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## (54) Title: FORMULATIONS AND METHODS FOR TREATING ACUTE CANNABINOID OVERDOSE

Effect of ANEB-001 on THC-induced hypocomotion

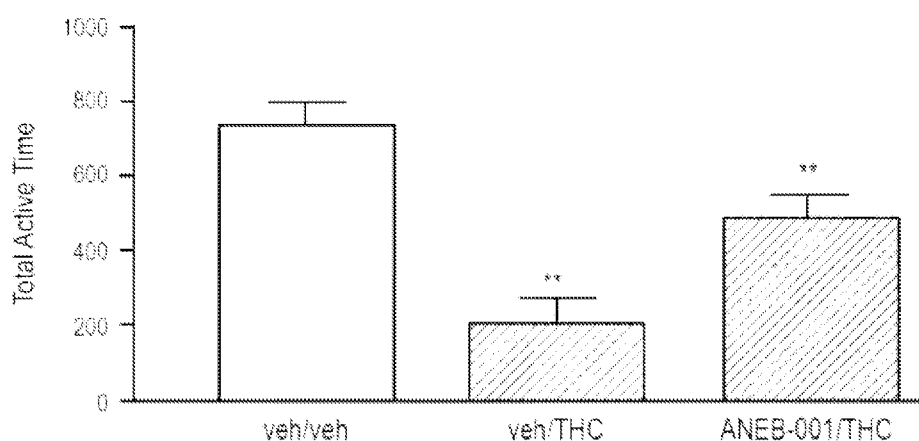


FIG. 1

(57) **Abstract:** Described herein are uses of the CB1 inhibitors (e.g., antagonists, neutral antagonists, inverse agonists) and various methods of using and administering a CB1 inhibitor to a patient, especially patients showing symptoms of drug overdose or suspected of a drug overdose. Further described herein are uses wherein the CB1 inhibitor is ANEB-001. Further described herein are treatments with a CB1 inhibitor for THC or synthetic cannabinoid overdose.

## FORMULATIONS AND METHODS FOR TREATING ACUTE CANNABINOID OVERDOSE

### CROSS-REFERENCE

[0001] This application claims the benefit of U.S. provisional patent application number 63/115,487 filed on November 18, 2020, which is incorporated herein by reference in its entirety.

### BACKGROUND

[0002] The widespread use of  $\Delta^9$ -tetrahydrocannabinol (THC) and synthetic cannabinoids (SCs) has resulted in an increased number of emergency room visits secondary to symptoms of cannabinoid overdose; this is especially notable after cannabis is legalized in a jurisdiction. A medical need therefore exists to treat THC and SC related-overdoses.

### INCORPORATION BY REFERENCE

[0003] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

### BRIEF DESCRIPTION OF THE DRAWINGS

[0004] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

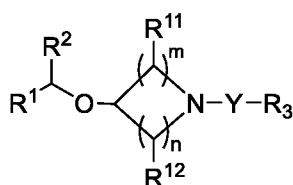
[0005] **Fig. 1** illustrates a plot of the effect of ANEB-001 on THC-induced hypolocomotion in mice. The total active time is plotted against conditions of vehicle only, treatment with THC, and treatment with ANEB-001 and THC. veh: vehicle; THC: tetrahydrocannabinol.

[0006] **Fig. 2** illustrates a plot of a single ascending oral dose study in humans of ANEB-001. Plasma concentrations (ng/mL) of ANEB-001 are plotted against time.

### BRIEF SUMMARY

[0007] Described herein are compositions, formulations, methods, and devices for treating THC and SC overdose. In some embodiments, the overdose is an acute overdose. In some embodiments, methods described herein comprise use of a CB1 inhibitor. Accordingly, described herein are compositions, formulations, and methods for reversing the symptoms of cannabinoid overdose using the CB1 antagonist ANEB-001, or a salt, adjunct, or polymorph thereof. Other aspects of the compositions and methods described herein are described below or throughout this specification.

**[0008]** Provided herein are methods of using a pharmaceutical composition comprising a CB1 inhibitor, the method comprising administering to a patient an effective amount of the CB1 inhibitor and a pharmaceutically acceptable carrier or excipient, wherein the patient has a known or suspected acute drug overdose reaction. Provided herein are methods of using a pharmaceutical composition comprising a CB1 inhibitor, the method comprising administering to a patient an effective amount of the CB1 inhibitor and a pharmaceutically acceptable carrier or excipient, wherein the patient has a known or suspected acute drug overdose reaction, wherein the CB1 inhibitor has the structure of formula (I):



formula (I), or a pharmaceutically acceptable salt or prodrug thereof,

wherein

R<sup>1</sup> is aryl or heteroaryl;

R<sup>2</sup> is alkyl, aryl or heteroaryl;

R<sup>3</sup> is alkyl, aryl, heteroaryl, NR<sup>9</sup>R<sup>10</sup>, OR<sup>15</sup>, or NR<sup>16</sup>C(O)R<sup>17</sup>;

Y is C=O, C=S, SO<sub>2</sub>, or (CR<sup>7</sup>R<sup>8</sup>)<sub>p</sub>;

R<sup>7</sup> and R<sup>8</sup> are independently selected from H and lower alkyl;

R<sup>9</sup> is selected from H, alkyl, aryl, heteroaryl, and non-aromatic heterocyclic groups, or together with R<sup>10</sup> forms a saturated 4, 5, 6, or 7 membered ring optionally containing an additional heteroatom selected from N and O;

R<sup>10</sup> is selected from H and lower alkyl, or together with R<sup>9</sup> forms a saturated 4, 5, 6, or 7 membered ring optionally containing an additional heteroatom selected from N and O;

R<sup>11</sup> and R<sup>12</sup> are independently selected from H and lower alkyl;

R<sup>15</sup> is selected from alkyl and aryl;

R<sup>16</sup> is selected from H and lower alkyl;

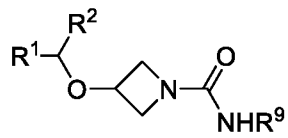
R<sup>17</sup> is selected from alkyl, aryl, and heteroaryl;

m is 1 or 2;

n is 1 or 2; and

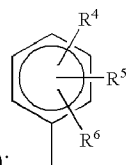
p is 1, 2, 3 or 4. Further provided herein are methods wherein m is 1 and n is 1. Further provided herein are methods wherein R<sup>1</sup> and R<sup>2</sup> are independently aryl. Further provided herein are methods wherein at least one of R<sup>1</sup> and R<sup>2</sup> has a non-hydrogen substituent in the ortho-position(s) thereof relative to the point of attachment to the [—CH—O—] group. Further provided herein are methods wherein R<sup>11</sup> and R<sup>12</sup> are hydrogen. Further provided herein are

methods wherein  $R^3$  is  $NR^9R^{10}$ , and  $R^9$  and  $R^{10}$  are independently lower alkyl or hydrogen. Further provided herein are methods wherein the CB1 inhibitor comprises the structure of formula (Ia):



formula (Ia), or a pharmaceutically acceptable salt or prodrug thereof.

Further provided herein are methods wherein  $R^1$  and  $R^2$  are independently selected from a group

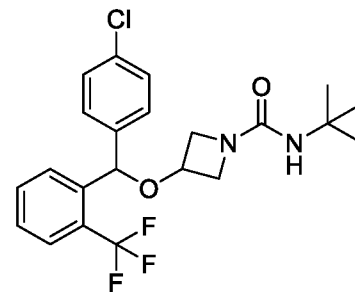


of formula (II): formula (II),

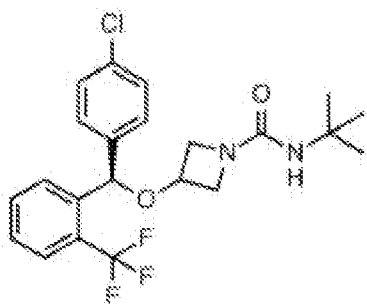
wherein

$R^4$ ,  $R^5$ , and  $R^6$  are independently selected from hydrogen, halo, alkyl (including haloalkyl), thioalkyl, alkoxy (including haloalkoxy), alkylsulfonyl, amino, mono- and di-alkyl amino, mono- and di-aryl amino, alkylaryl amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,  $NR^{14}C(O)R^{19}$ ,  $NR^{14}SO_2R^{20}$ ,  $COOR^{19}$ ,  $OC(O)R^{20}$ ,  $CONR^{13}R^{14}$  and  $SO_2NR^{13}R^{14}$ ,  $R^{13}$  and  $R^{14}$  are independently selected from hydrogen and alkyl or form a 5 or 6 membered ring optionally containing 1 or 2 additional heteroatoms selected from N, O, and S;  $R^{19}$  is selected from H, alkyl, aryl and heteroaryl, and  $R^{20}$  is selected from alkyl, aryl and heteroaryl. Further provided herein are methods wherein at least one of  $R^4$ ,  $R^5$ , and  $R^6$  are chloro or trifluoromethyl. Further provided herein are methods wherein the patient shows signs of an acute cannabinoid overdose. Further provided herein are methods wherein the patient shows signs of cannabinoid hyperemesis syndrome. Further provided herein are methods wherein the method comprises treatment for drug overdose prior to treatment with the CB1 inhibitor. Further provided herein are methods wherein the prior treatment comprises one or more of administration of an opiate antagonist, activated charcoal, or emetic. Further provided herein are methods wherein the prior treatment comprises one or more of orogastric lavage or whole bowel irrigation. Further provided herein are methods wherein the method further comprises a diagnostic test prior to treatment with the CB1 inhibitor. Further provided herein are methods wherein the diagnostic test is a blood test. Further provided herein are methods wherein the patient has a cannabinoid plasma concentration of at least 50  $\mu\text{g/L}$ . Further provided herein are methods wherein the patient has a cannabinoid plasma concentration of at least 100  $\mu\text{g/L}$ . Further provided herein are methods wherein the patient has a cannabinoid plasma concentration of 50  $\mu\text{g/L}$  to 300  $\mu\text{g/L}$ . Further provided herein are methods wherein the pharmaceutical composition is prepared as an oral, sublingual, buccal, rectal, nasal, or parenteral dose. Further provided herein are methods wherein the CB1 inhibitor is cannabigerol, ibipinabant,

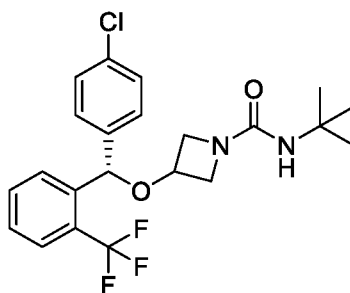
otenabant, tetrahydrocannabivarin, virodhamine, rimonabant, or taranabant. Further provided



herein are methods wherein the CB1 inhibitor has the structure:



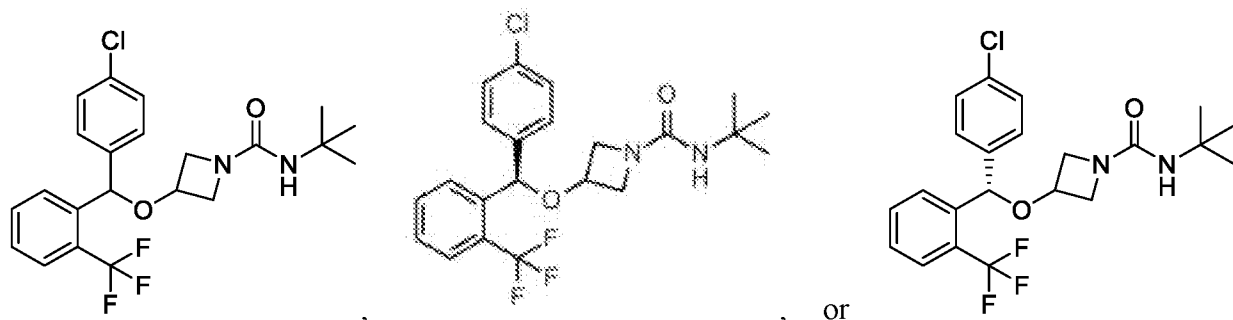
, or



. Further provided herein are

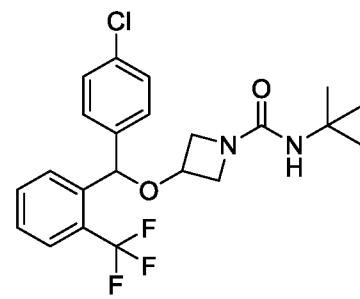
methods wherein the dose of the CB1 inhibitor is 1 mg to 200 mg. Further provided herein are methods wherein the dose of the CB1 inhibitor is 25 mg to 200 mg. Further provided herein are methods wherein the CB1 inhibitor is formulated as an oral, parenteral, intravenous (IV), intramuscular (IM), subcutaneous (SC), endotracheal, sublingual, buccal, intralingual, submental, transdermal, suppository, or intranasal administration. Further provided herein are methods wherein further comprising administering a pharmaceutically acceptable alkaline agent. Further provided herein are methods wherein the pharmaceutical composition is formulated to deliver an effective dose of the CB1 inhibitor in no more than 10 min. Further provided herein are methods wherein the dose of the CB1 inhibitor or pharmaceutical composition thereof is 50 mg to 200 mg. Further provided herein are methods wherein the dose of the CB1 inhibitor or pharmaceutical composition thereof delivers a therapeutically effective amount of the CB1 inhibitor in no more than 10 minutes. Further provided herein are methods wherein the dose of the CB1 inhibitor or pharmaceutical composition thereof delivers a therapeutically effective amount of the CB1 inhibitor in no more than 5 minutes. Further provided herein are methods wherein the amount of the CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within one hour after oral administration. Further provided herein are methods wherein the amount of the CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within 30 minutes after oral administration. Further provided herein are methods wherein the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 30 min. Further provided herein are methods wherein the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 1 hour.

Provided herein are methods of using a CB1 inhibitor as a pre-exposure prophylactic therapy comprising administering an effective amount of the CB1 inhibitor prior to exposure to a cannabinoid. Further provided herein are methods wherein the cannabinoid is tetrahydrocannabinol. Further provided herein are methods wherein CB1 inhibitor is formulated for oral, parenteral, intravenous (IV), intramuscular (IM), subcutaneous (SC), endotracheal, sublingual, buccal, intralingual, submental, transdermal, suppository, or intranasal administration. Further provided herein are methods wherein the CB1 inhibitor has the structure:

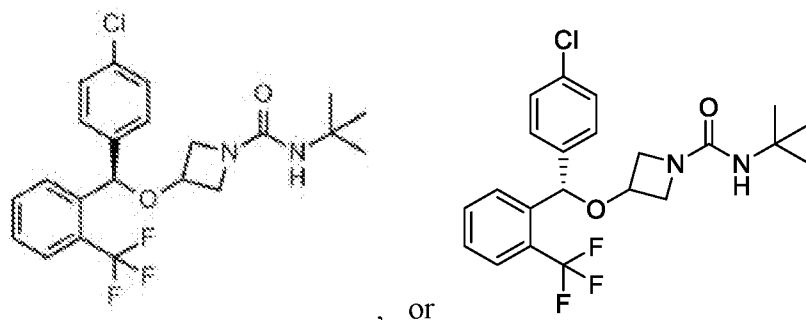


Further provided herein are methods wherein the dose of the CB1 inhibitor is 1 mg to 200 mg. Further provided herein are methods wherein the dose of the CB1 inhibitor is 25 mg to 200 mg.

**[0009]** Provided herein are methods of treating a patient suspected of a drug overdose comprising administering an effective amount of a CB1 inhibitor to a patient and monitoring the patient for reduced symptoms associated with overdose. Further provided herein are methods wherein monitoring comprises monitoring heart rate or respiration. Further provided herein are methods



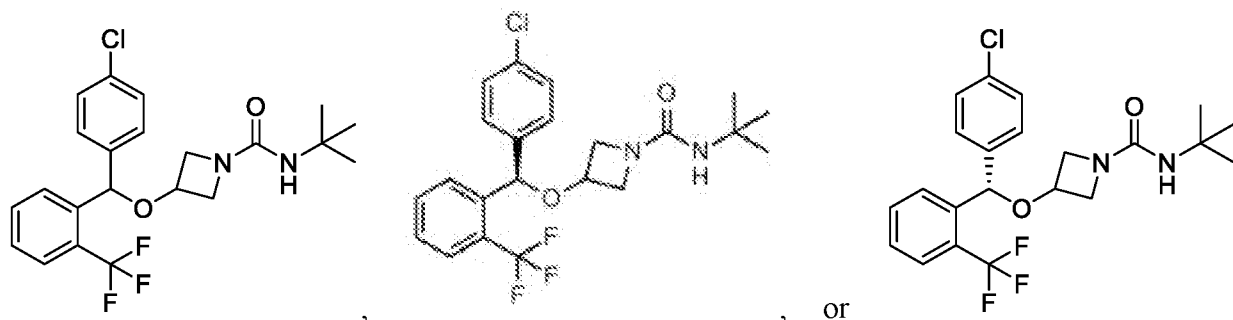
wherein the CB1 inhibitor has the structure:



Further provided herein are methods wherein the dose of the CB1 inhibitor is 1 mg to 200 mg. Further provided herein are methods wherein the dose of the CB1 inhibitor is 25 mg to 200 mg.

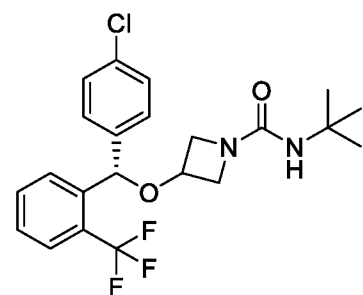
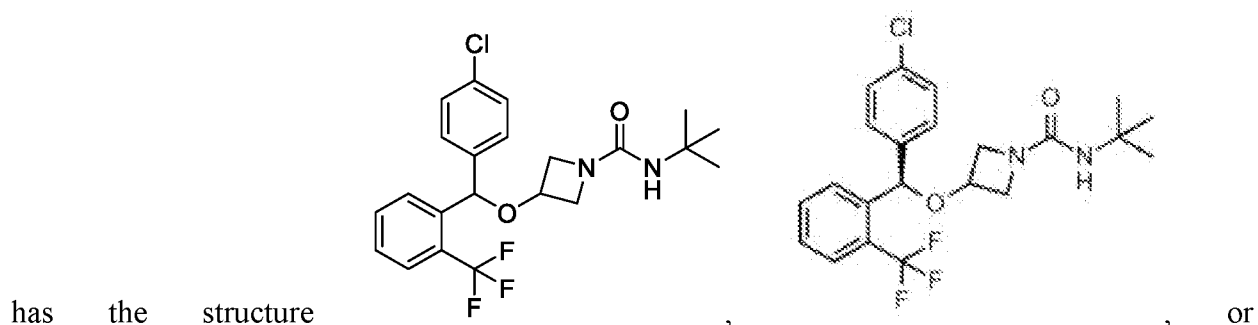
**[0010]** Provided herein are injectable compositions for treating a suspected drug overdose, the composition comprising a CB1 inhibitor, an opioid antagonist, and a benzodiazepine antagonist.

