some embodiments of Formula (IIa), R_{11} and R_{12} together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring. In some embodiments, R_{11} and R_{12} together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring. In some embodiments, R_{11} and R_{12} together with the atoms to which they are attached form a 5-membered heterocyclyl ring. In some embodiments, the heterocyclic ring is


or  . In some embodiments, the heterocyclic ring is  .

[0079] In some embodiments, the compound of the present disclosure is a compound of Formula (IIb):

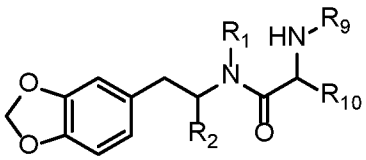


(IIb),

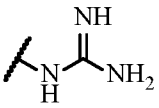
wherein R_1, R_2, R_3, R_4, R_7, and A are as defined above in Formula (II); and n is 1 or 2.

[0080] In some embodiments of Formula (II), n is 1. In some embodiments, n is 2.

[0081] In some embodiments, the compound of the present disclosure is a compound of Formula (IIc):

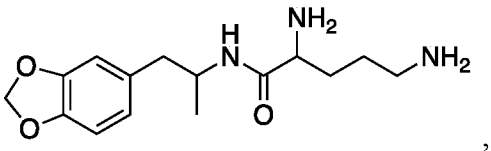


(IIc), wherein R_1, R_2, R_9 and R_{10} are as defined above in Formula (II). In some embodiments, R_1 is H or alkyl (e.g., Me, Et or *i*Pr); R_2 is alkyl (e.g., Me, Et, or *i*Pr); R_9 is H or -C(O)CH_3; and R_{10} is H, Ph or –$(CH_2)_m$–R_{11}, wherein R_{11} is –NH_2,

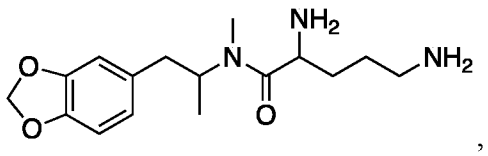


or –SCH_3 and m is an integer from 2-4.

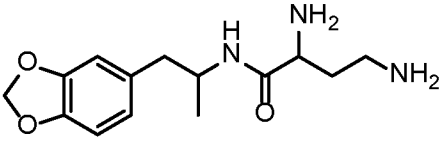
[0082] In some embodiments, the compound of the present disclosure is :



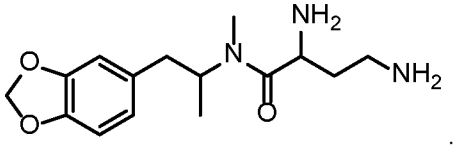
,



,

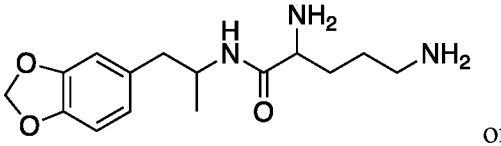


, or

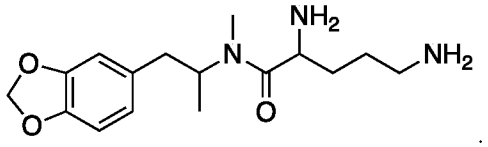


.

[0083] In some embodiments, the compound of the present disclosure is :

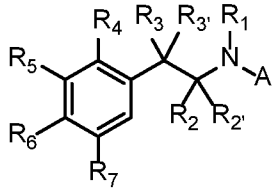


or



.

[0084] In some embodiments, the present disclosure provides a compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof;

wherein:

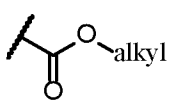
R_1 is H or alkyl;

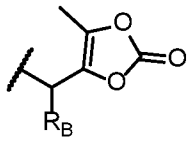
R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl, or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl; and

B is 

or 

, wherein R_B is H or alkyl.

[0085] In some embodiments of Formula (III), R_1 is H, alkyl, or cycloalkyl. In some embodiments, R_1 is H, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl. In some embodiments, R_1 is H or C_1-C_6 alkyl. In some embodiments, R_1 is H. In some embodiments, R_1 is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl. In some embodiments, R_1 is methyl, ethyl, or isopropyl. In some embodiments, R_1 is methyl or ethyl. In some embodiments R_1 is methyl. In some embodiments, R_1 is ethyl. In some embodiments, R_1 is isopropyl. In some embodiments, R_1 is cyclopropyl.

[0086] In some embodiments of Formula (III), R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl. In some embodiments, R_2 and $R_{2'}$ are each independently H, halogen, C_1-C_6 alkyl, –OH, or –O–C_1-C_6 alkyl. In some embodiments, R_2 and $R_{2'}$ are each independently H or alkyl. In some embodiments, R_2 and $R_{2'}$ are each independently H or C_1-C_6 alkyl. In some embodiments, the halogen is F. In some embodiments, the alkyl is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl.

[0087] In some embodiments, R_2 and $R_{2'}$ together with the atom to which they are attached form an oxo or a cycloalkyl ring. In some embodiments, R_2 and $R_{2'}$ together with the atom to which they are attached form an oxo. In some embodiments, R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring. In some embodiments, the cycloalkyl ring is a $C_{3\text{-}6}$ cycloalkyl ring. In some embodiments, the cycloalkyl ring is a cyclopropyl. In some embodiments, R_2 is alkyl and $R_{2'}$ is H. In some embodiments, R_2 is alkyl and $R_{2'}$ is absent. In some embodiments, R_2 is H and $R_{2'}$ is alkyl. In some embodiments, R_2 is H and $R_{2'}$ is F. In some embodiments, R_2 is H and $R_{2'}$ is –OH. In some embodiments, R_2 is H and $R_{2'}$ is $–OCH_3$. In some embodiments, R_2 is F and $R_{2'}$ is F. In some embodiments, R_2 is alkyl and $R_{2'}$ is alkyl. In some embodiments, the alkyl is methyl.

[0088] In some embodiments of Formula (III), R_3 and $R_{3'}$ are each independently H, halogen, alkyl, –OH, –O–alkyl or –O–cycloalkyl. In some embodiments, R_3 and $R_{3'}$ are each independently H, halogen, C_1-C_6 alkyl, –OH,–O–C_1-C_6 alkyl, or –O–$C_{3\text{-}6}$ cycloalkyl. In some embodiments, R_3 and $R_{3'}$ are each independently H or alkyl. In some embodiments, R_3 and $R_{3'}$ are each H. In some embodiments, R_3 and $R_{3'}$ are each independently H or C_1-C_6 alkyl. In some embodiments, the halogen is F. In some embodiments, the alkyl is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is selected from the group consisting of methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl.

[0089] In some embodiments, R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo or a cycloalkyl ring. In some embodiments, R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo. In some embodiments, R_3 and $R_{3'}$ together with the atom to which they are attached form a cycloalkyl ring. In some embodiments, the cycloalkyl ring is a $C_{3\text{-}6}$ cycloalkyl ring. In some embodiments, the cycloalkyl ring is a cyclopropyl. In some embodiments, R_3 is H and $R_{3'}$ is alkyl. In some embodiments, R_3 is H and $R_{3'}$ is F. In some embodiments, R_3 is H and $R_{3'}$ is –OH. In some embodiments, R_3 is H and $R_{3'}$ is $–OCH_3$. In some embodiments, R_3 is F and $R_{3'}$ is F. In some embodiments, R_3 is alkyl and $R_{3'}$ is alkyl. In some embodiments, the alkyl is methyl. In some embodiments, R_3 is H and $R_{3'}$ is absent.

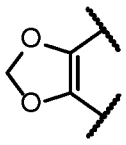
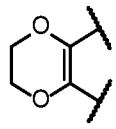
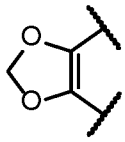
[0090] In some embodiments of Formula (III), R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, alkyl, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently

hydrogen, halogen, –OH, –O–C_1-C_6 alkyl, –O–C_3-C_6 cycloalkyl, alkylene–OR_8, –SH, –S–C_1-C_6 alkyl, –S–C_3-C_6 cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, or alkylene–OR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–C_1-C_6 alkyl, –O–C_3-C_6 cycloalkyl, or alkylene–OR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently H, halogen, alkyl, –OH, –O–alkyl or –O–cycloalkyl. In some embodiments, R_4, R_5, R_6 and R_7 are each independently H, halogen, C_1-C_6 alkyl, –OH,–O–C_1-C_6 alkyl, or –O–C_{3-6} cycloalkyl. In some embodiments, R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, or –O–alkyl. In some embodiments, R_4, R_5, R_6 and R_7 are each independently alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4, R_5, R_6 and R_7 are each independently H or –O–alkyl. In some embodiments, R_4, R_5, R_6 and R_7 are each independently H or –O–C_1-C_6 alkyl. In some embodiments, the halogen is F. In some embodiments, the alkyl is C_1-C_6 alkyl. In some embodiments, the C_1-C_6 alkyl is selected from the group consisting of methyl, ethyl, or isopropyl. In some embodiments, the C_1-C_6 alkyl is methyl or ethyl. In some embodiments, the C_1-C_6 alkyl is methyl. In some embodiments, the C_1-C_6 alkyl is ethyl. In some embodiments, the C_1-C_6 alkyl is isopropyl. In some embodiments, the alkyl is –O–C_1-C_6 alkyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–methyl, –O–ethyl, or –O–isopropyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–methyl or –O–ethyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–methyl. In some embodiments, the –O–C_1-C_6 alkyl is ethyl. In some embodiments, the –O–C_1-C_6 alkyl is –O–isopropyl. In some embodiments, alkylene is a C_{1-6} alkylene. In some embodiments, alkylene is a C_{1-3} alkylene. In some embodiments, alkylene is a methylene or ethylene. In some embodiments, alkylene is methylene.

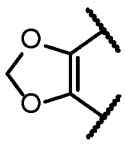
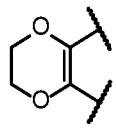
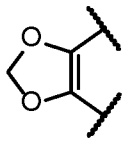
[0091] In some embodiments of Formula (III), R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl. In some embodiments, R_8 is H, alkyl, or alkylenecycloalkyl. In some embodiments, R_8 is H or alkyl. In some embodiments, the alkyl is a C_{1-6} alkyl. In some embodiments, the alkylenecycloalkyl is a C_{1-3}alkylene-C_{3-6}cycloalkyl.

[0092] In some embodiments of Formula (III), at least one of R_4, R_5, R_6 and R_7 is not H. In some embodiments, at least two of R_4, R_5, R_6 and R_7 are not H. In some embodiments, two of R_4, R_5, R_6 and R_7 are not H. In some embodiments, R_5 and R_6 are not H.

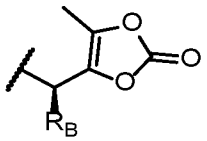
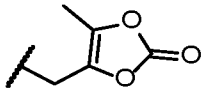
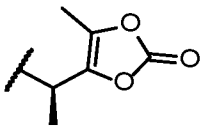
[0093] In some embodiments of Formula (III), R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring. In some embodiments of Formula (III), R_5 and R_6 together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring. In some embodiments of Formula (III), R_5 and R_6 together with the atoms

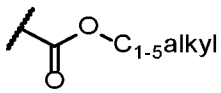
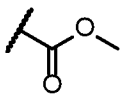
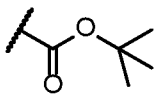
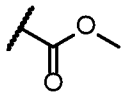
to which they are attached form a 5-membered heterocyclyl ring. In some embodiments of Formula (III), R_5 and R_6 together with the atoms to which they are attached form a 5-membered heterocyclyl ring. In some embodiments, the heterocyclyl ring has one or two oxygen atoms. In some embodiments, the heterocyclyl ring has two oxygen atoms. In some embodiments, the heterocyclic ring is  or  . In some embodiments, the heterocyclic ring is  .

[0094] In some embodiments of Formula (III), R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 are each independently –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8. In some embodiments, R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 are each independently –OH, –O–alkyl, –O–cycloalkyl, or alkylene–OR_8. In some embodiments, R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 are each independently –OH, –O–C_1-C_6 alkyl, –O–C_3-C_6 cycloalkyl, or alkylene–OR_8. In some embodiments, R_4 and R_7 are each H.

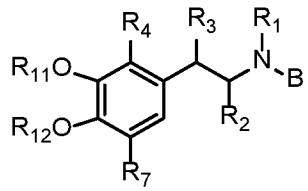
[0095] In some embodiments of Formula (III), R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 together with the atoms to which they are attached form heterocyclyl ring. In some embodiments of Formula (III), R_4 and R_7 are each independently H, halogen (e.g., F, Cl, or Br), or alkyl (e.g., methyl or ethyl) and R_5 and R_6 together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring. In some embodiments, the heterocyclyl ring has one or two oxygen atoms. In some embodiments, the heterocyclyl ring has two oxygen atoms. In some embodiments, the heterocyclic ring is  or  . In some embodiments, the heterocyclic ring is  . In some embodiments, R_4 and R_7 are each H.

[0096] In some embodiments, B is a cleavable promoiety that is cleaved at a pH of from about 7 to about 11. In some embodiments, B is a cleavable promoiety that is cleaved at a pH of from about 8 to about 10. In some embodiments, B is a cleavable promoiety that is cleaved at a pH of from about 8 to about 9. In some embodiments, B is a cleaved at pH 8. In some embodiments, A is a cleaved at pH 9.

[0097] In some embodiments of Formula (III), B is a cleavable promoiety having the structure  . In some embodiments of Formula (III), B is a cleavable promoiety having the structure  . In some embodiments of Formula (III), B is a cleavable promoiety having the structure  .

[0098] In some embodiments of Formula (III), B is a cleavable promoiety having the structure  . In some embodiments, B is a cleavable promoiety having the structure  or  . In some embodiments, B is a cleavable promoiety having the structure  .

[0099] In some embodiments, the present disclosure provides a compound of Formula (IIIa):

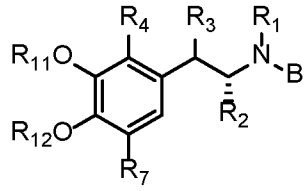


(IIIa),

wherein R_1, R_2, R_3, R_4, R_7, and B are as defined above in Formula (III); and

R_{11} and R_{12} are each independently H, alkyl, cycloalkyl, or R_{11} and R_{12} together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring.

[0100] In some embodiments, the present disclosure provides a compound of Formula (IIIa1):

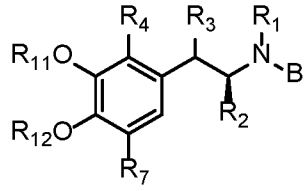


(IIIa1),

wherein R_1, R_2, R_3, R_4, R_7, and B are as defined above in Formula (III); and

R_{11} and R_{12} are each independently H, alkyl, cycloalkyl, or R_{11} and R_{12} together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring.

[0101] In some embodiments, the present disclosure provides a compound of Formula (IIIa2):



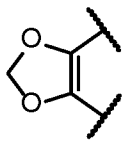
(IIIa2),

wherein R_1, R_2, R_3, R_4, R_7, and B are as defined above in Formula (III); and

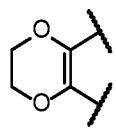
R_{11} and R_{12} are each independently H, alkyl, cycloalkyl, or R_{11} and R_{12} together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring.

[0102] In some embodiments of Formula (IIIa), R_{11} and R_{12} are each independently H, alkyl, alkylenecycloalkyl, or cycloalkyl. In some embodiments, R_{11} and R_{12} are each independently H, C_{1-5} alkyl, C_{1-3}alkylene-C_{3-6}cycloalkyl, or C_{3-6} cycloalkyl. In some embodiments, R_{11} and R_{12} are each independently H or C_{1-5} alkyl.

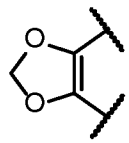
[0103] In some embodiments of Formula (IIIa), R_{11} and R_{12} together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring. In some embodiments, R_{11} and R_{12} together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring. In some embodiments, R_{11} and R_{12} together with the atoms to which they are attached form a 5-membered heterocyclyl ring. In some embodiments, the heterocyclic ring is



or

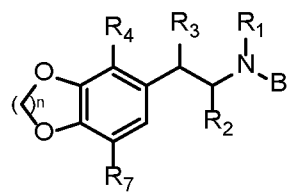


. In some embodiments, the heterocyclic ring is



.

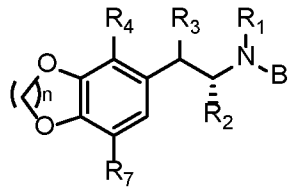
[0104] In some embodiments, the compound of the present disclosure is a compound of Formula (IIIb):



(IIIb),

wherein R_1, R_2, R_3, R_4, R_7, and B are as defined above in Formula (III); and n is 1 or 2.

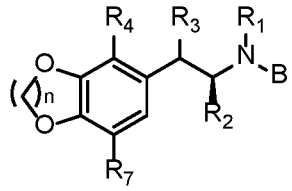
[0105] In some embodiments, the compound of the present disclosure is a compound of Formula (IIIb1):



(IIIb1),

wherein R_1, R_2, R_3, R_4, R_7, and B are as defined above in Formula (III); and n is 1 or 2.

[0106] In some embodiments, the compound of the present disclosure is a compound of Formula (IIIb2):

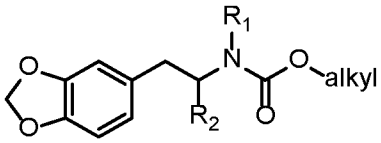


(IIIb2),

wherein R_1, R_2, R_3, R_4, R_7, and B are as defined above in Formula (III); and n is 1 or 2.

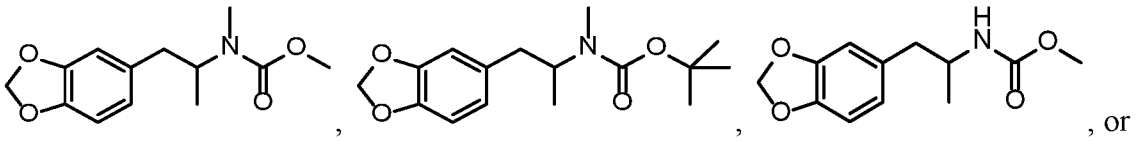
[0107] In some embodiments of Formula (III), n is 1. In some embodiments, n is 2.

[0108] In some embodiments, the compound of the present disclosure is a compound of Formula (IIIc):

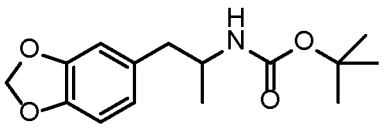


(IIIc), wherein R_1 and R_2 are as defined above in Formula (III). In some embodiments, R_1 is H or alkyl (e.g., Me or *i*Pr); and R_2 is alkyl (e.g., Me or *i*Pr). In some embodiments, R_1 is H or Me; and R_2 is Me or *i*Pr.

[0109] In some embodiments, the compound of the present disclosure is :

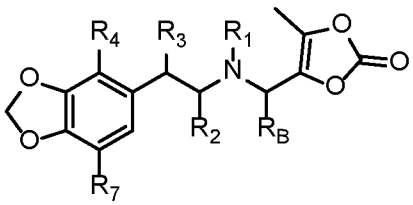


, or



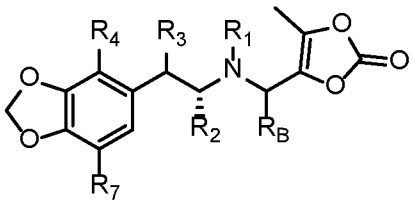
.

[0110] In some embodiments, the compound of the present disclosure is a compound of Formula (IIId):



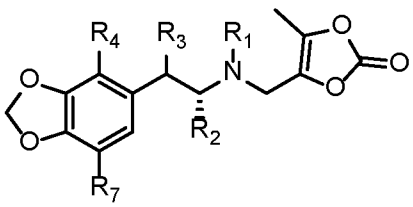
(IIId), wherein R_1, R_2, R_3, R_4, and R_7 are as defined above in Formula (III); and R_B is H or alkyl. In some embodiments, R_1 is H or alkyl (e.g., Me or *i*Pr); and R_2 is alkyl (e.g., Me or *i*Pr). In some embodiments, R_1 is H or Me; and R_2 is Me or *i*Pr.

[0111] In some embodiments, the compound of the present disclosure is a compound of Formula (IIId1):



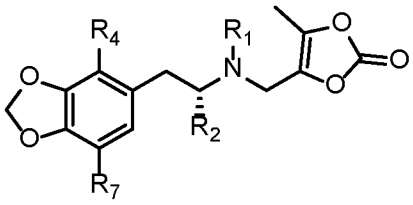
(IIId1), wherein R_1, R_2, R_3, R_4, and R_7 are as defined above in Formula (III); and R_B is H or alkyl. In some embodiments, R_1 is H or alkyl (e.g., Me or *i*Pr); and R_2 is alkyl (e.g., Me or *i*Pr). In some embodiments, R_1 is H or Me; and R_2 is Me or *i*Pr.

[0112] In some embodiments, the compound of the present disclosure is a compound of Formula (IIId1a):



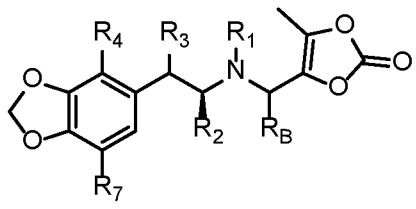
(IIId1a), wherein R_1, R_2, R_3, R_4, and R_7 are as defined above in Formula (III). In some embodiments, R_1 is H or alkyl (e.g., Me or *i*Pr); and R_2 is alkyl (e.g., Me or *i*Pr). In some embodiments, R_1 is H or Me; and R_2 is Me or *i*Pr.

