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(54) Title: N-SUBSTITUTED INDOLES AND USE AS ALLOSTERIC MODULATORS OF CANNABINOID RECEPTORS

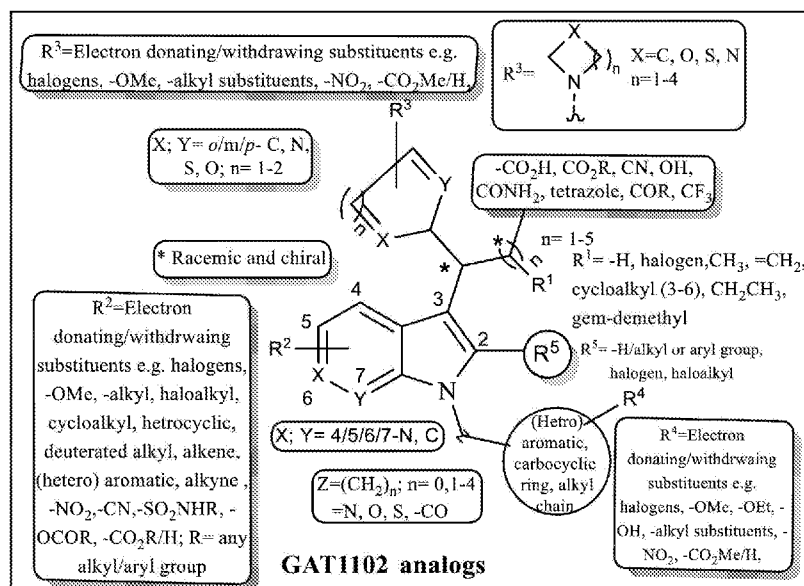


Fig. 1

(57) Abstract: Heteroaromatic compounds are provided which are allosteric modulators of the cannabinoid receptors and which are useful for the treatment of glaucoma, pain, neuropathic pain, post-traumatic stress disorder (PTSD), and neurodegenerative diseases such as Huntington's disease, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and other diseases where cannabinoid receptors are involved.

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
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TITLE

N-Substituted Indoles and Use as Allosteric Modulators of Cannabinoid Receptors

5 CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 62/690,317, filed June 26, 2018, the disclosure of which is hereby incorporated by reference in its entirety.

10 STATEMENT REGARDING FEDERALLY SPONSORED
RESEARCH OR DEVELOPMENT

This invention was made with government support under Grant No. NEI RO1 EY024717 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

15 The cannabinoid CB1 receptor is abundant in the central nervous system and regulates key physiological processes. (Caitlin E. Scott and Debra A. Kendall, *Methods in Enzymology* Volume 593, 2017, Pages 317-342). It is activated by the endogenous ligands (e.g., anandamide) and also by synthetic ligands including Δ^9 -tetrahydrocannabinol, the psychoactive component of *Cannabis sativa*. These CB1 ligands are orthosteric and target the endogenous ligand-binding site of CB1.
20 Allosteric modulators of CB1 receptor are also known (Paula Morales et al., *Cannabis and Cannabinoid Research*, Volume 1.1, 2016, pages 22-30). Allosteric modulators bind to topographically distinct sites and can noncompetitively impact the potency and efficacy of orthosteric compounds. Positive allosteric modulators (PAMs) activate whereas negative allosteric modulators (NAMs) inhibit receptor signaling.

25 The CB1 receptor is implicated in several diseases and conditions including, pain, and neurodegenerative disorders. As such, therapeutics that selectively target this receptor are of significant interest. In this regard, allosteric modulation of CB1 is advantageous as it offers more precise control of downstream pathways and potential circumvention of unwanted side effects.

Between 2001 and 2017, the cost of US opioid crisis (lost wages, lost productivity, health care costs etc.) was estimated to have exceeded \$1Trillion (<https://altarum.org/news/economic-toll-opioid-crisis-us-exceeded-1-trillion-2001>). Thus, there is an urgent need for developing non-addictive, effective and safer medications for treating pain, chronic pain as well as neuropathic and inflammatory pain. PAMs acting at CB1 receptors can provide a safer and effective alternative to opioid analgesics.

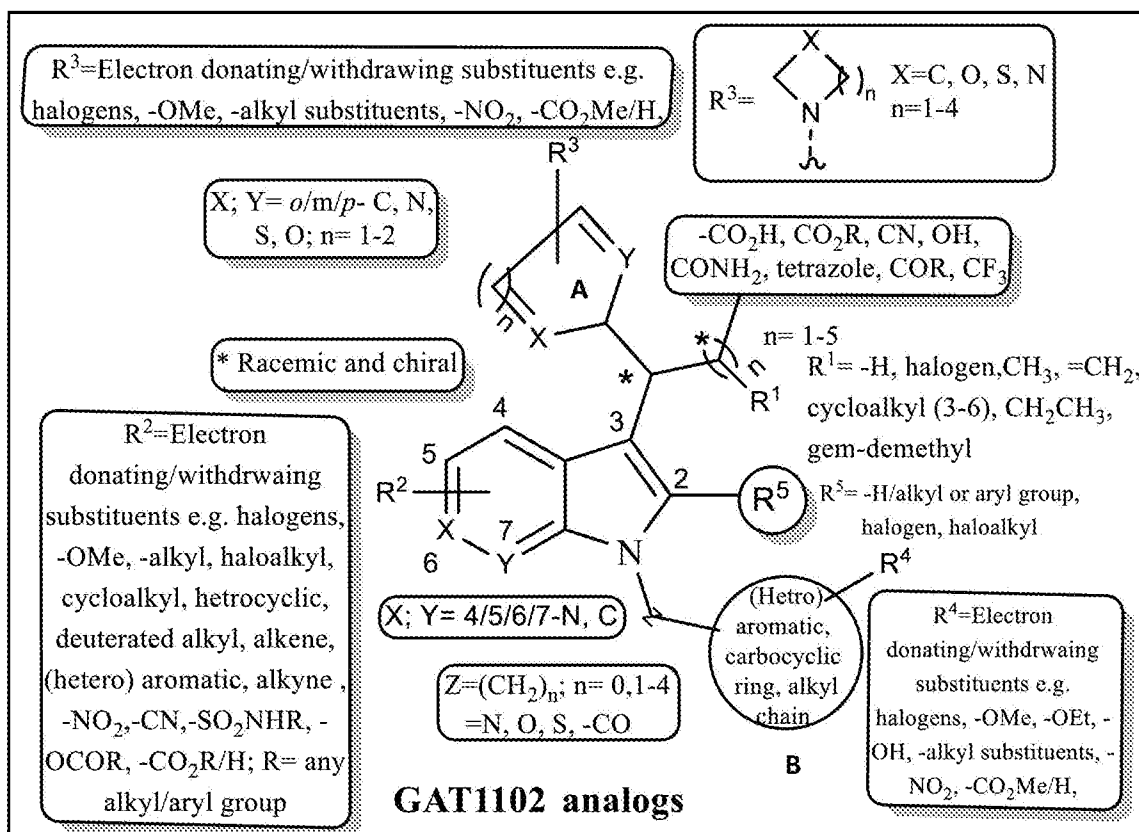
CB1 PAMs can also be effective in treating PTSD. An estimated 8% of Americans (24.4 million) have PTSD at any given time costing annually over ~42.2 billion dollars (www.ptsdunited.org/ptsd-statistics-2/). According to the VA (Veterans administrations), experts estimate that up to 20 % of Operation Enduring Freedom and Operation Iraqi Freedom veterans, up to 10 % of Gulf War veterans, and up to 30 % of Vietnam War veterans have experienced PTSD. Consequently, demand for PTSD treatment continues to grow.

There is a need for new allosteric modulators that can better function as drugs to provide relief in diseases and conditions where cannabinoid receptors play a role.

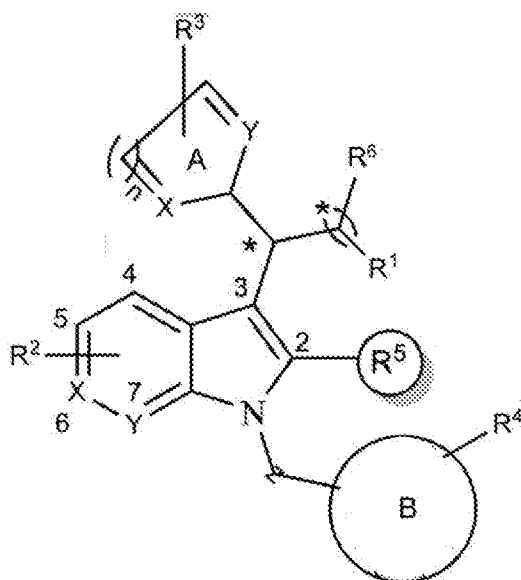
SUMMARY

Described herein are compounds that are positive allosteric modulators of the CB1 cannabinoid receptor that have better druggability (i.e., have higher solubility, plasma stability, and oral bioavailability) than previously described CB1 PAMs. These compounds constitute a novel class of compounds containing indole functionality and have robust PAM activity. GAT1102 is a representative compound of this class and was shown to be effective as a CB1 ago-PAM in cellular assays and in electrophysiological experiments and was found to be effective also in lowering intra ocular pressure in an animal model, thereby demonstrating utility in treating glaucoma. In addition to CB1PAM/ago-PAM activity, some of these compounds can also act as CB2 agonists, inverse agonist and PAMs. Additionally, the CB1 PAMs disclosed herein and their prodrugs have utility in treating pain, neuropathic pain, epilepsy, ocular disorders including glaucoma, and neurodegenerative disorders such as Huntington's disease, Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

Accordingly, in one aspect, the compound shown below is provided.