Further provided herein are methods wherein the benzodiazepine antagonist is flumazenil. Further provided herein are methods wherein the opioid antagonist is naloxone. Further provided herein are methods wherein the injectable composition is formulated in a single dose injectable device. Further provided herein are methods wherein the CB1 inhibitor has the structure



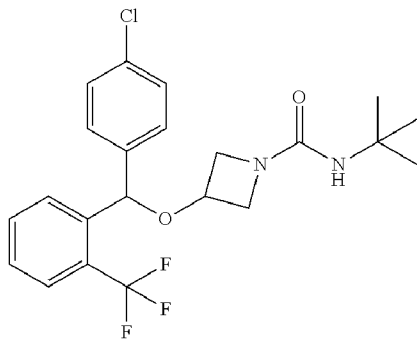
Further provided herein are methods wherein the dose of the CB1 inhibitor is 1 mg to 200 mg. Further provided herein are methods wherein the dose of the CB1 inhibitor is 25 mg to 200 mg.

**[0011]** Provided herein are compositions for treating a suspected drug overdose, the composition comprising a CB1 inhibitor and an anxiolytic agent. Further provided herein are methods wherein the anxiolytic agent is a cannabinoid. Further provided herein are methods wherein the cannabinoid is cannabidiol. Further provided herein are methods wherein composition is formulated for intranasal delivery. Further provided herein are methods wherein the CB1 inhibitor

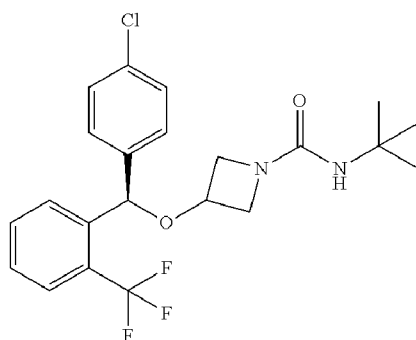


. Further provided herein are methods wherein the dose of the CB1 inhibitor is 1 mg to 200 mg. Further provided herein are methods wherein the dose of the CB1 inhibitor is 25 mg to 200 mg.

**[0012]** Provided herein are methods of using a pharmaceutical composition comprising a CB1 inhibitor, the method comprising orally administering to a patient an effective amount of the CB1 inhibitor and a pharmaceutically acceptable carrier or excipient, wherein the patient has an acute drug overdose reaction, wherein the CB1 inhibitor has the structure:



, or a pharmaceutically acceptable salt thereof, wherein the dose of the CB1 inhibitor is 50 mg to 300 mg, and wherein the amount of CB1 inhibitor in the bloodstream of the patient reaches at least 200 ng/mL within one hour after oral administration. Further provided herein are methods wherein the patient shows signs of an acute cannabinoid overdose. Further provided herein are methods wherein the acute cannabinoid overdose is caused by a compound from the *Cannabis* genus. Further provided herein are methods wherein the acute cannabinoid overdose is caused by a synthetic cannabinoid. Further provided herein are methods wherein the acute cannabinoid overdose is caused by oral ingestion of cannabinoids or synthetic cannabinoids. Further provided herein are methods wherein the patient shows signs of cannabinoid hyperemesis syndrome. Further provided herein are methods wherein the method further comprises treatment for drug overdose prior to treatment with the CB1 inhibitor. Further provided herein are methods wherein the prior treatment comprises one or more of administration of an opiate antagonist, activated charcoal, or emetic. Further provided herein are methods wherein the method further comprises a diagnostic test prior to treatment with the CB1 inhibitor. Further provided herein are methods wherein the diagnostic test is a blood test. Further provided herein are methods wherein the patient has a cannabinoid plasma concentration of at least 50 µg/L. Further provided herein are methods wherein the patient has a cannabinoid plasma concentration of 50 µg/L to 300 µg/L. Further provided herein are methods wherein the dose of the CB1 inhibitor is 50 mg to 200 mg. Further provided herein are methods wherein the dose of the CB1 inhibitor is 75 mg to 200 mg. Further provided herein are methods wherein the CB1 inhibitor has the



structure:

. Further provided herein are methods wherein the amount of CB1 inhibitor in the bloodstream of the patient reaches at least 200 ng/mL within 30 minutes after oral administration.

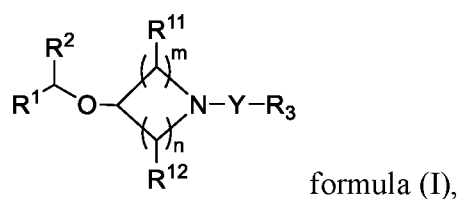
DETAILED DESCRIPTION

[0013] Described herein are compositions, formulations, and methods for reversing cannabinoid overdose and/or one or more symptoms thereof comprising administering a CB1 inhibitor in an amount sufficient to reduce the severity of one or more overdose symptoms or reverse the cannabinoid overdose in a patient. Further described herein are fast-acting formulations comprising CB1 inhibitors for emergency/rescue applications. Further described herein are formulations comprising combinations of CB1 inhibitors and other active agents.

*CB1 Inhibitors*

[0014] Compositions, formulations, and methods described herein may comprise use of a CB1 inhibitor. In some embodiments, the CB1 inhibitor is a CB1 antagonist. In some embodiments, the CB1 inhibitor is a CB1 inverse agonist. In some embodiments, the CB1 inhibitor is a CB1 neutral antagonist. Certain embodiments include the use of the CB1 antagonist and a specific cannabinoid antagonist.

[0015] Provided herein compounds having the structure of formula (I):



wherein

R<sup>1</sup> is aryl or heteroaryl;

R<sup>2</sup> is alkyl, aryl or heteroaryl;

R<sup>3</sup> is alkyl, aryl, heteroaryl, NR<sup>9</sup>R<sup>10</sup>, OR<sup>15</sup>, or NR<sup>16</sup>C(O)R<sup>17</sup>;

Y is C=O, C=S, SO<sub>2</sub>, or (CR<sup>7</sup>R<sup>8</sup>)<sub>p</sub>;

R<sup>7</sup> and R<sup>8</sup> are independently selected from H and lower alkyl;

R<sup>9</sup> is selected from H, alkyl, aryl, heteroaryl, and non-aromatic heterocyclic groups, or together with R<sup>10</sup> forms a saturated 4, 5, 6, or 7 membered ring optionally containing an additional heteroatom selected from N and O;

R<sup>10</sup> is selected from H and lower alkyl, or together with R<sup>9</sup> forms a saturated 4, 5, 6, or 7 membered ring optionally containing an additional heteroatom selected from N and O;

R<sup>11</sup> and R<sup>12</sup> are independently selected from H and lower alkyl;

R<sup>15</sup> is selected from alkyl and aryl;

R<sup>16</sup> is selected from H and lower alkyl;

R<sup>17</sup> is selected from alkyl, aryl and heteroaryl;

m is 1 or 2;

n is 1 or 2; and

p is 1, 2, 3 or 4.

**[0016]** In some embodiments,  $R^1$  and/or  $R^2$  is substituted with 1 to 3 substituents. In some embodiments,  $R^1$  and/or  $R^2$  is substituted with 1 or 2 substituents. In one embodiment,  $R^1$  and  $R^2$  are independently selected from a group  $-A(R^4)(R^5)(R^6)$ , where A is an aryl or heteroaryl ring, and where A may be selected from phenyl, naphthyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isooxazolyl, pyridyl, pyrazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl and isobenzofuryl. In some embodiments, one of  $R^1$  and  $R^2$  is aryl and the other is heteroaryl, or both  $R^1$  and  $R^2$  are aryl. In some embodiments, both  $R^1$  and  $R^2$  are monocyclic. In this embodiment,  $R^4$ ,  $R^5$ , and  $R^6$  are independently selected from hydrogen, halo, alkyl (including haloalkyl), thioalkyl, alkoxy (including haloalkoxy), alkylsulfonyl, amino, mono- and di-alkyl amino, mono- and di-aryl amino, alkylarylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,  $NR^{14}C(O)R^{19}$ ,  $NR^{14}SO_2R^{20}$ ,  $COOR^{19}$ ,  $OC(O)R^{20}$ ,  $CONR^{13}R^{14}$  and  $SO_2NR^{13}R^{14}$ , wherein  $R^{13}$  and  $R^{14}$  are independently selected from hydrogen and alkyl or may form a 5 or 6 membered ring optionally containing 1 or 2 additional heteroatoms selected from N, O and S; and  $R^{19}$  is selected from H, alkyl, aryl and heteroaryl and  $R^{20}$  is selected from alkyl, aryl and heteroaryl. The groups  $R^1$  and  $R^2$  may be the same or different, and in one embodiment are different. In some embodiments,  $R^3$  is  $NR^9R^{10}$ . In some embodiments,  $R^3$  is  $NR^9R^{10}$ , and  $R^9$  and  $R^{10}$  are independently lower alkyl or hydrogen. In some embodiments, Y is C=O. In some embodiments, Y is C=O and  $R^3$  is  $NR^9R^{10}$ . In some embodiments,  $R^3$  is  $NR^9R^{10}$ ,  $R^9$  is lower alkyl, and  $R^{10}$  is hydrogen.

**[0017]** In some embodiments of a compound of Formula (I) where  $R^4$ ,  $R^5$ , and  $R^6$  are selected from halo. In some embodiments, the halo group is fluoro, chloro, bromo or iodo. In some embodiments, the halo group is chloro or bromo. In some embodiments,  $R^4$ ,  $R^5$ , and  $R^6$  are selected from alkyl, thioalkyl, alkoxy and alkylsulfonyl. In some embodiments,  $R^4$ ,  $R^5$ , and  $R^6$  are selected from lower alkyl. In some embodiments,  $R^4$ ,  $R^5$ , and  $R^6$  are selected from methyl and ethyl. Where  $R^4$ ,  $R^5$ , and  $R^6$  are selected from haloalkyl, the alkyl is in some embodiments methyl, and the  $R^4$ ,  $R^5$ , or  $R^6$  group is trifluoromethyl. Where  $R^4$ ,  $R^5$ , and  $R^6$  are selected from haloalkoxy, the alkyl is in some embodiments methyl and the  $R^4$ ,  $R^5$ , or  $R^6$  group is trifluoromethoxy or difluoromethoxy. In some embodiments, one or two of  $R^4$ ,  $R^5$ , and  $R^6$  are hydrogen. In some embodiments, at least one of the  $R^1$  and  $R^2$  groups has a non-hydrogen substituent in the ortho-position(s) relative to the point of attachment to the  $[-CH-O-]$  group. The  $R^1$  or  $R^2$  groups may independently have one or two non-hydrogen substituents in said ortho position(s). Preferred ortho-substituents include halo and haloalkyl, as described herein. In some embodiments, ortho-substituents are chloro and trifluoromethyl. In some

embodiments, if  $\text{—Y—R}^3$  is  $\text{—C(O)NH(alkyl)}$  then:  $\text{R}^1$  and/or  $\text{R}^2$  is selected from heteroaryl; and/or m and/or n is 2; and/or  $\text{R}^{11}$  and/or  $\text{R}^{12}$  is lower alkyl. In some embodiments, if  $\text{—Y—R}^3$  is  $\text{—C(O)NH(alkyl)}$  then:  $\text{R}^1$  and/or  $\text{R}^2$  is selected from aryl, and m and n are 1.

**[0018]** In some embodiments of a compound of Formula (I) where  $\text{R}^{13}$  and  $\text{R}^{14}$  form a 5- or 6-membered ring, the ring is 6-membered. In some embodiments, the ring is saturated or partially saturated. In some embodiments where the ring contains additional heteroatoms, such as N and O. In some embodiments, there are 0 or 1 additional heteroatoms.

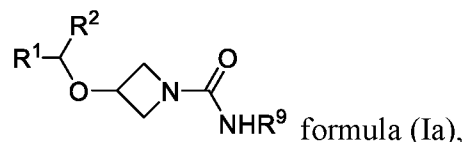
**[0019]** In some embodiments of a compound of Formula (I),  $\text{R}^1$  is selected from aryl. In some embodiments,  $\text{R}^2$  is selected from aryl or heteroaryl. In some embodiments,  $\text{R}^3$  is selected from  $\text{NR}^9\text{R}^{10}$ . In an alternative embodiment  $\text{R}^3$  is selected from alkyl, aryl and heteroaryl. In some embodiments, Y is selected from  $\text{C=O}$ ,  $\text{C=S}$  and  $\text{SO}_2$ . Where Y is selected from  $(\text{CR}^7\text{R}^8)_p$ , then  $\text{R}^7$  and/or  $\text{R}^8$  in some embodiments are hydrogen or methyl, and p is 1 or 2. Where Y is  $\text{SO}_2$ ,  $\text{R}^3$  is in some embodiments selected from alkyl, aryl and heteroaryl. Where Y is  $(\text{CR}^7\text{R}^8)_p$ , in some embodiments p is 1, and  $\text{R}^3$  is selected from alkyl, aryl, heteroaryl. In some embodiments,  $\text{R}^9$  is selected from piperidinyl (such as 1-piperidinyl) and morpholinyl (such as 4-morpholinyl). In some embodiments,  $\text{R}^9$  is cyclic, such as aryl or heteroaryl, and the  $\text{R}^9$  group may be substituted with one or more substituent groups. In some embodiments,  $\text{R}^9$  is substituted with halo, nitro, or alkoxy haloalkyl.

**[0020]** In some embodiments of a compound of Formula (I), the ring formed by  $\text{NR}^9\text{R}^{10}$  may be substituted, and substituents include hydroxy, methoxy, mono- and di-alkyl amino and alkoxycarbonyl. In one embodiment (hereinafter referred to as embodiment (i)),  $\text{R}^9$  is selected from aryl, heteroaryl and a non-aromatic heterocyclic group, and  $\text{R}^{10}$  is selected from H and lower alkyl. In an alternative embodiment (hereinafter referred to as embodiment (ii)),  $\text{R}^9$  is selected from alkyl and  $\text{R}^{10}$  is selected from lower alkyl. In a further alternative embodiment hereinafter referred to as embodiment (iii)),  $\text{R}^9$  and  $\text{R}^{10}$  form a 4, 5, 6, or 7-membered ring, or a 5, 6, or 7-membered ring, optionally containing an additional heteroatom selected from N and O.

**[0021]** In some embodiments of a compound of Formula (I), m is 1 and/or n is 1. In some embodiments, both m and n are 1. Where m is 2, the  $\text{R}^{11}$  groups may be the same or different, but at least one of the  $\text{R}^{11}$  groups in the  $(\text{CHR}^{11})_2$  moiety is hydrogen. Where n is 2, the  $\text{R}^{12}$  groups may be the same or different, but at least one and optionally both of the  $\text{R}^{12}$  groups in the  $(\text{CHR}^{12})_2$  moiety is/are hydrogen. In some embodiments,  $\text{R}^{11}$  and  $\text{R}^{12}$  are independently selected from hydrogen and methyl. In some embodiments, at least one of  $\text{R}^{11}$  and  $\text{R}^{12}$  is hydrogen. In some embodiments,  $\text{R}^{15}$  is selected from alkyl, such as lower alkyl (substituted or unsubstituted). In some embodiments,  $\text{R}^{15}$  is selected from aryl, such as phenyl (substituted or unsubstituted). In one embodiment,  $\text{R}^{15}$  is selected from lower alkyl, benzyl and phenyl. In some

embodiments,  $R^{16}$  is hydrogen. In some embodiments,  $R^{17}$  is lower alkyl, aryl, or heteroaryl, and in one embodiment is aryl.

**[0022]** Provided herein are compounds having the structure of formula (Ia)



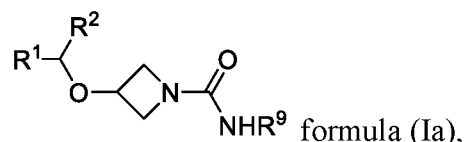
or a pharmaceutically acceptable salt or prodrug thereof,  
wherein

$R^1$  and  $R^2$  are independently selected from aryl or heteroaryl; and

$R^9$  is hydrogen or alkyl;

wherein at least one of  $R^1$  and  $R^2$  has a non-hydrogen substituent in the ortho-position(s) thereof relative to the point of attachment to the  $[-CH-O-]$  group.

**[0023]** Provided herein are compounds having the structure of formula (Ia)



or a pharmaceutically acceptable salt or prodrug thereof,  
wherein

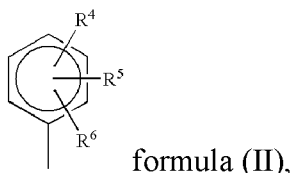
$R^1$  and  $R^2$  are independently selected from aryl; and

$R^9$  is hydrogen or alkyl;

wherein at least one of  $R^1$  and  $R^2$  has a non-hydrogen substituent in the ortho-position(s) thereof relative to the point of attachment to the  $[-CH-O-]$  group.

**[0024]** In the compounds of formula (I) or (Ia),  $R^1$  and  $R^2$  are independently selected from substituted or unsubstituted phenyl or naphthyl. In some embodiments,  $R^1$  and  $R^2$  are independently selected from phenyl or naphthyl having 1 to 3 substituents. In one embodiment the substituent groups are selected from halogen and haloalkyl. In some embodiments,  $R^1$  and  $R^2$  are selected from mono-cyclic aromatic groups.

**[0025]** In some embodiments of the compounds of formula (I) or (Ia),  $R^1$  and  $R^2$  are independently selected from a group of formula (II):



wherein

$R^4$ ,  $R^5$ , and  $R^6$  are independently selected from hydrogen, halo, alkyl (including haloalkyl), thioalkyl, alkoxy (including haloalkoxy), alkylsulfonyl, amino, mono- and di-alkyl amino, mono- and di-aryl amino, alkylarylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,  $NR^{14}C(O)R^{19}$ ,  $NR^{14}SO_2R^{20}$ ,  $COOR^{19}$ ,  $OC(O)R^{20}$ ,  $CONR^{13}R^{14}$  and  $SO_2NR^{13}R^{14}$ ,

$R^{13}$  and  $R^{14}$  are independently selected from hydrogen and alkyl or form a 5 or 6 membered ring optionally containing 1 or 2 additional heteroatoms selected from N, O, and S;

$R^{19}$  is selected from H, alkyl, aryl and heteroaryl, and

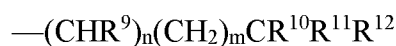
$R^{20}$  is selected from alkyl, aryl and heteroaryl.