[0113] In some embodiments, the compound of the present disclosure is a compound of Formula (IIId1b):



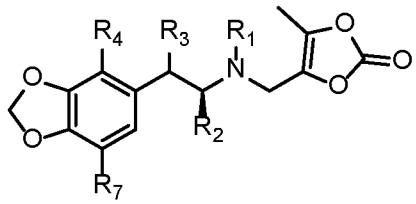
(IIId1b), wherein R_1, R_2, R_4, and R_7 are as defined above in Formula (III). In some embodiments, R_1 is H or alkyl (e.g., Me or *i*Pr); and R_2 is alkyl (e.g., Me or *i*Pr). In some embodiments, R_1 is H or Me; and R_2 is Me or *i*Pr.

[0114] In some embodiments, the compound of the present disclosure is a compound of Formula (IIId2):



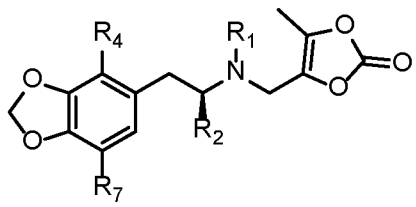
(IIId2), wherein R_1, R_2, R_3, R_4, and R_7 are as defined above in Formula (III); and R_B is H or alkyl. In some embodiments, R_1 is H or alkyl (e.g., Me or *i*Pr); and R_2 is alkyl (e.g., Me or *i*Pr). In some embodiments, R_1 is H or Me; and R_2 is Me or *i*Pr.

[0115] In some embodiments, the compound of the present disclosure is a compound of Formula (IIId2a):



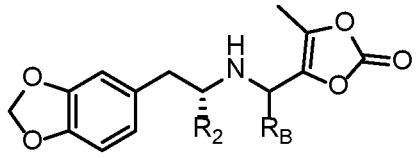
(IIId2a), wherein R_1, R_2, R_3, R_4, and R_7 are as defined above in Formula (III). In some embodiments, R_1 is H or alkyl (e.g., Me or *i*Pr); and R_2 is alkyl (e.g., Me or *i*Pr). In some embodiments, R_1 is H or Me; and R_2 is Me or *i*Pr.

[0116] In some embodiments, the compound of the present disclosure is a compound of Formula (IIId2b):

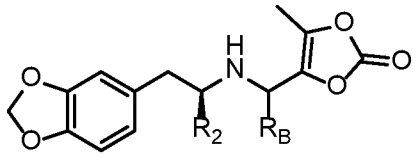


(IIId2b), wherein R_1, R_2, R_4, and R_7 are as defined above in Formula (III). In some embodiments, R_1 is H or alkyl (e.g., Me or *i*Pr); and R_2 is alkyl (e.g., Me or *i*Pr). In some embodiments, R_1 is H or Me; and R_2 is Me or *i*Pr.

[0117] In some embodiments, the compound of Formula (III) is:

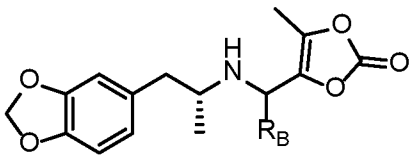
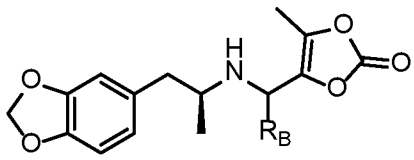


or

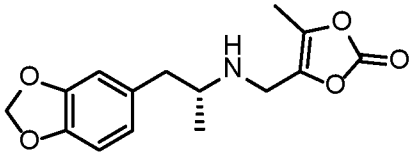


, wherein R_2 is as defined above in Formula (III); and R_B is H or alkyl.

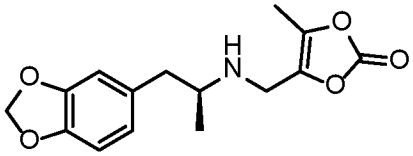
[0118] In some embodiments, the compound of Formula (III) is:

 or  , wherein R_B is H or alkyl.

[0119] In some embodiments, the compound of Formula (III) is:

 .

[0120] In some embodiments, the compound of Formula (III) is:

 .

[0121] In some embodiments, R_B is H or $C_{1\text{-}5}$alkyl. In some embodiments, R_B is H or Me. In some embodiments, R_B is H. In some embodiments, R_B is methyl.

[0122] It is contemplated that each of the therapeutic agents may be administered *per se* as well as in various forms including pharmaceutically acceptable esters, prodrugs, salts, solvates, enantiomers, stereoisomers, active metabolites, co-crystals, and other physiologically functional derivatives thereof. In some embodiments, the prodrugs disclosed herein comprise a mixture of enantiomers, including a racemic mixture thereof. In some embodiments, the prodrugs disclosed herein are enantiomerically pure. In some embodiments, the enantiomeric excess is from 0% (racemic) to 100% (enantiomerically pure), e.g., 0%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100%, including all ranges and values therebetween. In some embodiments, the enantiomeric excess is greater than 90%. In some embodiments, the enantiomeric excess is greater than 95%. In some embodiments, the enantiomeric excess is greater than 90%. In some embodiments, the enantiomeric excess is greater than 99%.

Pharmaceutical Compositions of the Present Disclosure

[0123] In various embodiments, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (II), Formula (IIa), Formula (IIb), Formula (IIc), Formula (III), Formula (IIIa), Formula (IIIb), Formula (IIIc), or Formula (IIId)) or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0124] In some embodiments, the pharmaceutically acceptable salt is a salt of 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, ascorbic acid (L), aspartic acid (L), benzenesulfonic acid, benzoic acid, camphoric acid (+), camphor-10-sulfonic acid (+), capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid (D), gluconic acid (D), glucuronic acid (D), glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid (DL), lactobionic acid, lauric acid, maleic acid, malic acid, (- L) malonic acid, mandelic acid (DL), methanesulfonic acid, naphthalene-1,5-disulfonic acid,naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, propionic acid, pyroglutamic acid (- L),salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid (+ L), thiocyanic acid, toluenesulfonic acid (*p*), and undecylenic acid.

[0125] The pharmaceutically acceptable excipients and adjuvants are added to the composition or formulation for a variety of purposes. In some embodiments, a pharmaceutical composition comprising one or more compounds disclosed herein, or a pharmaceutically acceptable salt thereof, further comprises a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutically acceptable carrier includes a pharmaceutically acceptable excipient, binder, and/or diluent. In some embodiments, suitable pharmaceutically acceptable carriers include, but are not limited to, inert solid fillers or diluents and sterile aqueous or organic solutions. In some embodiments, suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, and the like. General considerations in the formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy,* 21th Edition (Lippincott Williams & Wilkins, 2005).

[0126] For the purposes of this disclosure, the compounds disclosed herein can be formulated for administration by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used here includes subcutaneous, intravenous,

intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters.

Pharmacokinetics

[0127] The administration of pharmaceutical compositions comprising prodrugs of MDMA, MDA, and/or derivatives thereof disclosed herein can result in a measurable modification of the pharmacokinetic profile (e.g., circulating drug concentration) of free MDMA, MDA and/or derivative thereof relative to the administration of each as a free amine drug.

Formula (I)

[0128] Accordingly, in some embodiments of Formula (I), a pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by a Cmax of free amine of about 100 ng/mL to about 500 ng/mL, e.g., 100 ng/mL to about 500 ng/mL, about 100 ng/mL to about 450 ng/mL, 100 ng/mL to about 400 ng/mL, 100 ng/mL to about 350 ng/mL, 100 ng/mL to about 300 ng/mL or 100 ng/mL to about 250 ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

[0129] In some embodiments of Formula (I), the pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by an $AUC_{(0\text{-}24)}$ of free amine of about 1000 h*ng/mL to about 6000 h*ng/mL, e.g., 1000 h*ng/mL to about 6000 h*ng/mL, 1000 h*ng/mL to about 5500 h*ng/mL, 1000 h*ng/mL to about 5000 h*ng/mL, 1000 h*ng/mL to about 4500 h*ng/mL, 1000 h*ng/mL to about 4000 h*ng/mL, 1000 h*ng/mL to about 3500 h*ng/mL, or 1000 h*ng/mL to about 3000 h*ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

[0130] In some embodiments of Formula (I), the pharmaceutical composition of the present disclosure provides an *in vivo* $T_{1/2}$ of free amine of about 5 h to about 15 h, e.g., about 5 h to about 13 h, about 5 h to about 12 h, about 5 h to about 11 h, about 5 h to about 10 h, about 6 h to about 13 h, about 6 h to about 12 h, about 6 h to about 11 h, or about 6 h to about 10 h, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

[0131] In some embodiments of Formula (I), a pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by a Cmax of free amine that is about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of the Cmax achieved upon administration of a 125 mg dose of MDA to a human subject.

[0132] In some embodiments of Formula (I), when R_1 is H, the composition provides a Cmax of free amine within a range of about 50-90% of about 12 ng/mL to about 15 ng/mL, e.g., about

5.5 ng/mL, about 6 ng/mL, about 6.5 ng/mL, about 7 ng/mL, about 7.5 ng/mL, about 8 ng/mL, about 8.5 ng/mL, about 9 ng/mL, about 9.5 ng/mL, about 10 ng/mL, about 10.5 ng/mL, about 11 ng/mL, about 11.5 ng/mL, about 12 ng/mL, about 12.5 ng/mL, about 13 ng/mL, or about 13.5 ng/mL, achieved following oral administration of about a 125 mg dose of MDA to a human subject.

[0133] In some embodiments of Formula (I), a pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by a Cmax of free amine that is about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of the Cmax achieved upon administration of a 75 mg dose of MDA to a human subject.

[0134] In some embodiments of Formula (I), when R_1 is H, the composition provides a Cmax of free amine within a range of about 50-90% of about 7 ng/mL to about 8.5 ng/mL, e.g., about 3.2 ng/mL, about 3.5 ng/mL, about 3.8 ng/mL, about 4.1 ng/mL, about 4.4 ng/mL, about 4.7 ng/mL, about 5.0 ng/mL, about 5.3 ng/mL, about 5.6 ng/mL, about 5.9 ng/mL, about 6.2 ng/mL, about 6.5 ng/mL, about 6.8 ng/mL, about 7.1 ng/mL, about 7.4 ng/mL, or about 7.7 ng/mL, achieved following oral administration of about a 75 mg dose of MDA to a human subject.

[0135] In some embodiments of Formula (I), when R_1 is methyl, the composition provides a Cmax of free amine within a range of about 50-90% of about 220 ng/mL to about 250 ng/mL, e.g., about 100 ng/mL, about 110 ng/mL, about 120 ng/mL, about 130 ng/mL, about 140 ng/mL, about 150 ng/mL, about 160 ng/mL, about 170 ng/mL, about 180 ng/mL, about 190 ng/mL, about 200 ng/mL, about 210 ng/mL, about 220 ng/mL, or about 230 ng/mL, achieved following oral administration of a 125 mg dose of MDMA to a human subject.

[0136] In some embodiments of Formula (I), when R_1 is methyl, the composition provides a Cmax of free amine within a range of about 50-90% of about 120 ng/mL to about 140 ng/mL, e.g., about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 110 ng/mL, about 120 ng/mL, or about 130 ng/mL, achieved following oral administration of a 75 mg dose of MDMA to a human subject.

[0137] In some embodiments of Formula (I), when R_1 is methyl, the composition provides a $T_{1/2}$ of free amine within a range of about 105-150% of about 8 h to about 9 h, e.g., about 8.4 h, about 8.8 h, about 9.2 h, about 9.6 h, about 10 h, about 10.4 h, about 10.8 h, about 11.2 h, about 11.6 h, about 12 h, about 12.4 h, about 12.8 h, about 13.2 h, or about 13.6 h, achieved following oral administration of a 125 mg dose of MDMA to a human subject.

[0138] In some embodiments of Formula (I), when R_1 is methyl, the composition provides a $T_{1/2}$ of free amine within a range of about 105-150% of about 7 h to about 9 h, e.g., about 7.4

h, about 7.6 h, about 8 h, about 8.4 h, about 8.8 h, about 9.2 h, about 9.6 h, about 10 h, about 10.4 h, about 10.8 h, about 11.2 h, about 11.6 h, about 12 h, about 12.4 h, about 12.8 h, about 13.2 h, or about 13.6 h, achieved following oral administration of a 75 mg dose of MDMA to a human subject.

Formula (II)

[0139] In some embodiments of Formula (II), a pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by a Cmax of free amine of about 100 ng/mL to about 500 ng/mL, e.g., 100 ng/mL to about 500 ng/mL, about 100 ng/mL to about 450 ng/mL, 100 ng/mL to about 400 ng/mL, 100 ng/mL to about 350 ng/mL, 100 ng/mL to about 300 ng/mL or 100 ng/mL to about 250 ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (II) and release of promoiety A.

[0140] In some embodiments of Formula (II), the pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by an $AUC_{(0-24)}$ of free amine of about 1000 h*ng/mL to about 6000 h*ng/mL, e.g., 1000 h*ng/mL to about 6000 h*ng/mL, 1000 h*ng/mL to about 5500 h*ng/mL, 1000 h*ng/mL to about 5000 h*ng/mL, 1000 h*ng/mL to about 4500 h*ng/mL, 1000 h*ng/mL to about 4000 h*ng/mL, 1000 h*ng/mL to about 3500 h*ng/mL, or 1000 h*ng/mL to about 3000 h*ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (II) and release of promoiety A.

[0141] In some embodiments of Formula (II), the pharmaceutical composition of the present disclosure provides an *in vivo* $T_{1/2}$ of free amine of about 5 h to about 15 h, e.g., about 5 h to about 13 h, about 5 h to about 12 h, about 5 h to about 11 h, about 5 h to about 10 h, about 6 h to about 13 h, about 6 h to about 12 h, about 6 h to about 11 h, or about 6 h to about 10 h, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (II) and release of promoiety A.

[0142] In some embodiments of Formula (II), a pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by a Cmax of free amine that is about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of the Cmax achieved upon administration of a 75-125 mg dose of MDA to a human subject.

[0143] In some embodiments of Formula (II), when R_1 is H, the composition provides a Cmax of free amine within a range of about 50-90% of about 12 ng/mL to about 15 ng/mL, e.g., about 5.5 ng/mL, about 6 ng/mL, about 6.5 ng/mL, about 7 ng/mL, about 7.5 ng/mL, about 8 ng/mL, about 8.5 ng/mL, about 9 ng/mL, about 9.5 ng/mL, about 10 ng/mL, about 10.5 ng/mL, about 11 ng/mL, about 11.5 ng/mL, about 12 ng/mL, about 12.5 ng/mL, about 13 ng/mL, or about

13.5 ng/mL, achieved following oral administration of about a 125 mg dose of MDA to a human subject.

[0144] In some embodiments of Formula (II), when R_1 is H, the composition provides a Cmax of free amine within a range of about 50-90% of about 7 ng/mL to about 8.5 ng/mL, e.g., about 3.2 ng/mL, about 3.5 ng/mL, about 3.8 ng/mL, about 4.1 ng/mL, about 4.4 ng/mL, about 4.7 ng/mL, about 5.0 ng/mL, about 5.3 ng/mL, about 5.6 ng/mL, about 5.9 ng/mL, about 6.2 ng/mL, about 6.5 ng/mL, about 6.8 ng/mL, about 7.1 ng/mL, about 7.4 ng/mL, or about 7.7 ng/mL, achieved following oral administration of about a 75 mg dose of MDA to a human subject.

[0145] In some embodiments of Formula (II), a pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by a Cmax of free amine that is about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of the Cmax achieved upon administration of a 75-125 mg dose of MDMA to a human subject.

[0146] In some embodiments of Formula (II), when R_1 is methyl, the composition provides a Cmax of free amine within a range of about 50-90% of about 220 ng/mL to about 250 ng/mL, e.g., about 100 ng/mL, about 110 ng/mL, about 120 ng/mL, about 130 ng/mL, about 140 ng/mL, about 150 ng/mL, about 160 ng/mL, about 170 ng/mL, about 180 ng/mL, about 190 ng/mL, about 200 ng/mL, about 210 ng/mL, about 220 ng/mL, or about 230 ng/mL, achieved following oral administration of a 125 mg dose of MDMA to a human subject.

[0147] In some embodiments of Formula (II), when R_1 is methyl, the composition provides a Cmax of free amine within a range of about 50-90% of about 120 ng/mL to about 140 ng/mL, e.g., about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 110 ng/mL, about 120 ng/mL, or about 130 ng/mL, achieved following oral administration of a 75 mg dose of MDMA to a human subject.

[0148] In some embodiments of Formula (II), when R_1 is methyl, the composition provides a $T_{1/2}$ of free amine within a range of about 105-150% of about 8 h to about 9 h, e.g., about 8.4 h, about 8.8 h, about 9.2 h, about 9.6 h, about 10 h, about 10.4 h, about 10.8 h, about 11.2 h, about 11.6 h, about 12 h, about 12.4 h, about 12.8 h, about 13.2 h, or about 13.6 h, achieved following oral administration of a 125 mg dose of MDMA to a human subject.

[0149] In some embodiments of Formula (II), when R_1 is methyl, the composition provides a $T_{1/2}$ of free amine within a range of about 105-150% of about 7 h to about 9 h, e.g., about 7.4 h, about 7.6 h, about 8 h, about 8.4 h, about 8.8 h, about 9.2 h, about 9.6 h, about 10 h, about 10.4 h, about 10.8 h, about 11.2 h, about 11.6 h, about 12 h, about 12.4 h, about 12.8 h, about

13.2 h, or about 13.6 h, achieved following oral administration of a 75 mg dose of MDMA to a human subject.

Formula (III)

[0150] In some embodiments of Formula (III), a pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by a Cmax of free amine of about 100 ng/mL to about 500 ng/mL, e.g., 100 ng/mL to about 500 ng/mL, about 100 ng/mL to about 450 ng/mL, 100 ng/mL to about 400 ng/mL, 100 ng/mL to about 350 ng/mL, 100 ng/mL to about 300 ng/mL or 100 ng/mL to about 250 ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (III) and release of promoiety B.

[0151] In some embodiments of Formula (III), the pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by an $AUC_{(0-24)}$ of free amine of about 1000 h*ng/mL to about 6000 h*ng/mL, e.g., 1000 h*ng/mL to about 6000 h*ng/mL, 1000 h*ng/mL to about 5500 h*ng/mL, 1000 h*ng/mL to about 5000 h*ng/mL, 1000 h*ng/mL to about 4500 h*ng/mL, 1000 h*ng/mL to about 4000 h*ng/mL, 1000 h*ng/mL to about 3500 h*ng/mL, or 1000 h*ng/mL to about 3000 h*ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (III) and release of promoiety B.

[0152] In some embodiments of Formula (III), the pharmaceutical composition of the present disclosure provides an *in vivo* $T_{1/2}$ of free amine of about 5 h to about 15 h, e.g., about 5 h to about 13 h, about 5 h to about 12 h, about 5 h to about 11 h, about 5 h to about 10 h, about 6 h to about 13 h, about 6 h to about 12 h, about 6 h to about 11 h, or about 6 h to about 10 h, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (III) and release of promoiety B.

[0153] In some embodiments of Formula (III), a pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by a Cmax of free amine that is about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of the Cmax achieved upon administration of a 75-125 mg dose of MDA to a human subject.

[0154] In some embodiments of Formula (III), when R_1 is H, the composition provides a Cmax of free amine within a range of about 50-90% of about 12 ng/mL to about 15 ng/mL, e.g., about 5.5 ng/mL, about 6 ng/mL, about 6.5 ng/mL, about 7 ng/mL, about 7.5 ng/mL, about 8 ng/mL, about 8.5 ng/mL, about 9 ng/mL, about 9.5 ng/mL, about 10 ng/mL, about 10.5 ng/mL, about 11 ng/mL, about 11.5 ng/mL, about 12 ng/mL, about 12.5 ng/mL, about 13 ng/mL, or about 13.5 ng/mL, achieved following oral administration of about a 125 mg dose of MDA to a human subject.

[0155] In some embodiments of Formula (III), when R_1 is H, the composition provides a Cmax of free amine within a range of about 50-90% of about 7 ng/mL to about 8.5 ng/mL, e.g., about 3.2 ng/mL, about 3.5 ng/mL, about 3.8 ng/mL, about 4.1 ng/mL, about 4.4 ng/mL, about 4.7 ng/mL, about 5.0 ng/mL, about 5.3 ng/mL, about 5.6 ng/mL, about 5.9 ng/mL, about 6.2 ng/mL, about 6.5 ng/mL, about 6.8 ng/mL, about 7.1 ng/mL, about 7.4 ng/mL, or about 7.7 ng/mL, achieved following oral administration of about a 75 mg dose of MDA to a human subject.

[0156] In some embodiments of Formula (III), a pharmaceutical composition of the present disclosure provides an *in vivo* plasma level characterized by a Cmax of free amine that is about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of the Cmax achieved upon administration of a 75-125 mg dose of MDMA to a human subject.

[0157] In some embodiments of Formula (III), when R_1 is methyl, the composition provides a Cmax of free amine within a range of about 50-90% of about 220 ng/mL to about 250 ng/mL, e.g., about 100 ng/mL, about 110 ng/mL, about 120 ng/mL, about 130 ng/mL, about 140 ng/mL, about 150 ng/mL, about 160 ng/mL, about 170 ng/mL, about 180 ng/mL, about 190 ng/mL, about 200 ng/mL, about 210 ng/mL, about 220 ng/mL, or about 230 ng/mL, achieved following oral administration of a 125 mg dose of MDMA to a human subject.