5 In another aspect, the compound shown in Formula I below is provided:



Formula I

In the compound of Formula I,

5 X and Y are independently N or C at any of positions 4, 5, 6, and/or 7;

Z is an alkyl spacer, $(CH_2)_k$, optionally substituted and optionally including N, O, S, or a carbonyl group in the chain, and k is 0 to 4;

10 A is a saturated or unsaturated carbocyclic or heterocyclic ring, the heteroatom(s) being N, S, or O in any combination, and n is 1 or 2; A also can be a 5 or 6 membered substituted or unsubstituted hetero(aromatic) ring;

B is a substituted or unsubstituted carbocyclic, bicyclic, (hetero)aromatic, or heterocyclic ring, preferably a 3 to 10 membered ring, a 4 to 7 membered ring, or a 5 to 6 membered ring;

R^1 is H, alkyl, optionally substituted, $=CH_2$, $(CHR)_xCO_2R$, or $(CH_2)_xOH$, wherein each R is independently H or an alkyl, optionally substituted, and x is 0 to 5;

15 R^2 and R^4 are independently H, halogen, alkoxy, OH, alkyl, haloalkyl, optionally substituted, alkyne, NO_2 , CN, CO_2R , NR_2 , a deuterated alkyl group, a five- or six-membered heterocyclic ring, a (hetero)aromatic ring, or SO_2NHR , wherein R is independently H or alkyl, optionally substituted;

20 R^3 is independently H, halogen, alkoxy, OH, alkyl optionally substituted, alkyne, NO_2 , CN, CO_2R , a three to six membered heterocyclic ring containing N and optionally an O or S, or SO_2NHR , wherein R is independently H or alkyl, optionally substituted;

R⁵ is H, halogen, alkyl, optionally substituted, or aryl;

R⁶ is (CHR⁷)_pCO₂R⁷; CN; OH; CONH₂; alkyl, optionally substituted (e.g., CF₃), CONR⁷R⁸; aryl; heterocyclic ring; CH=CHCO₂R⁷; or (CHR⁷)_yCOR⁷; wherein R⁷ and R⁸, including each of R⁷, is independently H or alkyl, optionally substituted, and p and y are each 0 to 4;

* represents a chiral center; and

m is 0 to 5.

In another aspect, a composition comprising a compound of Formula I is provided.

In yet another aspect, a pharmaceutical composition comprising a compound of Formula I and one or more excipients is provided.

Further, in one aspect, a method of treating a medical condition selected from the group consisting of glaucoma, post-traumatic stress disorder, epilepsy, pain, neuropathic pain, a neurodegenerative disease, Huntington's disease, Alzheimer's disease, or Parkinson's disease is provided. The method comprises administering to a subject in need thereof an effective amount of the compound of Formula I, the composition comprising a compound of Formula I, or the pharmaceutical composition comprising a compound of Formula I. In one embodiment, the medical condition is glaucoma.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic diagram of a genus of compounds encompassed by the present technology.

Figures 2A, 2B, and 2C are graphs showing that GAT1102 exhibits both agonist and PAM properties. Figure 2A shows averaged direct inhibition of excitatory postsynaptic currents (EPSCs) upon applying 1μM GAT1102. Figure 2B shows depolarization response curves before and after GAT1102 treatment. Figure 2C shows sample DSE (depolarization-induced suppression of excitation) time course from a cell showing an enhanced DSE inhibition after GAT1102 treatment, which is consistent with a PAM-like response.

Figures 3A and 3B show the effects of PAM GAT1102 on IOP. Figure 3A shows that the IOP-lowering effect of subthreshold WIN55,212-2 (WIN) is potentiated by the GAT1102 in

normotensive C57Bl/6J mice. IOP was significantly lower in eyes receiving 0.2% GAT1102 combined with subthreshold 0.25% WIN at 6 and 12 hrs after topical administration compared to vehicle (n=5). Figure 3B shows that GAT1102 (0.2%) significantly decreased IOP in ocular hypertensive mice at 1 and 12 hrs after topical administration (n=6). Values are represented as a change in IOP from the baseline (time 0). Paired t-tests, $P < 0.05$.

Figure 4 is a graph showing variation in cAMP levels in response to administration of GAT1102 or THC (tetrahydrocannabinol).

DETAILED DESCRIPTION

A novel class of positive allosteric modulators of the CB1 cannabinoid receptor is provided. GAT1102 is a representative member of this class. Relative to earlier 2-phenylindole class of PAMs, the PAMs described herein, having a 1-substituted indole template, are structurally distinct and more druggable (e.g., have improved solubility) and also provide opportunities for administration as a prodrug. Through further structural manipulations these PAMs can be made either more lipophilic and therefore more brain permeable for treating CNS disorders such as post-traumatic stress disorder (PTSD), epilepsy, and neurodegenerative diseases, or can be made more polar with their activity restricted to the periphery (and exhibiting no CNS activity).

The 1-substituted indole derivatives preferably contain an N-aryl indole moiety and an additional carboxylate functionality. The compounds have been found to act as CB1 PAMs through cellular and electrophysiological assays. The representative compound from this class, GAT1102, was shown to be effective in reducing intraocular pressure in an animal model and thus, can be useful in treating glaucoma.

The compounds described herein can act as positive allosteric modulators (PAMs) or allosteric agonist-Positive allosteric modulators (ago-PAMs) on the CB1 and/or CB2 cannabinoid receptors. The racemic compounds as well as enantiomers, prodrugs, and pharmaceutical formulations are contemplated as included in the present class of compounds.

Referring to the schematic diagram shown in Figure 1, the compounds include all possible combinations of substituents as shown at the 1, 2, 3, 4, 5, 6, and 7, positions including all possible indicated variants for substituents R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 , as well as both racemic mixtures and both enantiomers at the indicated chiral centers. Compositions, including pharmaceutical compositions, containing any of these compounds or combinations thereof are also contemplated

herein as also the use of any of these compounds, compositions, and pharmaceutical compositions in treating, or to prepare a medicament for use in treating, glaucoma, pain, neuropathic pain, epilepsy, and neurodegenerative disorders such as Huntington's disease, Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

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Definitions

Terms listed below, when used in the present specification, will have the meaning as described below. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated.

10

The terms "alkyl" and "alk" refer to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms. Exemplary "alkyl" groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. The term "(C₁-C₄)alkyl" refers to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, and isobutyl. The term "(C₁-C₆)alkyl" refers to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 6 carbon atoms, such as n-hexyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl, 2,2-dimethylbutyl, in addition to those exemplified for "(C₁-C₄)alkyl." "Substituted alkyl" refers to an alkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (e.g., a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF₃ or an alkyl group bearing Cl₃), cyano, nitro, oxo (i.e., =O), CF₃, OCF₃, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, S(=O)R_e, S(=O)₂R_e, P(=O)₂R_e, S(=O)₂OR_e, P(=O)₂OR_e, NR_bR_c, NR_bS(=O)₂R_e, NR_bP(=O)₂R_e, S(=O)₂NR_bR_c, P(=O)₂NR_bR_c, C(=O)OR_d, C(=O)R_a, C(=O)NR_bR_c, OC(=O)R_a, OC(=O)NR_bR_c, NR_bC(=O)OR_e, NR_dC(=O)NR_bR_c, NR_dS(=O)₂NR_bR_c, NR_dP(=O)₂NR_bR_c, NR_bC(=O)R_a, or NR_bP(=O)₂R_e, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle;

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and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. In the aforementioned exemplary substitutents, groups such as alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, heterocycle and aryl can themselves be optionally substituted.

5 The term “alkoxy” refers to a group containing an alkyl group bonded to an oxygen atom.

The term “alkenyl” refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon-carbon double bond. Exemplaries of such groups include ethenyl or allyl. The term “C₂-C₆ alkenyl” refers to a straight or branched chain hydrocarbon radical containing from 2 to 6 carbon atoms and at least one carbon-carbon double bond, such as ethylenyl, propenyl, 2-propenyl, (E)-but-2-enyl, (Z)-but-2-enyl, 2-methy(E)-but-2-enyl, 2-methy(Z)-but-2-enyl, 2,3-dimethy-but-2-enyl, (Z)-pent-2-enyl, (E)-pent-1-enyl, (Z)-hex-1-enyl, (E)-pent-2-enyl, (Z)-hex-2-enyl, (E)-hex-2-enyl, (Z)-hex-1-enyl, (E)-hex-1-enyl, (Z)-hex-3-enyl, (E)-hex-3-enyl, and (E)-hex-1,3-dienyl. “Substituted alkenyl” refers to an alkenyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (e.g., a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF₃ or an alkyl group bearing Cl₃), cyano, nitro, oxo (i.e., =O), CF₃, OCF₃, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, S(=O)R_e, S(=O)₂R_e, P(=O)₂R_e, S(=O)₂OR_e, P(=O)₂OR_e, NR_bR_c, NR_bS(=O)₂R_e, NR_bP(=O)₂R_e, S(=O)₂NR_bR_c, P(=O)₂NR_bR_c, C(=O)OR_d, C(=O)R_a, C(=O)NR_bR_c, OC(=O)R_a, OC(=O)NR_bR_c, NR_bC(=O)OR_e, NR_dC(=O)NR_bR_c, NR_dS(=O)₂NR_bR_c, NR_dP(=O)₂NR_bR_c, NR_bC(=O)R_a, or NR_bP(=O)₂R_e, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted.