**[0026]** In some embodiments of the compounds of formula (I) or (Ia), the groups  $R^1$  and  $R^2$  in are the same or different, and in one embodiment are different. Where  $R^4$ ,  $R^5$ , and  $R^6$  are selected from halo, the halo group is in some embodiments fluoro, chloro, bromo or iodo. Where  $R^4$ ,  $R^5$  and  $R^6$  are selected from alkyl, thioalkyl, alkoxy and alkylsulfonyl, the alkyl is in some embodiments lower alkyl. Where  $R^4$ ,  $R^5$ , and  $R^6$  are selected from aminoalkyl, alkylaminoalkyl and dialkylaminoalkyl, the alkyl is selected from methyl and ethyl. Where  $R^4$ ,  $R^5$ , and  $R^6$  are selected from dialkylaminoalkyl, the dialkylamino fragment is in some embodiments selected from cyclicamino, such as morpholino and piperazino. Where  $R^4$ ,  $R^5$ , and  $R^6$  are selected from haloalkyl, the alkyl is in some embodiments methyl, and the  $R^4$ ,  $R^5$ , or  $R^6$  group is trifluoromethyl. Where  $R^4$ ,  $R^5$ , and  $R^6$  are selected from haloalkoxy, the alkyl is in some embodiments methyl and the  $R^4$ ,  $R^5$ , or  $R^6$  group is selected from trifluoromethoxy or difluoromethoxy. In some embodiments, one or two of  $R^4$ ,  $R^5$ , and  $R^6$  are hydrogen. At least one of the  $R^1$  and  $R^2$  groups has a non-hydrogen substituent in the ortho-position(s). The  $R^1$  or  $R^2$  groups in some embodiments independently have one or two non-hydrogen substituents in the ortho position(s) relative to the point of attachment to the  $[-CH-O-]$  group. Preferred ortho-substituents include halo and haloalkyl, as described herein. In some embodiments, ortho-substituents are chloro and trifluoromethyl. Where  $R^{13}$  and  $R^{14}$  form a 5- or 6-membered ring, the ring in some embodiments is 6-membered. Where the ring contains additional heteroatoms, in some embodiments, these are N and/or O. In some embodiments, there are 0 or 1 additional heteroatoms. In some embodiments,  $R^{13}$  and  $R^{14}$  are independently hydrogen or alkyl.

**[0027]** In some embodiments of the compounds of formula (I) or (Ia),  $R^9$  is selected from hydrogen or alkyl. In some embodiments,  $R^9$  is alkyl. In some embodiments,  $R^9$  is selected from methyl, ethyl, propyl, sec-butyl, or tert-butyl. The alkyl group in some embodiments are substituted or unsubstituted, and in one embodiment is substituted. In some embodiments, one or two substituent groups are present. In some embodiments, substituents are hydroxy, alkoxy,

thioalkyl, amino, mono- and dialkyl amino, alkoxycarbonyl, aryl, and heterocyclic groups including both heteroaryl and non-aromatic heterocyclic groups. Where  $R^9$  is an acyclic alkyl group, in some embodiments it is substituted by a cyclic alkyl group; and where  $R^9$  is a cyclic alkyl group in some embodiments it is substituted by an acyclic alkyl group. Where the substituent group is heteroaryl, in some embodiments the heteroaryl is a 5- or 6-membered ring containing one or more N, O, or S atoms, such as thiophenyl, furanyl, isoxazolyl, thiazolyl and benzothiophenyl. Other substituent groups in some embodiments include dihydrobenzofuranyl, dihydrobenzodioxinyl, tetrahydrofuranyl, pyrrolidinyl, oxopyrrolindyl and benzodioxolyl.

**[0028]** In one embodiment of a compound of formula (I),  $R^3$  has the structure:



wherein

$n$  is 0 or 1;

$m$  is 0, 1, 2 or 3;

$R^9$ ,  $R^{10}$ ,  $R^{11}$ , and  $R^{12}$  are selected from hydrogen, alkyl, hydroxy, alkoxy, thioalkyl, amino, mono- and di-alkyl amino, alkoxycarbonyl and  $R^{13}$ ;

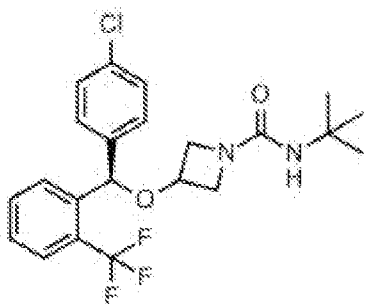
wherein  $R^{13}$  is selected from aryl, heteroaryl and non-aromatic heterocyclic optionally substituted by one or more groups selected from alkyl, halogen, alkoxy, oxo, aryl, heteroaryl and non-aromatic heterocycle.

**[0029]** In some embodiments of Formula (I) or (Ia),  $m$  is 0 or 1 or 2. In some embodiments,  $m$  is 0 or 1. In some embodiments,  $n$  is 0. In some embodiments,  $n$  is 1 and  $m$  is 1. In one embodiment, at least one or two of  $R^{10}$ ,  $R^{11}$ , and  $R^{12}$  are selected from hydrogen. In a further embodiment, at least two of  $R^{10}$ ,  $R^{11}$ , and  $R^{12}$  are selected from methyl. In a further embodiment,  $R^9$  is selected from cyclic alkyl, including cyclopentyl, cyclohexyl, norbornanyl and adamantyl. In some embodiments,  $R^9$  groups are tertiary butyl, sec-butyl, isobutyl, isopropyl, n-propyl and ethyl.

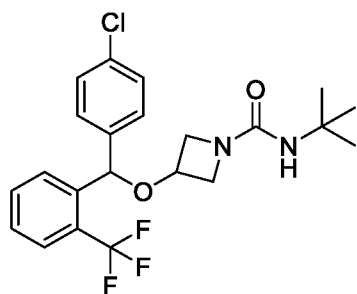
**[0030]** In some embodiments, the CB1 antagonist of Formula (I) or (Ia) is ((R)-(+)-N-tert-butyl-3-[(4-chloro)phenyl-(2-trifluoromethyl)phenyl]methoxyazetidine-1-carboxamide (Compound ANEB-001). In some embodiments, the CB1 antagonist is ((S)-(-)-N-tert-butyl-3-[(4-chloro)phenyl-(2-trifluoromethyl)phenyl]methoxyazetidine-1-carboxamide. In some embodiments, the CB1 antagonist is (N-tert-butyl-3-[(4-chloro)phenyl-(2-trifluoromethyl)phenyl]methoxyazetidine-1-carboxamide. In some embodiments, the CB1 antagonist is Cannabigerol. In some embodiments, the CB1 antagonist is ibipinabant. In some embodiments, the CB1 antagonist is otenabant. In some embodiments, the CB1 antagonist is tetrahydrocannabivarin. In some embodiments, the CB1 antagonist is virodhamine. In some embodiments, the CB1 inverse agonist is rimonabant. In some embodiments, the CB1 inverse

agonist is taranabant. In some embodiments, the CB1 inverse agonist is surinabant or drinabant. In some embodiments, a composition or formulation described herein comprises two or more CB1 inhibitors. In some embodiments, the CB1 inhibitor is a neutral antagonist. In some instances, the CB1 inhibitors comprise one or more substitutions at the phenyl groups that function as effective neutral antagonists of CB1.

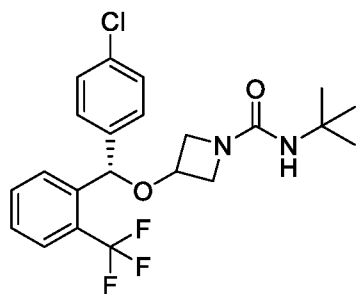
**[0031]** In some instances, a CB1 inhibitor comprises a structure of formula (Ia), wherein R<sup>1</sup> and R<sup>2</sup> are substituted aromatic groups, and R<sup>3</sup> is an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl group. In some instances, R<sup>3</sup> is tert-butyl. In some instances, R<sup>3</sup> is isopropyl. In some instances, R<sup>3</sup> is sec-butyl. In some instances, R<sup>1</sup> is a substituted aromatic group. In some instances, R<sup>1</sup> is an optionally substituted phenyl group. In some instances, R<sup>1</sup> is a phenyl group substituted with a halogen (e.g., F, Cl, Br, I). In some instances, R<sup>1</sup> is a phenyl group substituted with Cl. In some instances, R<sup>1</sup> is a phenyl group para substituted in (4-position) with a halogen (e.g., F, Cl, Br, I). In some instances, R<sup>1</sup> is a 4-chlorophenyl group. In some instances, R<sup>2</sup> is a substituted aromatic group. In some instances, R<sup>2</sup> is an optionally substituted phenyl group. In some instances, R<sup>2</sup> is a phenyl group substituted with a C<sub>1</sub>-C<sub>5</sub> alkyl group. In some instances, R<sup>2</sup> is a phenyl group substituted with a C<sub>1</sub>-C<sub>5</sub> trifluoroalkyl group. In some instances, R<sup>2</sup> is a phenyl group substituted with a trifluoromethyl group. In some instances, R<sup>2</sup> is a phenyl group ortho substituted in (4-position) with a C<sub>1</sub>-C<sub>5</sub> trifluoroalkyl group. In some instances, R<sup>2</sup> is a 2-trifluoromethylphenyl group. In some embodiments, the CB1 inhibitor is compound ANEB-001, having the following structure:



Methods of producing ANEB-001 and related compounds (and enantiomers thereof) are known in the art (*see* Example 81 of US 7,504,522 which is incorporated by reference). In some embodiments, the CB1 inhibitor has the structure:



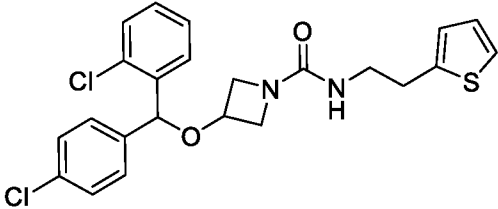
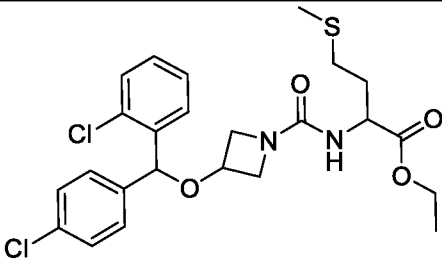
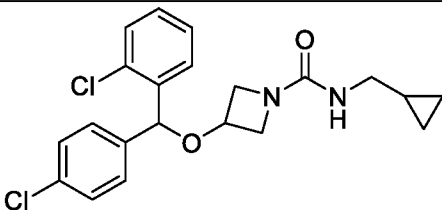
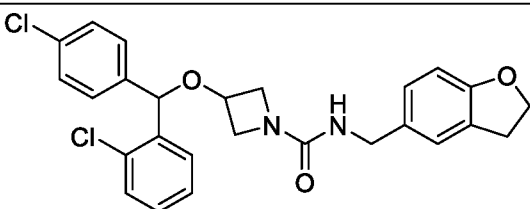
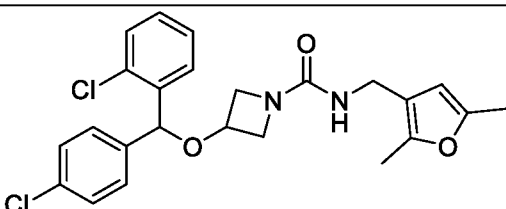
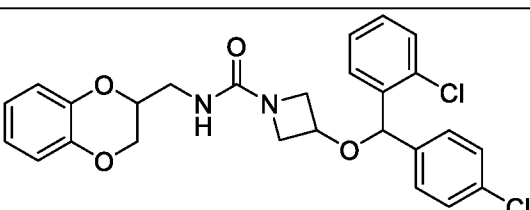
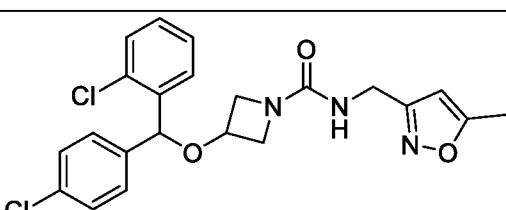
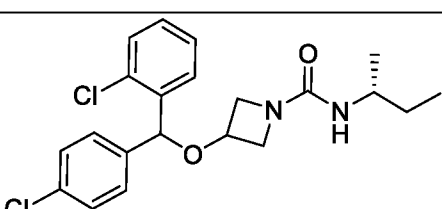
. In some embodiments, the CB1 inhibitor has the structure:



**[0032]** In some embodiments, a CB1 inhibitor is a compound of **Table 1**.

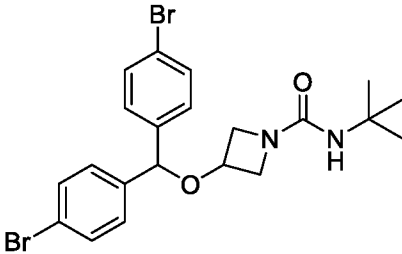
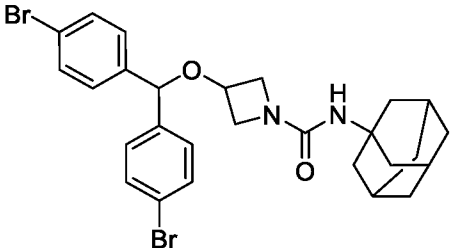
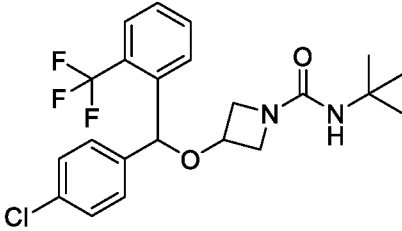
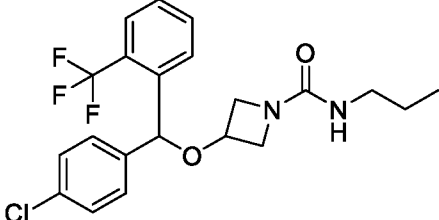
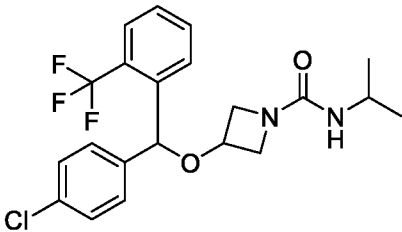
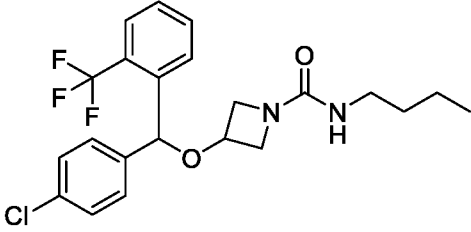
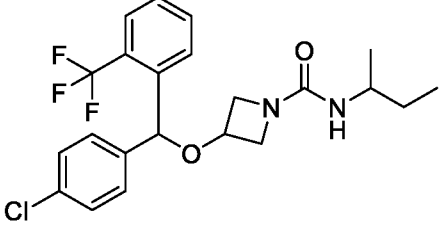
**Table 1**

| # | Name                                                                                                | Structure |
|---|-----------------------------------------------------------------------------------------------------|-----------|
| 1 | 3-[(R)-2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(tert-butyl)azetidine-1-carboxamide (ANEB-001) |           |
| 2 | 3-(2,4,4'-trichlorobenzhydryloxy)-N-(tert-butyl)azetidine-1-carboxamide                             |           |
| 3 | 3-(2,4'-dichlorobenzhydryloxy)-N-(ethyl propionate-2-yl)azetidine-1-carboxamide                     |           |
| 4 | 3-(2,4'-dichlorobenzhydryloxy)-N-(tert-butyl)azetidine-1-carboxamide                                |           |

|    |                                                                                                   |                                                                                      |
|----|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 5  | 3-(2,4'-dichlorobenzhydryloxy)-N-(2-thiophen-2-ylethyl)azetidine-1-carboxamide                    |    |
| 6  | 3-(2,4'-dichlorobenzhydryloxy)-N-[ethyl 4-(methylthio)butyrate-2-yl]azetidine-1-carboxamide       |    |
| 7  | 3-(2,4'-dichlorobenzhydryloxy)-N-(cyclopropylmethyl)azetidine-1-carboxamide                       |    |
| 8  | 3-(2,4'-dichlorobenzhydryloxy)-N-(2,3-dihydrobenzofuran-5-yl-methyl)azetidine-1-carboxamide       |   |
| 9  | 3-(2,4'-dichlorobenzhydryloxy)-N-(2,5-dimethylfuran-3-yl-methyl)azetidine-1-carboxamide           |  |
| 10 | 3-(2,4'-dichlorobenzhydryloxy)-N-(2,3-Dihydrobenzo[1,4]dioxin-2-yl-methyl)azetidine-1-carboxamide |  |
| 11 | 3-(2,4'-dichlorobenzhydryloxy)-N-(5-methylisoxazol-3-yl-methyl)azetidine-1-carboxamide            |  |
| 12 | 3-(2,4'-dichlorobenzhydryloxy)-N-[(R)-sec-butyl]azetidine-1-carboxamide                           |  |