[0158] In some embodiments of Formula (III), when R_1 is methyl, the composition provides a Cmax of free amine within a range of about 50-90% of about 120 ng/mL to about 140 ng/mL, e.g., about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 110 ng/mL, about 120 ng/mL, or about 130 ng/mL, achieved following oral administration of a 75 mg dose of MDMA to a human subject.

[0159] In some embodiments of Formula (III), when R_1 is methyl, the composition provides a $T_{1/2}$ of free amine within a range of about 105-150% of about 8 h to about 9 h, e.g., about 8.4 h, about 8.8 h, about 9.2 h, about 9.6 h, about 10 h, about 10.4 h, about 10.8 h, about 11.2 h, about 11.6 h, about 12 h, about 12.4 h, about 12.8 h, about 13.2 h, or about 13.6 h, achieved following oral administration of a 125 mg dose of MDMA to a human subject.

[0160] In some embodiments of Formula (III), when R_1 is methyl, the composition provides a $T_{1/2}$ of free amine within a range of about 105-150% of about 7 h to about 9 h, e.g., about 7.4 h, about 7.6 h, about 8 h, about 8.4 h, about 8.8 h, about 9.2 h, about 9.6 h, about 10 h, about 10.4 h, about 10.8 h, about 11.2 h, about 11.6 h, about 12 h, about 12.4 h, about 12.8 h, about 13.2 h, or about 13.6 h, achieved following oral administration of a 75 mg dose of MDMA to a human subject.

Methods of Treatment

[0161] In some embodiments, the present disclosure provides a method of treating or preventing neurological disorders in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, e.g., a compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (II), Formula (IIa), Formula (IIB), Formula (IIc), Formula (III), Formula (IIIa), Formula (IIIb), Formula (IIIc), or Formula (IIId), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0162] In some embodiments, the neurological disorder is a mood disorder. In some embodiments, the mood disorder is clinical depression, postnatal depression or postpartum depression, perinatal depression, atypical depression, melancholic depression, psychotic major depression, cationic depression, seasonal affective disorder, dysthymia, double depression, depressive personality disorder, recurrent brief depression, major depressive disorder, minor depressive disorder, bipolar disorder or manic depressive disorder, depression caused by chronic medical conditions, treatment-resistant depression, refractory depression, suicidality, suicidal ideation, or suicidal behavior. In some embodiments, the method described herein provides therapeutic effect to a subject suffering from depression (e.g., moderate or severe depression). In some embodiments, the mood disorder is associated with neuroendocrine diseases and disorders, neurodegenerative diseases and disorders (e.g., epilepsy), movement disorders, tremor (e.g., Parkinson's Disease), or women's health disorders or conditions. In certain embodiments the mood disorder is depression. In some embodiments, the mood disorder is treatment-resistant depression or major depressive disorder. In some embodiments, the mood disorder is major depressive disorder. In some embodiments, the mood disorder is treatment-resistant depression.

[0163] In some embodiments, the present disclosure provides a method of treating or preventing PTSD, mood disorders, general anxiety disorder, addictive disorders, and/or drug dependence in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, e.g., a compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (II), Formula (IIa), Formula (IIB), Formula (IIc), Formula (III), Formula (IIIa), Formula (IIIb), Formula (IIIc), or Formula (IIId), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0164] In one embodiment, the prodrug of the present disclosure is used to treat PTSD. In one embodiment, the prodrug of the present disclosure is used for induction and maintenance

therapy to treat PTSD. In one embodiment, the prodrug of the present disclosure is used to treat PTSD with an improved safety profile when compared to treatment with the entactogenic, oneirophrenic or psychedelic compound (e.g. MDMA or related compound, psilocybin or dimethyltryptamine) alone. In one embodiment, the prodrug of the present disclosure is used for induction and maintenance therapy to treat PTSD with an improved safety profile when compared to treatment with the entactogenic, oneirophrenic or psychedelic compound (e.g. MDMA or related compound, psilocybin or dimethyltryptamine) alone.

[0165] In one embodiment, the prodrug of the present disclosure is used to treat behavioral or mood disorders. Examples of behavioral or mood disorders include anxiety, such as social anxiety in autistic subjects (e.g. autistic adults) and anxiety related to life-threatening illnesses, stress (where moderation thereof is measured, for example, by effects on amygdala responses). In some embodiments, the anxiety disorder is panic disorder, obsessive-compulsive disorder, or general anxiety disorder. Other examples include lack of motivation, attention, accuracy, speed of response, perseveration, and/or cognitive engagement. Further examples include depression (e.g., MDD or TRD), attention disorders, disorders of executive function and/or cognitive engagement, obsessive compulsive disorder, bipolar disorder, panic disorder, phobia, schizophrenia, psychopathy, antisocial personality disorder and/or neurocognitive disorders.

[0166] In one embodiment, the prodrug of the present disclosure is used to treat an addictive disorder. In some embodiments, the addictive disorder is alcohol abuse, substance abuse, smoking, or obesity. In some embodiments, the disorder is an eating disorder (anorexia nervosa, bulimia, nervosa, binge eating disorder, etc.) or an auditory disorder.

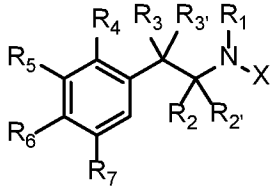
[0167] In some embodiments, the disorder is an impulsive disorder. In some embodiments, the impulsive disorder is attention deficit hyperactivity disorder (ADHD), attention deficit disorder (ADD), Tourette's syndrome or autism.

[0168] In some embodiments, the disorder is a compulsive disorder. In some embodiments, the compulsive disorder is obsessive compulsive disorder (OCD), gambling, or aberrant sexual behavior.

[0169] In some embodiments, the disorder is a personality disorder. In some embodiments, the personality disorder is conduct disorder, antisocial personality, or aggressive behavior.

NUMBERED EMBODIMENTS OF THE DISCLOSURE

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt or enantiomer thereof;

wherein,

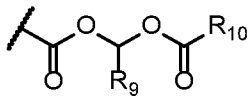
R_1 is H or alkyl;

R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl, or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

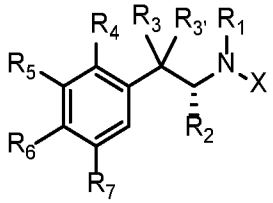
R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl;

X is a cleavable promoiety having the structure 

, wherein:

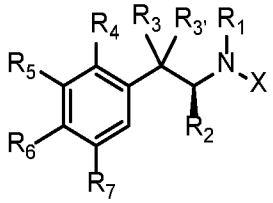
R_9 and R_{10} are each independently alkyl.

1a. The compound of embodiment 1, having the structure:



, or a pharmaceutically acceptable salt thereof.

1b. The compound of embodiment 1, having the structure:



, or a pharmaceutically acceptable salt thereof.

2. The compound of embodiment 1, wherein at least one of R_4, R_5, R_6 and R_7 is not H.

3. The compound of embodiment 1 or 2, wherein R_1 is H or C_1-C_6 alkyl.

4. The compound of embodiment 1 or 2, wherein R_1 is H.

5. The compound of embodiment 1 or 2, wherein R_1 is CH_3.

6. The compound of any one of embodiments 1-5, wherein R_2 and $R_{2'}$ are each independently H, alkyl, or –OH.

7. The compound of any one of embodiments 1-5, wherein R_2 is alkyl and $R_{2'}$ is H.

8. The compound of any one of embodiments 1-5, wherein R_2 and $R_{2'}$ are each alkyl.

9. The compound of any one of embodiments 6-8, wherein the alkyl is methyl or isopropyl.

10. The compound of any one of embodiments 1-9, wherein R_3 and $R_{3'}$ are each independently H, –OH, or –O–alkyl, or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo.

10a. The compound of any one of embodiments 1-9, wherein R_3 and $R_{3'}$ are each H.

11. The compound of any one of embodiments 1-10, wherein R_4 is H.

12. The compound of any one of embodiments 1-11, wherein R_7 is H.

13. The compound of any one of embodiments 1-12, wherein R_5 and R_6 are each independently halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8.

14. The compound of any one of embodiments 1-12, wherein R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring.

15. The compound of any one of embodiments 1-14, wherein R_8 is alkyl.

16. The compound of any one of embodiments 1-15, wherein R_9 is C_{1-5} alkyl.

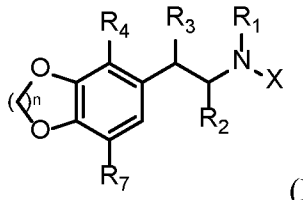
17. The compound of any one of embodiments 1-16, wherein R_9 is methyl or isopropyl.

18. The compound of any one of embodiments 1-17, wherein R_{10} is C_{1-5} alkyl.

19. The compound of embodiment 18 , wherein R_{10} is methyl or isopropyl.

19a. The compound of embodiment 18 , wherein R_{10} is methyl, isopropyl, or *tert*-butyl.

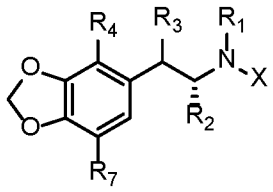
20. The compound of any one of embodiments 1-12 and 14-19a, having the structure of Formula (Ib):



(Ib),

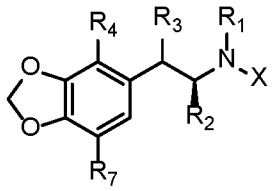
wherein n is 1 or 2.

20a. The compound of embodiment 20, having the structure:



, or a pharmaceutically acceptable salt thereof.

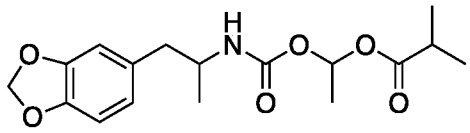
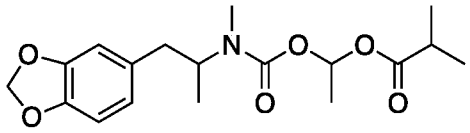
20b. The compound of embodiment 20, having the structure:



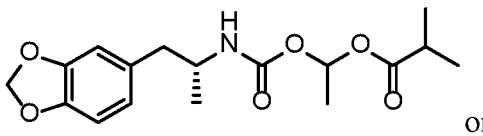
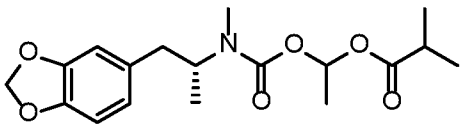
, or a pharmaceutically acceptable salt thereof.

20c. The compound of any one of embodiments 20-20b, wherein R_3 is H.

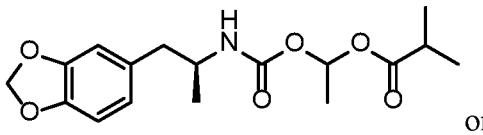
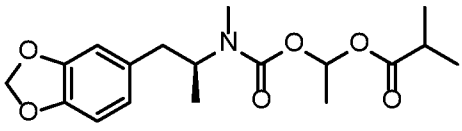
21. The compound of any one of embodiments 1-12 and 14-20, wherein the compound is:

 or  .

21a. The compound of embodiment 21, wherein the compound is:

 or  .

21b. The compound of embodiment 21, wherein the compound is:

 or  .

22. The compound of any one of embodiments 1-21b, wherein X is cleavable at a pH of from about 1 to about 5.

23. The compound of any one of embodiments 1-21b, wherein X is cleavable at a pH of from about 2 to about 4.

24. A pharmaceutical composition comprising the compound of any one of embodiments 1-23 and a pharmaceutically acceptable excipient.

25. The pharmaceutical composition of embodiment 24, capable of providing an *in vivo* plasma level characterized by a Cmax of free amine of about 100 ng/mL to about 500 ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

26. The pharmaceutical composition of embodiment 24 or 25, capable of providing an *in vivo* plasma level characterized by an $AUC_{(0-24)}$ of free amine of about 1000 h*ng/mL to about 6000 h*ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

27. The pharmaceutical composition of any one of embodiments 24-26, capable of providing an *in vivo* $T_{1/2}$ of free amine of about 5 h to about 15 h, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

28. The pharmaceutical composition of embodiment 24, wherein when R_1 is H, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 12 ng/mL to about 15 ng/mL achieved following oral administration of a 125 mg dose of MDA to a human subject.

29. The pharmaceutical composition of embodiment 24, wherein when R_1 is H, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 7 ng/mL to about 8.5 ng/mL achieved following oral administration of a 75 mg dose of MDA to a human subject.

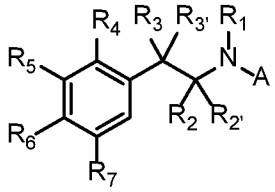
30. The pharmaceutical composition of embodiment 22, wherein when R_1 is methyl, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 220 ng/mL to about 250 ng/mL achieved following oral administration of a 125 mg dose of MDMA to a human subject.

31. The pharmaceutical composition of embodiment 24, wherein R_1 is methyl, the composition is capable of providing a $T_{1/2}$ of free amine within a range of about 105-150% of about 8 h to about 9 h achieved following oral administration of a 125 mg dose of MDMA to a human subject.

32. The pharmaceutical composition of embodiment 24, wherein when R_1 is methyl, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 120 ng/mL to about 140 ng/mL achieved following oral administration of a 75 mg dose of MDMA to a human subject.

33. The pharmaceutical composition of embodiment 24, wherein when R_1 is methyl, the composition is capable of providing a $T_{1/2}$ of free amine within a range of 105-150% of about 7 h to about 9 h achieved following oral administration of a 75 mg dose of MDMA to a human subject.

34. A compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof;

wherein,

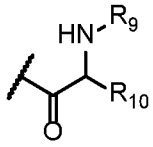
R_1 is H or alkyl;

R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl, or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl; and

A is a cleavable promoiety having the structure  , wherein:

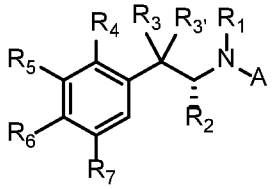
R_9 is H, alkyl or acyl; and

R_{10} is H, aryl, or $–(CH_2)_m–R_{11}$, wherein:

m is an integer from 1-5; and

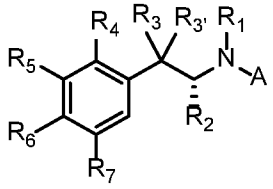
R_{11} is amino, guanidino, thioalkyl, or aryl.

34a. The compound of embodiment 34, having the structure:



, or a pharmaceutically acceptable salt thereof.

34b. The compound of embodiment 34, having the structure:



, or a pharmaceutically acceptable salt thereof.

35. The compound of any one of embodiments 34-34b, wherein at least one of R_4, R_5, R_6 and R_7 is not H.

36. The compound of any one of embodiments 34-35, wherein R_1 is H or C_1-C_6 alkyl.

37. The compound of any one of embodiments 34-35, wherein R_1 is H.

38. The compound of any one of embodiments 34-35, wherein R_1 is CH_3.

39. The compound of any one of embodiments 34-38, wherein R_2 and $R_{2'}$ are each independently H, alkyl, or –OH.

40. The compound of any one of embodiments 34-38, wherein R_2 is alkyl and $R_{2'}$ is H.

41. The compound of any one of embodiments 34-38, wherein R_2 and $R_{2'}$ are each alkyl.

42. The compound of any one of embodiments 39-41, wherein the alkyl is methyl or isopropyl.

43. The compound of any one of embodiments 34-42, wherein R_3 and $R_{3'}$ are each independently H, –OH, or –O–alkyl or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo.

43a. The compound of any one of embodiments 34-42, wherein R_3 and $R_{3'}$ are each H.

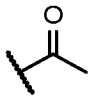
44. The compound of any one of embodiments 34-43, wherein R_4 is H.

45. The compound of any one of embodiments 34-44, wherein R_7 is H.

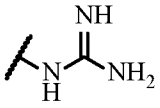
46. The compound of any one of embodiments 34-45, wherein R_5 and R_6 are each independently halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8.

47. The compound of any one of embodiments 34-45, wherein R_5 and R_6 together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring.

48. The compound of any one of embodiments 34-47, wherein R_8 is alkyl.

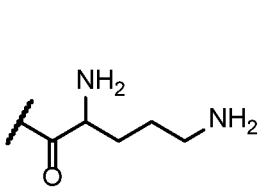
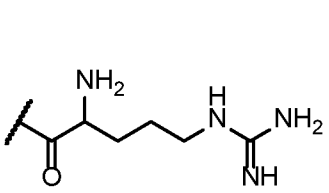
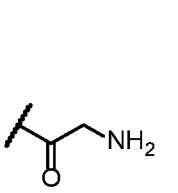
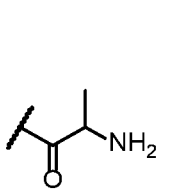
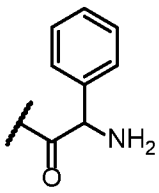
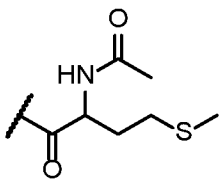
49. The compound of any one of embodiments 34-48, wherein R_9 is H or  .

50. The compound of any one of embodiments 34-49, wherein R_9 is H.

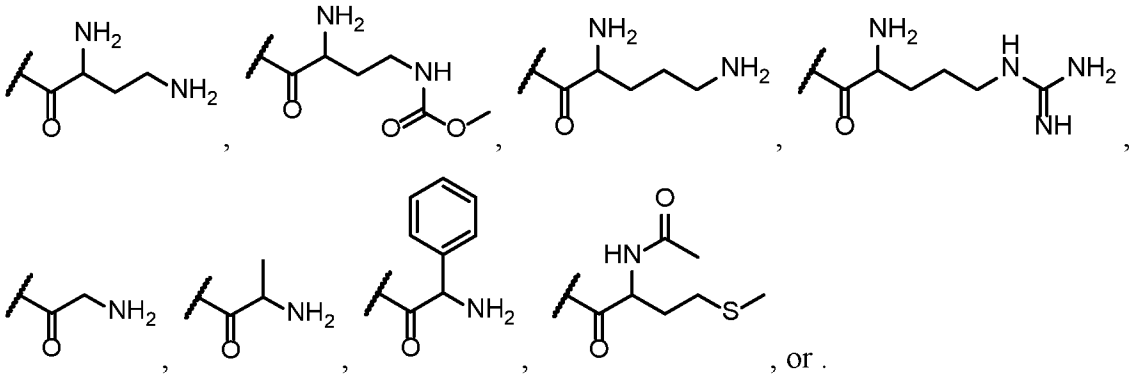
51. The compound of any one of embodiments 34-50, wherein R_{10} is H, Ph or –$(CH_2)_m$–R_{11}, and wherein R_{11} is –NH_2,  or –SCH_3.

52. The compound of embodiment 50 or 51, wherein m is an integer from 2-4.

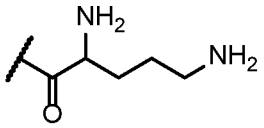
53. The compound of any one of embodiments 34-52, wherein promoiety A is :

 ,  ,  ,  ,  , or  .

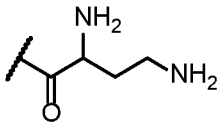
53a. The compound of any one of embodiments 34-52, wherein promoiety A is :



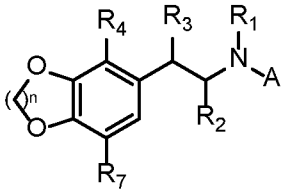
54. The compound of any one of embodiments 34-53, wherein promoiety A is



54a. The compound of any one of embodiments 34-53, wherein promoiety A is



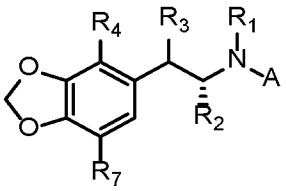
55. The compound of any one of embodiments 34-45 and 47-54a, having the structure of Formula (IIa):



(IIb),

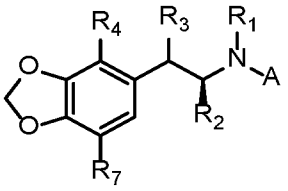
wherein n is 1 or 2.

55a. The compound of embodiment 55, having the structure:



, or a pharmaceutically acceptable salt thereof.

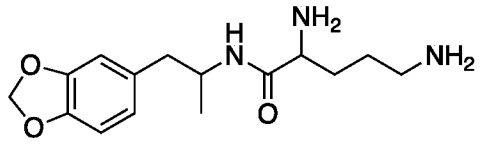
55b. The compound of embodiment 55, having the structure:



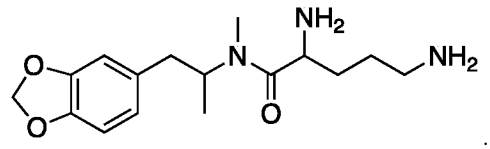
, or a pharmaceutically acceptable salt thereof.

55c. The compound of any one of embodiments 55-55b, wherein R_3 is H.

56. The compound of any one of embodiments 34-45 and 47-54, wherein the compound is:

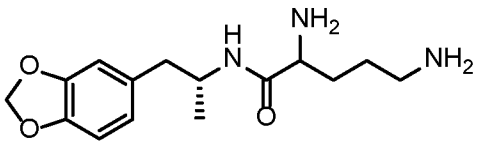


or

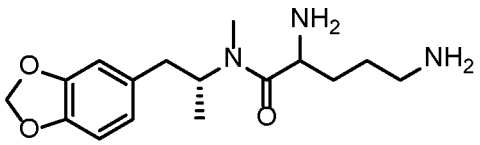


.