The term “alkynyl” refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond. An exemplary of such groups includes ethynyl. The term “C₂-C₆ alkynyl” refers to a straight or branched chain hydrocarbon radical containing from 2 to 6 carbon atoms and at least one carbon-carbon triple

bond, such as ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, pent-1-ynyl, pent-2-ynyl, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl. "Substituted alkynyl" refers to an alkynyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups:

5 hydrogen, halogen (e.g., a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF₃ or an alkyl group bearing Cl₃), cyano, nitro, oxo (i.e., =O), CF₃, OCF₃, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, S(=O)R_e, S(=O)₂R_e, P(=O)₂R_e, S(=O)₂OR_e, P(=O)₂OR_e, NR_bR_c, NR_bS(=O)₂R_e, NR_bP(=O)₂R_e, S(=O)₂NR_bR_c, P(=O)₂NR_bR_c, C(=O)OR_d, C(=O)R_a, C(=O)NR_bR_c, OC(=O)R_a, OC(=O)NR_bR_c, NR_bC(=O)OR_e, NR_dC(=O)NR_bR_c, NR_dS(=O)₂NR_bR_c, NR_dP(=O)₂NR_bR_c, NR_bC(=O)R_a, or NR_bP(=O)₂R_e, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is

10 independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted.

The term "cycloalkyl" refers to a fully saturated cyclic hydrocarbon group containing from 1 to 4 rings and 3 to 8 carbons per ring. "C₃-C₇ cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. "Substituted cycloalkyl" refers to a cycloalkyl group

20 substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (e.g., a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF₃ or an alkyl group bearing Cl₃), cyano, nitro, oxo (i.e., =O), CF₃, OCF₃, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, S(=O)R_e, S(=O)₂R_e, P(=O)₂R_e, S(=O)₂OR_e, P(=O)₂OR_e, NR_bR_c, NR_bS(=O)₂R_e, NR_bP(=O)₂R_e, S(=O)₂NR_bR_c, P(=O)₂NR_bR_c, C(=O)OR_d, C(=O)R_a, C(=O)NR_bR_c, OC(=O)R_a, OC(=O)NR_bR_c, NR_bC(=O)OR_e, NR_dC(=O)NR_bR_c, NR_dS(=O)₂NR_bR_c, NR_dP(=O)₂NR_bR_c, NR_bC(=O)R_a, or NR_bP(=O)₂R_e, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is

25 independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is

30 independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is

independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cyclic substituents, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused
 5 cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

The term “cycloalkenyl” refers to a partially unsaturated cyclic hydrocarbon group containing 1 to 4 rings and 3 to 8 carbons per ring. Exemplaries of such groups include cyclobutenyl, cyclopentenyl, cyclohexenyl, etc. “Substituted cycloalkenyl” refers to a
 10 cycloalkenyl group substituted with one more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (e.g., a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF₃ or an alkyl group bearing Cl₃), cyano, nitro, oxo (i.e., =O), CF₃, OCF₃, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a,
 15 SR_a, S(=O)R_e, S(=O)₂R_e, P(=O)₂R_e, S(=O)₂OR_e, P(=O)₂OR_e, NR_bR_c, NR_bS(=O)₂R_e, NR_bP(=O)₂R_e, S(=O)₂NR_bR_c, P(=O)₂NR_bR_c, C(=O)OR_d, C(=O)R_a, C(=O)NR_bR_c, OC(=O)R_a, OC(=O)NR_bR_c, NR_bC(=O)OR_e, NR_dC(=O)NR_bR_c, NR_dS(=O)₂NR_bR_c, NR_dP(=O)₂NR_bR_c, NR_bC(=O)R_a, or NR_bP(=O)₂R_e, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is
 20 independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cyclic substituents, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused
 25 cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

The term “aryl” refers to cyclic, aromatic hydrocarbon groups that have 1 to 5 aromatic rings, especially monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where
 30 containing two or more aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group may be joined at a single point (e.g., biphenyl), or fused (e.g., naphthyl, phenanthrenyl and the like).

“Substituted aryl” refers to an aryl group substituted by one or more substituents, preferably 1 to 3 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (e.g., a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF₃ or an alkyl group bearing Cl₃), cyano, nitro, oxo (i.e., =O), CF₃, OCF₃, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, S(=O)R_e, S(=O)₂R_e, P(=O)₂R_e, S(=O)₂OR_e, P(=O)₂OR_e, NR_bR_c, NR_bS(=O)₂R_e, NR_bP(=O)₂R_e, S(=O)₂NR_bR_c, P(=O)₂NR_bR_c, C(=O)OR_d, C(=O)R_a, C(=O)NR_bR_c, OC(=O)R_a, OC(=O)NR_bR_c, NR_bC(=O)OR_e, NR_dC(=O)NR_bR_c, NR_dS(=O)₂NR_bR_c, NR_dP(=O)₂NR_bR_c, NR_bC(=O)R_a, or NR_bP(=O)₂R_e, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted. Exemplary substituents also include fused cyclic groups, especially fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

The terms “heterocycle” and “heterocyclic” refer to fully saturated, or partially or fully unsaturated, including aromatic (i.e., “heteroaryl”) cyclic groups (for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 8 to 16 membered tricyclic ring systems) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. (The term “heteroarylium” refers to a heteroaryl group bearing a quaternary nitrogen atom and thus a positive charge.) The heterocyclic group may be attached to the remainder of the molecule at any heteroatom or carbon atom of the ring or ring system. Exemplary monocyclic heterocyclic groups include azetidiny, pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl,

hexahydrodiazepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like. Exemplary bicyclic heterocyclic groups include indolyl, isoindolyl, benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzothienyl, benzo[d][1,3]dioxolyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, quinuclidinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofurazanyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), triazinylazepinyl, tetrahydroquinolinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

“Substituted heterocycle” and “substituted heterocyclic” (such as “substituted heteroaryl”) refer to heterocycle or heterocyclic groups substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (e.g., a single halogen substituent or multiple halo substituents forming, in the latter case, groups such as CF₃ or an alkyl group bearing Cl₃), cyano, nitro, oxo (i.e., =O), CF₃, OCF₃, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, S(=O)R_e, S(=O)₂R_e, P(=O)₂R_e, S(=O)₂OR_e, P(=O)₂OR_e, NR_bR_c, NR_bS(=O)₂R_e, NR_bP(=O)₂R_e, S(=O)₂NR_bR_c, P(=O)₂NR_bR_c, C(=O)OR_d, C(=O)R_a, C(=O)NR_bR_c, OC(=O)R_a, OC(=O)NR_bR_c, NR_bC(=O)OR_e, NR_dC(=O)NR_bR_c, NR_dS(=O)₂NR_bR_c, NR_dP(=O)₂NR_bR_c, NR_bC(=O)R_a, or NR_bP(=O)₂R_e, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substituents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cyclic substituents at any available point or points of attachment, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused

heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

The term “alkylamino” refers to a group having the structure —NHR', wherein R' is hydrogen, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, as defined herein.

5 Examples of alkylamino groups include, but are not limited to, methylamino, ethylamino, n-propylamino, iso-propylamino, cyclopropylamino, n-butylamino, tert-butylamino, neopentylamino, n-pentylamino, hexylamino, cyclohexylamino, and the like.

The term “dialkylamino” refers to a group having the structure —NRR', wherein R and R' are each independently alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, aryl or substituted aryl, heterocyclyl or substituted heterocyclyl, as defined herein. R and R' may be the same or different in an dialkylamino moiety. Examples of dialkylamino groups include, but are not limited to, dimethylamino, methyl ethylamino, diethylamino, methylpropylamino, di(n-propyl)amino, di(iso-propyl)amino, di(cyclopropyl)amino, di(n-butyl)amino, di(tert-butyl)amino, di(neopentyl)amino, di(n-pentyl)amino, di(hexyl)amino, di(cyclohexyl)amino, and the like. In certain embodiments, R and R' are linked to form a cyclic structure. The resulting cyclic structure may be aromatic or non-aromatic. Examples of cyclic diaminoalkyl groups include, but are not limited to, aziridinyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrrolyl, imidazolyl, 1,3,4-trianolyl, and tetrazolyl.

The terms “halogen” or “halo” refer to chlorine, bromine, fluorine or iodine.