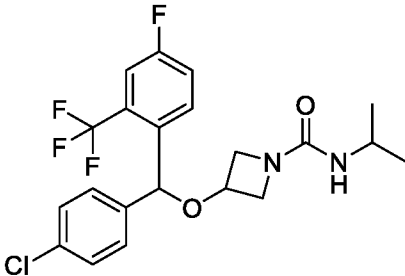
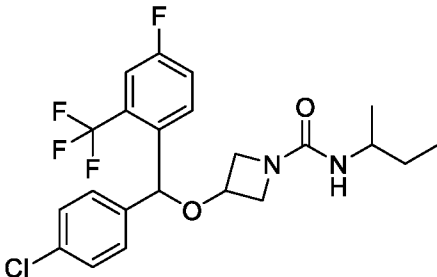
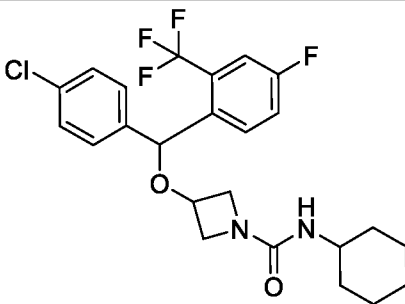
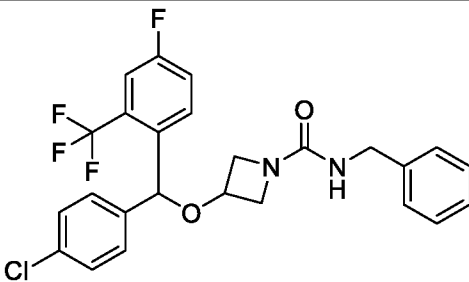
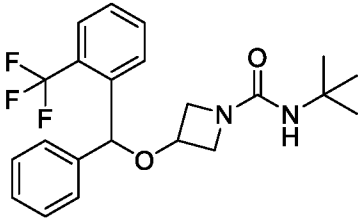
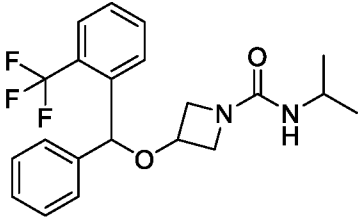
|    |                                                                                       |  |
|----|---------------------------------------------------------------------------------------|--|
| 13 | 3-(2,4'-dichlorobenzhydryloxy)-N-(2-bromothiophen-3-yl-methyl)azetidine-1-carboxamide |  |
| 14 | 3-(2,4'-dichlorobenzhydryloxy)-N-[(S)-sec-butyl]azetidine-1-carboxamide               |  |
| 15 | 3-(2,4'-dichlorobenzhydryloxy)-N-(thiophen-3-yl-methyl)azetidine-1-carboxamide        |  |
| 16 | 3-(2,4'-dichlorobenzhydryloxy)-N-(2-methoxyphenylmethyl)azetidine-1-carboxamide       |  |
| 17 | 3-(2,4'-dichlorobenzhydryloxy)-N-(2-furanylmethyl)azetidine-1-carboxamide             |  |
| 18 | 3-(2,4'-dichlorobenzhydryloxy)-N-(3-ethoxypropyl)azetidine-1-carboxamide              |  |
| 19 | 3-(2,4'-dichlorobenzhydryloxy)-N-(2-tetrahydrofuranylmethyl)azetidine-1-carboxamide   |  |
| 20 | 3-(2,4'-dichlorobenzhydryloxy)-N-(exo-2-norbornanyl)azetidine-1-carboxamide           |  |

|    |                                                                                        |  |
|----|----------------------------------------------------------------------------------------|--|
| 21 | 3-(2,4'-dichlorobenzhydryloxy)-N-(1-phenylpropyl)azetidine-1-carboxamide               |  |
| 22 | 3-(2,4'-dichlorobenzhydryloxy)-N-[(R)-α-methylbenzyl]azetidine-1-carboxamide           |  |
| 23 | 3-(2,4'-dichlorobenzhydryloxy)-N-[(R)-1-(3-methoxyphenyl)ethyl]azetidine-1-carboxamide |  |
| 24 | 3-(2,4'-dichlorobenzhydryloxy)-N-[(S)-1-(3-methoxyphenyl)ethyl]azetidine-1-carboxamide |  |
| 25 | 3-(4,4'-dichlorobenzhydryloxy)-N-(1-adamantyl)azetidine-1-carboxamide                  |  |
| 26 | 3-(4,4'-dichlorobenzhydryloxy)-N-(benzo[b]thiophen-2-yl-methyl)azetidine-1-carboxamide |  |
| 27 | 3-(2,2'-dichlorobenzhydryloxy)-N-(1-adamantyl)azetidine-1-carboxamide                  |  |

|    |                                                                                      |                                                                                      |
|----|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 28 | 3-(4,4'-dibromobenzhydryloxy)-N-(tert-butyl)azetidine-1-carboxamide                  |    |
| 29 | 3-(4,4'-dibromobenzhydryloxy)-N-(1-adamantyl)azetidine-1-carboxamide                 |    |
| 30 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(tert-butyl)azetidine-1-carboxamide |    |
| 31 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(n-propyl)azetidine-1-carboxamide   |   |
| 32 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(iso-propyl)azetidine-1-carboxamide |  |
| 33 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(n-butyl)azetidine-1-carboxamide    |  |
| 34 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(sec-butyl)azetidine-1 carboxamide  |  |

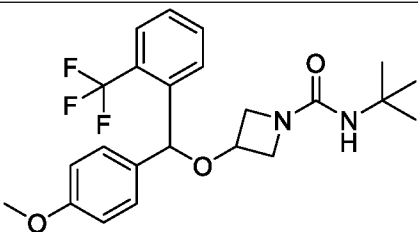
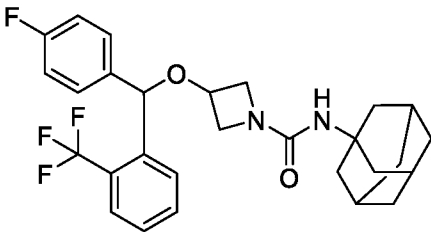
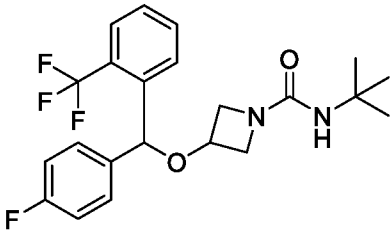
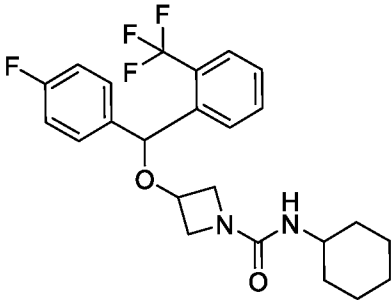
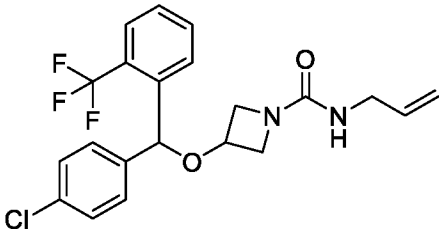
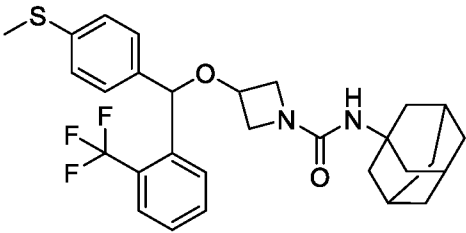
|    |                                                                                                         |  |
|----|---------------------------------------------------------------------------------------------------------|--|
| 35 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(ethyl propionate-3-yl)azetidine-1-carboxamide         |  |
| 36 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(ethyl 3-phenylpropionate-2-yl)azetidine-1-carboxamide |  |
| 37 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(ethyl)azetidine-1-carboxamide                         |  |
| 38 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-[(S)-α-methyl-benzyl]azetidine-1-carboxamide           |  |
| 39 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(2,2,4-trimethylpent-4-yl)azetidine-1-carboxamide      |  |
| 40 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(cyclopentyl)azetidine-1-carboxamide                   |  |
| 41 | 3-(2,4'-dichlorobenzhydryloxy)-N-(2,2,4-trimethylpent-4-yl)azetidine-1-carboxamide                      |  |

|    |                                                                                               |  |
|----|-----------------------------------------------------------------------------------------------|--|
| 42 | 3-(2,4'-dichlorobenzhydryloxy)-N-(2-methylbut-2-yl)azetidine-1-carboxamide                    |  |
| 43 | 3-[2-(trifluoromethyl)-2'-fluoro-4'-bromobenzhydryloxy]-N-(tert-butyl)azetidine-carboxamide   |  |
| 44 | 3-[2-(trifluoromethyl)-4'-(methylthio)benzhydryloxy]-N-(tert-butyl)azetidine-1-carboxamide    |  |
| 45 | 3-[2-(trifluoromethyl)-4'-(methylthio)benzhydryloxy]-N-(isopropyl)azetidine-1-carboxamide     |  |
| 46 | 3-[2-(trifluoromethyl)-4'-(methylthio)benzhydryloxy]-N-(sec-butyl)azetidine-1-carboxamide     |  |
| 47 | 3-[2-(trifluoromethyl)-4'-(methylthio)benzhydryloxy]-N-(benzyl)azetidine-1-carboxamide        |  |
| 48 | 3-[2-(trifluoromethyl)-4-fluoro-4'-chlorobenzhydryloxy]-N-(tert-butyl)azetidine-1-carboxamide |  |

|    |                                                                                               |                                                                                      |
|----|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 49 | 3-[2-(trifluoromethyl)-4-fluoro-4'-chlorobenzhydryloxy]-N-(iso-propyl)azetidine-carboxamide   |    |
| 50 | 3-[2-(trifluoromethyl)-4-fluoro-4'-chlorobenzhydryloxy]-N-(sec-butyl)azetidine-1-carboxamide  |    |
| 51 | 3-[2-(trifluoromethyl)-4-fluoro-4'-chlorobenzhydryloxy]-N-(cyclohexyl)azetidine-1-carboxamide |   |
| 52 | 3-[2-(trifluoromethyl)-4-fluoro-4'-chlorobenzhydryloxy]-N-(benzyl)azetidine-1-carboxamide     |  |
| 53 | 3-[2-(trifluoromethyl)benzhydryloxy]-N-(tert-butyl)azetidine-1-carboxamide                    |  |
| 54 | 3-[2-(trifluoromethyl)benzhydryloxy]-N-(iso-propyl)azetidine-1-carboxamide                    |  |

|    |                                                                                                          |  |
|----|----------------------------------------------------------------------------------------------------------|--|
| 55 | 3-[2-(trifluoromethyl)benzhydryloxy]-N-(sec-butyl)azetidine-1-carboxamide                                |  |
| 56 | 3-[2-(trifluoromethyl)benzhydryloxy]-N-(cyclohexyl)azetidine-1-carboxamide                               |  |
| 57 | 3-[2-(trifluoromethyl)benzhydryloxy]-N-(benzyl)azetidine-1-carboxamide                                   |  |
| 58 | N-(tert-butyl)-3-((4-(trifluoromethoxy)phenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide |  |
| 59 | 3-[2-(trifluoromethyl)-4'-(trifluoromethoxy)benzhydryloxy]-N-(isopropyl)azetidine-1-carboxamide          |  |
| 60 | 3-[2-(trifluoromethyl)-4'-(trifluoromethoxy)benzhydryloxy]-N-(sec-butyl)azetidine-1-carboxamide          |  |
| 61 | 3-[2-(trifluoromethyl)-4'-(trifluoromethoxy)benzhydryloxy]-N-(benzyl)azetidine-1-carboxamide             |  |

|    |                                                                                        |  |
|----|----------------------------------------------------------------------------------------|--|
| 62 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(1-adamantyl)azetidine-1-carboxamide  |  |
| 63 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(cyclohexyl)azetidine-1-carboxamide   |  |
| 64 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(tert-amyl)azetidine-1-carboxamide    |  |
| 65 | 3-[2-(trifluoromethyl)-4'-methylbenzhydryloxy]-N-(1-adamantyl)azetidine-1-carboxamide  |  |
| 66 | 3-[2-(trifluoromethyl)-4'-methylbenzhydryloxy]-N-(tert-butyl)azetidine-1-carboxamide   |  |
| 67 | 3-[2-(trifluoromethyl)-4'-methylbenzhydryloxy]-N-(cyclohexyl)azetidine-1-carboxamide   |  |
| 68 | 3-[2-(trifluoromethyl)-4'-methoxybenzhydryloxy]-N-(1-adamantyl)azetidine-1-carboxamide |  |

|    |                                                                                             |                                                                                      |
|----|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 69 | 3-[2-(trifluoromethyl)-4'-methoxybenzhydryloxy]-N-(tert-butyl)azetidine-1-carboxamide       |    |
| 70 | 3-[2-(trifluoromethyl)-4'-fluorobenzhydryloxy]-N-(1-adamantyl)azetidine-1-carboxamide       |    |
| 71 | 3-[2-(trifluoromethyl)-4'-fluorobenzhydryloxy]-N-(tert-butyl)azetidine-1-carboxamide        |    |
| 72 | 3-[2-(trifluoromethyl)-4'-fluorobenzhydryloxy]-N-(cyclohexyl)azetidine-1-carboxamide        |   |
| 73 | 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(allyl)azetidine-1-carboxamide             |  |
| 74 | 3-[2-(trifluoromethyl)-4'-(methylthio)benzhydryloxy]-N-(1-adamantyl)azetidine-1-carboxamide |  |

|    |                                                                                                         |  |
|----|---------------------------------------------------------------------------------------------------------|--|
| 75 | 3-[2-(trifluoromethyl)-4'-(methylthio)benzhydryloxy]-N-(cyclohexyl)azetidine-1-carboxamide              |  |
| 76 | N-(tert-butyl)-3-((4-(difluoromethoxy)phenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide |  |
| 77 | 3-[2-(trifluoromethyl)-4'-(difluoromethoxy)benzhydryloxy]-N-(sec-butyl)azetidine-1-carboxamide          |  |
| 78 | 3-[2-(trifluoromethyl)-4'-(difluoromethoxy)benzhydryloxy]-N-(isopropyl)azetidine-1-carboxamide          |  |
| 79 | 3-[2-(trifluoromethyl)-4'-(difluoromethoxy)benzhydryloxy]-N-(cyclohexyl)azetidine-1-carboxamide         |  |
| 80 | 3-[2-(trifluoromethyl)-4'-(difluoromethoxy)benzhydryloxy]-N-(allyl)azetidine-1-carboxamide              |  |

|    |                                                                                                                  |  |
|----|------------------------------------------------------------------------------------------------------------------|--|
| 81 | 3-[2-(trifluoromethyl)-4'-fluorobenzhydryloxy]-N-(sec-butyl)azetidine-1-carboxamide                              |  |
| 82 | 3-[2-(trifluoromethyl)-4'-fluorobenzhydryloxy]-N-(iso-propyl)azetidine-1-carboxamide                             |  |
| 83 | 3-[2-(trifluoromethyl)-4'-fluorobenzhydryloxy]-N-[(S)-a-methylbenzyl]azetidine-1-carboxamide                     |  |
| 84 | 3-[2-(trifluoromethyl)-2'-fluoro-4'-(1-piperidinyloxomethyl)benzhydryloxy]-N-(tert-butyl)azetidine-1-carboxamide |  |
| 85 | 3-[2-(trifluoromethyl)-2'-fluorobenzhydryloxy]-N-(tert-butyl)azetidine-1-carboxamide                             |  |

### Formulations

**[0033]** Formulations described herein may comprise a CB1 inhibitor and one or more excipients. In some aspects, described herein is a CB1 inhibitor co-formulated or co-administered with one or more agents that alkalinizes the tissues or body fluids in contact with the drug when disbursed. In some instances, the CB1 inhibitor is ANEB-001. A buccal delivery or sublingual delivery is in some instances particularly useful for this aspect of the methods described herein. Without being bound by theory, alkalinizing the solution in some instances resulting in the absorption of a CB1 inhibitor is hastened as the nitrogen in a CB1 inhibitor is less likely to exist in the protonated state, where the protonated state reduces its ability to traverse biologic membranes. The use of an alkaline formulation in combination with a CB1 inhibitor treatment in some instances facilitates the improved and faster absorption of the

compound, especially in buccal or sublingual delivery. Accordingly, combinations of a CB1 inhibitor with appropriate alkalinizing compounds can either modify the protonation of a CB1 inhibitor or modify the buccal or sublingual tissue to promote improved transmission of a CB1 inhibitor into the bloodstream. Similarly, surfactants, including sodium dodecyl (lauryl) sulfate, polysorbates, laureths, Brij, and benzalkonium chloride are predominantly water-soluble compounds that form associations (micelles) in aqueous solution. These associations in some instances enhance the sublingual or transbuccal permeation of a CB1 inhibitor into the bloodstream.

**[0034]** The active compound (e.g., CB1 inhibitor) may be used in a pharmaceutical formulation including a pharmaceutically acceptable carrier. Accordingly, described herein are pharmaceutical formulations comprising a compound or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) is “acceptable” in the sense of being compatible with the other ingredients of the formulation, the activity of the CB1 inhibitor, and not deleterious to the patient. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art (*see, e.g.,* Remington: The Science and Practice of Pharmacy, Twenty Second Edition, Pharmaceutical Press, 2015, hereby incorporated by reference). The pharmaceutical compositions of the CB1 inhibitors described herein may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

**[0035]** The formulations for CB1 inhibitors (e.g., ANEB-001), include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, suppository or rectal, and topical (including dermal, buccal, sublingual and intraocular) administration, although the most suitable route may depend upon the condition and disorder of the patient. In some instances, such formulations reverse one or more overdose symptoms. In one embodiment, the method comprises using a composition formulated for oral, sublingual, intranasal, absorbed by suppository, or parenteral administration comprising an effective amount of a CB1 inhibitor or a salt or polymorph thereof that is effective to reverse cannabinoid overdose or one or more symptoms of overdose in a patient. In some instances, formulations are fast-acting to reverse or ameliorate an overdose, such as in an emergency or rescue situation. In some instances, fast-acting formulations include methods of administration which deliver an effective amount of a formulation comprising a CB1 inhibitor to the bloodstream in a rapid manner. In some instances, a formulation is delivered in effective concentrations in no more than 1 hr, 30 min, 15 min, 10

min, 5 min, 2 min, 1 min, 30 sec or no more than 15 sec. In some instances, a formulation is delivered in effective concentrations in 10 sec-2 hr, 30 sec-2 hr, 1 min-2 hr, 10 sec- 30 sec, 10 sec-1 min, 10-sec-2 min, or 15 min-2 hr. In some instances, a fast-acting formulation is delivered via intranasal, rectal, buccal, inhalation, or transdermal routes.

**[0036]** The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound described herein (e.g., CB1 inhibitor) or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof (“active ingredient”) with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation. In some instances, the carrier is a biopolymer, such as methyl cellulose.

**[0037]** Formulations of CB1 inhibitors described herein for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. The a CB1 inhibitor compound can be a powder or granules, a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water liquid emulsion, or a water-in-oil liquid emulsion. a CB1 inhibitor may also be used as a bolus, electuary or paste.

**[0038]** Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricants, surface active agents or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer

solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

**[0039]** For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in a conventional manner (*Remington: The Science and Practice of Pharmacy*, Twenty Second Edition, Pharmaceutical Press, 2015). Such compositions may comprise the active ingredient in a flavored basis such as with sucrose or other sweetener, and/or acceptable flavorings.

**[0040]** Pharmaceutically acceptable carriers (e.g., excipients) for formulations described herein (e.g., with a CB1 inhibitor) may comprise one or more polymers. In some embodiments, the pharmaceutically acceptable carrier is a polymer. Examples of polymers suitable for oral, buccal, intranasal, transdermal, thin-film, suppository or other administration include biocompatible and biodegradable polymers. Further examples of biocompatible polymers include natural or synthetic polymers such as polystyrene, polylactic acid, polyketal, butadiene styrene, styreneacrylic-vinyl terpolymer, polymethylmethacrylate, polyethylmethacrylate, polyalkylcyanoacrylate, styrene-maleic anhydride copolymer, polyvinyl acetate, polyvinylpyridine, polydivinylbenzene, polybutyleneterephthalate, acrylonitrile, vinylchloride-acrylates, polycaprolactone, poly(alkyl cyanoacrylates), poly(lactic-co-glycolic acid), and the like. In some instances, the carrier is Labrasol. In some instances, the carrier is methyl cellulose. In further embodiments, the pharmaceutically acceptable carrier comprises one or more biodegradable polymers. Use of biodegradable polymers provides the advantages of using a formulation that will eventually disintegrate, which facilitates release of the benzofuran compound and elimination of the carrier in vivo. However, benzofuran compounds can also be released from the matrix of non-biodegradable polymers as a result of gradual efflux from channels within the polymer matrix, including those formed by soluble materials included in the polymer matrix.