56a. The compound of embodiment 56, wherein the compound is:

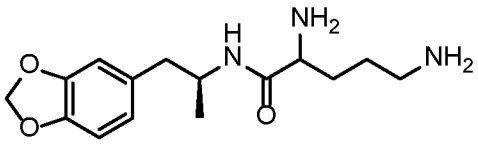


or

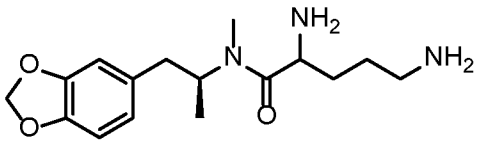


.

56b. The compound of embodiment 56, wherein the compound is:



or



.

57. The compound of any one of embodiments 34-56b, wherein the promoiety A is cleavable at a pH of from about 8 to about 10.

58. The compound of any one of embodiments 34-56b, wherein the promoiety A is cleavable at a pH of from about 8 or 9.

59. A pharmaceutical composition comprising a compound of any one of embodiments 34-58 and a pharmaceutically acceptable excipient.

60. The pharmaceutical composition of embodiment 59, wherein when R_1 is H, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of

about 12 ng/mL to about 15 ng/mL achieved following oral administration of a 125 mg dose of MDA to a human subject.

61. The pharmaceutical composition of embodiment 59, wherein when R_1 is H, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 7 ng/mL to about 8.5 ng/mL achieved following oral administration of a 75 mg dose of MDA to a human subject.

62. The pharmaceutical composition of embodiment 59, wherein when R_1 is methyl, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 220 ng/mL to about 250 ng/mL achieved following oral administration of a 125 mg dose of MDMA to a human subject.

63. The pharmaceutical composition of embodiment 59, wherein R_1 is methyl, the composition is capable of providing a $T_{1/2}$ of free amine within a range of about 105-150% of about 8 h to about 9 h achieved following oral administration of a 125 mg dose of MDMA to a human subject.

64. The pharmaceutical composition of embodiment 59, wherein when R_1 is methyl, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 120 ng/mL to about 140 ng/mL achieved following oral administration of a 75 mg dose of MDMA to a human subject.

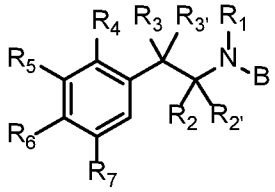
65. The pharmaceutical composition of embodiment 59, wherein when R_1 is methyl, the composition is capable of providing a $T_{1/2}$ of free amine within a range of 105-150% of about 7 h to about 9 h achieved following oral administration of a 75 mg dose of MDMA to a human subject.

66. The pharmaceutical composition of embodiment 59, capable of providing an *in vivo* plasma level characterized by a Cmax of free amine of about 100 ng/mL to about 500 ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (II) and release of promoiety A.

67. The pharmaceutical composition of embodiment 59 or 66, capable of providing an *in vivo* plasma level characterized by an $AUC_{(0-24)}$ of free amine of about 1000 h*ng/mL to about 6000 h*ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (II) and release of promoiety A.

68. The pharmaceutical composition of any one of embodiments 59 and 66-67, capable of providing an *in vivo* $T_{1/2}$ of free amine of about 5 h to about 15 h, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (II) and release of promoiety A.

69. A compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof;

wherein,

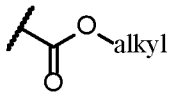
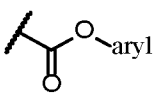
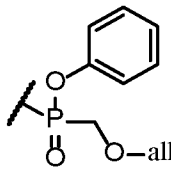
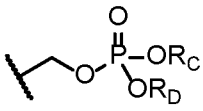
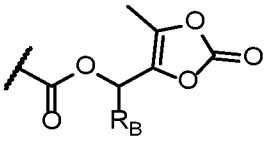
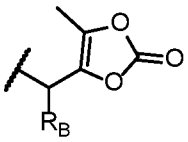
R_1 is H or alkyl;

R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

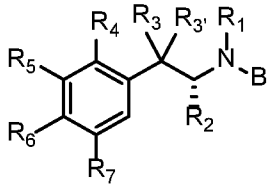
R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl, or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

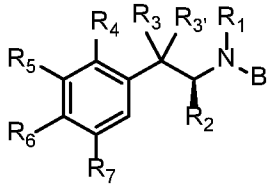
R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl; and

B is  ,  ,  ,  ,  ,  , or , wherein R_B is H or alkyl; and R_C and R_D are each independently H or alkyl.

69a. The compound of embodiment 69, having the structure:

 , or a pharmaceutically acceptable salt thereof.

69b. The compound of embodiment 69, having the structure:

 , or a pharmaceutically acceptable salt thereof.

70. The compound of any one of embodiments 69-69b, wherein at least one of R_4, R_5, R_6 and R_7 is not H.

71. The compound of any one of embodiments 69-70, wherein R_1 is H or C_1-C_6 alkyl.

72. The compound of any one of embodiments 69-70, wherein R_1 is H.

73. The compound of any one of embodiments 69-70, wherein R_1 is CH_3.

74. The compound of any one of embodiments 69-73, wherein R_2 and $R_{2'}$ are each independently H, alkyl, or –OH.

75. The compound of any one of embodiments 69-73, wherein R_2 is alkyl and $R_{2'}$ is H.

76. The compound of any one of embodiments 69-73, wherein R_2 and $R_{2'}$ are each alkyl.

77. The compound of any one of embodiments 74-76, wherein the alkyl is methyl or isopropyl.

78. The compound of any one of embodiments 69-77, wherein R_3 and $R_{3'}$ are each independently H, –OH, or –O–alkyl or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo.

78a. The compound of any one of embodiments 69-77, wherein R_3 and $R_{3'}$ are each H.

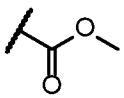
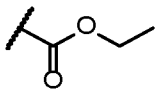
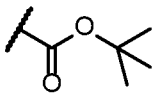
79. The compound of any one of embodiments 69-78, wherein R_4 is H.

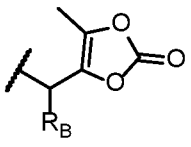
80. The compound of any one of embodiments 69-79, wherein R_7 is H.

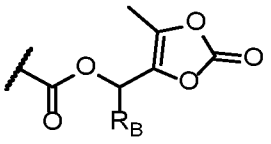
81. The compound of any one of embodiments 69-80, wherein R_5 and R_6 are each independently halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8.

82. The compound of any one of embodiments 69-80, wherein R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring.

83. The compound of any one of embodiments 69-82, wherein R_8 is alkyl.

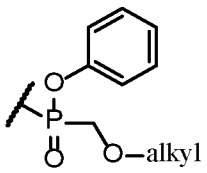
84. The compound of any one of embodiments 69-83, wherein B is  ,  , or  .

84a. The compound of any one of embodiments 69-83, wherein B is  , wherein R_B is H or alkyl.

84b. The compound of any one of embodiments, 69-83, wherein B is  , wherein R_B is H or alkyl.

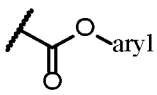
84c. The compound of embodiment 84a or 84b, wherein R_B is H or Me.

84d. The compound of embodiment 84a or 84b, wherein R_B is H.

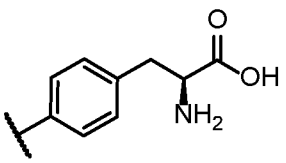
84e. The compound of any one of embodiments 69-83, wherein B is  .

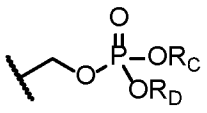
84f. The compound of embodiment 84e, wherein alkyl is methyl, ethyl, or isopropyl.

84g. The compound of embodiment 84e or 84f, wherein alkyl is methyl.

84h. The compound of any one of embodiments 69-83, wherein B is  .

84i. The compound of embodiment 84h, wherein aryl is optionally substituted phenyl.

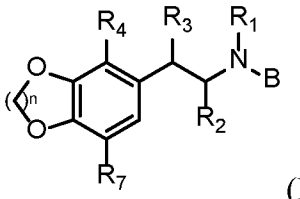
84j. The compound of embodiment 84i, wherein optionally substituted phenyl is  .

84k. The compound of any one of embodiments 69-83, wherein B is  .

84l. The compound of embodiment 84k, wherein R_C and R_D are each independently H, Me, Et, or *i*-Pr.

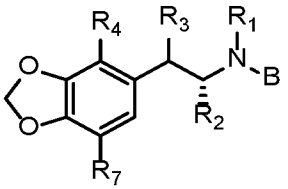
84m. The compound of embodiment 84k or 84l, wherein R_C and R_D are each H.

85. The compound of any one of embodiments 69-80 and 82-84m, having the structure of Formula (IIIb):

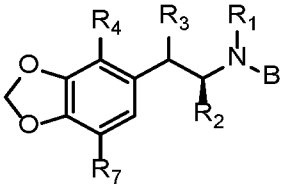
 (IIIb),

wherein n is 1 or 2.

85a. The compound of embodiment 85, having the structure:

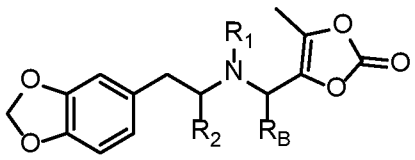
 , or a pharmaceutically acceptable salt thereof.

85b. The compound of embodiment 85, having the structure:

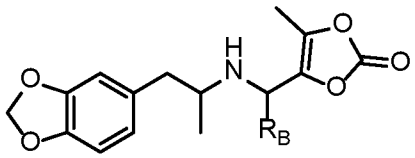
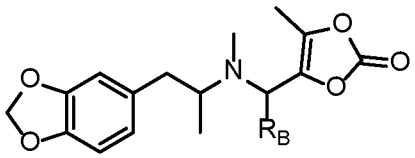
 , or a pharmaceutically acceptable salt thereof.

85c. The compound of any one of embodiments 85-85b, wherein R_3 is H.

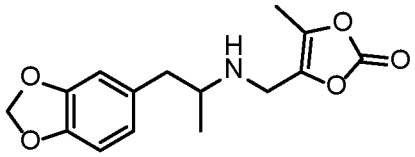
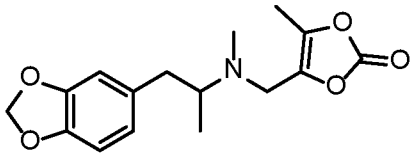
85d. The compound of any one of embodiments 69-83 and 84a-85, having the structure:



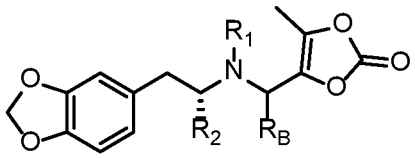
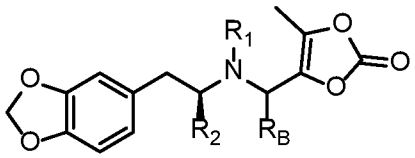
85e. The compound of any one of embodiments 69-83 and 84a-85, having the structure:


or


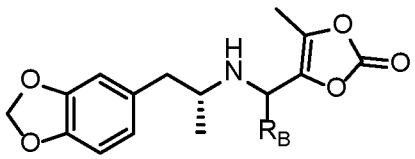
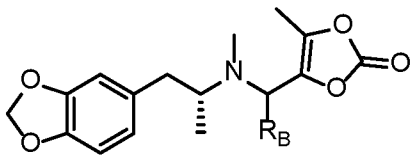
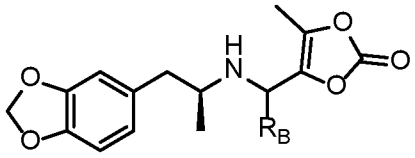
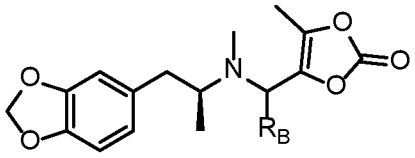
85f. The compound of any one of embodiments 69-83 and 84a-85, having the structure:


or


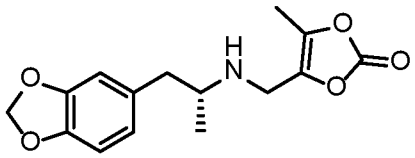
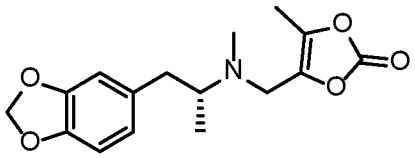
85g. The compound of any one of embodiments 69-83 and 84a-85c, having the structure:


or


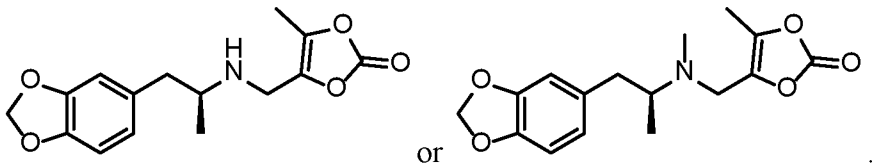
85h. The compound of embodiment 85g, having the structure:


,

,

, or


85i. The compound of embodiment 85g or 85h, having the structure:


or


85j. The compound of embodiment 85h or 85i, having the structure:



86. A pharmaceutical composition comprising a compound of any one of embodiments 69-85j and a pharmaceutically acceptable excipient.

87. The pharmaceutical composition of embodiment 86, capable of providing an *in vivo* plasma level characterized by a Cmax of free amine of about 100 ng/mL to about 500 ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (III) and release of promoiety B.

88. The pharmaceutical composition of embodiment 86 or 87, capable of providing an *in vivo* plasma level characterized by an $AUC_{(0-24)}$ of free amine of about 1000 h*ng/mL to about 6000 h*ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (III) and release of promoiety B.

89. The pharmaceutical composition of any one of embodiments 86-88, capable of providing an *in vivo* $T_{1/2}$ of free amine of about 5 h to about 15 h, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (III) and release of promoiety B.

90. A method of treating post-traumatic stress disorder (PTSD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition of any one of embodiments 24-33, 59-68, and 86-89.

91. A method of treating an eating disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition of any one of embodiments 24-33, 59-68, and 86-89.

92. A method of treating depression in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition of any one of embodiments 24-33, 59-68, and 86-89.

93. The method of embodiment 92, wherein the depression is major depressive disorder (MDD) or treatment-resistant depression (TRD).

94. A method of treating an anxiety disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition of any one of embodiments 24-33, 59-68, and 86-89.

95. The method of embodiment 94, wherein the anxiety disorder is generalized anxiety disorder.

96. A compound selected from compounds 1-11 of Table 6.

97. A compound selected from compounds 1-45 of Table 1.

EXAMPLES

[0170] Example 1. Preparation of Prodrug Compounds of the Present Disclosure

[0171] Compounds of the present disclosure are prepared from MDA, MDMA or derivative thereof in a one or two-step synthetic route that relies on standard amide and ester bond-forming reactions between commercially available reagents.

[0172] Specific enantiomers (or diastereomers in some cases) are obtained by separation of the mixtures and identification of the desired isomer.

[0173] General reaction conditions are provided, and reaction products can be purified by known methods including silica gel chromatography using various organic solvents such as hexane, dichloromethane, ethyl acetate, methanol and the like or preparative reverse phase high pressure liquid chromatography.

[0174] Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene and Wuts, *Protective Groups in Organic Synthesis,* 44th. Ed., Wiley & Sons, 2006, as well as in Jerry March, *Advanced Organic Chemistry,* 4th edition, John Wiley & Sons, publisher, New York, 1992 which are incorporated herein by reference in their entirety.

[0175] Example 2. PK Measurements in Healthy Human Subjects Administered MDMA

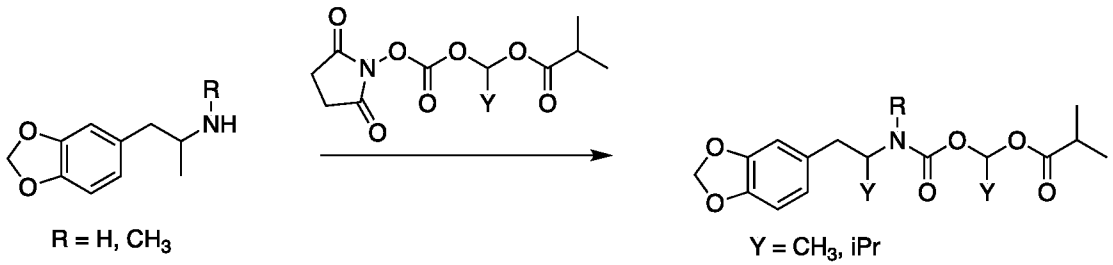
Dose	75 mg MDMA	125 mg MDMA
C_{max} (ng/mL)	130.9	236.4
AUC_{0-24} (ng/ml*h^{-1})	1331	2623
T_{max} (h)	1.8	2.4
$T_{1/2}$ (h)	7.7	8.6

[0176] Example 3. PK Measurements in Healthy Human Subjects Administered MDA

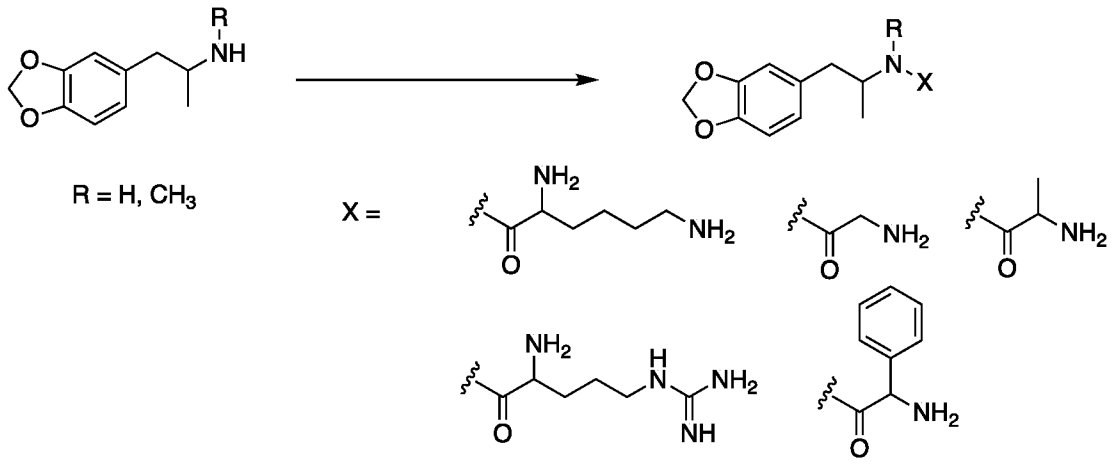
Dose	75 mg MDA	125 mg MDA
C_{max} (ng/mL)	7.8	13.7
AUC_{0-24} (ng/ml*h^{-1})	122	215
T_{max} (h)	5	7

[0177] Prodrugs have been exemplified in the following classes:

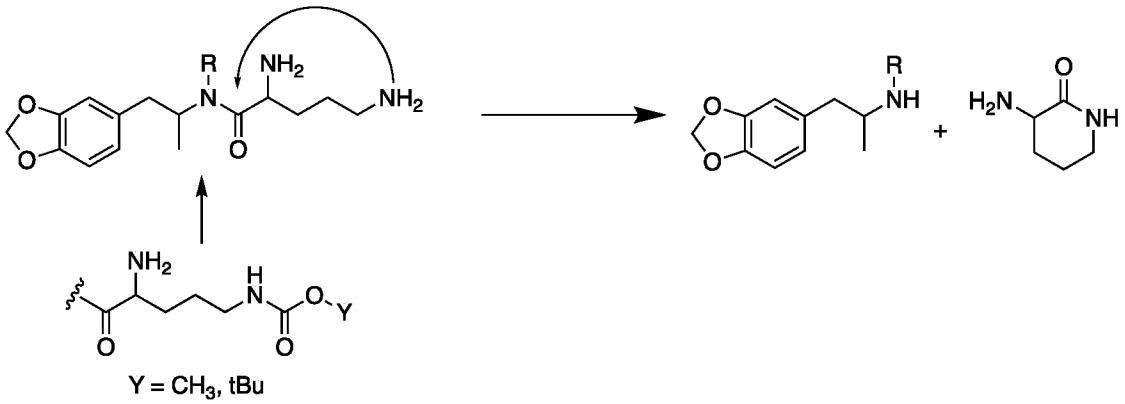
1. **Enacarbil (N-acyloxyalkoxy carbonyl) derivatives**



2. **Simple amino acids**

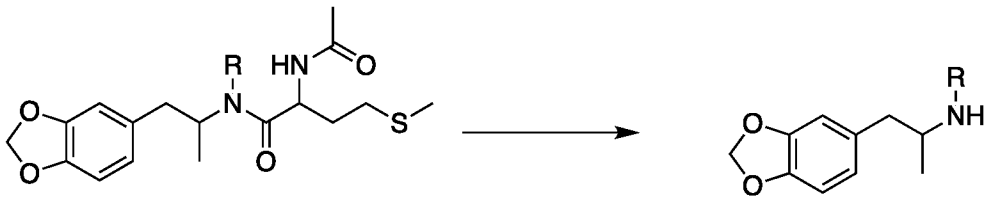


[0178] In some embodiments, amino acids provide a group that can be internally released to provide the MDMA, MDA, or a derivative thereof. A specific example of an internally released protecting group utilizes ornithine. prodrug can be stabilized to prevent cyclization and release by dosing a salt of the amine or by utilizing a slow release of a secondary protecting group such as a carbamate. The α-amino group is an optional substituent.