20 Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

The compounds of the present invention may form salts which are also within the scope of this invention. Reference to a compound of the present invention is understood to include reference to salts thereof, unless otherwise indicated. The term “salt(s),” as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of the present invention contains both a basic moiety, such as but not limited to a pyridine or imidazole, and an acidic moiety such as but not limited to a carboxylic acid, zwitterions (“inner salts”) may be formed and are included within the term “salt(s)” as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, e.g., in isolation or purification steps which may be employed during preparation. Salts of a compound of the present invention may be formed, for example, by

reacting a compound I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

The compounds of the present invention which contain a basic moiety, such as but not limited to an amine or a pyridine or imidazole ring, may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, hydroxyethanesulfonates (e.g., 2-hydroxyethanesulfonates), lactates, maleates, methanesulfonates, naphthalenesulfonates (e.g., 2-naphthalenesulfonates), nicotines, nitrates, oxalates, pectinates, persulfates, phenylpropionates (e.g., 3-phenylpropionates), phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates, tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

Compounds of the present invention which contain an acidic moiety, such as but not limited to a carboxylic acid, may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl) ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glycamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term “prodrug” as employed herein denotes a compound that, upon administration to a subject, undergoes chemical conversion by metabolic (e.g., enzymatic) or chemical processes to yield a compound of the present invention, or a salt and/or solvate thereof. Solvates of the compounds of the present invention include, for example, hydrates.

Compounds of the present invention, and salts or solvates thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

5 All stereoisomers of the present compounds (for example, those which may exist due to asymmetric carbons on various substituents), including enantiomeric forms and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers (e.g., as a pure or substantially pure optical isomer having a specified activity, wherein “pure” can be, for example, at least 70% pure, 80% pure, 90% pure, 95% pure, 98% pure, or 99% pure), or may be
10 admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention may have the S or R configuration as defined by the International Union of Pure and Applied Chemistry (IUPAC) 1974 Recommendations. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The
15 individual optical isomers can be obtained from the racemates by any suitable method, including without limitation, conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater
20 than 90%, for example, equal to greater than 95%, equal to or greater than 99% pure (“substantially pure” compound I), which is then used or formulated as described herein. Such “substantially pure” compounds of the present invention are also contemplated herein as part of the present invention.

25 All configurational isomers of the compounds of the present invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds of the present invention embraces both cis (Z) and trans (E) alkene isomers, as well as cis and trans isomers of cyclic hydrocarbon or heterocyclic rings.

Throughout the specifications, groups and substituents thereof may be chosen to provide stable moieties and compounds.

30 Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this invention, the chemical elements are identified in accordance with the

Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry," Thomas Sorrell, University Science Books, Sausalito: 1999, the entire contents of which are incorporated herein by reference.

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are all contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer mixtures.

The present invention also includes isotopically labeled compounds, which are identical to the compounds disclosed herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ²H, ³H, ¹³C, ¹¹C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³⁵S, ¹⁸F, and ³⁶Cl, respectively. Compounds of the present invention, or an enantiomer, diastereomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ³H and ¹⁴C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ³H, and carbon-14, i.e., ¹⁴C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ²H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred

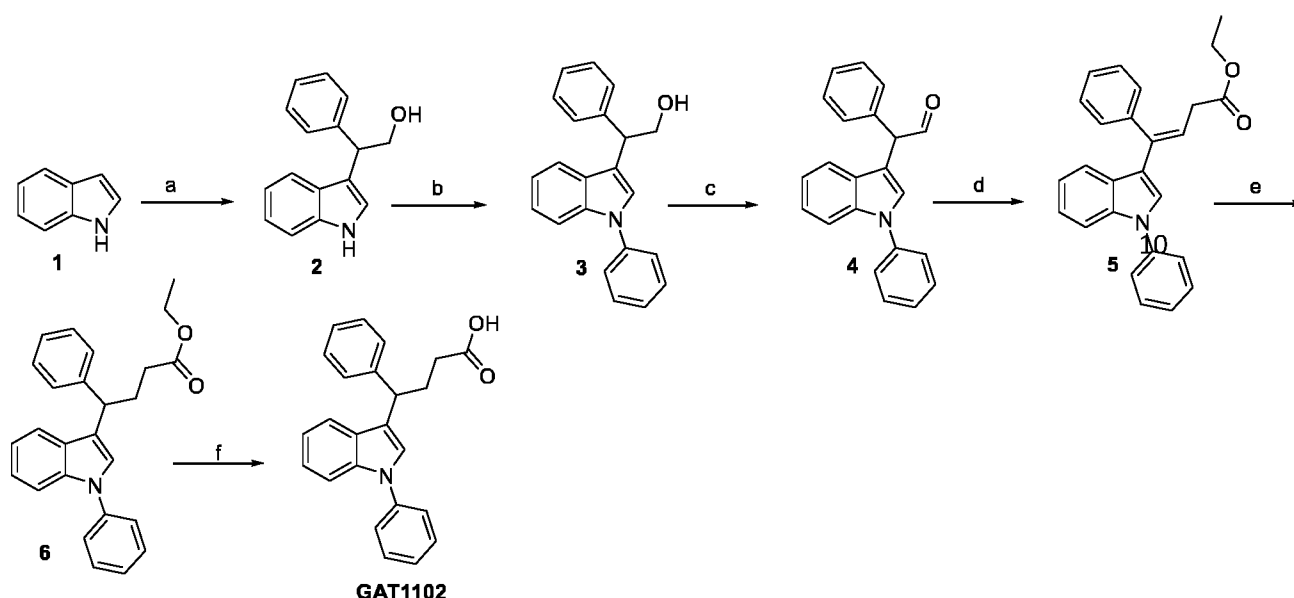
in some circumstances. Isotopically labeled compounds can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

If a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

The compounds described herein may be substituted with any number of substituents or functional moieties. In general, the term “substituted” whether preceded by the term “optionally” or not, and substituents contained in formulas of this invention, refer to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. Furthermore, this invention is not intended to be limited in any manner by the permissible substituents of organic compounds. Combinations of substituents and variables envisioned by this invention are preferably those that result in the formation of stable compounds useful in the treatment, for example, of infectious diseases or proliferative disorders. The term “stable,” as used herein, preferably refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

Method of preparation of GAT1102 and analogs

The synthesis of **GAT 1102** was commenced with the epoxide ring opening of racemic styrene oxide with indole (**1**). The coupled product **2** was treated under standard Buchwald coupling reaction to get N-arylated compound **3** in quantitative yield. The hydroxyl functionality of compound **3** was oxidized with DMP and further treated two carbon Wittig reaction condition to get unsaturated ester **5**. The double bond of unsaturated ester was reduced under Raney Ni mediated hydrogenation reaction condition and finally ester was hydrolyzed to get acid, **GAT1102** in good yield. This synthetic route can be potentially used for synthesizing **GAT1102** analogs.



Reagents and conditions: a) (±)-styrene oxide, $\text{CF}_3\text{CF}_2\text{OH}$, reflux, 7 hrs, 72%; b) bromobenzene, CuI , K_3PO_4 , *trans*-1,2-diaminocyclohexane, toluene, 120°C , 12 hrs, quant; c) DMP, DCM , 15 min, 44%; d) diethyl ethylphosphonate, NaH , 0°C to rt, 72%; e) Raney Ni, H_2 , MeOH , rt, 3 hrs, 98%; f) LiOH , $\text{THF}:\text{H}_2\text{O}$ (9:1), 84%.

2-(1H-Indol-3-yl)-2-phenylethan-1-ol (2): Indole **1** (1 gm, 8.50 mmol) and (±)-styrene oxide (1.025 gm, 8.50 mmol) were dissolved in $\text{CF}_3\text{CH}_2\text{OH}$ (10 mL) and refluxed at 100°C for overnight. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure then reaction mixture was purified by silica gel column chromatography to give pure coupled product **2** (1.46 gm, 72%) as a white solid.

2-Phenyl-2-(1-phenyl-1H-indol-3-yl)ethan-1-ol (3): 2-(1H-indol-3-yl)-2-phenylethan-1-ol, **2** (1 gm, 0.421 mol), bromobenzene (13.2 ml, 1.20 mol), potassium phosphate (2.12 gm, 1.68 mol), *trans* (±)-diamine cyclohexane (20 mol%) and CuI (5 mol%) were added to anhydrous toluene in

100 ml round bottom flask under inert atmosphere. The reaction mixture was refluxed at 120 °C for overnight. The reaction mixture was cooled, filtered through small pad of celite and residue was washed with ethyl acetate for 2-3 times then the mother liquor was concentrated under vacuum. Purification of the reaction mixture on a silica gel column using ethyl acetate/ hexane (5:95) as eluent furnished the *N*-arylated compound, **3** (1.32 gm, quant.) as a colorless liquid.

2-Phenyl-2-(1-phenyl-1H-indol-3-yl)acetaldehyde (4): Dess Martin periodinane (4.06 gm, 9.59 mmol) was added to the stirred solution of alcohol, **3** (1 gm, 3.19 mmol) in DCM and further stirred for 15 min in room temperature. The reaction mixture was concentrated under vacuum and directly loaded for column. . Purification of the reaction mixture on a silica gel column using ethyl acetate/ hexane (4:96) as eluent furnished the aldehyde compound, **4** (437 mg, 44%).