**[0041]** Examples of biodegradable polymers include polylactide polymers include poly(D,L-lactide)s; poly(lactide-co-glycolide) (PLGA) copolymers; polyglycolide (PGA) and polydioxanone; caprolactone polymers; chitosan; hydroxybutyric acids; polyanhydrides and polyesters; polyphosphazenes; and polyphosphoesters. In some instances, the biodegradable polymer for use in the nanoparticles is poly-(D,L-lactide-co-glycolide).

**[0042]** Functionalized poly (D,L-lactide)s can also be used as biodegradable polymers in the nanoparticles described herein. Examples of functionalized poly(D,L-lactide)s include poly(L-lactide), acrylate terminated; poly(L-lactide), amine terminated; poly(L-lactide), azide terminated; poly(L-lactide), 2-bromoisobutyryl terminated; poly(L-lactide), 2-bromoisobutyryl

terminated; poly(L-lactide) 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentonate; poly(L-lactide) N-2-hydroxyethylmaleimide terminated; poly(L-lactide) 2-hydroxyethyl, methacrylate terminated; poly(L-lactide), propargyl terminated; or poly(L-lactide), thiol terminated.

**[0043]** Other biodegradable polymers that can be used in the nanoparticles include AB - 31 -eblock copolymers such as poly(ethylene glycol) methyl ether-block-poly(D,L-lactide); poly(ethylene glycol) methyl ether-block-poly(lactide-co-glycolide) PEG; poly(ethylene glycol)-block-poly( $\epsilon$ -caprolactone) methyl ether PEG; and polypyrrole-block-poly(caprolactone). Further biodegradable polymers include ABA triblock copolymers such as polylactide-block-poly(ethylene glycol)-block-polylactide PLA; poly(lactide-co-glycolide)-block-poly(ethylene glycol)-block-poly(lactide-co-glycolide); poly(lactide-co-caprolactone)-block-poly(ethylene glycol)-block-poly(lactide-co-caprolactone); polycaprolactone-block-polytetrahydrofuran-block-polycaprolactone; and polyglycolide-block-poly(ethylene glycol)-block-polyglycolide PEG.

**[0044]** Biodegradable polymers also include various natural polymers. Examples of natural polymers include polypeptides including those modified non-peptide components, such as saccharide chains and lipids; nucleotides; sugar-based biopolymers such as polysaccharides; cellulose; carbohydrates and starches; dextrans; lignins; polyamino acids; adhesion proteins; lipids and phospholipids (e.g., phosphorylcholine). In some embodiments, the polymer is a cellulose derivative such as hydroxypropyl methylcellulose polymers. Hydroxypropyl methyl cellulose (HPMC) is a non-ionic cellulose ether made through a series of chemical processes, with the natural polymer cellulose as the raw material. The product is a non-ionic cellulose ether in the shape of white powder, odorless and tasteless. HPMC is also known as hypromellose, is a methylcellulose modified with a small amount of propylene glycol ether groups attached to the anhydroglucose of the cellulose.

**[0045]** Useful pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of a CB1 inhibitor described herein. The term “solubilizing agent” generally includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, e.g., polyethylene glycol 400, and glycol ethers. The solubilizing agent can be selected from the group consisting of a cyclodextrin, a glycol, a glycerol, and combinations thereof. In some embodiments, the solubilizing agent includes a cyclodextrin. For example, the solubilizing agent can be selected from the group consisting of a  $\beta$ -cyclodextrin derivative, a  $\gamma$ -cyclodextrin, and combinations thereof. In some embodiments, the solubilizing agent includes a hydroxy alkyl- $\gamma$ -cyclodextrin. The solubilizing

agent can include a  $\beta$ -cyclodextrin selected from the group consisting of a hydroxy alkyl- $\beta$ -cyclodextrin, a sulfoalkyl ether- $\beta$ -cyclodextrin, and combinations thereof. In some embodiments, the solubilizing agent includes hydroxypropyl- $\beta$ -cyclodextrin. In some embodiments, the cyclodextrin can include an  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin derivative, a  $\delta$ -cyclodextrin derivative, a  $\gamma$ -cyclodextrin, or a combination derivative thereof. For example, the solubilizing agent can include a cyclodextrin. The solubilizing agent can include a  $\beta$ -cyclodextrin derivative, a  $\gamma$ -cyclodextrin, or a mixture thereof. For example, the solubilizing agent can include a hydroxy alkyl- $\gamma$ -cyclodextrin. In some embodiments, the solubilizing agent includes a  $\beta$ -cyclodextrin including at least one of a hydroxy alkyl- $\beta$ -cyclodextrin (e.g., hydroxypropyl- $\beta$ -cyclodextrin) or a sulfoalkyl ether- $\beta$ -cyclodextrin (e.g., sulfobutyl ether- $\beta$ -cyclodextrin). For example, the liquid the solubilizing agent can include hydroxypropyl- $\beta$ -cyclodextrin. In some embodiments, the cyclodextrin is CAVASOL® W7 HP (hydroxypropyl- $\beta$ -cyclodextrin). In some embodiments, the cyclodextrin is KLEPTOSE® HP (hydroxypropyl- $\beta$ -cyclodextrin). In some embodiments, the cyclodextrin is CAVAMAX® W7 ( $\beta$ -cyclodextrin). In some embodiments, the cyclodextrin is CAPTISOL® (sulfoalkyl ether- $\beta$ -cyclodextrin). In some embodiments, the cyclodextrin is CAVASOL® W7 M (methyl- $\beta$ -cyclodextrin). In some embodiments, the cyclodextrin is CAVASOL® W8 HP (hydroxypropyl- $\gamma$ -cyclodextrin). In some embodiments, the cyclodextrin is CAVAMAX® W8 ( $\gamma$ -cyclodextrin). In some embodiments, the cyclodextrin is CAVAMAX® W6 ( $\alpha$ -cyclodextrin).

**[0046]** Furthermore, useful pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

**[0047]** Additionally, useful compositions also, optionally, include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

**[0048]** Still other useful compositions include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid

glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

### *Injectable Compositions*

**[0049]** In some embodiments, the CB1 inhibitors as described herein are formulated into an injectable composition. In some embodiments, the injectable composition comprises a CB1 inhibitor, or the pharmaceutical composition described herein, an opioid antagonist, and a benzodiazepine antagonist. In some embodiments, the benzodiazepine antagonist is flumazenil. In some embodiments, the opioid antagonist is naloxone or naltrexone. In some embodiments, the injectable composition is formulated in a single dose injectable device.

**[0050]** CB1 inhibitors described herein may be formulated with one or more pharmaceutically active agents. In some embodiments described herein, the CB1 inhibitor is formulated with naloxone or an opioid antidote. In some instances, an opioid antidote or opioid antagonist includes nalmefene or nalorphine. These can be administered with a Luer-Jet or Luer Lock Prefilled Syringe of 2 mg/2 mL naloxone hydrochloride. The IMS Luer-Jet™ system is a needleless prefilled emergency syringe. In some instances, the CB1 inhibitor is administered with flumazenil or other benzodiazepine antagonist. And similarly, in some instances the CB1 inhibitor is administered with both an opioid and a benzodiazepine antagonist in a single formulation. In another aspect, devices and methods described herein provide an overdose rescue pen that an emergency responder or others can use to treat an unresponsive person suspected of a drug overdose where the drug(s) in question are unknown. Said pen in some instances includes one or more of a narcotic antagonist, a benzodiazepine antagonist, and a cannabinoid antagonist such as ANEB-001, or a CB1 neutral antagonist. Formulations described herein are in some instances are configured for IV, IM, subcutaneous or other injection, or for intranasal delivery. Intranasal formulations comprising certain polymers in some instances increase the residence time of active compounds on the mucosal membranes. Similarly, the pH of the formulation and/or the ionization state of the active compound(s) are in some instances taken into consideration for more effective transport across the nasal mucosa.

**[0051]** A formulation described herein may comprise a CB1 inhibitor and one or more active agents. In some instances, a CB1 inhibitor is administered with an active agent in a 0.1:1, 0.2:1, 0.5:1, 1:1, 1.5:1, 2:1, 5:1, or 10:1 (w/w). In some instances, a CB1 inhibitor is administered with an active agent in a 0.1:1, 0.2:1, 0.5:1, 1:1, 1.5:1, 2:1, 5:1, or 10:1 (molar ratio). In some instances, the CB1 inhibitor is administered with the one or more active agents as a single formulation. In some instances, the CB1 inhibitor is administered with the one or more active agents as two or more formulations. A CB1 inhibitor may be administered in combination with one or more active

agents. In some instances, the active agent is an anxiolytic agent. In some instances, the active agent is a cannabinoid. In some instances, the cannabinoid is cannabidiol (CBD). In some instances, the active agent is CBG (Cannabigerol), CBD (Cannabidiol), CBC (Cannabichromene), CBGV (Cannabigerivarin), THCV (Tetrahydrocannabivarin), CBDV (Cannabidivarin), or CBCV (Cannabichromevarin).

**[0052]** Formulations comprising a CB1 inhibitors (such as ANEB-001) may comprise one or more active agents (e.g., CBD). In some instances, a formulation comprises about 1 mg, 2 mg, 5 mg, 10 mg, 25 mg, 40 mg, 60 mg, 75 mg, 100 mg, 125 mg, or 150 mg of ANEB-001 and 0.5, 1, 2, 5, 10, 20, 50, 75, 100, 150, 300, 500, or 800 mg of CBD. Formulations comprising a CB1 inhibitors (such as ANEB-001) may comprise one or more active agents (e.g., CBD). In some instances, a formulation comprises about 10-150 mg of ANEB-001 and 0.5, 1, 2, 5, 10, 20, 50, 75, 100, or 150 mg of CBD. In some instances, a formulation comprises about 50-150 mg of ANEB-001 and 0.5, 1, 2, 5, 10, 20, 50, 75, 100, 150, 300, 500, or 800 mg of CBD. In some instances, a formulation comprises about 60-120 mg of ANEB-001 and 0.5, 1, 2, 5, 10, 20, 50, 75, 100, or 150, 300, 500, or 800 mg CBD. In some instances, a formulation comprises about 10-150 mg of ANEB-001 and 5-800 mg of CBD. In some instances, a formulation comprises about 1 mg, 2 mg, 5 mg, 10 mg, 25 mg, 40 mg, 60 mg, 75 mg, 100 mg, 125 mg, or 150 mg of ANEB-001 and 5-800 mg of CBD.

#### *Methods of Treatment*

**[0053]** Compositions and formulations described herein may be administered as single or multiple doses. In one aspect, described herein are methods of using a CB1 inhibitor (e.g., ANEB-001) as a single dose, one-time treatment for overdose of THC or SCs, or both. The overdose can also be from consumption of cannabis, a synthetic cannabinoid, or any compound that is an agonist at the CB1 receptor. In some instances, methods described herein include treatments to children who inadvertently consume cannabis or cannabinoid edibles. In related aspects, any suspected overdose patient that presents as mentally disoriented or psychotic or cannot articulate the nature of their condition or the substances that have been ingested or administered can be treated with a CB1 inhibitor. In some instances, a THC or SC overdose is treated by administration of a CB1 inhibitor and one or more active agents (e.g., opioid antagonist, benzodiazepine antagonist, cannabinoid, or other active agent). In some instances, the CB1 inhibitor and one or more active agents are administered as a single formulation.

**[0054]** Described herein are methods of treating patients for one or more of the following: a CB1 antagonist (e.g., ANEB-001) formulated for oral, intravenous (IV), intramuscular (IM), subcutaneous (SC), endotracheal, sublingual, buccal, intralingual, submental, transdermal, and intranasal administration. In some instances, a CB1 inhibitor is formulated in an injector pen for

on-site administration to an overdose patient as well as the use of a CB1 inhibitor by emergency responders to treat THC or SC overdose outside of the hospital. The methods described herein also include the use of a CB1 inhibitor to treat cannabinoid hyperemesis syndrome and the use of various formulations and administration methods for that treatment, including the use of a CB1 inhibitor in suppository form to treat cannabinoid hyperemesis syndrome. In some instances, a CB1 inhibitor is formulated for rapid nasal injection.

**[0055]** In some instances, CB1 antagonists prevent, treat or reduce the severity of various medical conditions and symptoms, including, but not limited to obesity, appetite disorder, another metabolic disorder, drug addiction and/or mental illness. In some instances, CB1 antagonists are used for the treatment of: addiction, alcoholism, Alzheimer's disease, anorexia nervosa, anxiety disorder, appetite disorders, attention deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, cancer, cardiovascular disorders, central nervous system disease, cerebral ischemia, cerebral apoplexy, chemotherapy induced emesis, cocaine addiction, cognitive disorder, dementia, demyelination related disorders, diabetes, diabetic neuropathy, diarrhea, drug dependence, dystonia, eating disorder, emesis, epilepsy, female sexual dysfunction, functional bowel disorder, gastrointestinal disorders, gastric ulcers, generalized anxiety disorder, glaucoma, headache, Huntington's disease, impulse control disorders, inflammation, irritable bowel syndrome, male sexual dysfunction, major depressive disorder, memory disorders, menopause, migraine, muscle spasticity, multiple sclerosis, myalgia, nausea, neuralgia, neurodegenerative disorders, neuroinflammatory disorders, neuropathic pain, obesity, obsessive compulsive disorder, osteoarthritis, pain, panic disorder, Parkinson's disease, plaque sclerosis, premature ejaculation, premenstrual syndrome, psychosexual disorder, psychosis, rheumatoid arthritis, septic shock, schizophrenia, sexual disorders, sleep disorder, spinal cord injury, stroke, Tourette's syndrome, traumatic brain injury, tremor, urinary incontinence, and viral encephalitis.

**[0056]** The methods described herein include pre-exposure prophylaxis treatments. The long term effects of CB1 antagonism, which in some instances includes anhedonia, potentially makes them unsuitable for chronic use. However, in the same way an alcoholic might consume disulfiram before entering a situation when tempted to consume alcohol, one can take a CB1 antagonist, such as ANEB-001, before encountering a situation where they may likely be exposed to or tempted to ingest THC or SCs or both. Similarly, in some instances, a CB1 inhibitor is used to prevent effects from second hand smoke from marijuana. The method of using a CB1 inhibitor in some instances includes use by someone who wishes to gain acceptance to a situation or group by smoking marijuana or SCs, but also wants to remain mentally alert, such as during an undercover police or law enforcement investigation.

**[0057]** In various embodiments, the method reduces the subject's ability to experience euphoria after inhaling or consuming Cannabis or a synthetic cannabinoid.

**[0058]** The methods described herein include use of a CB1 inhibitor to treat cannabinoid hyperemesis syndrome. In one aspect, the use of the CB1 inhibitor in a suppository form is used to treat cannabinoid hyperemesis syndrome.

**[0059]** Methods described herein may be used to treat a patient with a known or suspected acute drug overdose. In some instances, this is determined by the judgement of a qualified healthcare professional or emergency medical technician. In some instances, a lack of or reduced response to prior overdose treatments indicates a potential cannabinoid overdose. Such a patient is in some instances subsequently treated using the CB1 inhibitors described herein. In some instances, a patient is treated with a prior treatment comprising administration of an opiate antagonist, activated charcoal, or emetic. In some instances, the prior treatment is orogastric lavage or whole bowel irrigation.

**[0060]** A CB1 inhibitor may be administered after confirmation of a cannabinoid overdose by one or more testing methods. In some instances, the testing method is a blood test. In some instances, the blood test comprises determination of the cannabinoid (or synthetic cannabinoid) plasma concentration. In some instances, a patient is administered a CB1 inhibitor (e.g., ANEB-001) when his or her cannabinoid plasma concentration is at least 25, 50, 125, 150, 175, 200, 225, 250, 275, 300, 325, or at least 350 ug/L. In some instances, a patient is administered a CB1 inhibitor (e.g., ANEB-001) when his or her cannabinoid plasma concentration is 25-300 ug/L, 50-300 ug/L, 75-300 ug/L, 100-300 ug/L, 125-300 ug/L, or 200-400 ug/L.

**[0061]** A CB1 inhibitor (e.g., ANEB-001) may be administered to obtain diagnostic information about whether a patient is suffering from a cannabinoid or synthetic cannabinoid overdose. If a patient's mental state fails to improve upon administration of a CB1 inhibitor, other etiologies of confusion or altered mental state in some instances are considered, including intoxication with other substances, psychiatric illnesses, metabolic conditions and inflammatory, infectious or traumatic conditions of the brain. Treatment with a CB1 inhibitor in some instances is used for diagnostic purposes.

**[0062]** A CB1 inhibitor may be administered in combination with one or more active agents. In some instances, the active agent is an anxiolytic agent. In some instances, the active agent is a cannabinoid. In some instances, the cannabinoid is cannabidiol (CBD). In some instances, the active agent is CBG (Cannabigerol), CBD (Cannabidiol), CBC (Cannabichromene), CBGV (Cannabigerivarin), THCV (Tetrahydrocannabivarin), CBDV (Cannabidivarin), or CBCV (Cannabichromevarin).

**[0063]** In some instances, a CB1 inhibitor is administered with an active agent in a 0.1:1, 0.2:1, 0.5:1, 1:1, 1.5:1, 2:1, 5:1, or 10:1 (w/w). In some instances, a CB1 inhibitor is administered with an active agent in a 0.1:1, 0.2:1, 0.5:1, 1:1, 1.5:1, 2:1, 5:1, or 10:1 (molar ratio). In some instances, the CB1 inhibitor is administered with the one or more active agents as a single formulation. In some instances, the CB1 inhibitor is administered with the one or more active agents as two or more formulations.

**[0064]** After administration of a CB1 inhibitor (e.g., ANEB-001) described herein, a patient may be monitored for improvement. Monitoring in some instances comprises heart rate monitoring, respiration monitoring, or measures such as patient cognitive function or behavior. In some instances, monitoring comprises patient-reported feelings or answers to verbal or written interrogatories.

#### *Dosages*

**[0065]** CB1 inhibitors may be dosed in various amounts. In some instances, the CB1 inhibitor is dosed at about 1, 2, 5, 10, 25, 40, 50, 75, 90, 100, or about 150 mg. In some instances, the CB1 inhibitor is dosed at no more than 1, 2, 5, 10, 25, 40, 50, 75, 90, 100, or no more than 150 mg. In some instances, the CB1 inhibitor is dosed at least at 1, 2, 5, 10, 25, 40, 50, 75, 90, 100, or at least 150 mg. In some instances, the CB1 inhibitor is dosed at 1-200, 1-100, 1-50, 2-100, 5-100, 10-150, 10-200, 20-120, 50-125, 50-200, or 75-150 mg. In some instances, the CB1 inhibitor is dosed orally. In some instances, the CB1 inhibitor is dosed rectally.