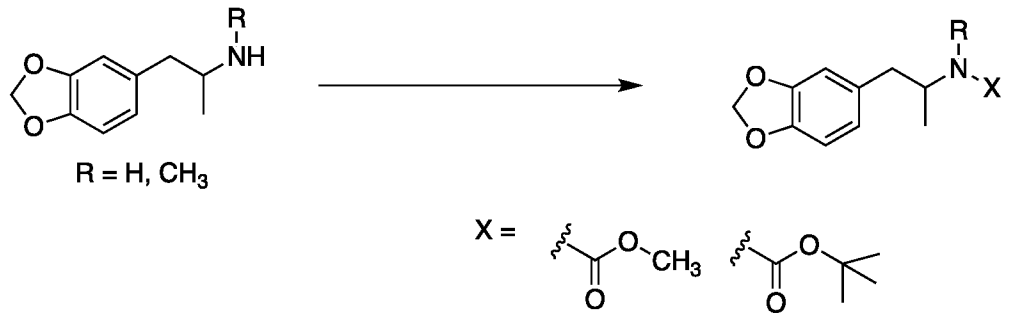
3. Amides/amino acid variants

[0179] Below is a pro-drug amide derived from docarpamine. Amide groups can be cleaved enzymatically *in vivo*.



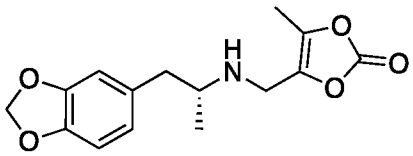
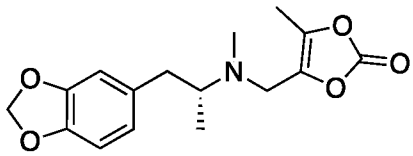
4. Carbamates

[0180] The non-limiting carbamate examples shown below are generally freed via simple hydrolysis.

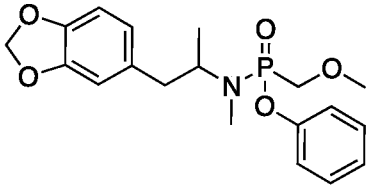
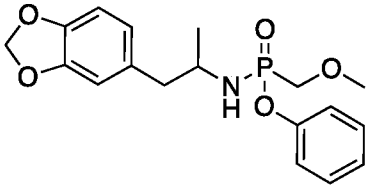


[0181]

5. Dialkyl-1,3-dioxol-2-one

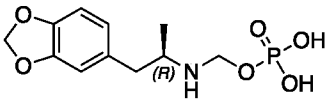
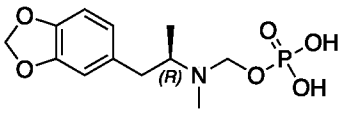



6. Methoxymethyl phosphinyl amide (Kirby and Dowd, 2022)

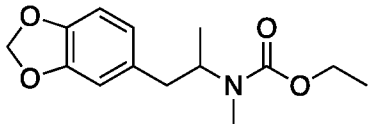
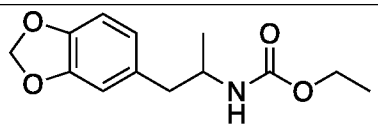
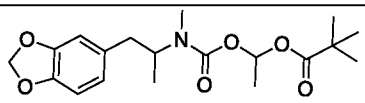
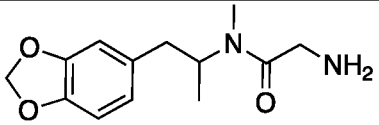



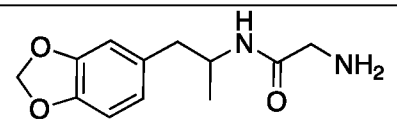
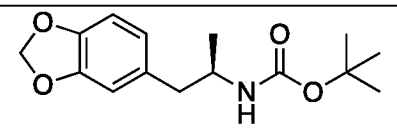
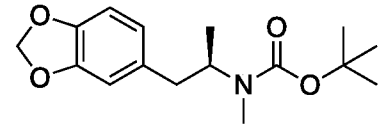
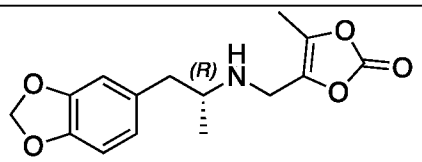
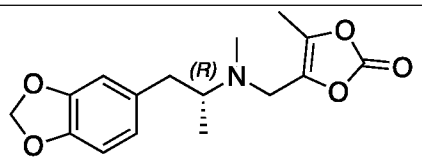
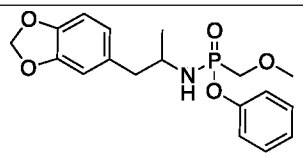
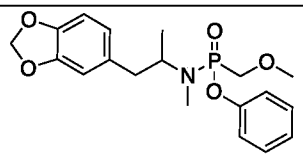
[0182] Syntheses of the prodrugs may be accomplished from MDA or MDMA and commercially available reagents in one or two steps. Isolation of specific enantiomers can be achieved by separation of the mixtures or by enantioselective synthesis methods.

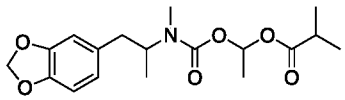
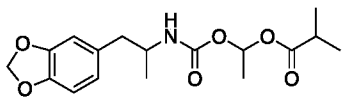
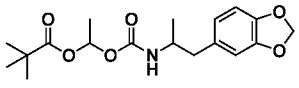
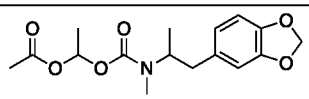
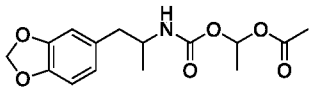
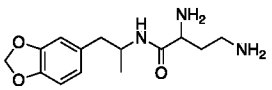
7. Methoxymethyl phosphate

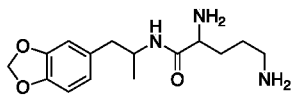
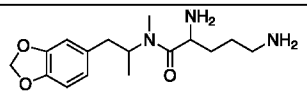
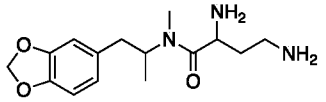
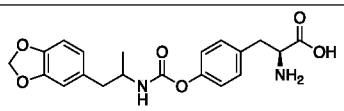
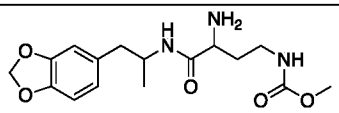
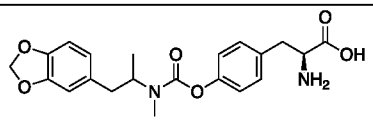
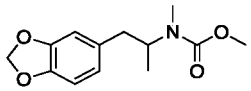
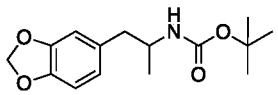
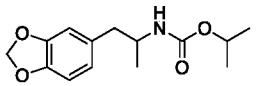
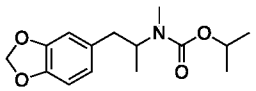
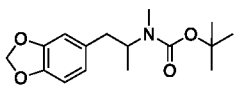
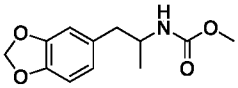
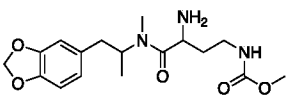
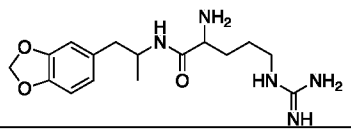



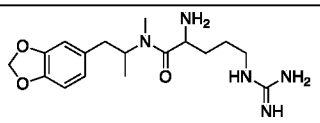
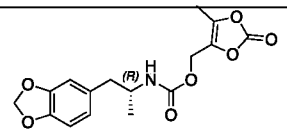
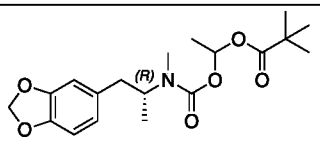
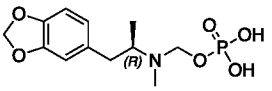
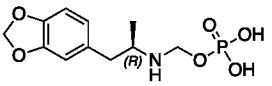
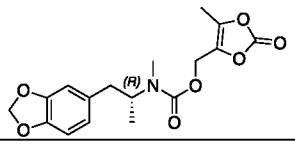
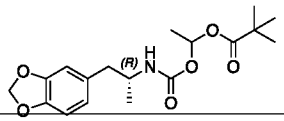
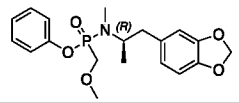
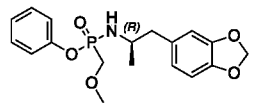
[0183] Table 1. Compounds of the invention

ID	Structure	Chemical name
1		ethyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamate
2		ethyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate
3		1-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamoyl)oxy)ethyl pivalate
4		2-amino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*N*-methylacetamide

5		2-amino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)acetamide
6		*tert*-butyl (*R*)-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate
7		*tert*-butyl (*R*)-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamate
8		(*R*)-4-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one
9		(*R*)-4-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)amino)methyl)-5-methyl-1,3-dioxol-2-one
10		phenyl *N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*P*-(methoxymethyl)phosphonamidate
11		phenyl *N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*P*-(methoxymethyl)-*N*-methylphosphonamidate

12		1-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamoyl)oxy)ethyl isobutyrate
13		1-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamoyl)oxy)ethyl isobutyrate
14		1-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamoyl)oxy)ethyl pivalate
15		1-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamoyl)oxy)ethyl acetate
16		1-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamoyl)oxy)ethyl acetate
17		2,4-diamino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)butanamide

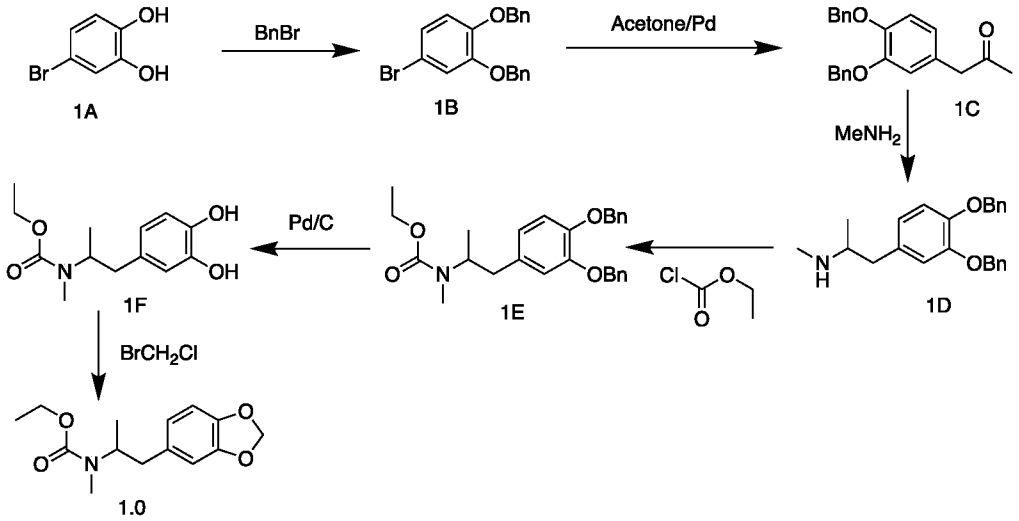
18		2,5-diamino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)pentanamide
19		2,5-diamino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*N*-methylpentanamide
21		2,4-diamino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*N*-methylbutanamide
22		(2*S*)-2-amino-3-(4-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamoyl)oxy)phenyl)propanoic acid
23		methyl (3-amino-4-((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)amino)-4-oxobutyl)carbamate
25		(2*S*)-2-amino-3-(4-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamoyl)oxy)phenyl)propanoic acid
26		methyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamate
29		*tert*-butyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate
30		isopropyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate
31		isopropyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamate
32		*tert*-butyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamate
34		methyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate
35		methyl (3-amino-4-((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)amino)-4-oxobutyl)carbamate
36		2-amino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-5-guanidinopentanamide

37		2-amino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-5-guanidino-*N*-methylpentanamide
38		(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl (*R*)-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate
39		1-((((*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamoyl)oxy)ethyl pivalate
40		(*R*)-((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)amino)methyl dihydrogen phosphate
41		(*R*)-((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)amino)methyl dihydrogen phosphate
42		(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl (*R*)-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamate
43		1-((((*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamoyl)oxy)ethyl pivalate
44		phenyl *N*-((*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*P*-(methoxymethyl)-*N*-methylphosphonamidate
45		phenyl *N*-((*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*P*-(methoxymethyl)phosphonamidate

Example 1: Synthesis of Compounds

[0184] Synthesis of Prodrug 1.0: Ethyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamate

[0185] Compound **1.0** was synthesized from commercially available compound **1A** in six steps (Scheme 1).



Scheme 1

[0186] Synthesis of 1A

[0187] To a stirred solution of 4-bromocatechol (5.0 g, 26.45 mmol, 1.0 equiv) and potassium carbonate (7.3 g, 52.91 mmol, 2.0 equiv) in acetone (50.0 mL) was added (bromomethyl)benzene (6.8 g, 39.68 mmol, 1.5 equiv) dropwise at 25°C under nitrogen atmosphere. The mixture was stirred for 16h at 60°C. Added 100 mL of water to the reaction, the aqueous layer was extracted with ethyl acetate (3 x 300 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in Water (0.05% NH_4HCO_3), 10% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in **1A** (5.0 g, 51%) as a white solid. MS m/z $[M+H]^+$ (ESI): 369.04.

[0188] Synthesis of 1B

[0189] To a stirred solution of **1A** (1.0 g, 2.71 mmol, 1.0 equiv) and K_3PO_4 (1.7 g, 8.12 mmol, 3.0 equiv) in acetone (10.0 mL) was added XPhos Pd(crotyl)Cl (182.5 mg, 0.27 mmol, 0.1 equiv) at 25°C under nitrogen atmosphere. The mixture was stirred for 6h at 50°C. The reaction was diluted with 50 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in Water (0.05% NH_4HCO_3), 10% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in **1B** (480.0 mg, 51%) as a white solid. MS m/z $[M+H]^+$ (ESI): 347.16.

[0190] Synthesis of 1C

[0191] To a solution of methanamine hydrochloride (935.5 mg, 13.86 mmol, 10.0 equiv) in methyl alcohol (5.0 mL) was added sodium cyanoborohydride (435.4 mg, 6.93 mmol, 5.0 equiv) and **1B** (480.0 mg, 1.39 mmol, 1.0 equiv) at 0°C. The resulting mixture was stirred for 16h at room temperature. The reaction was diluted with 50 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in Water (0.1% TFA), 10% to 100% gradient in 20 min; detector, UV 254 nm. to afford **1C** (450.0 mg, 90%) as a white solid. MS m/z $[M+H]^+$ (ESI): 362.20.

[0192] Synthesis of 1D

[0193] To a stirred solution of **1C** (450.0 mg, 1.25 mmol, 1.0 equiv) and triethylamine (377.9 mg, 3.74 mmol, 3.0 equiv) in dichloromethane (5.0 mL) was added ethyl chloroformate (270.2 mg, 2.49 mmol, 2.0 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature. The reaction was diluted with 50 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in Water (0.05% NH_4HCO_3), 10% to 100% gradient in 20 min; detector, UV 254 nm. 300 mg of **1D** was obtained as a colorless oil. MS m/z $[M+H]^+$ (ESI): 434.23.

[0194] Synthesis of 1E and final product 1.0

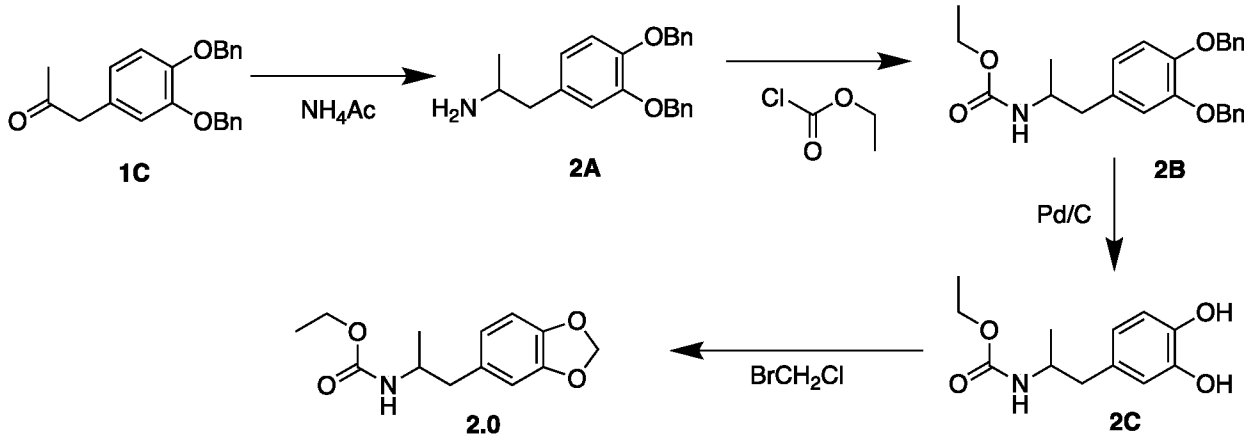
[0195] A mixture of **1D** (300.0 mg, 0.69 mmol, 1.0 equiv) and 10%Pd/C (60.0 mg) in tetrahydrofuran (1.0 mL) was stirred for 3 h at room temperature under hydrogen atmosphere. The solid was filtered and washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure. The crude product **1E** was used in the next step directly without further purification. To a stirred solution of **1E** (100.0 mg, 0.40 mmol, 1.0 equiv) and cesium carbonate (231.5 mg, 0.71 mmol, 1.8 equiv) in DMF (1.0 mL) was added bromo(chloro)methane (91.9 mg, 0.71 mmol, 1.8 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature. The reaction was diluted with 50 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried

over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in Water (0.05% NH_4HCO_3), 10% to 100% gradient in 20 min; detector, UV 254 nm. 28.9 mg (27%) of **1.0, Ethyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamate** was obtained as a colorless oil.

[0196] MS m/z [M+H]+ (ESI): 266.10. ^{1}H NMR (300 MHz, DMSO-d6) δ 6.81-6.60 (m, 3H), 5.95 (s, 2H), 4.31-4.25 (m, 1H), 3.96-3.81 (m, 2H), 2.64-2.59 (m, 5H), 1.08-0.99 (m, 6H).

[0197] Synthesis of Prodrug 2.0: Ethyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate

[0198] Prodrug **2.0** was synthesized from the previous intermediate **1C** in 4 steps (Scheme 2).



Scheme 2

[0199] Synthesis of 2A

[0200] To a solution of NH_4OAc (2.22g, 28.83 mmol, 10.0 equiv.) in methyl alcohol (10.0 mL) was added sodium cyanoborohydride (0.91g, 14.44 mmol, 5.0 equiv.), **1C** (1g, 2.89 mmol, 1.0 equiv.) and AcOH (1mL) at 0°C. The resulting mixture was stirred for 16h at room temperature. The reaction was diluted with 100 mL of dichloromethane, washed with 2 x 50 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in Water (0.1% TFA), 10% to 100% gradient in 20 min; detector, UV 254 nm. to afford **2A** (840 mg, 84%) as a white solid.

[0201] Synthesis of 2B

[0202] To a solution of **2A** (300.0 mg, 0.86 mmol, 1.0 equiv) and triethylamine (262.1 mg, 2.58 mmol, 3.0 equiv) in dichloromethane was added ethyl chloroformate (93.7 mg, 0.86 mmol, 1.0 equiv) dropwise at 0°C under nitrogen atmosphere. The mixture was stirred at 25°C for 16h. The reaction was diluted with 50 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in water (0.1% $NH_3.H_2O$), 10% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in **2B** (160 mg, 44%) as a yellow solid. MS m/z $[M+H]^+$ (ESI): 420.21.

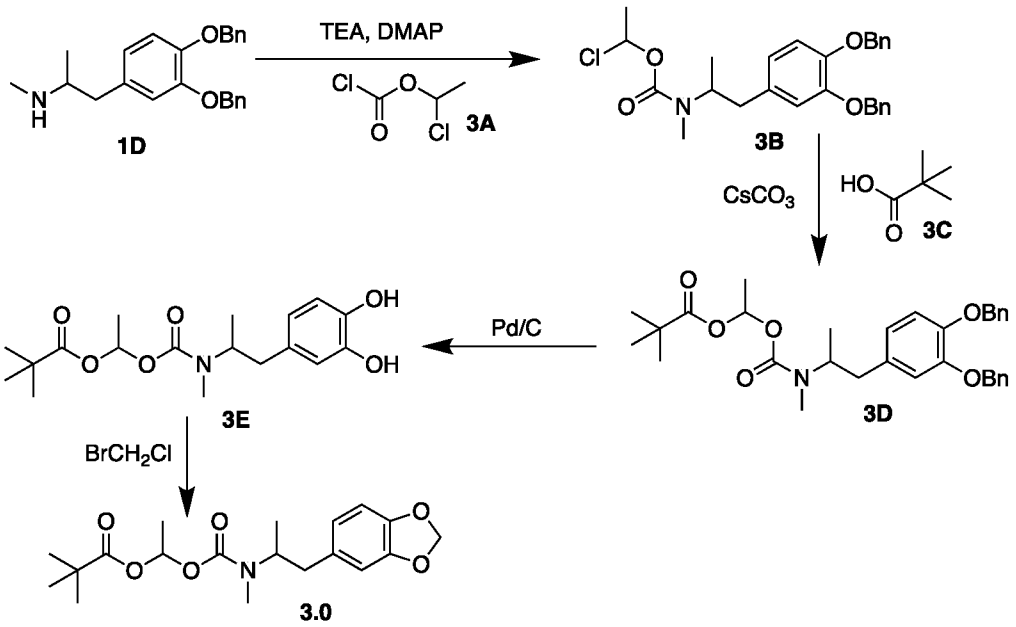
[0203] Synthesis of 2C and final product 2.0

[0204] A mixture of **2B** (150.0 mg, 0.36 mmol, 1.0 equiv) and 10%Pd/C (30.0 mg) in tetrahydrofuran (5.0 mL) was stirred for 3 h at room temperature under hydrogen atmosphere. The solid was filtered and washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure to crude material **2C**. The crude product (**2C**) was used in the next step directly without further purification.