Ethyl 4-phenyl-4-(1-phenyl-1H-indol-3-yl)but-3-enoate (5): To a solution of phosphonate ester (863 mg, 3.85 mmol) in THF (10 mL) was added NaH (145 mg, 3.6 mmol, 60%) at 0 °C under inert atmosphere. After 30 min, a solution of 2-phenyl-2-(1-phenyl-1H-indol-3-yl)acetaldehyde, **4** (400 mg, 1.28 mmol) in THF (5 mL) was added to the mixture. The mixture was warmed to room temperature and stirred for overnight, quenched with saturated solution of NH₄Cl, extracted with ethyl acetate, washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuum. Purification of the reaction mixture on a silica gel column using ethyl acetate/ hexane (4:96) as eluent furnished the unsaturated ester, **5** (354 mg, 72%) as a colorless liquid.

Ethyl 4-phenyl-4-(1-phenyl-1H-indol-3-yl)butanoate (6): To a solution of unsaturated ester, **5** (300 mg, 0.787 mmol) in ethanol, catalytic amount Raney Ni was added and stirred overnight under H₂ atmosphere at room temperature. The reaction mixture was filtered through short celite pad and concentrated under vacuum. The saturated ester **6** (294 mg, 98%) was taken to the next step without further purification.

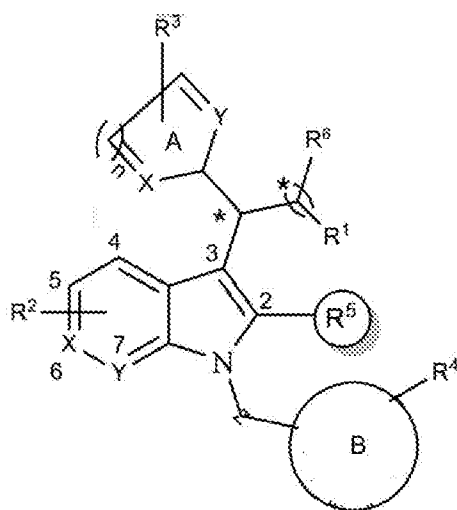
4-Phenyl-4-(1-phenyl-1H-indol-3-yl)butanoic acid (GAT 1102): Ester (200 mg, 0.520 mmol) was dissolved in 10 ml of THF:H₂O (9:1) and then LiOH (195 mg, 5.20 mmol) was added portion wise. The reaction mixture was stirred for overnight at RT. The reaction mixture was quenched by addition of 10% HCl solution and stirred for further 15 min. Then residue was dissolved in water and EtOAc was added to extract the product. The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate/ hexane as eluent furnished

the acid, **GAT1102** (158 mg, 84%) as a white solid. ^1H NMR (CDCl_3 , 500 MHz): δ 7.52 (d, $J=8.1$ Hz, 1H), 7.49-7.47 (m, 4H), 7.35-7.27 (m, 5H), 7.21-7.15 (m, 3H), 7.07-7.05 (m, 1H), 4.30 (t, $J=8.7$ Hz, 1H), 2.63-2.56 (m, 1H), 2.48-2.33 (m, 3H); MS-ESI (m/z) 356 $[\text{M} + \text{H}]^+$.

Compounds, Compositions and Methods of Use

5 Compounds and compositions and methods of treatment included in the present technology are summarized in the numbered embodiments below.

1. A compound having a structure according to Formula I



Formula I

wherein

Y is independently N or C;

Z is an alkyl, optionally substituted, and optionally having N, O, or S in the chain; or a carbonyl; and k is a number from 0 to 4;

A is a saturated or unsaturated carbocyclic or heterocyclic ring, the hetero atom being N, S, or O in any combination, and "n" is 1 or 2;

B is a substituted or unsubstituted carbocyclic ring, bicyclic ring, aromatic ring, or heterocyclic ring;

R¹ is H; alkyl, optionally substituted; $=\text{CH}_2$, $(\text{CHR})_n\text{CO}_2\text{R}$, or $(\text{CH}_2)_n\text{OH}$, wherein each R is independently H or an alkyl, optionally substituted, and n is a number between 0 and 5;

R² and R⁴ are independently; H; halogen; alkoxy; OH; alkyl, optionally substituted;

alkyne; NO₂; CN; CO₂R; a five- or six-member heterocyclic ring; or SO₂NHR; wherein R is independently H or alkyl, optionally substituted;

R³ is independently halogen; H; alkoxy; OH; alkyl, optionally substituted; alkyne; NO₂; CN; COX and Y are independently N or C at any of positions 4, 5, 6, and/or 7;

5 Z is an alkyl spacer, (CH₂)_k, optionally substituted and optionally including N, O, S, or a carbonyl group in the chain, and k is 0 to 4;

A is a saturated or unsaturated carbocyclic or heterocyclic ring, the heteroatom(s) being N, S, or O in any combination, and n is 1 or 2; A also can be a 5 or 6 membered substituted or unsubstituted hetero(aromatic) ring;

10 B is a substituted or unsubstituted carbocyclic, bicyclic, (hetero)aromatic, or heterocyclic ring, preferably a 3 to 10 membered ring, a 4 to 7 membered ring, or a 5 to 6 membered ring;

R¹ is H, alkyl, optionally substituted, =CH₂, (CHR)_xCO₂R, or (CH₂)_xOH, wherein each R is independently H or an alkyl, optionally substituted, and x is 0 to 5;

15 R² and R⁴ are independently H, halogen, alkoxy, OH, alkyl, haloalkyl, optionally substituted, alkyne, NO₂, CN, CO₂R, NR₂, a deuterated alkyl group, a five- or six-membered heterocyclic ring, a (hetero)aromatic ring, or SO₂NHR, wherein R is independently H or alkyl, optionally substituted;

20 R³ is independently H, halogen, alkoxy, OH, alkyl optionally substituted, alkyne, NO₂, CN, CO₂R, a three to six membered heterocyclic ring containing N and optionally an O or S, or SO₂NHR, wherein R is independently H or alkyl, optionally substituted;

R⁵ is H, halogen, alkyl, optionally substituted, or aryl;

25 R⁶ is (CHR⁷)_pCO₂R⁷; CN; OH; CONH₂; alkyl, optionally substituted (e.g., CF₃), CONR⁷R⁸; aryl; heterocyclic ring; CH=CHCO₂R⁷; or (CHR⁷)_yCOR⁷; wherein R⁷ and R⁸, including each of R⁷, is independently H or alkyl, optionally substituted, and p and y are each 0 to 4;