**[0066]** CB1 inhibitors (such as ANEB-001) may be administered in an oral dosage form. In some instances, ANEB-001 is dosed (oral) at 1 mg, 2 mg, 5 mg, 10 mg, 25 mg, 40 mg or more, typically taken once, or once daily. ANEB-001 at 30 mg/kg to 10 mg/kg i.p. is in some instances administered subcutaneously. Similarly, a single dose of ANEB-001 i.p. at 0.1 mg/kg is in some instances used. For example, a CB1 inhibitor test employing forty-two male volunteers to receive one of three oral drug regimens, 40 mg daily for 15 days, placebo for 14 days, then 90 mg on day 15, or placebo for 15 days can be used test effectiveness. Oral dosages of ANEB-001 are in some instances selected from one or more of 1 mg, 2 mg, 5 mg, 10 mg, 25 mg, or 40 mg once daily. In some instances, oral dosages of ANEB-001 are about 1 mg, 2 mg, 5 mg, 10 mg, 25 mg, 40 mg, 50 mg, 60 mg, 75 mg, 90 mg, or about 100 mg. While preferably delivered as an acute therapy, ANEB-001 is administered daily for up to 2, 4, 6, 10, 12, 15, 20, 25, or up to 28 days. In some instances, ANEB-001 is administered as a single acute dosage. CB1 inhibitors (such as ANEB-001) may be administered with one or more active agents, such as CBD. In some instances, a CB1 inhibitor is administered with 0.5, 1, 2, 5, 10, 20, 50, 75, 100, or 150 mg of CBD.

[0067] In one aspect, the present disclosure provides a method of treating known or suspected acute drug overdose reaction in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of CB1 inhibitor, or the pharmaceutical composition as described herein.

[0068] In some embodiments, the subject shows signs of an acute cannabinoid overdose. In some embodiments, the acute cannabinoid overdose is caused by a compound from the *Cannabis* genus. In some embodiments, the acute cannabinoid overdose is caused by a synthetic cannabinoid. In some embodiments, the acute cannabinoid overdose is caused by oral ingestion of cannabinoids or synthetic cannabinoids. In some embodiments, the acute cannabinoid overdose is caused by oral ingestion of cannabinoids or synthetic cannabinoids. In some embodiments, the synthetic cannabinoid is capable of binding to the Cannabinoid (CB1) receptor. In some embodiments, the subject shows signs of cannabinoid hyperemesis syndrome.

[0069] In some embodiments, the method further comprising treatment for drug overdose prior to treatment with the CB1 inhibitor. In some embodiments, the prior treatment comprises one or more of administration of an opiate antagonist, activated charcoal, or emetic.

[0070] In another aspect, the present disclosure provides a method of using the CB1 inhibitor, or the pharmaceutical composition as described herein, comprising administering a therapeutically effective amount of the CB1 inhibitor prior to exposure to a cannabinoid. In some embodiments, the cannabinoid is tetrahydrocannabinol (THC).

[0071] In another aspect, the present disclosure provides a method of treating a subject suspected of a drug overdose, comprising administering a therapeutically effective amount of the CB1 inhibitor to the subject and monitoring said subject for reduced symptoms associated with overdose. In some embodiments, the monitoring comprises monitoring heart rate or respiration.

[0072] In various embodiments of the methods described herein, the method further comprising a diagnostic test prior to treatment with the CB1 inhibitor. In some embodiments, the diagnostic test is a blood test. In some embodiments, the subject has a cannabinoid plasma concentration of at least 25 µg/L. In some embodiments, the diagnostic test is a blood test. In some embodiments, the subject has a cannabinoid plasma concentration of at least 50 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 25 µg/L to 350 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 50 µg/L to 350 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 75 µg/L to 350 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 100 µg/L to 350 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 150 µg/L to 350 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 200 µg/L to 350 µg/L.

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the amount of the CB1 inhibitor is 25-500, 25-400, 25-300, 25-250, 25-200, 25-150, 25-100, or 25-75 mg. In another embodiment, the amount of the CB1 inhibitor is 50-500, 50-400, 50-300, 50-250, 50-200, 50-150, 50-100, or 50-75 mg. In another embodiment, the amount of the CB1 inhibitor is 75-500, 75-400, 75-300, 75-250, 75-200, 75-150, 75-100, or 75-125 mg. In another embodiment, the amount of the CB1 inhibitor is 100-500, 100-400, 100-300, 100-250, 100-200, 100-150, 100-125 mg.

**[0074]** In various embodiments, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 30 minutes. In another embodiment, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 1 hour. In various embodiments, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 10 minutes. In another embodiment, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 15 minutes. In various embodiments, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 45 minutes. In another embodiment, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 20 minutes. In various embodiments, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in 5-60, 5-45, 5-30, 5-25, 5-20, 5-15, 5-10, 10-60, 10-120, 10-30, 20-60, 20-120, 50-120, 60-120, or 90-120 minutes.

**[0075]** In various embodiments of the methods described herein, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within one hour after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within 50 minutes after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within 40 minutes after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within 30 minutes after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within 20 minutes after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within 10 minutes after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within 5 minutes after oral administration.

**[0076]** In various embodiments of the methods described herein, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within one hour after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the

subject reaches at least 150 ng/mL within 50 minutes after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 150 ng/mL within 40 minutes after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 150 ng/mL within 30 minutes after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 150 ng/mL within 20 minutes after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 150 ng/mL within 10 minutes after oral administration. In another embodiment, the amount of CB1 inhibitor in the bloodstream of the subject reaches at least 150 ng/mL within 5 minutes after oral administration.

**[0077]** In some instances, CB1 inhibitor is dosed to provide a T<sub>max</sub> of no more than 5, 4, 3, 2.5, 2.25, 2, 1.75, 1.5, 1.25, 1, 0.75, 0.5, or 0.25 hours. In some instances, CB1 inhibitor is dosed to provide a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75 hr. In some instances, CB1 inhibitor dosed at 100-200 mg provides a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75 hr. In some instances, CB1 inhibitor dosed at 25-250 mg provides a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75 hr. In some instances, CB1 inhibitor dosed at no more than 200 mg provides a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75 hr. In some instances, CB1 inhibitor dosed at no more than 150 mg provides a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75 hr. In some instances, CB1 inhibitor dosed at no more than 100 mg provides a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75 hr.

**[0078]** In one aspect, the present disclosure provides a method of treating known or suspected acute drug overdose reaction in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide, or the pharmaceutical composition as described herein.

**[0079]** In some embodiments, the subject shows signs of an acute cannabinoid overdose. In some embodiments, the acute cannabinoid overdose is caused by a compound from the *Cannabis* genus. In some embodiments, the acute cannabinoid overdose is caused by a synthetic cannabinoid. In some embodiments, the acute cannabinoid overdose is caused by oral ingestion

of cannabinoids or synthetic cannabinoids. In some embodiments, the acute cannabinoid overdose is caused by oral ingestion of cannabinoids or synthetic cannabinoids. In some embodiments, the synthetic cannabinoid is capable of binding to the Cannabinoid (CB1) receptor. In some embodiments, the subject shows signs of cannabinoid hyperemesis syndrome.

**[0080]** In some embodiments, the method further comprising treatment for drug overdose prior to treatment with the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide. In some embodiments, the prior treatment comprises one or more of administration of an opiate antagonist, activated charcoal, or emetic.

**[0081]** In another aspect, the present disclosure provides a method of using the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide, or the pharmaceutical composition as described herein, comprising administering a therapeutically effective amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide prior to exposure to a cannabinoid. In some embodiments, the cannabinoid is tetrahydrocannabinol (THC).

**[0082]** In another aspect, the present disclosure provides a method of treating a subject suspected of a drug overdose, comprising administering a therapeutically effective amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide to the subject and monitoring said subject for reduced symptoms associated with overdose. In some embodiments, the monitoring comprises monitoring heart rate or respiration.

**[0083]** In various embodiments of the methods described herein, the method further comprising a diagnostic test prior to treatment with the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide. In some embodiments, the diagnostic test is a blood test. In some embodiments, the subject has a cannabinoid plasma concentration of at least 25 µg/L. In some embodiments, the diagnostic test is a blood test. In some embodiments, the subject has a cannabinoid plasma concentration of at least 50 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 25 µg/L to 350 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 50 µg/L to 350 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 75 µg/L to 350 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 100 µg/L to 350 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 150 µg/L to 350 µg/L. In some embodiments, the subject has a cannabinoid plasma concentration of about 200 µg/L to 350 µg/L.

**[0084]** In various embodiments of the methods as described here, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is

between about 1 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 5 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 10 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 15 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 20 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 25 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 30 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 35 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 40 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 45 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 50 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 75 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 100 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 125 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 150 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is between about 175 mg to about 200 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is 25-500, 25-400, 25-300, 25-250, 25-200, 25-150, 25-100, or 25-75 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is 50-500, 50-400, 50-300, 50-250,

50-200, 50-150, 50-100, or 50-75 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is 75-500, 75-400, 75-300, 75-250, 75-200, 75-150, 75-100, or 75-125 mg. In another embodiment, the amount of the (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is 100-500, 100-400, 100-300, 100-250, 100-200, 100-150, 100-125 mg.

**[0085]** In various embodiments, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 30 minutes. In another embodiment, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 1 hour. In various embodiments, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 10 minutes. In another embodiment, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 15 minutes. In various embodiments, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 45 minutes. In another embodiment, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 20 minutes. In various embodiments, the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in 5-60, 5-45, 5-30, 5-25, 5-20, 5-15, 5-10, 10-60, 10-120, 10-30, 20-60, 20-120, 50-120, 60-120, or 90-120 minutes.

**[0086]** In various embodiments of the methods described herein, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 200 ng/mL within one hour after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 200 ng/mL within 50 minutes after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 200 ng/mL within 40 minutes after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 200 ng/mL within 30 minutes after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 200 ng/mL within 20 minutes after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-

(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 200 ng/mL within 10 minutes after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 200 ng/mL within 5 minutes after oral administration.

**[0087]** In various embodiments of the methods described herein, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 200 ng/mL within one hour after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 150 ng/mL within 50 minutes after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 150 ng/mL within 40 minutes after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 150 ng/mL within 30 minutes after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 150 ng/mL within 20 minutes after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 150 ng/mL within 10 minutes after oral administration. In another embodiment, the amount of (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide in the bloodstream of the subject reaches at least 150 ng/mL within 5 minutes after oral administration.

**[0088]** In some instances, (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is dosed to provide a T<sub>max</sub> of no more than 5, 4, 3, 2.5, 2.25, 2, 1.75, 1.5, 1.25, 1, 0.75, 0.5, or 0.25 hours. In some instances, (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide is dosed to provide a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75 hr. In some instances, (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide dosed at 100-200 mg provides a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75

hr. In some instances, (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide dosed at 25-250 mg provides a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75 hr. In some instances, (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide dosed at no more than 200 mg provides a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75 hr. In some instances, (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide dosed at no more than 150 mg provides a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75 hr. In some instances, (R)-N-(tert-butyl)-3-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methoxy)azetidine-1-carboxamide dosed at no more than 100 mg provides a T<sub>max</sub> of 0.1-5, 0.1-4, 0.1-3, 0.1-2, 0.1-1.5, 0.1-1, 0.25-3, 0.25-2, 0.25-1.5, 0.25-1, 0.5-3, 0.5-2.5, 0.5-2, 0.5-1.5, 0.5-1.25, 0.5-1, 0.5-0.75, or 0.75 hr.

**[0089]** In some embodiments, the CB1 inhibitor (e.g., ANEB-001) has a half-life of at least 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18 or at least 24 hours. In some embodiments, the CB1 inhibitor has a half-life of 2-24, 2-12, 2-8, 4-24, 4-16, 4-12, 4-8, 6-12, 6-16, 6-10, 8-24, 8-16, 8-12, 12-24, or 12-48 hours.

**[0090]** In some embodiments, the CB1 inhibitor (e.g., ANEB-001) has a reduced seizure liability relative to other CB1 inhibitors. In some embodiments, ANEB-001 has a reduced seizure liability relative to other CB1 inhibitors. In some embodiments, ANEB-001 has a reduced seizure liability relative to other CB1 inhibitors. In some embodiments, ANEB-001 has a reduced seizure liability relative to drinabant, taranabant, or rimonabant. In some instances, seizure liability is reduced by 10, 20, 50, 75, 100, 200, 400, 500, 1000, or 2000 percent.

**[0091]** In some instances, the CB1 inhibitor (e.g., ANEB-001) does not inhibit one or more P450 enzymes. In some embodiments, the CB1 inhibitor is metabolized by one or more of CYP3A4, CYP2C9, CYP2C19, CYP1A2, CYP2E1, CYP2D6, and CYP2A6. In some instances, the CB1 inhibitor does not inhibit CYP3A4. In some embodiments, the CB1 inhibitor comprises an IC<sub>50</sub> of individual CYP450s of less than 100, 80, 70, 60, 50, 40, 30, 20, or 10 micromolar in human liver microsomes.

### *Definitions*

**[0092]** As used herein, the term "about" is intended to qualify the numerical values which it modifies, denoting such a value as variable within a range. When no range, such as a margin of error or a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean the greater of the range which would encompass the

recited value and the range which would be included by rounding up or down to that figure as well, considering significant figures, and the range which would encompass the recited value plus or minus 20%.

**[0093]** As used herein, the term "agonist" refers to a moiety that interacts with, and activates, a receptor and thereby initiates a physiological or pharmacological response characteristic of that receptor.

**[0094]** As used herein, the term "antagonist" refers to a compound that binds to a receptor, such as CB1, but which does not activate the intracellular response(s) initiated by an active agonist compound of the receptor. The antagonist can thereby inhibit the intracellular responses that would be elicited by an agonist or partial agonist if present. An antagonist does not diminish the baseline intracellular response in the absence of an agonist or partial agonist. The term "inverse agonist" refers to a moiety that binds to the endogenous form of the receptor or to the constitutively activated form of the receptor and which inhibits the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of an agonist or partial agonist. It is noted that under certain conditions a compound can behave like an antagonist while under other conditions it can behave as an inverse agonist. Functionally, both an antagonist and an inverse agonist can block and/or reverse the effects of an agonist or partial agonist. In some instances, a CB1 inhibitor includes compounds which act as antagonists or inverse agonists. In some instances, the term "neutral antagonist" is an antagonist that does not change the baseline response level of the receptor when it binds to receptor. In some instances, a neutral antagonist comprises ANEB-001.

**[0095]** As used herein, symptom(s) of cannabinoid overdose is "apparent" or "suspected" when, in the judgment of a trained healthcare provider or emergency responder, the patient has one or more symptom(s) associated with a cannabinoid overdose. In some instances, a cannabinoid overdose is suspected from an absence or reduced response to other overdose related medical treatments (e.g., opioid antagonists, antipsychotics, or other overdose treatment).

**[0096]** As used herein, reversal of symptom(s) of cannabinoid overdose is "apparent" when, in the judgment of a trained healthcare provider or emergency responder, the symptom(s) have been reduced or abated to a noticeable degree. Such a provider may use any appropriate measure to quantify the reversal of symptom(s), e.g., a visual analog scale for self-reporting, a heart rate monitor for tachycardia, an improved affect, etc. "Apparent" reversal of symptom(s) includes, but need not extend to, complete reversal.

**[0097]** As used herein, the term "cannabinoid" is synonymous with "cannabinoid receptor agonist" and refers to a compound which binds to and activates a cannabinoid receptor. The term includes both natural and synthetic compounds.

**[0098]** As used herein, the term "synthetic cannabinoid" ("SC") means a non-naturally-occurring cannabinoid. Most SCs are lipid-soluble, non-polar, small molecules that are fairly volatile, and often have a side-chain of 5-9 saturated carbon atoms. SCs are associated with psychotropic activity from binding CB1 receptors. There are at least five major structural categories for synthetic cannabinoids: classical cannabinoids, non-classical cannabinoids, hybrid cannabinoids, aminoalkylindoles (and their analogues), and eicosanoids. Classical cannabinoids are analogs of THC that are based on a dibenzopyran ring; examples include nabilone, dronabinol, and the (-)-1,1-dimethylheptyl analog of 11-hydroxy- $\Delta^8$ -tetrahydrocannabinol. Non-classical cannabinoids include cyclohexylphenols such as cannabicyclohexanol. Hybrid cannabinoids have a combination of classical and non-classical cannabinoid structural features. Aminoalkylindoles are structurally dissimilar to THC and include naphthoylindoles such as 1-pentyl-3-(1-naphthoyl)indole, phenylacetylindoles such as 1-pentyl-3-(2-methoxyphenylacetyl)indole (JWH-250), and benzoylindoles such as 1-[(N-methylpiperidin-2-yl)methyl]-3-(2-iodobenzoyl)indole; they are the most common SCs found in SC blends due to relative ease of synthesis. Other compounds structurally similar to aminoalkylindoles include naphthoylpyrroles, naphthylmethylindenes, phenylacetylindoles/benzoylindoles, tetramethylcyclopropylindoles, adamantoylindoles, indazole carboxamides, indolecarboxylates, and quinolinyl esters. Eicosanoid SCs are analogs of endocannabinoids such as anandamide. In some instances, SCs are CB1 activators, such as agonists.

**[0099]** As used herein, the term "cannabinoid receptor antagonist" or "CB1 antagonist" refers to a compound that binds to and blocks or dampens the normal biological function of the CB1 receptor and its signaling. This activity can occur in the presence of a natural or synthetic agonist or partial agonist. The term includes cannabinoid receptor antagonists that are selective or nonselective for the CB1 receptor subtype.

**[00100]** As used herein, "active agent" is used to indicate a chemical entity which has biological activity. In certain embodiments, an "active agent" is a compound having pharmaceutical utility. For example an active agent may be an anti-cancer therapeutic.

**[00101]** As used herein, "modulation" refers to a change in activity as a direct or indirect response to the presence of a chemical entity as described herein, relative to the activity of in the absence of the chemical entity. The change may be an increase in activity or a decrease in activity, and may be due to the direct interaction of the compound with the target or due to the interaction of the compound with one or more other factors that in turn affect the target's activity. For example, the presence of the chemical entity may, for example, increase or decrease the target activity by directly binding to the target, by causing (directly or indirectly) another

factor to increase or decrease the target activity, or by (directly or indirectly) increasing or decreasing the amount of target present in the cell or organism.

**[00102]** As used herein, “therapeutically effective amount” of a chemical entity described herein refers to an amount effective, when administered to a human or non-human subject, to provide a therapeutic benefit such as amelioration of symptoms, slowing of disease progression, or prevention of disease.

**[00103]** “Treating” or “treatment” encompasses administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a mammalian subject, particularly a human subject, in need of such an administration and includes (i) arresting the development of clinical symptoms of the disease, such as cancer, (ii) bringing about a regression in the clinical symptoms of the disease, such as cancer, and/or (iii) prophylactic treatment for preventing the onset of the disease, such as cancer.

**[00104]** As used herein, a “pharmaceutically acceptable” component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

**[00105]** “Pharmaceutically acceptable salts” include, but are not limited to salts with inorganic acids, such as hydrochlorate, carbonate, phosphate, hydrogenphosphate, diphosphate, hydrobromate, sulfate, sulfinate, nitrate, and like salts; as well as salts with an organic acid, such as malate, malonate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, gluconate, methanesulfonate, Tris (hydroxymethyl-aminomethane), p-toluenesulfonate, propionate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, oxalate, pamoate, and alkanoate such as acetate,  $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$  where  $n$  is 0-4, and like salts. Other salts include sulfate, methanesulfonate, bromide, trifluoroacetate, picrate, sorbate, benzilate, salicylate, nitrate, phthalate or morpholine. Pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium, and ammonium.