[0205] To a solution of **2C** (100.0 mg, 0.42 mmol, 1.0 equiv) and cesium carbonate (217.8 mg, 0.67 mmol, 1.6 equiv) in N, N-Dimethylformamide was added bromo(chloro)methane (86.5 mg, 0.67 mmol, 1.6 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. The reaction was diluted with 50 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (0.1%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 55% B in 9 min, 55% B; Wavelength: 254 nm) to afford Prodrug **2.0, ethyl (1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate** (18 mg) as a colorless oil. MS m/z $[M+H]^+$ (ESI): 252.05. ^1H NMR (300 MHz, Methanol-d_4) δ 6.72-6.62 (m, 3H), 5.88 (s, 2H), 4.04-3.97 (m, 2H), 3.81-3.70 (m, 1H), 2.73-2.52 (m, 2H), 1.21-1.07 (m, 6H).

[0206] Synthesis of Prodrug 3.0: 1-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamoyl)oxy)ethyl pivalate

[0207] Compound **3.0** was synthesized from previously synthesized intermediate **1D** (scheme 1) in four steps (**Scheme 3**).



Scheme 3

[0208] Synthesis of 3B

[0209] To a solution of **1D** (200.0 mg, 0.55 mmol, 1.0 equiv) and TEA (167.9 mg, 1.65 mmol, 3.0 equiv), DMAP (33.8 mg, 0.27 mmol, 0.5 equiv) in dichloromethane was added 1-chloroethyl carbonochloridate, **3A** (237.3 mg, 1.65 mmol, 3.0 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 16h at room temperature. The reaction was diluted with 50 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude (**3B**) was used in next step directly without further purification.

[0210] Synthesis of 3D

[0211] To a solution of **3B** (150.0 mg, 0.32 mmol, 1.0 equiv) and pivalic acid, **3C** (65.4 mg, 0.64 mmol, 2.0 equiv) in DMF was added cesium carbonate (125.32 mg, 0.385 mmol, 1.2 equiv), potassium iodide (10.6 mg, 0.06 mmol, 0.20 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 4h at 100°C under nitrogen atmosphere. The reaction was diluted with 30 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase,

acetonitrile in water (0.1% NH3.H2O), 10% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in **3D** (114.0 mg, 66%) as a yellow oil. MS m/z $[M+H]^+$ (ESI): 534.28.

[0212] A mixture of **3D** (150.0 mg, 0.28 mmol, 1.0 equiv) and 10%Pd/C (40.0 mg) in tetrahydrofuran (1.0 mL) was stirred for 3 h at room temperature under hydrogen atmosphere. The solid was filtered and washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure to provide **3E**. The crude product (**3E**) was used in the next step directly without further purification.

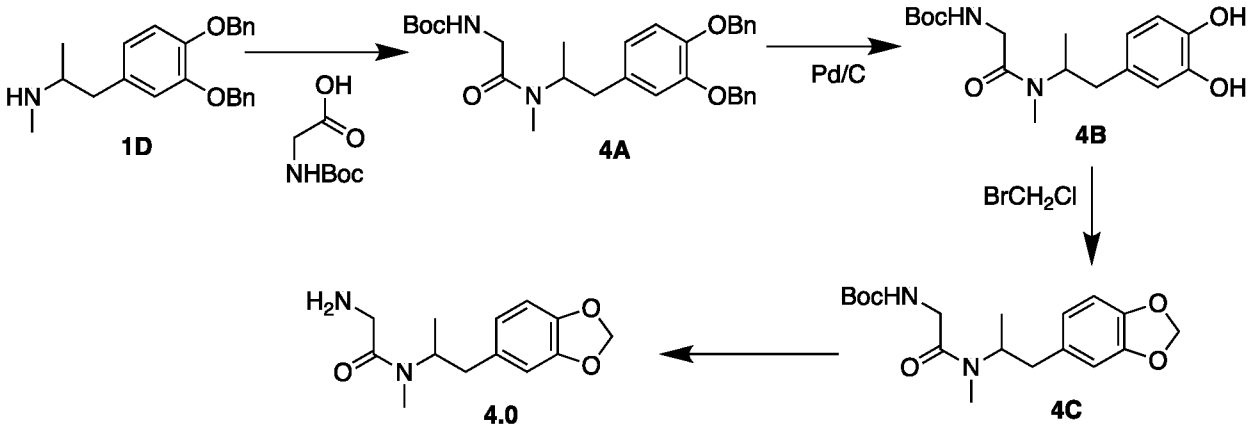
[0213] Synthesis of 3.0

[0214] To a solution of 3E (90.0 mg, 0.25 mmol, 1.0 equiv) and cesium carbonate (132.7 mg, 0.41 mmol, 1.6 equiv) in DMF was added bromo(chloro)methane (52.7 mg, 0.41 mmol, 1.6 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. The reaction was diluted with 50 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (0.1% TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 50% B to 80% B in 9 min, 80% B; Wavelength: 254 nm) to afford

[0215] Prodrug 3.0, 1-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamoyl)oxy)ethyl pivalate (18 mg, 18%) as a colorless oil. MS m/z [M+H] + (ESI): 366.05. 1H NMR (400 MHz, Methanol-d4) δ 6.70-6.32 (m, 4H), 5.94-5.88 (m, 2H), 4.43-4.31 (m, 1H), 2.79-2.66 (m, 5H), 1.48-1.40 (m, 2H), 1.33-1.22 (m, 1H), 1.19-1.13 (m, 12H).

[0216] Synthesis of Prodrug 4.0: 2-amino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*N*-methylacetamide

[0217] Compound 4.0 was synthesized from commercially available compound NBoc protected glycine and previously synthesized intermediate **1D** (Scheme 1) in four steps (Scheme 4).



Scheme 4

[0218] Synthesis of 4A

[0219] To a stirred solution of **1A** (500.0 mg, 1.38 mmol, 1.0 equiv) and HATU (1.1 g, 2.77 mmol, 2.0 equiv) in DMF (5.0 mL) was added [(tert-butoxycarbonyl)amino]acetic acid (290.8 mg, 1.66 mmol, 1.2 equiv) and DIEA (536.3 mg, 4.15 mmol, 3.0 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16h at room temperature. The reaction was diluted with 50 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in Water (0.05% NH_4HCO_3), 10% to 100% gradient in 20 min; detector, UV 254 nm. 450 mg of **4A** was obtained as a colorless oil. MS m/z [M+H]+ (ESI): 519.28.

[0220] Synthesis of 4B

[0221] A mixture of **4A** (450.0 mg, 0.87 mmol, 1.0 equiv) and 10% Pd/C (90.0 mg) in Tetrahydrofuran (5.0 mL) was stirred for 3 h at room temperature under hydrogen atmosphere. The solids were filtered and washed with Tetrahydrofuran. The filtrate was concentrated under reduced pressure and crude **product 4B** was obtained. The crude product **4B** was used in the next step directly without further purification.

[0222] Synthesis of 4C

[0223] To a stirred mixture of **4B** (250.0 mg, 0.74 mmol, 1.0 equiv) and cesium carbonate (433.3 mg, 1.33 mmol, 1.8 equiv) in DMF (3.0 mL) was added bromo(chloro)methane (172.1 mg, 1.33 mmol, 1.8 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature. The reaction was diluted with 30 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried

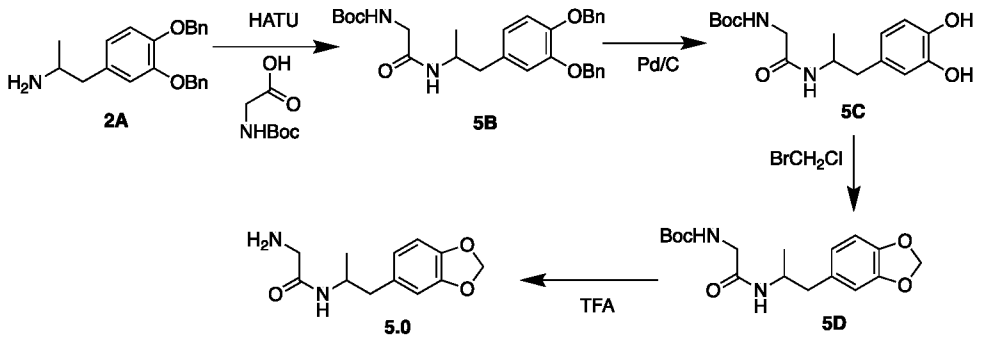
over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in Water (0.05% NH_4HCO_3), 10% to 100% gradient in 20 min; detector, UV 254 nm. 200 mg of **4C** was obtained as a colorless oil. MS m/z $[M+H]^+$ (ESI): 351.18.

[0224] Synthesis of product, Prodrug 4.0

[0225] To a stirred solution of **4C** (100.0 mg, 0.29 mmol, 1.0 equiv) in dichloromethane (1.0 mL) was added TFA (0.2 mL, 2.69 mmol) dropwise at room temperature. The resulting mixture was stirred for 1h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in Water (0.1% TFA), 10% to 100% gradient in 20 min; detector, UV 254 nm. 35.4 mg of **4.0, 2-amino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*N*-methylacetamide,** was obtained as a yellow oil (TFA Salt). MS m/z $[M+H]^+$ (ESI): 251.10. ^1H NMR (300 MHz, Methanol-d4) δ 6.77-6.65 (m, 3H), 5.90 (d, J = 8.7 Hz, 2H), 4.87-4.76 (m, 1H), 3.92-3.70 (m, 2H), 3.06-2.84 (m, 3H), 2.80-2.70 (m, 2H), 1.32-1.16 (m, 3H).

[0226] Synthesis of Prodrug 5.0: 2-amino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)acetamide

[0227] Prodrug **5.0** was synthesized from the previous intermediate **2A** in 4 steps (Scheme 5).



Scheme 5

[0228] Synthesis of 5B

[0229] To a solution of **2A** (500.0 mg, 1.44 mmol, 1.0 equiv) and [(tert-butoxycarbonyl)amino]acetic acid (378.1 mg, 2.16 mmol, 1.5 equiv), DIEA (557.9 mg, 4.32

mmol, 3.0 equiv) in DMF (5mL) was added HATU (1367.9 mg, 3.59 mmol, 2.5 equiv) at 25°C under nitrogen atmosphere. The resulting mixture was stirred for 16h at room temperature under nitrogen atmosphere. The reaction was diluted with 50 mL of dichloromethane, washed with 2 x 20 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in water (0.1% FA), 10% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in **5B** (582 mg, 80%) as a white solid. MS m/z $[M+H]^+$ (ESI): 505.26.

[0230] Synthesis of 5C

[0231] A mixture of **5B** (500.0 mg, 0.99 mmol, 1.0 equiv) and 10%Pd/C (100.0 mg) in tetrahydrofuran (10.0 mL) was stirred for 3 h at room temperature under hydrogen atmosphere. The solid was filtered and washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure. The crude product **(5C)** was used in the next step directly without further purification.

[0232] Synthesis of 5D

[0233] To a mixture of **5C** (500.0 mg, 1.54 mmol, 1.0 equiv) and cesium carbonate (803.5 mg, 2.46 mmol, 1.6 equiv) in DMF (5mL) was added bromo(chloro)methane (319.1 mg, 2.46 mmol, 1.6 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature. The reaction was diluted with 50 mL of dichloromethane, washed with 2 x 30 mL saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in water (0.1% FA), 10% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in **5D** (400.0 mg, 77%) as a white solid. MS m/z $[M+H]^+$ (ESI): 337.17.

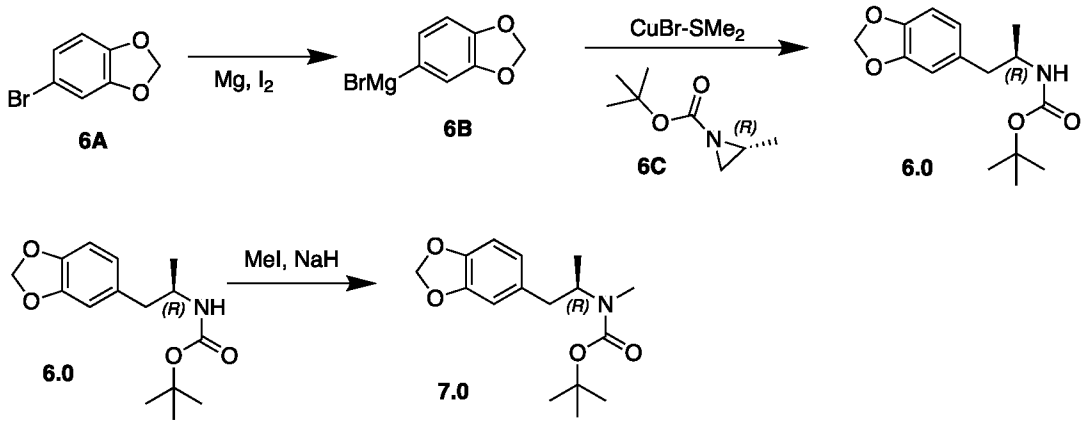
[0234] Synthesis of 5.0

[0235] To a solution of **5D** (70.0 mg, 0.21 mmol, 1.0 equiv) in dichloromethane (1mL) was added TFA (0.2 mL) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (0.1%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min;

Gradient: 5% B to 28% B in 9 min, 28% B; Wavelength: 254 nm) to afford **Prodrug 5.0, 2-amino-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)acetamide,** (42 mg, 82%) as a white solid (TFA Salt). MS m/z $[M+H]^+$ (ESI): 237.10. ^{1}H NMR (300 MHz, Methanol-d4) δ 6.73-6.64 (m, 3H), 5.89 (s, 2H), 4.17-4.05 (m, 1H), 3.64-3.51 (m, 2H), 2.76-2.61 (m, 2H), 1.13 (d, J=6.6Hz 3H).

[0236] Synthesis of Prodrug 6.0: *tert*-butyl (*R*)-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate. Synthesis of Prodrug 7.0: *tert*-butyl (*R*)-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamate.

[0237] Prodrugs **6.0 and 7.0** were synthesized from the previously described chemistry from commercially available intermediate **6A** and **6C** in a few steps (Scheme 6).



Scheme 6

[0238] Synthesis of 6B

[0239] To a 100 mL flask was charged magnesium (60.4 mg, 2.487 mmol, 2.00 equiv.), iodine (one crystal) and tetrahydrofuran (1.5 mL) at room temperature under nitrogen. 5-Bromo-2H-1,3-benzodioxole (50 mg) was added to the mixture and heated to 50 °C at which time the iodine color disappeared, and the internal temperature rose to 56 °C. 5-Bromo-2H-1,3-benzodioxole (450 mg, total added 500 mg, 2.487 mmol, 2.0 equiv.) was added, via syringe, to the mixture dropwise maintaining an internal temperature of 45-55° over 10 minutes. After addition was complete the syringe was rinsed with THF (0.1 mL) and the rinse charged to the reaction at 49 °C. After stirring for 1.5 hours the batch was a clear amber color with an internal temperature of 19.6 °C. THF (1 mL) was added. This crude material 6B was used directly for the next steps.

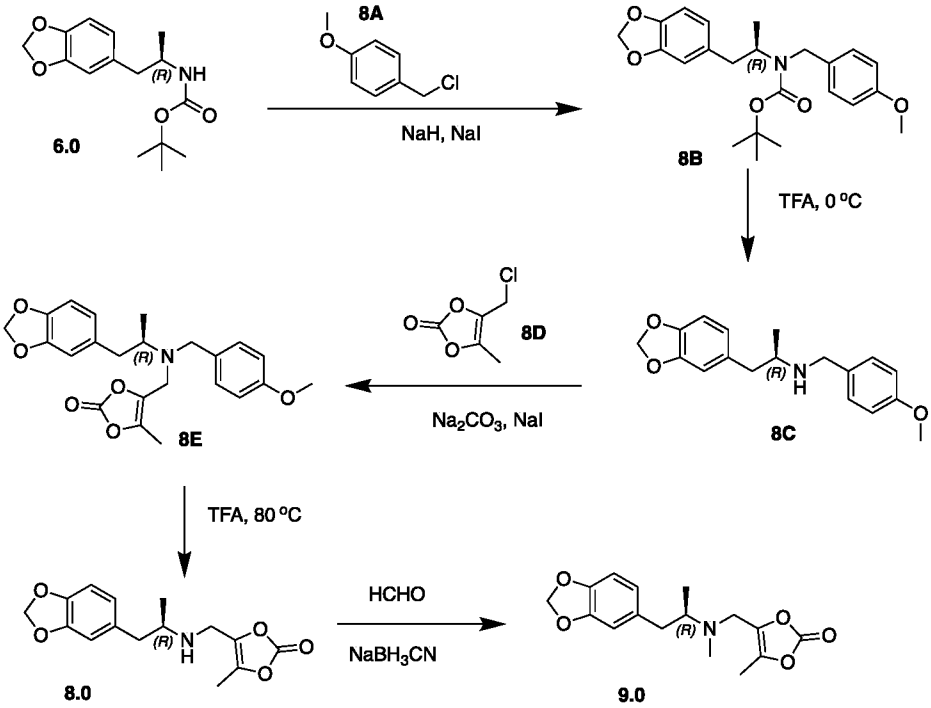
[0240] 2. Synthesis of 6.0

[0241] The flask was cooled to 0.8 °C using an ice/water bath then solid CuBr•SMe2 (52.3 mg, 0.254 mmol, 0.2 equiv) was charged in one portion. An exotherm to 6 °C was observed. After cooling to 0.5 °C a solution of tert-butyl (2R)-2-methylaziridine-1-carboxylate (200 mg, 1.272 mmol, 1.0 equiv.) in tetrahydrofuran (0.5 mL) was added over 20 minutes, while maintaining an internal temperature <6 °C. After stirring for 4 hours TLC analysis (5:1 heptane/EA) of the brown slurry showed complete reaction. After a further 20 minutes the reaction was quenched with dropwise addition sat. ammonium chloride (5.0 mL), while maintaining an internal temperature <18°C (3 minutes). After stirring for 12 minutes at room temperature the biphasic mixture was diluted with Ethyl acetate (1.5 mL). The layers were separated, and the aqueous layer was extracted with Ethyl acetate (2 x 1.5 mL). The combined organic layers dried over sodium sulfate (1.3 g), filtered, and concentrated under reduced pressure. Chromatographic purification in silica, eluting with 0-15% Ethyl acetate/heptane afforded **6.0, *tert*-butyl (*R*)-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate,** (130 mg, 36 % yield) as a white solid. 50 mg purified by reversed Flash with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: 10mmol NH_4HCO_3+0.05%NH_3H_2O, Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 53% B in 8 min, 53% B; Wavelength: 254 nm. The fractions of desired product were lyophilized. This resulted in 28.0 mg as a white solid. MS m/z $[M-H]^-$ (ESI):278.15. ^1H NMR (400 MHz, DMSO-d_6) δ 6.81-6.61 (m, 4H), 5.95-5.94 (m, 2H), 3.61-3.53 (m, 1H), 2.63-2.58 (m, 1H), 2.49-2.44 (m, 1H), 1.34 (s, 9H), 0.98 (d, J = 6.8 Hz, 3H).

[0242] Synthesis of Prodrug 7.0

[0243] A solution of prodrug **6.0** (100 mg, 0.358 mmol, 1 equiv) in DMF (2 mL) was treated with sodium hydride (12.89 mg, 0.537 mmol, 1.5 equiv) for 30min at 0°C under nitrogen atmosphere followed by the addition of methyl iodide (101.63 mg, 0.716 mmol, 2 equiv) dropwise at 0°C. The resulting mixture was stirred for 16 hours at room temperature. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 55% B in 8 min, 55% B; Wavelength: 254 nm) to afford **7.0, *tert*-butyl (*R*)-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)carbamate,** (34.5 mg, 32% yield) as a light-yellow oil. MS m/z $[M+H]^+$ (ESI): 294.05. ^1H NMR (300 MHz, DMSO-d_6) δ 6.81-6.59 (m, 3H), 5.93 (s, 2H), 4.33-4.10 (m, 1H), 2.61-2.55 (m, 5H), 1.30-1.08 (m, 12H). ee purity: 99.29%, $[\alpha]_D^{25.6}$ =-118°(c=1mg/mL, ACN)

[0244] Synthesis of Prodrug 8.0: (*R*)-4-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one.



Scheme 7

[0245] Synthesis of 8B

[0246] To a solution of **6.0** (4 g, 14.320 mmol, 1 equiv) in DMF (40 mL) was added sodium hydride (60% in oil, 859.1 mg, 1.5 equiv) at 0°C. The mixture was stirred for 15 minutes. 4-methoxybenzyl chloride **8A** (4.49 g, 28.640 mmol, 2 equiv) was added by dropwise and the mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was quenched by saturated ammonium chloride aqueous solution and extracted with dichloromethane (2 x 200 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with petroleum ether / ethyl acetate (9:1) to afford **8B** (4.2 g, 73% yield) as a yellow oil. MS m/z $[M+Na]^+$ (ESI):422.15.