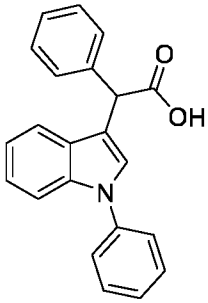
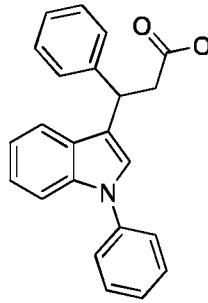
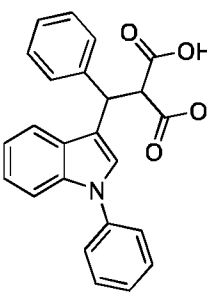
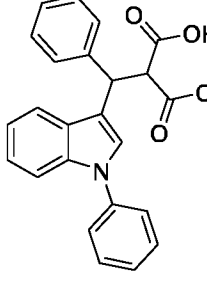
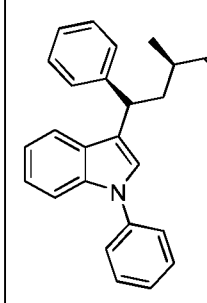
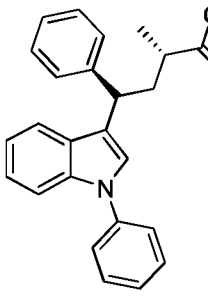
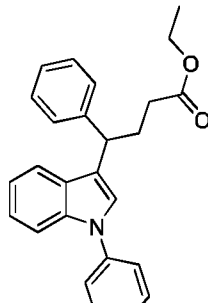
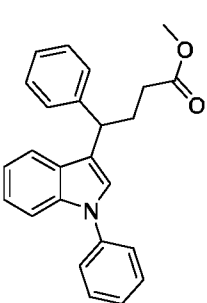
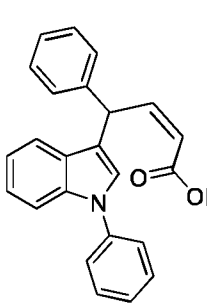
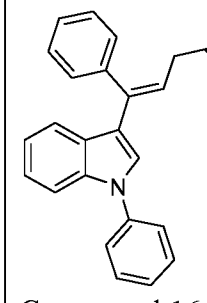
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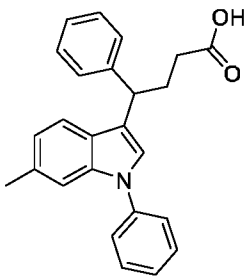
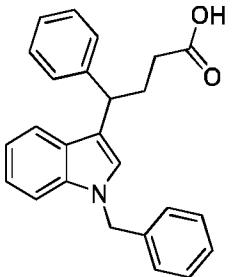
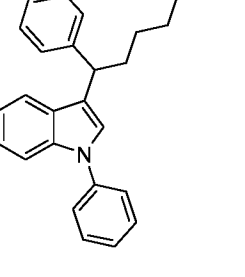
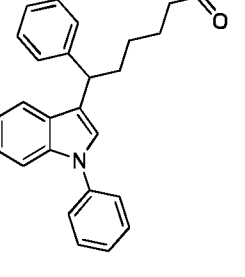
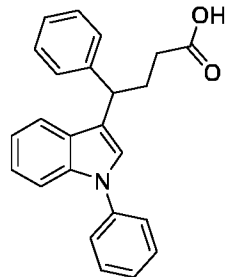
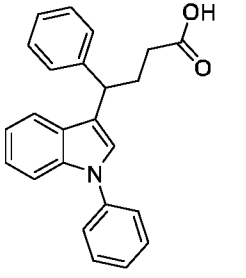
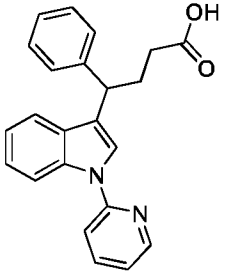
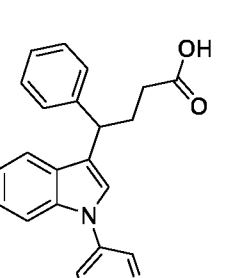
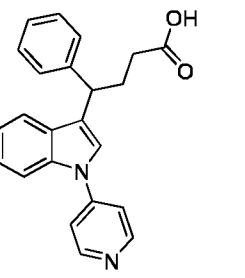
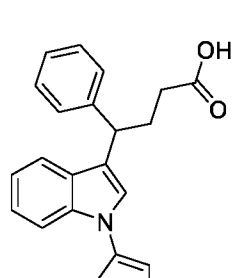
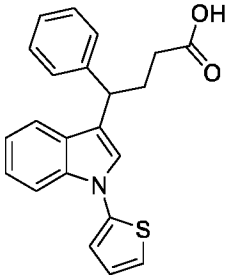
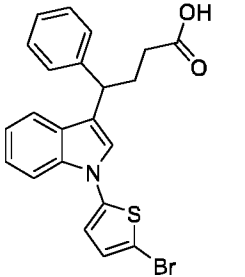
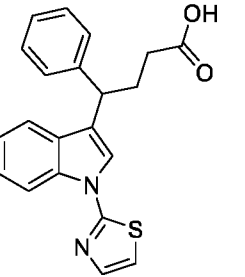
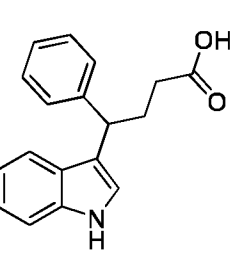
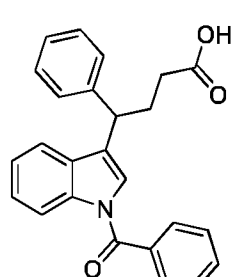
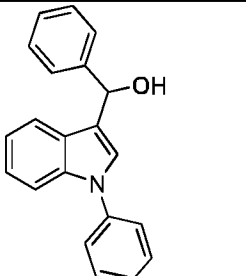
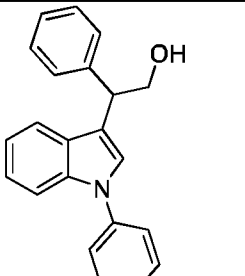
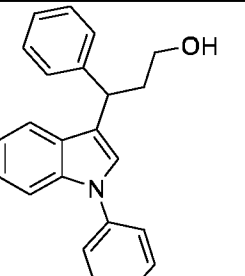
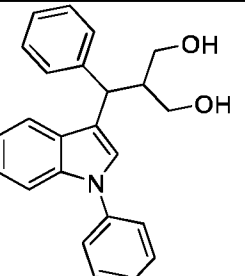
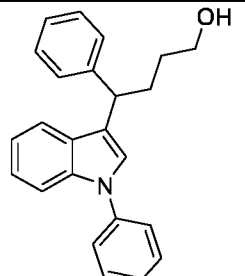
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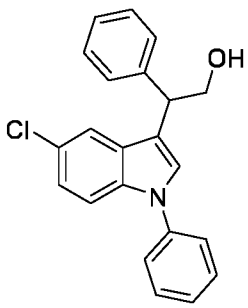
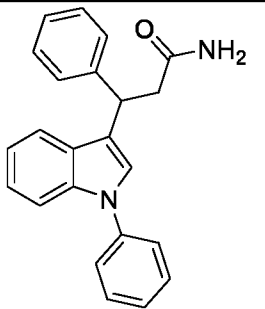
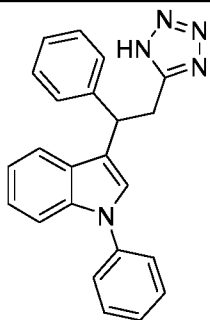
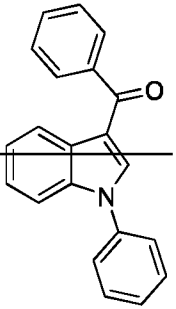
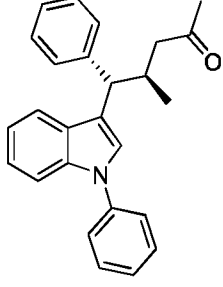
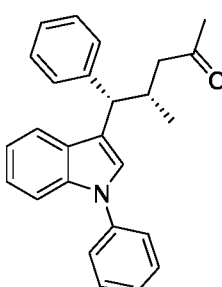
2. The compound of embodiment 1, wherein R⁶ is CO₂H.

30 3. The compound of embodiment 1, wherein R⁶ is CO₂H and m is 1.

4. The compound of embodiment 1, wherein each of R^1 and R^6 is CO_2H .
5. The compound of embodiment 1, wherein each of R^1 and R^6 is CO_2H and m is 1.
6. The compound of embodiment 1, wherein R^1 is CH_2OH and m is 1.
7. The compound of embodiment 1, wherein each of R^1 and R^6 is CH_2OH and m is 1.
8. The compound of embodiment 1, wherein R^6 is a heterocyclic ring.
9. The compound of embodiment 8, wherein the heterocyclic ring is tetrazole.
10. The compound of embodiment 1, wherein R^6 is CH_2COR^7 and R^7 is alkyl and m is 1.
11. The compound of embodiment 10, wherein R^1 is H.
12. The compound of embodiment 10, wherein each of R^1 and R^7 is CH_3 .
13. The compound of embodiment 1, wherein R^3 is piperidine, piperazine, or pyrrolidine.
14. The compound of embodiment 1 selected from the group consisting of

 Compound 7	 Compound 8	 Compound 9	 Compound 10	 Compound 11
 Compound 12	 Compound 13	 Compound 14	 Compound 15	 Compound 16

 Compound 17	 Compound 18	 Compound 19	 Compound 20	 (+)-GAT1102
 (-)-GAT1102	 Compound 21	 Compound 22	 Compound 23	 Compound 24
 Compound 25	 Compound 26	 Compound 27	 Compound 28	 Compound 29
 Compound 30	 Compound 31	 Compound 32	 Compound 33	 Compound 34

 Compound 35			 Compound 38	 Compound 39
 Compound 40	 Compound 41	 Compound 42		

15. The compound of any of embodiments 1-14 that binds to a CB1 receptor.

5 16. The compound of any of embodiments 1-14 that binds to a CB2 receptor.

17. The compound of embodiments 15 or 16 that is a positive allosteric modulator.

18. A composition comprising a compound of any of embodiments 1-17.

10

19. A pharmaceutical composition comprising a compound of any of embodiments 1-17 and one or more excipients.

20. A method of treating a medical condition selected from the group consisting of glaucoma, post-traumatic stress disorder, epilepsy, pain, neuropathic pain, a neurodegenerative disease, Huntington's disease, Alzheimer's disease, or Parkinson's disease, the method comprising administering the compound of any of embodiments 1-17, the composition of embodiment 18, or the pharmaceutical composition of embodiment 19 to a subject in need thereof.