**[00106]** In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts.

**[00107]** As used herein, “subject” refers to a mammal that has been or will be the object of treatment, observation or experiment. The methods described herein can be useful in both human therapy and veterinary applications. In some embodiments, the subject is a human.

**[00108]** “Prodrugs” described herein include any compound that becomes Compound 1 when administered to a subject, e.g., upon metabolic processing of the prodrug. Similarly, “pharmaceutically acceptable salts” includes “prodrugs” of pharmaceutically acceptable salts. Examples of prodrugs include derivatives of functional groups, such as a carboxylic acid group, in Compound 1. Exemplary prodrugs of a carboxylic acid group include, but are not limited to, carboxylic acid esters such as alkyl esters, hydroxyalkyl esters, arylalkyl esters, and aryloxyalkyl esters. Other exemplary prodrugs include lower alkyl esters such as ethyl ester, acyloxyalkyl esters such as pivaloyloxymethyl (POM), glycosides, and ascorbic acid derivatives. Other exemplary prodrugs include amides of carboxylic acids. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, in Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, and in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

**[00109]** A “solvate” is formed by the interaction of a solvent and a compound. The term “compound” is intended to include solvates of compounds. Similarly, “pharmaceutically acceptable salts” includes solvates of pharmaceutically acceptable salts. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates, including monohydrates and hemi-hydrates. Also included are solvates formed with the one or more crystallization solvents.

**[00110]** Pharmaceutically acceptable forms of the compounds recited herein include pharmaceutically acceptable salts, chelates, non-covalent complexes, prodrugs, and mixtures thereof.

**[00111]** A “chelate” is formed by the coordination of a compound to a metal ion at two (or more) points. The term “compound” is intended to include chelates of compounds. Similarly, “pharmaceutically acceptable salts” includes chelates of pharmaceutically acceptable salts.

**[00112]** A “non-covalent complex” is formed by the interaction of a compound and another molecule wherein a covalent bond is not formed between the compound and the molecule. For example, complexation can occur through van der Waals interactions, hydrogen bonding, and electrostatic interactions (also called ionic bonding). Such non-covalent complexes are included in the term “compound”. Similarly, pharmaceutically acceptable salts include “non-covalent complexes” of pharmaceutically acceptable salts.

**[00113]** When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and sub combinations of ranges and specific embodiments therein are intended to be included.

[00114] As used herein, “significant” refers to any detectable change that is statistically significant in a standard parametric test of statistical significance such as Student's T-test, where  $p < 0.05$ .

### EXAMPLES

#### Example 1: *In vivo* Model of CB1 Antagonist Efficacy

[00115] Reversal of THC-induced hypolocomotion in mice: Six C57 mice (Charles River, Wilmington, MA) were administered  $\Delta^9$ -tetrahydrocannabinol (THC) 3 mg/kg ip, 10 min pre-test. The mice exhibited reduced locomotor activity when placed in automated locomotor activity cages for 15 min. In this apparatus, four qualitatively different measures of locomotor activity are automatically scored. In a preliminary screen to identify active CB1 antagonists, ANEB-001 (compound 1) given orally at a dose of 30 mg/kg and 30 min pre-test, significantly reversed the action of THC on the total active time parameter of these locomotor measures (**FIG. 1**). The magnitude of the effect is similar to that elicited by rimonabant given at 3 mg/kg po, and given 30 min pre-test.

[00116] Repeated dose (28 day) toxicity studies were conducted using ANEB-001 in two species, rat and primate, selected on the basis of acceptable bioavailability and comparison of metabolite profiles with those in human liver microsomes. No adverse effects were observed at the highest dose tested in the rat, therefore the no observed adverse effect level in the rat was 75 mg/kg/day. Dose levels of 75 mg/kg/day were associated with hepatic changes consistent with an adaptive response to repeated administration of high doses of ANEB-001 to rats.

[00117] In repeat dose (28 day) toxicity studies no adverse effects were observed at the highest dose level studied in the cynomolgus monkey, 160 mg/kg/day.

#### Example 2: *In vivo* Single Ascending Dose Pharmacokinetics in Humans

[00118] Human subjects were assigned to six different dosage groups of ANEB-001. Groups assigned to receive dosages of 1 mg, 5 mg, 25 mg, 100 mg, or 200 mg had six subjects each, and the 150 mg dosage group had four subjects. ANEB-001 was administered orally to subjects in each group, and the plasma concentration of ANEB-001 in each subject was measured as a function of time after dosing (**FIG. 2**). ANEB-001 had a  $T_{max}$  of approximately 1-1.6 hours, and a terminal elimination half-life up to 19 days.

#### Example 3: Treatment of THC overdose

[00119] A patient admitted to the emergency room is diagnosed with acute THC poisoning from overconsumption of cannabinoid products, such as edibles. The patient is administered a 75 mg oral dose of a CB1 inhibitor, such as ANEB-001, and monitored for signs of improvement (heart rate, cognitive response, etc.).

Example 4: Fast administration for treatment of THC overdose

**[00120]** A human subject diagnosed or suspected of acute THC poisoning from overconsumption of cannabinoid products is treated by a clinician or first responder with a fast-acting nasal formulation comprising a CB1 inhibitor (e.g., ANEB-001) via nasal injector. The fast-acting nasal formulation is designed to provide effective amounts of the CB1 inhibitor in no more than 10 minutes.

Example 5: Combination treatment of THC overdose

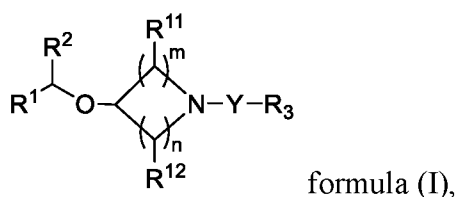
**[00121]** A patient admitted to the emergency room is diagnosed with acute THC poisoning from overconsumption of cannabinoid products, such as edibles. The patient is administered a formulation comprising a 75 mg oral dose of a CB1 inhibitor such as ANEB-001 and CBD (150 mg) and monitored for signs of improvement (heart rate, cognitive response, etc.).

**[00122]** The description and examples presented above and the contents of the application define and describe examples of the many combinations, apparatus, and methods that can be produced or used according to the teachings here. None of the examples and no part of the description should be taken as a limitation on the scope of the inventions or of the meaning of the following claims.

CLAIMS

What is claimed is:

1. A method of using a pharmaceutical composition comprising a CB1 inhibitor, the method comprising administering to a patient an effective amount of the CB1 inhibitor and a pharmaceutically acceptable carrier or excipient, wherein the patient has a known or suspected acute drug overdose reaction, wherein the CB1 inhibitor has the structure of formula (I):



or a pharmaceutically acceptable salt or prodrug thereof,

wherein

$R^1$  is aryl or heteroaryl;

$R^2$  is alkyl, aryl or heteroaryl;

$R^3$  is alkyl, aryl, heteroaryl,  $NR^9R^{10}$ ,  $OR^{15}$ , or  $NR^{16}C(O)R^{17}$ ;

$Y$  is  $C=O$ ,  $C=S$ ,  $SO_2$ , or  $(CR^7R^8)_p$ ;

$R^7$  and  $R^8$  are independently selected from H and lower alkyl;

$R^9$  is selected from H, alkyl, aryl, heteroaryl, and non-aromatic heterocyclic groups, or together with  $R^{10}$  forms a saturated 4, 5, 6, or 7 membered ring optionally containing an additional heteroatom selected from N and O;

$R^{10}$  is selected from H and lower alkyl, or together with  $R^9$  forms a saturated 4, 5, 6, or 7 membered ring optionally containing an additional heteroatom selected from N and O;

$R^{11}$  and  $R^{12}$  are independently selected from H and lower alkyl;

$R^{15}$  is selected from alkyl and aryl;

$R^{16}$  is selected from H and lower alkyl;

$R^{17}$  is selected from alkyl, aryl and heteroaryl;

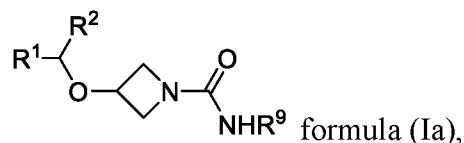
$m$  is 1 or 2;

$n$  is 1 or 2; and

$p$  is 1, 2, 3 or 4.

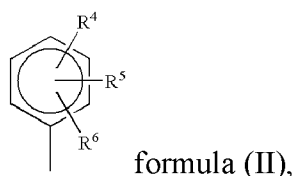
2. The method of claim 1, wherein  $m$  is 1 and  $n$  is 1.
3. The method of claim 1 or 2, wherein  $R^1$  and  $R^2$  are independently aryl.
4. The method of any one of claims 1-3, wherein at least one of  $R^1$  and  $R^2$  has a non-hydrogen substituent in the ortho-position(s) thereof relative to the point of attachment to the  $[-CH-O-]$  group.

5. The method of any one of claims 1-4, wherein  $R^{11}$  and  $R^{12}$  are hydrogen.
6. The method of any one of claims 1-5, wherein  $R^3$  is  $NR^9R^{10}$ , and  $R^9$  and  $R^{10}$  are independently lower alkyl or hydrogen.
7. The method of claim 1, wherein the CB1 inhibitor comprises the structure of formula (Ia):



or a pharmaceutically acceptable salt or prodrug thereof.

8. The method of claim 7, wherein  $R^1$  and  $R^2$  are independently selected from a group of formula (II):



wherein

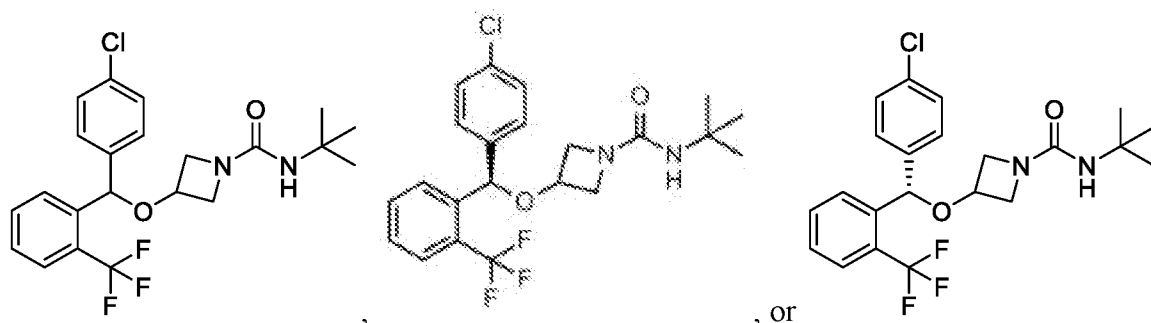
$R^4$ ,  $R^5$ , and  $R^6$  are independently selected from hydrogen, halo, alkyl (including haloalkyl), thioalkyl, alkoxy (including haloalkoxy), alkylsulfonyl, amino, mono- and di-alkyl amino, mono- and di-aryl amino, alkylaryl amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,  $NR^{14}C(O)R^{19}$ ,  $NR^{14}SO_2R^{20}$ ,  $COOR^{19}$ ,  $OC(O)R^{20}$ ,  $CONR^{13}R^{14}$  and  $SO_2NR^{13}R^{14}$ ,

$R^{13}$  and  $R^{14}$  are independently selected from hydrogen and alkyl or form a 5 or 6 membered ring optionally containing 1 or 2 additional heteroatoms selected from N, O and S;

$R^{19}$  is selected from H, alkyl, aryl and heteroaryl, and

$R^{20}$  is selected from alkyl, aryl and heteroaryl.

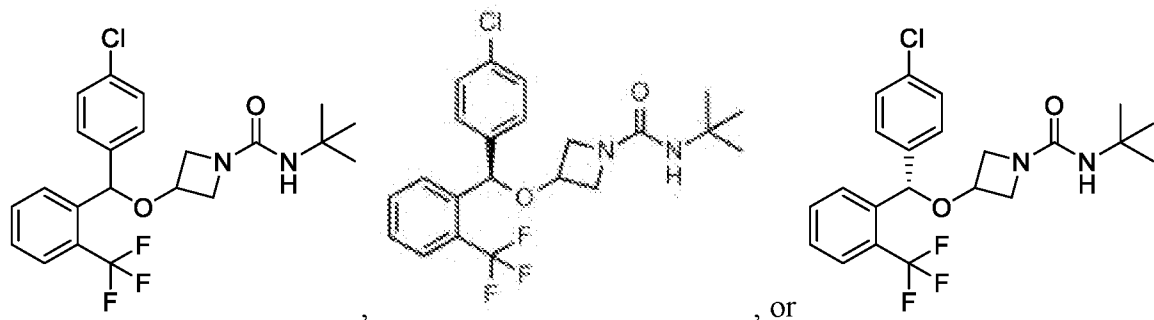
9. The method of claim 8, wherein at least one of  $R^4$ ,  $R^5$ , and  $R^6$  are chloro or trifluoromethyl.
10. The method of claim 1, wherein the CB1 inhibitor has the structure:



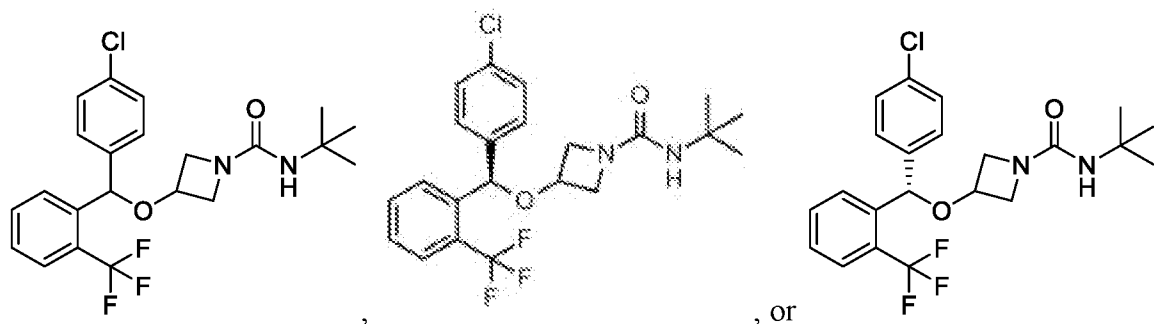
11. The method of any one of claims 1-10, wherein the patient shows signs of an acute cannabinoid overdose.

12. The method of any one of claims 1-10, wherein the patient shows signs of cannabinoid hyperemesis syndrome.
13. The method of any one of claims 1-10, wherein the method comprises treatment for drug overdose prior to treatment with the CB1 inhibitor.
14. The method of any one of claims 1-10, wherein the prior treatment comprises one or more of administration of an opiate antagonist, activated charcoal, or emetic.
15. The method of claim 14, wherein the prior treatment comprises one or more of orogastric lavage or whole bowel irrigation.
16. The method of any one of claims 1-10, wherein the method further comprises a diagnostic test prior to treatment with the CB1 inhibitor.
17. The method of claim 16, wherein the diagnostic test is a blood test.
18. The method of claim 1, wherein the patient has a cannabinoid plasma concentration of at least 50 µg/L.
19. The method of claim 18, wherein the patient has a cannabinoid plasma concentration of at least 100 µg/L.
20. The method of claim 1, wherein the patient has a cannabinoid plasma concentration of 50 µg/L to 300 µg/L.
21. The method of any one of claims 1-20, wherein the pharmaceutical composition is prepared as an oral, sublingual, buccal, rectal, nasal, or parenteral dose.
22. The method of any one of claims 1-20, wherein the dose of the CB1 inhibitor is 1 mg to 200 mg.
23. The method of claim 22, wherein the dose of the CB1 inhibitor is 25 mg to 200 mg.
24. The method of claim 22, wherein the dose of the CB1 inhibitor is 50 mg to 200 mg.
25. The method of claim 22 wherein the dose of the CB1 inhibitor delivers a therapeutically effective amount of the CB1 inhibitor in no more than 10 minutes.
26. The method of claim 22 wherein the dose of the CB1 inhibitor delivers a therapeutically effective amount of the CB1 inhibitor in no more than 5 minutes.
27. The method of claim 22 wherein the amount of the CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within one hour after oral administration.
28. The method of claim 22 wherein the amount of the CB1 inhibitor in the bloodstream of the subject reaches at least 200 ng/mL within 30 minutes after oral administration.
29. The method of claim 22, wherein the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 30 min.
30. The method of claim 22, wherein the method is capable of ameliorating one or more symptoms of the acute drug overdose reaction in no more than 1 hour.