[0247] Synthesis 8C

[0248] To a stirred solution of **8B** (4.2 g, 10.513 mmol, 1 equiv) in dichloromethane (56 mL) was added trifluoroacetic acid (28 mL) by dropwise at 0°C. The resulting mixture was stirred for 10 minutes at 0°C. The value of pH was adjusted to ~8 with saturated sodium bicarbonate aqueous solution at 0°C. The resulting mixture was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under

reduced pressure. The residue was purified by silica gel column chromatography, eluted with dichloromethane / methanol (20:1) to afford 8C (2 g, 63% yield) as a yellow oil. MS m/z [M+H]+ (ESI):300.20.

[0249] Synthesis 8E

[0250] To a solution of **8C** (300 mg, 1.002 mmol, 1 equiv) in DMF (3 mL), Na_2CO_3 (214.4 mg, 2.004 mmol, 2 equiv), sodium iodide (30.0 mg, 0.200 mmol, 0.2 equiv) and 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one **8D** (297.7 mg, 2.004 mmol, 2 equiv) was added. The mixture was stirred for 4 hours. Then, the solid was filtered. The filtrate was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in water (0.05% ammonium bicarbonate), 20% to 100% gradient in 15 min; detector, UV 220 nm. The fractions of desired product were concentrated under reduced pressure. This resulted in **8E** (300 mg, 73% yield) as a yellow oil. MS m/z $[M+H]^+$ (ESI):412.20.

[0251] Synthesis of 8.0: (*R*)-4-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one

[0252] A solution of **8E** (300 mg, 0.729 mmol, 1 equiv) in TFA (3 mL) was stirred for 2 days at 80°C. Then, it was cooled to room temperature and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in water (0.05% TFA), 10% to 50% gradient in 15 min; detector, UV 220 nm. The fractions of desired product were concentrated under reduced pressure. This resulted in crude product. It was purified by Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 13% B to 23% B in 8 min, 23% B; Wavelength: 254 nm. The fractions of desired product were lyophilized. This resulted in **8.0, (*R*)-4-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)amino)methyl)-5-methyl-1,3-dioxol-2-one,** (15.7 mg) as a grey semi-solid (FA salt). MS m/z $[M+H]^+$ (ESI):292.05. ^1H NMR (300 MHz, Methanol-d_4) δ 6.82-6.71 (m, 3H), 5.94 (s, 2H), 4.21 (s, 2H), 3.58-3.49 (m, 1H), 3.15-3.09 (m, 1H), 2.70-2.63 (m, 1H), 2.20 (s, 3H), 1.27 (d, J = 6.6 Hz, 3H). ee purity: 100%, $[\alpha]_D^{25.6}$ =-168° (c=1mg/mL, ACN)

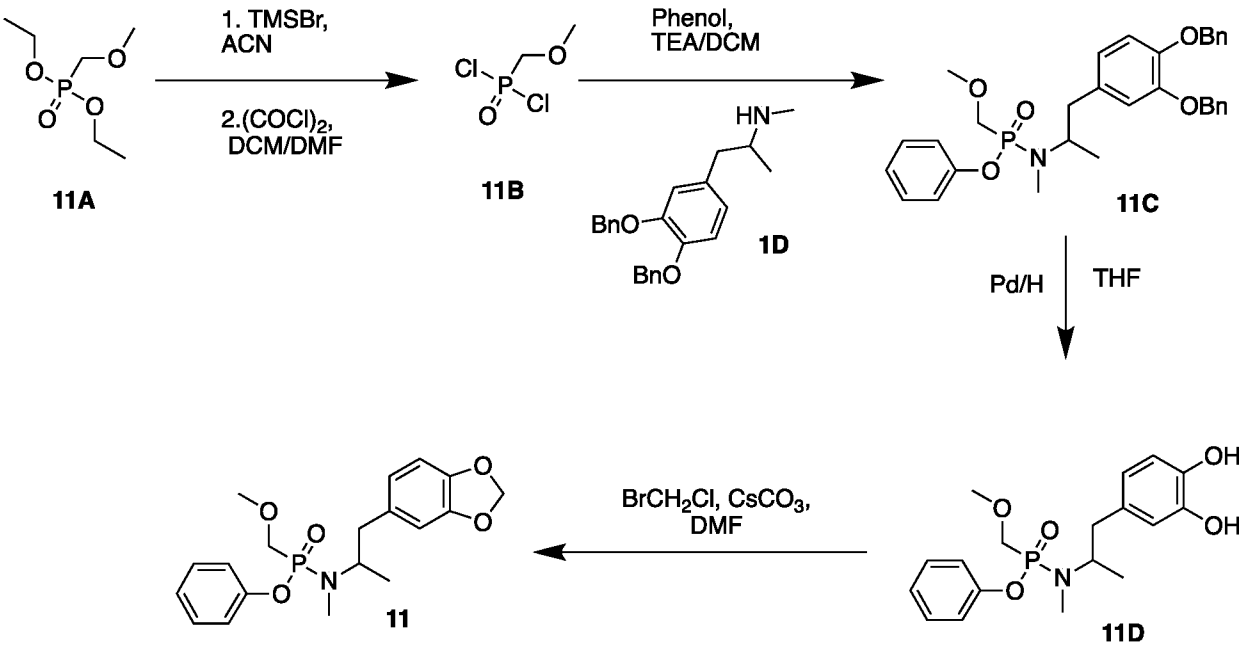
[0253] Synthesis of Prodrug 9.0: (*R*)-4-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)amino)methyl)-5-methyl-1,3-dioxol-2-one.

[0254] To a solution of **8.0** (290 mg, 0.996 mmol, 1 equiv) in methanol (4.35 mL), sodium cyanoborohydride (125.12 mg, 1.992 mmol, 2 equiv) and formaldehyde (161.58 mg, 1.992 mmol, 2 equiv, 37% in water) was added at 0°C. It was stirred for 2 hours at room temperature. Then, it was quenched with saturated ammonium chloride aqueous solution. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. It was purified by Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 40% B in 8 min, 40% B; Wavelength: 254 nm. The fractions of desired product were lyophilized. This resulted in **9.0, (*R*)-4-(((1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)(methyl)amino)methyl)-5-methyl-1,3-dioxol-2-one,** (44.8 mg) as a light grey oil (FA salt). MS m/z $[M+H]^+$ (ESI):306.10. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 6.80-6.72 (m, 2H), 6.70-6.64 (m, 1H), 5.93 (s, 2H), 3.45-3.35 (m, 2H), 3.00-2.91 (m, 1H), 2.81-2.76 (m, 1H), 2.49-2.41 (m, 1H), 2.25 (s, 3H), 2.04 (s, 3H), 0.96 (d, J = 6.4 Hz, 3H). ee purity: 100%, $[\alpha]_D^{25.6}$ =-95° (c=1mg/mL, ACN).

[0255] It will be appreciated that the prodrugs of the invention afford increased exposure and bioavailability relative to parent drug itself. Prodrugs generated across different sites of the MDMA/MDA scaffold have specific pharmacokinetic profiles and afford distinct advantages to fine tune exposure, duration of exposure and overall intensity of entactogenic effects. Underlying these advantages are increased metabolic stability, increased absorption and decreased maximal plasma concentrations of parent drug over time. Prodrugs of the invention which limit maximal plasma concentrations of parent drug over time also limit amphetaminergic-like side effects of MDMA including hypertension. Limiting these side effects expands the suitability of MDMA for its intended PTSD population, of which many are obese and diagnosed with chronic hypertension.

[0256] Synthesis of Prodrug 11: phenyl *N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*P*-(methoxymethyl)-*N*-methylphosphonamidate

[0257] Prodrug 11 was synthesis in 6 steps from commercially available intermediate (10A). and described in Scheme 8.



Scheme 8

[0258] Synthesis of intermediate 11B:

[0259] To a solution of **11A** (200 mg, 1.098 mmol, 1 equiv) in acetonitrile (2 mL), bromotrimethylsilane (504.27 mg, 3.294 mmol, 3 equiv) was added. It was stirred for 2 hours at 50°C. Then, it was cooled to room temperature and concentrated under reduced pressure. The crude was dissolved in dichloromethane (4 mL), one drop of N,N-Dimethylformamide and oxalyl chloride (418.06 mg, 3.294 mmol, 3 equiv) was added at 0°C under nitrogen atmosphere. It was stirred for 1 hour at room temperature. Then, the solvent was removed under reduced pressure. This resulted in **11B** (175 mg, 97% yield) as a yellow oil. The crude was used at next step directly.

[0260] Synthesis of intermediate 11C:

[0261] To a solution of **11B** (175 mg, 1.074 mmol, 1.2 equiv) in dichloromethane (2 mL), a solution phenol (84.24 mg, 0.895 mmol, 1 equiv) and triethylamine (271.72 mg, 2.685 mmol, 3 equiv) in dichloromethane (2 mL) was added by dropwise at -10°C under nitrogen atmosphere. The mixture was stirred for 1 hour at room temperature. Then, a solution of **1D** (258.84 mg, 0.716 mmol, 0.8 equiv) in dichloromethane (2 mL) was added into the system. It was stirred for 1 hour at room temperature. The reaction was diluted with DCM, washed with saturated sodium phosphate monobasic. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase,

acetonitrile in water (0.05% TFA), 20% to 100% gradient in 15 min; detector, UV 220 nm. This resulted in **11C** (200 mg, 31% yield) as a colorless oil. MS m/z $[M+H]^+$ (ESI): 546.35. This product (**11C**) was used directly for the next step without further characterization.

[0262] Synthesis of intermediate 11D:

[0263] To a solution of **11C** (200 mg, 0.275 mmol, 1 equiv, 75%) in tetrahydrofuran (4 mL) was added Pd/C (10%, 100 mg) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 3 hours under hydrogen atmosphere using a hydrogen balloon, filtered through a celite pad and concentrated under reduced pressure. The crude (**11D:** MS m/z $[M+H]^+$ (ESI):366.20) was used at next step directly.

[0264] Synthesis of final Prodrug 11: Phenyl *N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*P*-(methoxymethyl)-*N*-methylphosphonamidate

[0265] To a mixture of **11D** (150 mg, 0.287 mmol, 1 equiv, 70%) in DMF (1.5 mL) was added bromochloromethane (59.49 mg, 0.459 mmol, 1.6 equiv) dropwise at room temperature under nitrogen atmosphere. It was stirred for 2 hours at room temperature. Then, the resulting mixture was filtered. The filtrate was purified by Column: XBridge Shield RP18 OBD Column19*250 mm, 5μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 0% B to 25% B in 10 min; Wavelength: 254 nm nm; RT1(min): 9.0. The fractions of desired product were lyophilized. This resulted in **prodrug 11,** phenyl *N*-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-*P*-(methoxymethyl)-*N*-methylphosphonamidate (33.1 mg, 30% yield) as a yellow oil. MS m/z $[M+H]^+$ (ESI): 378.10. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40-7.24 (m, 2H), 7.20-6.99 (m, 3H), 6.85-6.69 (m, 2H), 6.67-6.56 (m, 1H), 5.98-5.92 (m, 2H), 4.03-3.63 (m, 2H), 3.37-3.35 (m, 2H), 3.32-3.26 (m, 1H), 3.25-3.22 (m, 2H), 2.60-2.51 (m, 4H), 0.99-0.84 (m, 3H). ^{31}P NMR (400 MHz, DMSO-d_6) δ 24.51, 24.23.

Example 2: Evaluation of Compound Stability

[0266] Table 2. Compound Chemical stability PBS (pH6.5)

ID	% Remaining at 0, 30, 60, 120 and 240 minutes	Prodrug-class
1	100.00, 90.48, 90.36, 89.59, 90.28	carbamate
2	100.00, 89.05, 87.87, 91.21, 88.66	carbamate
3	100.00, 103.45, 107.91, 105.56, 96.60	N-acyloxy alkoxy carbonyl
4	100.00, 88.84, 92.54, 92.04, 92.48	Amide/ amino Acids

5	100.00, 95.53, 97.09, 98.67, 105.87	Amide/ amino Acids
6	100.00, 84.81, 93.60, 103.65, 91.66	carbamate
7	100.00, 94.54, 105.49, 105.72, 102.75	carbamate
8	100, 96, 93, 75, 72	Dialkyl-1,3-dioxol-2-one
9	100, 83, 75, 55, 32	Dialkyl-1,3-dioxol-2-one

[0267] Table 3. Compound Chemical stability SGF with pepsin

ID	**% Remaining at 0, 30, 60, 120 and 240 minutes**	**Prodrug-class**
1	100.00, 101.86, 98.61, 103.31, 100.50	carbamate
2	100.00, 100.95, 97.74, 98.18, 99.08	carbamate
3	100.00, 106.44, 108.51, 103.98, 106.17	N-acyloxy alkoxy carbonyl
4	100.00, 108.06, 98.50, 106.18, 103.88	Amide/ amino Acids
5	100.00, 99.68, 105.84, 94.42, 91.97	Amide/ amino Acids
6	100.00, 85.17, 79.89, 56.87, 31.48	carbamate
7	100.00, 74.97, 63.49, 56.42, 28.25	carbamate
8	**100, 103, 98, 96, 92**	Dialkyl-1,3-dioxol-2-one
9	**100, 97, 92, 87, 71**	Dialkyl-1,3-dioxol-2-one

[0268] Table 4. Compound Chemical stability SGF without pepsin

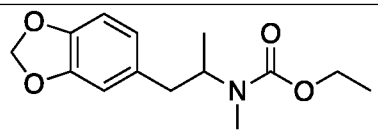
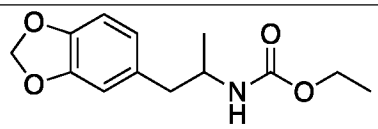
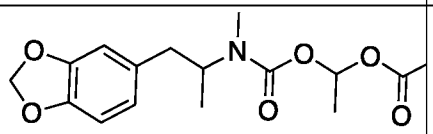
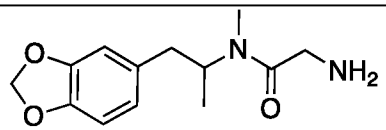
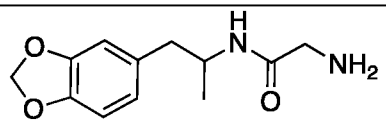
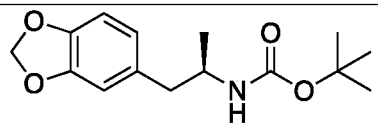
ID	**% Remaining at 0, 30, 60, 120 and 240 minutes**	**Prodrug-class**
1	100.00, 103.81, 101.90, 103.81, 104.29	carbamate
2	100.00, 102.53, 101.64, 90.45, 99.40	carbamate
3	100.00, 97.82, 97.35, 93.65, 94.12	N-acyloxy alkoxy carbonyl
4	100.00, 94.49, 96.72, 96.67, 96.46	Amide/ amino acids
5	100.00, 101.17, 91.48, 95.49, 100.41	Amide/ amino acids
6	100.00, 87.96, 77.20, 57.49, 28.57	carbamate
7	100.00, 89.90, 73.62, 61.79, 30.52	carbamate
8	100, 97, 94, 90, 86	Dialkyl-1,3-dioxol-2-one
9	1000, 94, 89, 83, 72	Dialkyl-1,3-dioxol-2-one

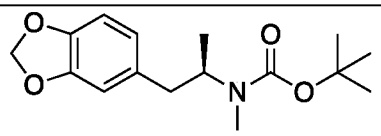
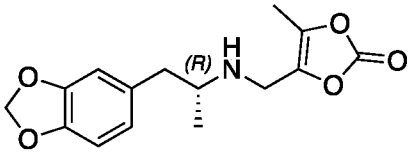
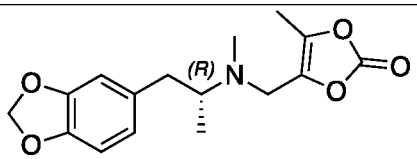
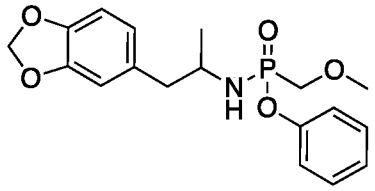
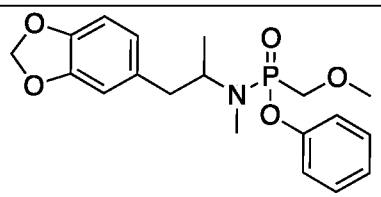
[0269] Table 5. Compound Mouse Plasma stability

ID	% Remaining at 0, 15, 30, 60, and 120 minutes	Prodrug-class
1	100.00, 108.51, 87.67, 98.49, 89.31	carbamate
2	100.00, 101.77, 86.60, 89.02, 84.42	carbamate
3	100, 0.0, 0.0, 0.0, 0.0	N-acyloxy alkoxy carbonyl
4	100.00, 102.99, 83.50, 94.51, 87.42	Amide/ amino acids
5	100.00, 103.33, 87.64, 90.78, 83.06	Amide/ amino acids
6	100, 102, 106, 92, 95	carbamate
7	100, 101, 92, 83, 92	carbamate
8	100, 72, 54, 25, 6	Dialkyl-1,3-dioxol-2-one
9	100, 70, 22, 4	Dialkyl-1,3-dioxol-2-one

Example 3: Evaluation of Compound Solubility

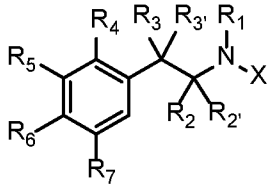
[0270] Table 6. Compound Solubility

ID	Structure	MW	Prodrug-class	FaSSIF Solubility (uM)
1		265.31	carbamate	309.11
2		251.28	carbamate	313.43
3		365.43	N-acyloxy alkoxy carbonyl	101.28
4		250.3	Amide/ amino Acids	291.11
5		236.27	Amide/ amino Acids	304.05
6		279.34	carbamate	175.28

7		293.36	carbamate	256.53
8		291.3	Dialkyl-1,3-dioxol-2-one	282.91
9		305.33	Dialkyl-1,3-dioxol-2-one	223.28
10		363.35	Methoxymethyl phosphinyl	NA
11		377.38	Methoxymethyl phosphinyl	NA

CLAIMS

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof;

wherein,

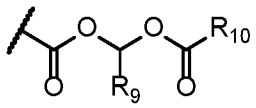
R_1 is H or alkyl;

R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl, or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl;

X is a cleavable promoiety having the structure  , wherein:

R_9 and R_{10} are each independently alkyl.

2. The compound of claim 1, wherein at least one of R_4, R_5, R_6 and R_7 is not H.

3. The compound of claim 1, wherein R_1 is H or C_1-C_6 alkyl.

4. The compound of claim 1, wherein R_1 is H.

5. The compound of claim 1, wherein R_1 is CH_3.

6. The compound of claim 1, wherein R_2 and $R_{2'}$ are each independently H, alkyl, or –OH.

7. The compound of claims 1-5, wherein R_2 is alkyl and $R_{2'}$ is H.

8. The compound of claim 1, wherein R_2 and $R_{2'}$ are each alkyl.

9. The compound of claim 6, wherein the alkyl is methyl or isopropyl.

10. The compound of claim 1, wherein R_3 and $R_{3'}$ are each independently H, –OH, or –O–alkyl, or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo.

11. The compound of claims 1, wherein R_4 is H.

12. The compound of claim 1, wherein R_7 is H.

13. The compound of claim 1, wherein R_5 and R_6 are each independently halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8.

14. The compound of claims 1, wherein R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring.

15. The compound of claim 1, wherein R_8 is alkyl.

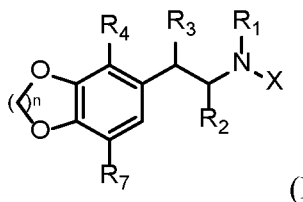
16. The compound of claim 1, wherein R_9 is $C_{1\text{-}5}$ alkyl.

17. The compound of claim 1, wherein R_9 is methyl or isopropyl.

18. The compound of claim 1, wherein R_{10} is $C_{1\text{-}5}$ alkyl.

19. The compound of claim 18, wherein R_{10} is methyl or isopropyl.

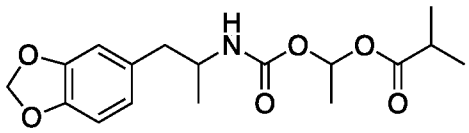
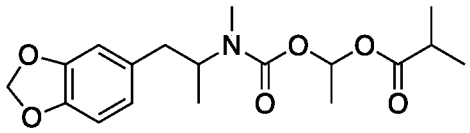
20. The compound of claim 1, having the structure of Formula (Ib):



(Ib),

wherein n is 1 or 2.

21. The compound of claim 1, wherein the compound is:

 or  .

22. The compound of claim 1, wherein X is cleavable at a pH of from about 1 to about 5.

23. The compound of claim 1-21, wherein X is cleavable at a pH of from about 2 to about 4.

24. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient.

25. The pharmaceutical composition of claim 24, capable of providing an *in vivo* plasma level characterized by a Cmax of free amine of about 100 ng/mL to about 500 ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

26. The pharmaceutical composition of claim 24, capable of providing an *in vivo* plasma level characterized by an $AUC_{(0\text{-}24)}$ of free amine of about 1000 h*ng/mL to about 6000 h*ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

27. The pharmaceutical composition of claim 24, capable of providing an *in vivo* $T_{1/2}$ of free amine of about 5 h to about 15 h, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (I) and release of promoiety X.

28. The pharmaceutical composition of claim 24, wherein when R_1 is H, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 12 ng/mL to about 15 ng/mL achieved following oral administration of a 125 mg dose of MDA to a human subject.