15

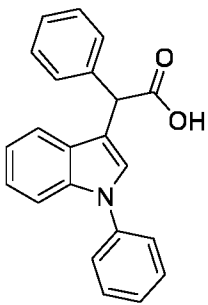
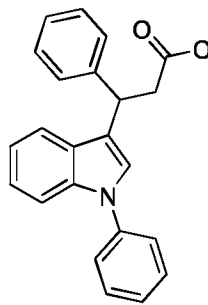
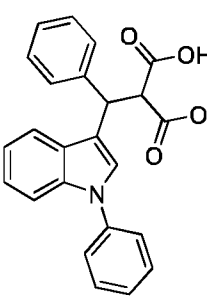
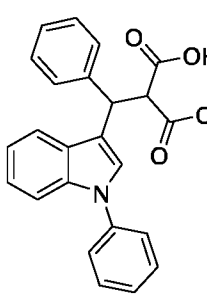
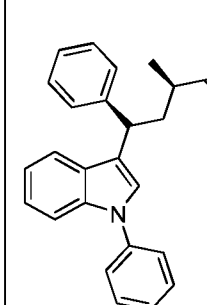
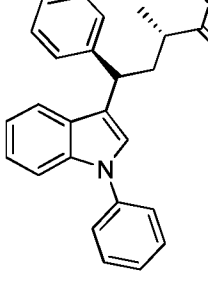
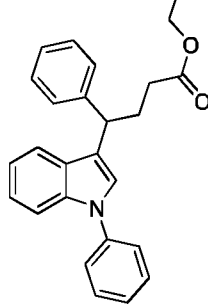
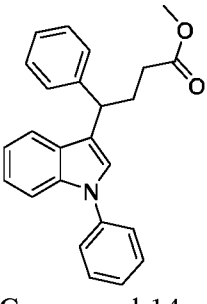
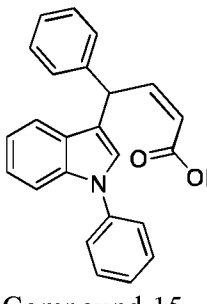
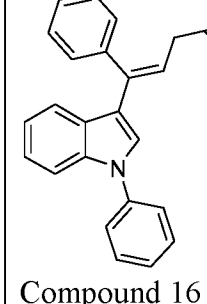
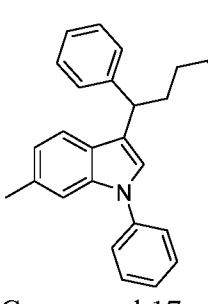
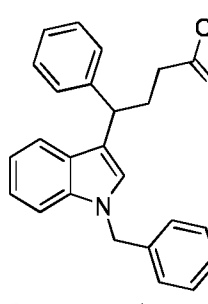
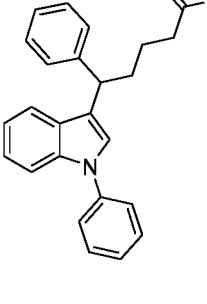
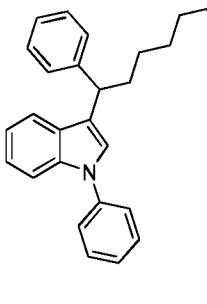
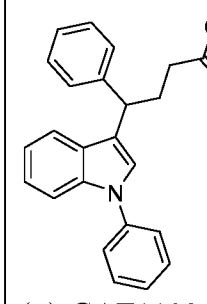
21. The method of embodiment 20, wherein the medical condition is glaucoma.

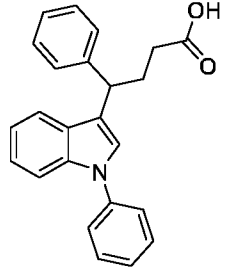
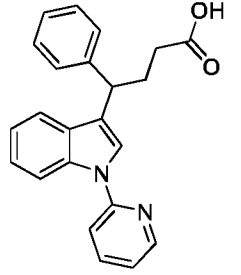
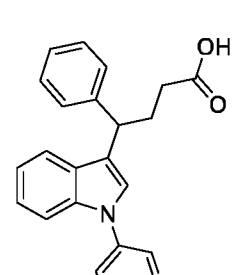
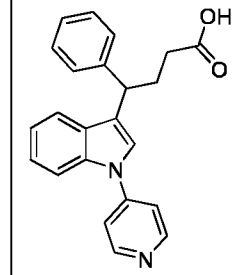
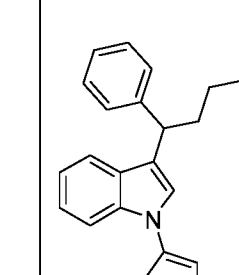
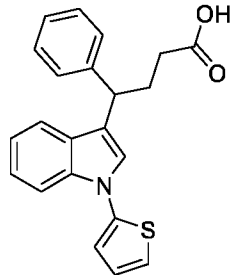
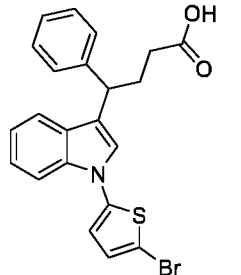
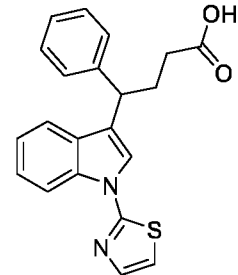
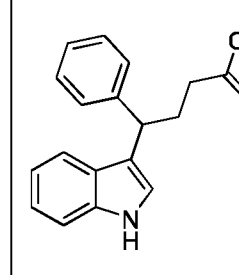
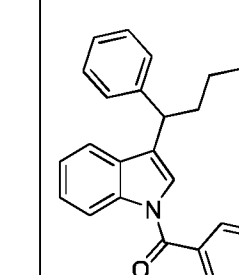
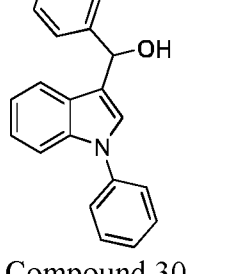
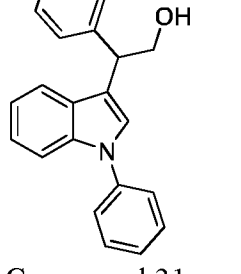
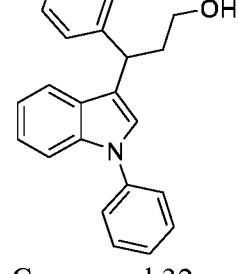
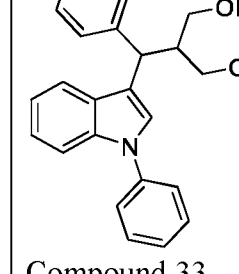
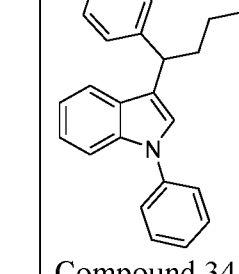
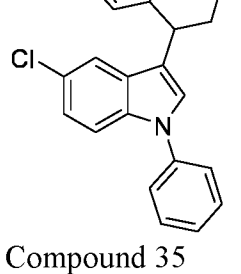
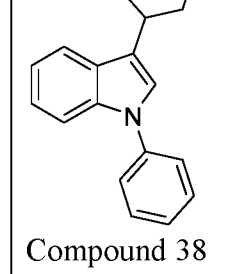
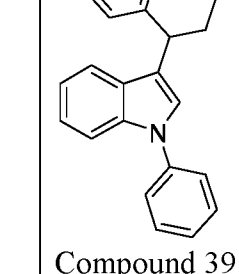
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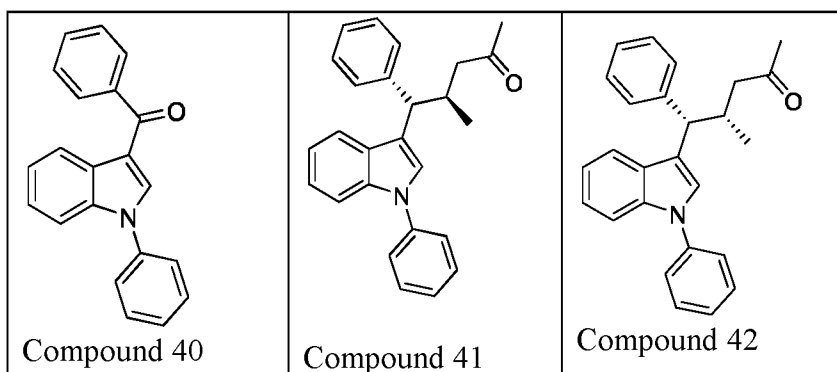
EXAMPLES

Example 1: Synthesis of GAT1102 analogs

The following GAT1102 analogs were synthesized.

 Compound 7	 Compound 8	 Compound 9	 Compound 10	 Compound 11
 Compound 12	 Compound 13	 Compound 14	 Compound 15	 Compound 16
 Compound 17	 Compound 18	 Compound 19	 Compound 20	 (+)-GAT1102

				
(-)-GAT1102	Compound 21	Compound 22	Compound 23	Compound 24
				
Compound 25	Compound 26	Compound 27	Compound 28	Compound 29
				
Compound 30	Compound 31	Compound 32	Compound 33	Compound 34
				
Compound 35			Compound 38	Compound 39



Example 2: Chemical characterization of GAT1102 analogs

NMR spectroscopic characterization of the synthesized GAT1102 analogs are provided below.

5 **2-Phenyl-2-(1-phenyl-1H-indol-3-yl)acetic acid [Compound 7]:** ^1H NMR (CDCl_3 , 500 MHz): δ 7.53 (dd, $J=8.3$, 1.0 Hz, 1H), 7.50-7.47 (m, 6H), 7.38 (s, 1H), 7.34-7.31 (m, 3H), 7.29-7.26 (m, 1H), 7.23-7.18 (m, 1H), 7.12-7.09 (m, 1H), 5.31 (s, 1H); MS-ESI (m/z) 328 $[\text{M} + \text{H}]^+$.

10 **3-Phenyl-3-(1-phenyl-1H-indol-3-yl)propanoic acid [Compound 8]:** ^1H NMR (CDCl_3 , 500 MHz): δ 7.53-7.45 (m, 5H), 7.37-7.33 (m, 3H), 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 7.06 (t, $J=7.9$ Hz, 1H), 4.83 (t, $J=7.3$ Hz, 1H), 3.22 (dd, $J=15.6$, 7.34 Hz, 1H), 3.08 (dd, $J=15.6$, 7.65 Hz, 1H); MS-ESI (m/z) 342 $[\text{M} + \text{H}]^+$.