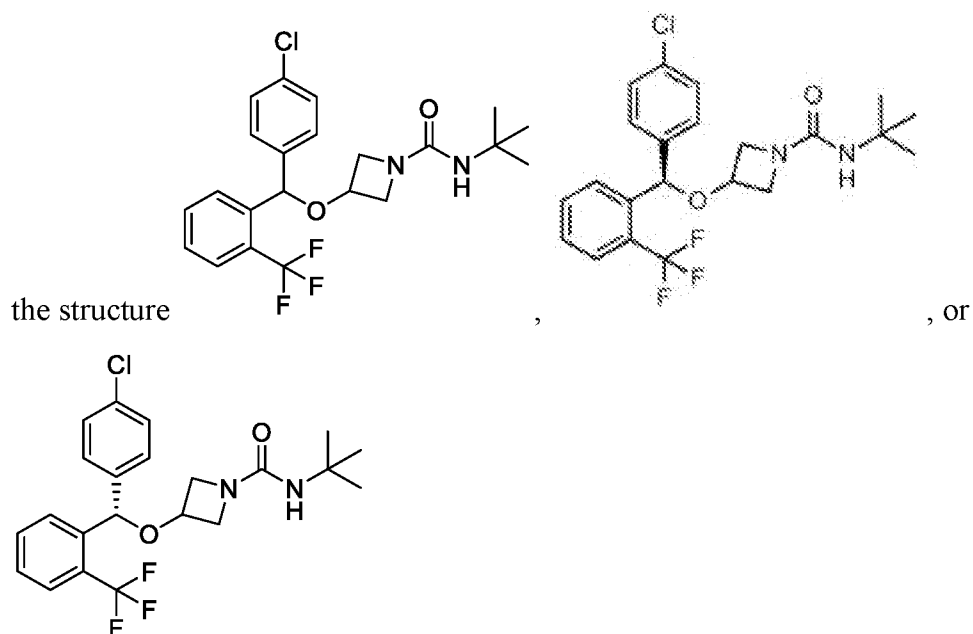
31. The method of any one of claims 1-20, wherein the CB1 inhibitor is formulated as an oral, parenteral, intravenous (IV), intramuscular (IM), subcutaneous (SC), endotracheal, sublingual, buccal, intralingual, submental, transdermal, suppository, or intranasal administration.
32. The method of any one of claims 1-31, further comprising administering a pharmaceutically acceptable alkaline agent.
33. The method of any one of claims 1-32, wherein the pharmaceutical composition is formulated to deliver an effective dose of the CB1 inhibitor in no more than 10 min.
34. A method of using a CB1 inhibitor as a pre-exposure prophylactic therapy comprising administering an effective amount of the CB1 inhibitor prior to exposure to a cannabinoid.
35. The method of claim 34, wherein the cannabinoid is tetrahydrocannabinol.
36. The method of claim 34 or 35 wherein CB1 inhibitor is formulated for oral, parenteral, intravenous (IV), intramuscular (IM), subcutaneous (SC), endotracheal, sublingual, buccal, intralingual, submental, suppository, or intranasal administration.
37. The method of any one of claims 34-36, wherein the CB1 inhibitor has the structure



38. The method of any one of claims 1-37, wherein the excipient comprises a cyclodextrin.
39. The method of claim 34, wherein the dose of the CB1 inhibitor is 1 mg to 200 mg.
40. A method of treating a patient suspected of a drug overdose comprising administering an effective amount of a CB1 inhibitor to a patient and monitoring the patient for reduced symptoms associated with overdose.
41. The method of claim 40, wherein monitoring comprises monitoring heart rate or respiration.
42. The method of claim 40 or 41, wherein the CB1 inhibitor has the structure:

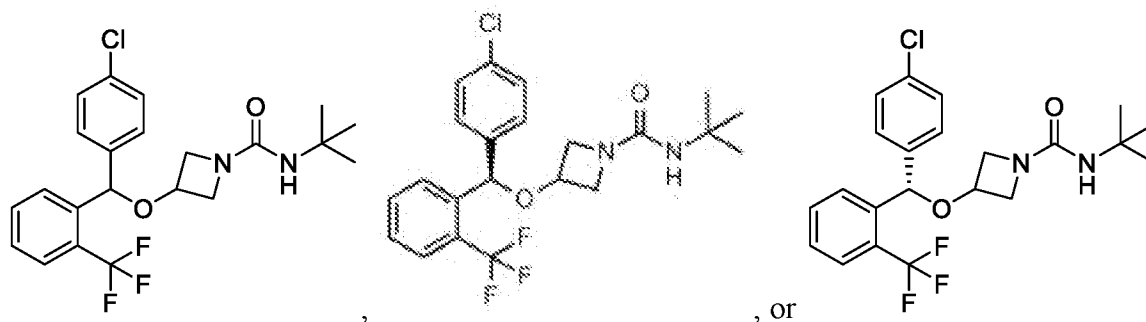


43. The method of claim 42, wherein the dose of the CB1 inhibitor is 1 mg to 200 mg.
44. The method of claim 42, wherein the dose of the CB1 inhibitor is 25 mg to 200 mg.
45. The method of claim 42, wherein the dose of the CB1 inhibitor is 50 mg to 200 mg.
46. An injectable composition for treating a suspected drug overdose, the composition comprising a CB1 inhibitor, an opioid antagonist, and a benzodiazepine antagonist.
47. The injectable composition of claim 46, wherein the benzodiazepine antagonist is flumazenil.
48. The injectable composition of claim 46 or 47, wherein the opioid antagonist is naloxone.
49. The injectable composition of any one of claims 46-48, wherein the injectable composition is formulated in a single dose injectable device.
50. The injectable composition of any one of claims 46-49, wherein the CB1 inhibitor has



51. The injectable composition of claim 50, wherein the dose of the CB1 inhibitor is 1 mg to 200 mg.
52. A composition for treating a suspected drug overdose, the composition comprising a CB1 inhibitor and an anxiolytic agent.
53. The composition of claim 52, wherein the anxiolytic agent is a cannabinoid.
54. The composition of claim 53, wherein the cannabinoid is cannabidiol (CBD).
55. The composition of any one of claims 52-54, wherein composition is formulated for intranasal delivery.

56. The composition of any one of claims 52-55, wherein the CB1 inhibitor has the structure



57. The composition of claim 56, wherein the dose of the CB1 inhibitor is 1 mg to 200 mg.

Effect of ANEB-001 on THC-induced hypolocomotion

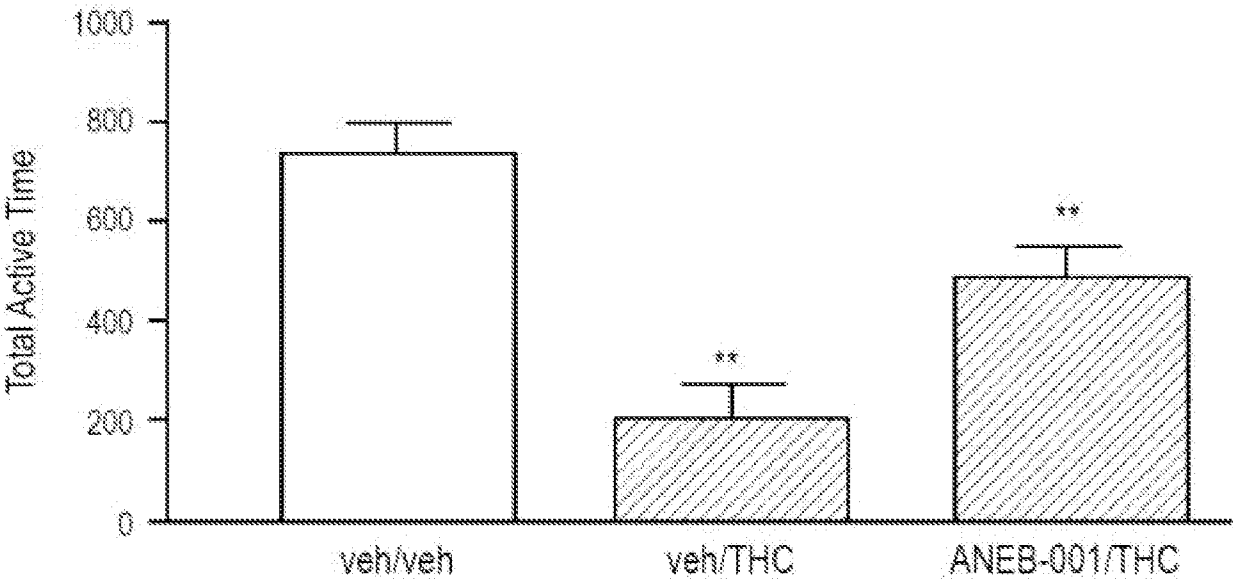


FIG. 1

Single Ascending Dose PK

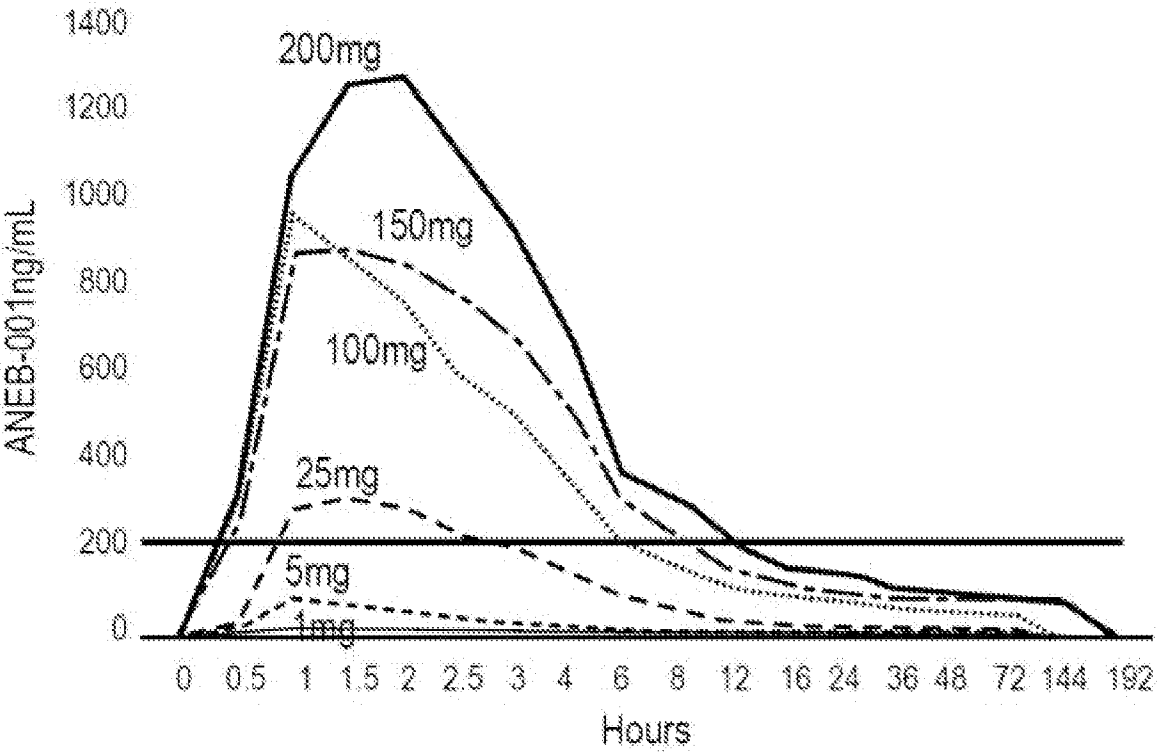


FIG. 2

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/059747

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/397; A61P 25/30; A61P 43/00; C07D 205/00; C07D 205/02; C07D 205/04 (2022.01)

CPC - A61K 31/397; A61P 25/30; A61P 43/00; C07D 205/00; C07D 205/02; C07D 205/04 (2022.02)

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 data base consulted during the international search (name of data base 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.     |
|-----------|--------------------------------------------------------------------------------------------------------------------------|---------------------------|
| A         | WO 2018/204689 A1 (THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM) 08 November 2018 (08.11.2018) entire document | 1, 2, 18-20, 34-36, 39-41 |
| A         | WO 2008/024408 A2 (THERAQUEST BIOSCIENCES INC) 28 February 2008 (28.02.2008) entire document                             | 1, 2, 18-20, 34-36, 39-41 |
| A         | US 2007/0054891 A1 (DAVIDSON et al) 08 March 2007 (08.03.2007) entire document                                           | 1, 2, 18-20, 34-36, 39-41 |
| A         | US 6,403,574 B1 (ADAMS et al) 11 June 2002 (11.06.2002) entire document                                                  | 1, 2, 18-20, 34-36, 39-41 |
| P. A      | US 11,141,404 B1 (ANEBULO PHARMACEUTICALS INC) 12 October 2021 (12.10.2021) entire document                              | 1, 2, 18-20, 34-36, 39-41 |

☐ 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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

23 February 2022

Date of mailing of the international search report

MAR 08 2022

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

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Facsimile No. 571-273-8300

Authorized officer

Harry Kim

Telephone No. PCT Helpdesk: 571-272-4300

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/059747

## 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.: 4-6, 11-17, 21-33, 37, 38, 49-51, 56, 57  
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.:
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.:  
1, 2, 18-20, 34-36, 39-41

### 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/US2021/059747

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

Claims 1, 2, 18-20, 34-36, and 39-41 have been analyzed subject to the restriction that the claims read on a method of using a pharmaceutical composition comprising a CB1 inhibitor, the method comprising administering to a patient an effective amount of the CB1 inhibitor and a pharmaceutically acceptable carrier or excipient, wherein the patient has a known or suspected acute drug overdose reaction, wherein the CB1 inhibitor has the structure of formula (I); or a pharmaceutically acceptable salt or prodrug thereof, wherein R1 is aryl, wherein the aryl is unsubstituted phenyl; R2 is alkyl, wherein the alkyl is methyl; R3 is alkyl, wherein the alkyl is methyl; Y is C=O; R11 and R12 are independently H; m is 1; and n is 1.

## INTERNATIONAL SEARCH REPORT

International application No.

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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 1-3, 7-10, 18-20, 34-36, and 39-45 are drawn to methods of using a pharmaceutical composition, methods of using a CB1 inhibitor as a pre-exposure prophylactic therapy, and methods of treating a patient suspected of a drug overdose.

Group II+: claims 46-48 and 52-55 are drawn to injectable compositions for treating a suspected drug overdose and compositions for treating a suspected drug overdose.

The first invention of Group I+ is restricted to a method of using a pharmaceutical composition comprising a CB1 inhibitor, the method comprising administering to a patient an effective amount of the CB1 inhibitor and a pharmaceutically acceptable carrier or excipient, wherein the patient has a known or suspected acute drug overdose reaction, wherein the CB1 inhibitor has the structure of formula (I): or a pharmaceutically acceptable salt or prodrug thereof, wherein R1 is aryl, wherein the aryl is unsubstituted phenyl; R2 is alkyl, wherein the alkyl is methyl; R3 is alkyl, wherein the alkyl is methyl; Y is C=O; R11 and R12 are independently H; m is 1; and n is 1; methods of using a CB1 inhibitor as a pre-exposure prophylactic therapy; and methods of treating a patient suspected of a drug overdose. It is believed that claims 1, 2, 18-20, 34-36, and 39-41 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.

The first invention of Group II+ is restricted to an injectable composition for treating a suspected drug overdose, the composition comprising a CB1 inhibitor, an opioid antagonist, and a benzodiazepine antagonist, wherein the CB1 inhibitor is the first shown structure in instant claim 50; and compositions for treating a suspected drug overdose thereof.

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 method of using a pharmaceutical composition comprising a CB1 inhibitor, the method comprising administering to a patient an effective amount of the CB1 inhibitor and a pharmaceutically acceptable carrier or excipient, wherein the patient has a known or suspected acute drug overdose reaction, wherein the CB1 inhibitor has the structure of formula (I): or a pharmaceutically acceptable salt or prodrug thereof, wherein R1 is aryl, wherein the aryl is unsubstituted phenyl; R2 is alkyl, wherein the alkyl is methyl; R3 is alkyl, wherein the alkyl is methyl; Y is C=S; R11 and R12 are independently H; m is 1; and n is 1; methods of using a CB1 inhibitor as a pre-exposure prophylactic therapy; and methods of treating a patient suspected of a drug overdose. 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+ and II+ 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 special technical features of Group I+, methods of using a pharmaceutical composition, methods of using a CB1 inhibitor as a pre-exposure prophylactic therapy, and methods of treating a patient suspected of a drug overdose, are not present in Group II+, and the special technical features of Group II+, injectable compositions for treating a suspected drug overdose and compositions for treating a suspected drug overdose, are not present in Group I+.

The Groups I+ and II+ formulae do not share a significant structural element requiring the selection of alternatives for the CB1 inhibitor and the compound variables R1, R2, R3, R11, R12, Y, m, n and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ and II+ were considered to share the technical features of a method of using a pharmaceutical composition comprising a CB1 inhibitor, the method comprising administering to a patient an effective amount of the CB1 inhibitor and a pharmaceutically acceptable carrier or excipient, wherein the patient has a known or suspected acute drug overdose reaction, wherein the CB1 inhibitor has the core structure of formula (I): or a pharmaceutically acceptable salt or prodrug thereof; a method of using a CB1 inhibitor as a pre-exposure prophylactic therapy comprising administering an effective amount of the CB1 inhibitor prior to exposure to a cannabinoid; a method of treating a patient suspected of a drug overdose comprising administering an effective amount of a CB1 inhibitor to a patient and monitoring the patient for reduced symptoms associated with overdose; an injectable composition for treating a suspected drug overdose, the composition comprising a CB1 inhibitor, an opioid antagonist, and a benzodiazepine antagonist; and a composition for treating a suspected drug overdose, the composition comprising a CB1 inhibitor and an anxiolytic agent, these shared technical features do not represent a contribution over the prior art as disclosed by WO 2018/204689 A1 to The Board of Regents of the University of Texas System, WO 2008/024408 A2 to Theraquest Biosciences, Inc., and US 2007/0054891 A1 to Davidson et al.

WO 2018/204689 A1 to The Board of Regents of the University of Texas System discloses a method of using a pharmaceutical composition comprising a CB1 inhibitor (Claim 1, administering to the subject a therapeutically effective amount of rimonabant; Pg. 7, Lns. 30-31, Rimonabant is a selective CB1 receptor blocker; see also Pg. 8, Lns. 27-29), the method comprising administering to a patient an effective amount of the CB1 inhibitor and a pharmaceutically acceptable carrier or excipient (Claim 1, administering to the subject a therapeutically effective amount of rimonabant; Pg. 8, Lns. 27-29, a pharmaceutical composition comprising rimonabant and a pharmaceutically acceptable carrier), wherein the patient has a known or suspected acute drug overdose reaction (Claim 1, method of treating or preventing synthetic cannabinoid toxicity or overdose in a subject; Pg. 8, Lns. 1-2, Rimonabant can also be useful for the treatment of subjects that are non-dependent subjects suffering from synthetic cannabinoid toxicity or overdose); a method of using a CB1 inhibitor as a pre-exposure prophylactic therapy (Claim 1, administering to the subject a therapeutically effective amount of rimonabant; Pg. 8, Lns. 27-29, a pharmaceutical composition comprising rimonabant; Pg. 9, Ln. 10, Therapeutic administration encompasses prophylactic applications) comprising administering an effective amount of the CB1 inhibitor prior to exposure to a cannabinoid (Claim 1, administering to the subject a therapeutically effective amount of rimonabant; Pg. 20, Ln. 1, rimonabant was administered prior to synthetic cannabinoids); a method of treating a patient suspected of a drug overdose (Claim 1, A method of treating or preventing synthetic cannabinoid toxicity or overdose in a subject,) comprising administering an effective amount of a CB1 inhibitor to a patient and monitoring the patient for reduced symptoms associated with overdose (Claims 1, 6 and 7, wherein administration of the rimonabant reduces one or more symptoms of drug toxicity or overdose ... wherein the symptoms of drug toxicity or overdose are reduced over a period of at least 15 to about 30 minutes); an injectable composition for treating a suspected drug

# INTERNATIONAL SEARCH REPORT

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PCT/US2021/059747

overdose (Claims 1 and 3, wherein rimonabant is administered intravenously; Pg. 8, Lns. 27-29), the composition comprising a CB1 inhibitor (Pg. 8, Lns. 27-29).

WO 2008/024408 A2 to Theraquest Biosciences, Inc. discloses a composition (Claim 1, dosage form) comprising a CB1 inhibitor (Claim 74, wherein the cannabinoid agonist is an inhibitor of CB1), an opioid antagonist (Claim 14, wherein said additional therapeutic agent is selected from the group consisting of: an opioid antagonist), and a benzodiazepine antagonist (Claim 57, benzodiazepine antagonists); and an anxiolytic agent (Claim 66, cannabidiol).

US 2007/0054891 A1 to Davidson et al. disclose wherein the CB1 inhibitor has the core structure of formula (I) (Para. [0060], 3-(2,4,4'-trichlorobenzhydryloxy)-N-(tert-butyl)azetidine-1-carboxamide).

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