29. The pharmaceutical composition of claim 24, wherein when R_1 is H, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 7 ng/mL to about 8.5 ng/mL achieved following oral administration of a 75 mg dose of MDA to a human subject.

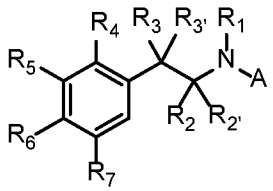
30. The pharmaceutical composition of claim 22, wherein when R_1 is methyl, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 220 ng/mL to about 250 ng/mL achieved following oral administration of a 125 mg dose of MDMA to a human subject.

31. The pharmaceutical composition of claim 24, wherein R_1 is methyl, the composition is capable of providing a $T_{1/2}$ of free amine within a range of about 105-150% of about 8 h to about 9 h achieved following oral administration of a 125 mg dose of MDMA to a human subject.

32. The pharmaceutical composition of claim 24, wherein when R_1 is methyl, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 120 ng/mL to about 140 ng/mL achieved following oral administration of a 75 mg dose of MDMA to a human subject.

33. The pharmaceutical composition of claim 24, wherein when R_1 is methyl, the composition is capable of providing a $T_{1/2}$ of free amine within a range of 105-150% of about 7 h to about 9 h achieved following oral administration of a 75 mg dose of MDMA to a human subject.

34. A compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof;

wherein,

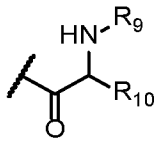
R_1 is H or alkyl;

R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl, or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl; and

A is a cleavable promoiety having the structure 

, wherein:

R_9 is H, alkyl or acyl; and

R_{10} is H, aryl, or $–(CH_2)_m–R_{11}$, wherein:

m is an integer from 1-5; and

R_{11} is amino, guanidino, thioalkyl, or aryl.

35. The compound of claim 34, wherein at least one of R_4, R_5, R_6 and R_7 is not H.

36. The compound of claim 34, wherein R_1 is H or C_1-C_6 alkyl.

37. The compound of claim 34, wherein R_1 is H.

38. The compound of claim 34, wherein R_1 is CH_3.

39. The compound of claim 34, wherein R_2 and $R_{2'}$ are each independently H, alkyl, or –OH.

40. The compound of claim 34, wherein R_2 is alkyl and $R_{2'}$ is H.

41. The compound of claim 34, wherein R_2 and $R_{2'}$ are each alkyl.

42. The compound of claim 39, wherein the alkyl is methyl or isopropyl.

43. The compound of claim 34, wherein R_3 and $R_{3'}$ are each independently H, –OH, or –O–alkyl or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo.

44. The compound of claim 34, wherein R_4 is H.

45. The compound of claim 34, wherein R_7 is H.

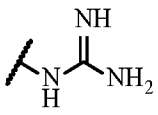
46. The compound of claim 34, wherein R_5 and R_6 are each independently halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8.

47. The compound of claim 34, wherein R_5 and R_6 together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring.

48. The compound of claim 34, wherein R_8 is alkyl.

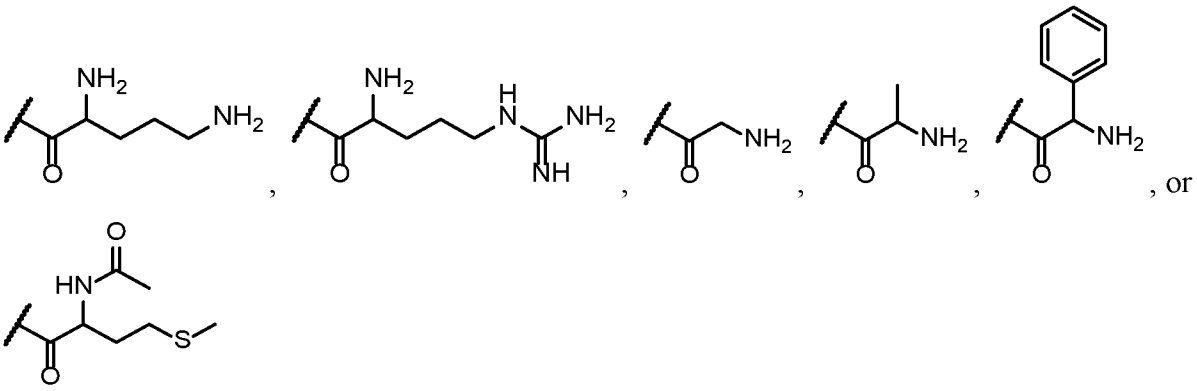
49. The compound of claims 34, wherein R_9 is H or .

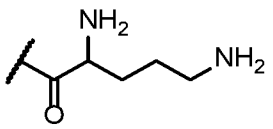
50. The compound of claim 34, wherein R_9 is H.

51. The compound of claim 34, wherein R_{10} is H, Ph or –$(CH_2)_m$–R_{11}, and wherein R_{11} is –NH_2,  or –SCH_3.

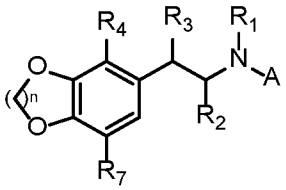
52. The compound of claim 50, wherein m is an integer from 2-4.

53. The compound of claim 34, wherein promoiety A is :



54. The compound of claim 34, wherein promoiety A is  .

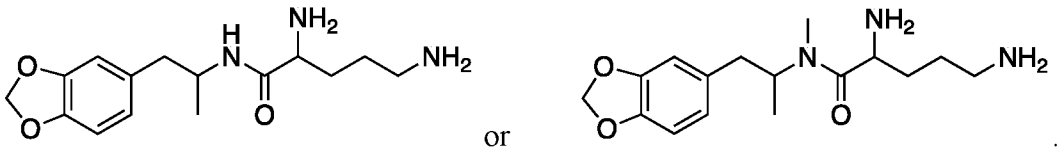
55. The compound of claim 34, having the structure of Formula (IIa):



(IIb),

wherein n is 1 or 2.

56. The compound of claim 34, wherein the compound is:



57. The compound of claim 34, wherein the promoiety A is cleavable at a pH of from about 8 to about 10.

58. The compound of claims 34, wherein the promoiety A is cleavable at a pH of from about 8 or 9.

59. A pharmaceutical composition comprising a compound of claim 34 and a pharmaceutically acceptable excipient.

60. The pharmaceutical composition of claim 59, wherein when R_1 is H, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 12 ng/mL to about 15 ng/mL achieved following oral administration of a 125 mg dose of MDA to a human subject.

61. The pharmaceutical composition of claim 59, wherein when R_1 is H, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 7 ng/mL to about 8.5 ng/mL achieved following oral administration of a 75 mg dose of MDA to a human subject.

62. The pharmaceutical composition of claim 59, wherein when R_1 is methyl, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 220 ng/mL to about 250 ng/mL achieved following oral administration of a 125 mg dose of MDMA to a human subject.

63. The pharmaceutical composition of claim 59, wherein R_1 is methyl, the composition is capable of providing a $T_{1/2}$ of free amine within a range of about 105-150% of about 8 h to about 9 h achieved following oral administration of a 125 mg dose of MDMA to a human subject.

64. The pharmaceutical composition of claim 59, wherein when R_1 is methyl, the composition is capable of providing a Cmax of free amine within a range of about 60-90% of about 120 ng/mL to about 140 ng/mL achieved following oral administration of a 75 mg dose of MDMA to a human subject.

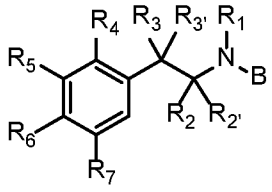
65. The pharmaceutical composition of claim 59, wherein when R_1 is methyl, the composition is capable of providing a $T_{1/2}$ of free amine within a range of 105-150% of about 7 h to about 9 h achieved following oral administration of a 75 mg dose of MDMA to a human subject.

66. The pharmaceutical composition of claim 59, capable of providing an *in vivo* plasma level characterized by a Cmax of free amine of about 100 ng/mL to about 500 ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (II) and release of promoiety A.

67. The pharmaceutical composition of claim 59, capable of providing an *in vivo* plasma level characterized by an $AUC_{(0\text{-}24)}$ of free amine of about 1000 h*ng/mL to about 6000 h*ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (II) and release of promoiety A.

68. The pharmaceutical composition of claim 59, capable of providing an *in vivo* $T_{1/2}$ of free amine of about 5 h to about 15 h, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (II) and release of promoiety A.

69. A compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof;

wherein,

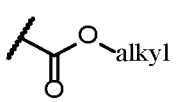
R_1 is H or alkyl;

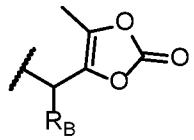
R_2 and $R_{2'}$ are each independently H, halogen, alkyl, –OH, or –O–alkyl, or R_2 and $R_{2'}$ together with the atom to which they are attached form a cycloalkyl ring;

R_3 and $R_{3'}$ are each independently hydrogen, alkyl, –OH, –O–alkyl, or –O–cycloalkyl, or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo;

R_4, R_5, R_6 and R_7 are each independently hydrogen, halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8, or R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring;

R_8 is H, alkyl, cycloalkyl, or alkylenecycloalkyl; and

B is 

or 

, wherein R_B is H or alkyl.

70. The compound of claim 69, wherein at least one of R_4, R_5, R_6 and R_7 is not H.

71. The compound of claim 69, wherein R_1 is H or C_1-C_6 alkyl.

72. The compound of claim 69, wherein R_1 is H.

73. The compound of claim 69, wherein R_1 is CH_3.

74. The compound of claim 69, wherein R_2 and $R_{2'}$ are each independently H, alkyl, or –OH.

75. The compound of claim 69, wherein R_2 is alkyl and $R_{2'}$ is H.

76. The compound of claims 69, wherein R_2 and $R_{2'}$ are each alkyl.

77. The compound of claim 74, wherein the alkyl is methyl or isopropyl.

78. The compound of claim 69, wherein R_3 and $R_{3'}$ are each independently H, –OH, or –O–alkyl or R_3 and $R_{3'}$ together with the atom to which they are attached form an oxo.

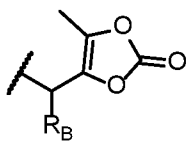
79. The compound of claim 69, wherein R_4 is H.

80. The compound of claims 69, wherein R_7 is H.

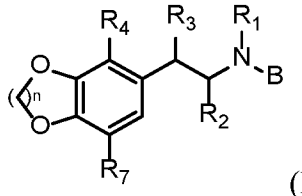
81. The compound of claim 69, wherein R_5 and R_6 are each independently halogen, –OH, –O–alkyl, –O–cycloalkyl, alkylene–OR_8, –SH, –S–alkyl, –S–cycloalkyl, or alkylene–SR_8.

82. The compound of claim 69, wherein R_5 and R_6 together with the atoms to which they are attached form a 5- to 8-membered heterocyclyl ring.

83. The compound of any one of claim 69, wherein R_8 is alkyl.

84. The compound of claim 69, wherein B is or  , wherein R_B is H or alkyl..

85. The compound of claim 69, having the structure of Formula (IIIb):

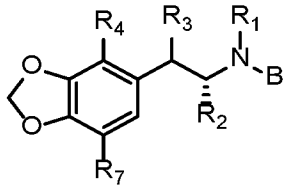


(IIIb),

or a pharmaceutically acceptable salt thereof,

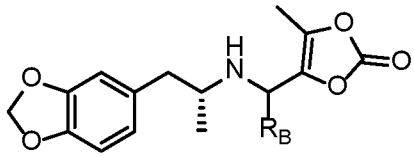
wherein n is 1 or 2.

86. The compound of claim 85, having the structure:

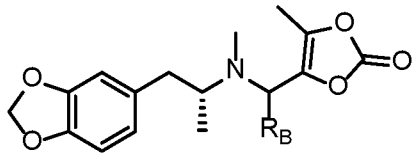


, or a pharmaceutically acceptable salt thereof.

87. The compound of claim 86, having the structure:

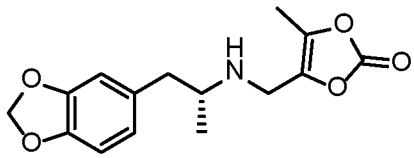


or

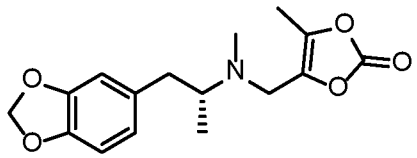


.

88. The compound of claim 86, having the structure:



or



.

89. A pharmaceutical composition comprising a compound of claim 69 and a pharmaceutically acceptable excipient.

90. The pharmaceutical composition of claim 89, capable of providing an *in vivo* plasma level characterized by a Cmax of free amine of about 100 ng/mL to about 500 ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (III) and release of promoiety B.

91. The pharmaceutical composition of claim 89, capable of providing an *in vivo* plasma level characterized by an $AUC_{(0-24)}$ of free amine of about 1000 h*ng/mL to about 6000 h*ng/mL, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (III) and release of promoiety B.

92. The pharmaceutical composition of claim 89, capable of providing an *in vivo* $T_{1/2}$ of free amine of about 5 h to about 15 h, after oral administration of from about 80 mg to about 125 mg of a compound of Formula (III) and release of promoiety B.

93. A method of treating post-traumatic stress disorder (PTSD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition of claim 89.

94. A method of treating an eating disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition of claim 89.

95. A method of treating depression in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition of claim 89.

96. The method of claim 95, wherein the depression is major depressive disorder (MDD) or treatment-resistant depression (TRD).

97. A method of treating an anxiety disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition of claim 89.

98. The method of claim 97, wherein the anxiety disorder is generalized anxiety disorder.

99. A compound selected from compounds 1-11 of Table 6.

100. A compound selected from compounds 1-45 of Table 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/045587

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - C07D 317/44 (2022.01)
ADD. - A61K 31/36; A61P 25/24 (2022.01)

CPC - INV. - C07D 317/44 (2022.08)

ADD. - A61P 25/24; A61K 31/36 (2022.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	1st invention:	
X	PUBCHEM, SID 38492237, Available Date: 05 December 2007 [retrieved on 08 November 2022].,Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/substance/38492237> entire document	1, 3, 4, 6, 10-12, 16-19, 22
A	US 2008/0146567 A1 (Kolczewski et al.) 19 June 2008 (19.06.2008) entire document	1, 3, 4, 6, 10-12, 16-19, 22, 24-33
A	US 2003/0171303 A1 (GALLOP et al) 11 September 2003 (11.09.2003) entire document	1, 3, 4, 6, 10-12, 16-19, 22, 24-33
A	US 2008/0045588 A1 (GANT et al) 21 February 2008 (21.02.2008) entire document	1, 3, 4, 6, 10-12, 16-19, 22, 24-33
A	PUBCHEM, SID 439624087, Available Date: 15 January 2021 [retrieved on 08 November 2022].,Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/substance/439624087> entire document	1, 3, 4, 6, 10-12, 16-19, 22, 24-33
A	PUBCHEM, SID 406789554, Available Date: 18 July 2020 [retrieved on 08 November 2022].,Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/substance/406789554> entire document	1, 3, 4, 6, 10-12, 16-19, 22, 24-33

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 December 2022	FEB 01 2023
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Taina Matos Telephone No. PCT Helpdesk: 571-272-4300

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	2nd invention:	
A	PUBCHEM, SID 243280603, Modify Date: 24 June 2015 [retrieved on 27 December 2022].,Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/substance/243280603> entire document	1, 3, 4, 6, 7, 9-12, 14, 16-20, 22, 24-33
A	US 2003/0171303 A1 (GALLOP et al) 11 September 2003 (11.09.2003) entire document	1, 3, 4, 6, 7, 9-12, 14, 16-20, 22, 24-33
A	US 2008/0045588 A1 (GANT et al) 21 February 2008 (21.02.2008) entire document	1, 3, 4, 6, 7, 9-12, 14, 16-20, 22, 24-33
	3rd invention:	
A	PUBCHEM, SID 243280603, Modify Date: 24 June 2015 [retrieved on 27 December 2022].,Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/substance/243280603> entire document	1, 3, 4, 6, 7, 9-12, 14, 16-20, 22, 24-33, 69, 71, 74, 75, 77-80, 82, 83, 85, 86, 89-98
A	US 2003/0171303 A1 (GALLOP et al) 11 September 2003 (11.09.2003) entire document	1, 3, 4, 6, 7, 9-12, 14, 16-20, 22, 24-33, 69, 71, 74, 75, 77-80, 82, 83, 85, 86, 89-98
A	US 2008/0045588 A1 (GANT et al) 21 February 2008 (21.02.2008) entire document	1, 3, 4, 6, 7, 9-12, 14, 16-20, 22, 24-33, 69, 71, 74, 75, 77-80, 82, 83, 85, 86, 89-98

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/045587

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 23
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1st invention: claims 1, 3, 4, 6, 10-12, 16-19, 22, 24-33
2nd invention: claims 1, 3, 4, 6, 7, 9-12, 14, 16-20, 22, 24-33
3rd invention: claims 1, 3, 4, 6, 7, 9-12, 14, 16-20, 22, 24-33, 69, 71, 74, 75, 77-80, 82, 83, 85, 86, 89-98

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/045587

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-22 and 24-100 are drawn to compounds of Formula (I), or a pharmaceutically acceptable salt thereof, compounds of Formula (II), or a pharmaceutically acceptable salt thereof, compounds of Formula (III), or a pharmaceutically acceptable salt thereof, pharmaceutical compositions thereof, methods of treating post-traumatic stress disorder (PTSD) in a subject in need thereof, methods of treating an eating disorder in a subject in need thereof, methods of treating depression in a subject in need thereof, and methods of treating an anxiety disorder in a subject in need thereof.

The first invention of Group I+ is restricted to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R1 is H; R2 and R2' are each independently H; R3 and R3' are each independently hydrogen; R4, R5, R6, and R7 are each independently hydrogen; X is a cleavable promoiety having the structure –C(O)OCH(R9)OC(O)R10 wherein R9 and R10 are each independently alkyl, specifically wherein R9 and R10 are each independently unsubstituted methyl, pharmaceutical compositions thereof, methods of treating post-traumatic stress disorder (PTSD) in a subject in need thereof, methods of treating an eating disorder in a subject in need thereof, methods of treating depression in a subject in need thereof, and methods of treating an anxiety disorder in a subject in need thereof. It is believed that claims 1, 3, 4, 6, 10, 11, 12, 16-19, 22, and 24-33 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R1 is alkyl, specifically unsubstituted methyl; R2 and R2' are each independently H; R3 and R3' are each independently hydrogen; R4, R5, R6, and R7 are each independently hydrogen; X is a cleavable promoiety having the structure –C(O)OCH(R9)OC(O)R10 wherein R9 and R10 are each independently alkyl, specifically wherein R9 and R10 are each independently unsubstituted methyl, pharmaceutical compositions thereof, methods of treating post-traumatic stress disorder (PTSD) in a subject in need thereof, methods of treating an eating disorder in a subject in need thereof, methods of treating depression in a subject in need thereof, and methods of treating an anxiety disorder in a subject in need thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, R2', R3, R3', R4, R5, R6, R7, X, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structure of Formula (I), or a pharmaceutically acceptable salt thereof; a compound having the core structure of Formula (II), or a pharmaceutically acceptable salt thereof; a compound having the core structure of Formula (III), or a pharmaceutically acceptable salt thereof; a pharmaceutical composition comprising a compound and a pharmaceutically acceptable excipient; a method of treating post-traumatic stress disorder (PTSD) in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a composition; a method of treating an eating disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a composition; a method of treating depression in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a composition; and a method of treating an anxiety disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a composition, these shared technical features do not represent a contribution over the prior art as disclosed by the publication entitled "SID 38492237" by PubChem (hereinafter, "PubChem '237"), the publication entitled "SID 406789554" by PubChem (hereinafter, "PubChem '554"), the publication entitled "SID 439624087" by PubChem (hereinafter, "PubChem '087"), and US 2008/0146567 A1 to Kolczewski et al. (hereinafter, "Kolczewski").

PubChem '237 teaches a compound having the core structure of Formula (I) (Pg. 2, compound as shown).

PubChem '554 teaches a compound having the core structure of Formula (II) (Pg. 2, compound as shown).

PubChem '087 teaches a compound having the core structure of Formula (III) (Pg. 2, compound as shown).

Kolczewski teaches a pharmaceutical composition comprising a compound and a pharmaceutically acceptable excipient (Claim 21, pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically-acceptable excipient); a method of treating post-traumatic stress disorder (PTSD) in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a composition (Para. [0326], a method for treating or preventing a disease or disorder in a patient comprising administering a therapeutically-effective amount of a compound of the present invention to a patient; Para. [0321], compounds of the present invention are ... suitable for the treatment of ... post-traumatic stress disorders); a method of treating an eating disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a composition (Para. [0326], a method for treating or preventing a disease or disorder in a patient comprising administering a therapeutically-effective amount of a compound of the present invention to a patient; Para. [0321], compounds of the present invention are ... suitable for the treatment of ... disorders of eating behaviors); a method of treating depression in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a composition (Para. [0326], a method for treating or preventing a disease or disorder in a patient comprising administering a therapeutically-effective amount of a compound of the present invention to a patient; Para. [0321], compounds of the present invention are ... suitable for the treatment of depression); and a method of treating an anxiety disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a composition (Para. [0326], a method for treating or preventing a disease or disorder in a patient comprising administering a therapeutically-effective amount of a compound of the present invention to a patient; Para. [0321], compounds of the present invention are ... suitable for the treatment of ... anxiety disorders).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/045587

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.