15 **2-(Phenyl(1-phenyl-1H-indol-3-yl)methyl)malonic acid [Compound 9]:** ^1H NMR (CDCl_3 , 500 MHz): δ 7.54 (d, $J=7.9$, 1H), 7.50-7.43 (m, 5H), 7.38-7.37 (3H), 7.34-7.31 (m, 1H), 7.25-7.22 (m, 2H), 7.17-7.13 (m, 2H), 7.05 (t, $J=7.6$ Hz, 1H), 5.08 (d, $J=11.3$ Hz, 1H), 4.32 (d, $J=11.6$ Hz, 1H); MS-ESI (m/z) 386 $[\text{M} + \text{H}]^+$.

20 **3-Ethoxy-3-oxo-2-(phenyl(1-phenyl-1H-indol-3-yl)methyl)propanoic acid [Compound 10]:** ^1H NMR (CDCl_3 , 500 MHz): δ 7.53 (d, $J=8.0$ Hz, 1H), 7.50-7.45 (m, 5H), 7.41 (s, 1H), 7.38 (d, $J=7.8$ Hz, 2H), 7.34-7.31 (m, 1H), 7.25-7.22 (m, 2H), 7.15 (q, $J=7.6$ Hz, 2H), 7.05 (t, $J=7.1$ Hz, 1H), 5.07 (d, 11.4 Hz, 1H), 4.32 (d, $J=11.9$ Hz, 1H), 3.93 (q, $J=7.3$ Hz, 2H), 0.94 (t, $J=7.4$ Hz, 3H); MS-ESI (m/z) 414 $[\text{M} + \text{H}]^+$.

($\pm$)-2-Methyl-4-phenyl-4-(1-phenyl-1H-indol-3-yl)butanoic acid [($\pm$)-Compound 11, *cis*]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.54-7.48 (m, 5H), 7.38-7.35 (m, 2H), 7.33-7.28 (m, 3H), 7.21-7.15

(m, 3H), 7.08-7.05 (m, 1H), 4.35 (dd, $J=9.0, 6.7$ Hz, 1H), 2.76-2.70 (m, 1H), 2.57-2.44 (m, 1H), 2.10-2.04 (m, 1H), 1.23 (d, $J=6.9$ Hz, 3H); MS-ESI (m/z) 370 $[M + H]^+$.

(±)-2-Methyl-4-phenyl-4-(1-phenyl-1H-indol-3-yl)butanoic acid [(±)-Compound 12, *trans*]:

^1H NMR (CDCl_3 , 500 MHz): δ 7.52-7.48 (m, 5H), 7.38-7.36 (m, 2H), 7.33-7.26 (m, 3H), 7.19-7.15 (m, 3H), 7.08-7.05 (m, 1H), 4.35 (t, $J=8.0$, 1H), 2.60-2.54 (m, 1H), 2.52-2.45 (m, 1H), 2.31-2.25 (m, 1H), 1.29 (d, $J=7.3$ Hz, 3H); MS-ESI (m/z) 370 $[M + H]^+$.

Ethyl 4-phenyl-4-(1-phenyl-1H-indol-3-yl)butanoate [Compound 13]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.54-7.48 (m, 6H), 7.36-7.27 (m, 5H), 7.24-7.16 (m, 3H), 7.08-7.05 (m, 1H), 4.29 (t, $J=7.3$ Hz, 1H), 4.14 (q, $J=6.7$ Hz, 2H), 2.60-2.54 (m, 1H), 2.39-2.35 (m, 3H), 1.23 (t, $J=7.3$ Hz, 3H); MS-ESI (m/z) 384 $[M + H]^+$.

Methyl 4-phenyl-4-(1-phenyl-1H-indol-3-yl)butanoate [Compound 14]: ^1H NMR (CDCl_3 , 400 MHz): 7.55-7.50 (m, 6H), 7.35-7.30 (m, 5 H), 7.23-7.18 (m, 3H), 7.09-7.07 (m, 1H), 4.27-4.25 (m, 1H), 3.85 (s, 3H), 2.62-2.57 (m, 1H), 2.43-2.35 (m, 3H); MS-ESI (m/z) 397 $[M + H]^+$.

(Z)-4-phenyl-4-(1-phenyl-1H-indol-3-yl)but-2-enoic acid [Compound 15]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.55 (d, $J=8.3$ Hz, 1H), 7.51-7.49 (m, 4H), 7.40-7.39 (m, 3H), 7.35-7.30 (m, 3H), 7.25-7.23 (m, 1H), 7.19 (t, $J=7.7$ Hz, 1H), 7.13 (s, 1H), 7.06 (t, $J=7.8$ Hz, 1H), 6.84 (t, $J=11.0$ Hz, 1H), 6.51 (d, $J=10.7$ Hz, 1H), 5.97 (d, $J=11.3$ Hz, 1H); MS-ESI (m/z) 354 $[M + H]^+$.

(E and Z)-4-Phenyl-4-(1-phenyl-1H-indol-3-yl)but-3-enoic acid [Compound 16; mix of *trans*:*cis* (94:6)]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.69 (d, $J=8.2$ Hz, 0.07H), 7.60 (d, $J=8.2$ Hz, 1H), 7.57-7.52 (m, 4H), 7.49-7.46 (m, 0.21 H), 7.44-7.41 (m, 3H), 7.38-7.32 (m, 1H), 7.31-7.28 (m, 3H), 7.23-7.20 (m, 1H), 7.13-7.11 (m, 1H), 7.06-7.03 (m, 1H), 6.41 (t, $J=7.8$ Hz, 0.06 H), 6.33 (t, $J=7.4$ Hz, 1H), 3.40 (d, $J=7.6$ Hz, 2H), 3.28 (d, $J=7.6$ Hz, 0.14 Hz) MS-ESI (m/z) 354 $[M + H]^+$.

4-(6-Methyl-1-phenyl-1H-indol-3-yl)-4-phenylbutanoic acid [Compound 17]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.52-7.48 (m, 4H), 7.35-7.32 (m, 5H), 7.29 (t, $J=7.6$ Hz, 2H), 7.20-7.17 (m, 1H), 7.14 (s, 1H), 6.90 (d, $J=8.0$ Hz, 1H), 4.23 (t, $J=8.04$ Hz, 1H), 2.62-2.55 (m, 1H), 2.48-2.32 (m, 6H); MS-ESI (m/z) 370 $[M + H]^+$.

4-(1-Penzyl-1H-indol-3-yl)-4-phenylbutanoic acid [Compound 18]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.43 (d, $J=8.4$ Hz, 1H), 7.31-7.27 (m, 7H), 7.23-7.16 (m, 2H), 7.13-7.08 (m, 3H), 7.01-6.98 (m, 2H), 5.29 (s, 2H), 4.22 (t, $J=8.0$ Hz, 1H), 2.57-2.50 (m, 1H), 2.44-2.28 (m, 3H); MS-ESI (m/z) 370 $[\text{M} + \text{H}]^+$.

5 **5-Phenyl-5-(1-phenyl-1H-indol-3-yl)pentanoic acid [Compound 19]:** ^1H NMR (CDCl_3 , 500 MHz): δ 7.54-7.47 (m, 6H), 7.34-7.31 (m, 3H), 7.29-7.26 (m, 2H), 7.22 (s, 1H), 7.19-7.15 (m, 2H), 7.06 (t, $J=7.4$ Hz, 1H), 4.22 (t, $J=7.4$ Hz, 1H), 2.40 (t, $J=7.44$ Hz, 2H), 2.32-2.25 (m, 1H), 2.13-2.05 (m, 1H), 1.81-1.75 (m, 1H), 1.72-1.65 (m, 1H); MS-ESI (m/z) 370 $[\text{M} + \text{H}]^+$.

10 **6-Phenyl-6-(1-phenyl-1H-indol-3-yl)hexanoic acid [Compound 20]:** ^1H NMR (CDCl_3 , 500 MHz): δ 7.54-7.47 (m, 6H), 7.34-7.31 (m, 3H), 7.29-7.28 (m, 2H), 7.19-7.15 (m, 3H), 7.06 (t, $J=7.6$ Hz, 1H), 4.20 (t, $J=7.2$ Hz, 1H), 2.33 (t, $J=8.0$ Hz, 2H), 2.29-2.22 (m, 1H), 2.10-2.03 (m, 1H), 1.76-1.63 (m, 2H), 1.51-1.44 (m, 1H), 1.41-1.35 (m, 1H); MS-ESI (m/z) 384 $[\text{M} + \text{H}]^+$.

15 **4-Phenyl-4-(1-(pyridin-2-yl)-1H-indol-3-yl)butanoic acid [Compound 21]:** ^1H NMR (CDCl_3 , 500 MHz): δ 8.57 (dd, $J=4.8, 1.1$ Hz, 1H), 8.10 (d, $J=8.0$ Hz, 1H), 7.84-7.80 (m, 1H), 7.66 (s, 1H), 7.51 (d, $J=8.0$ Hz, 1H), 7.44 (d, $J=8.0$ Hz, 1H), 7.36 (s, 1H), 7.34 (s, 1H), 7.28 (t, $J=7.7$ Hz, 2H), 7.24-7.23 (m, 1H), 7.20-7.15 (m, 2H), 7.09 (t, $J=7.5$ Hz, 1H), 4.25 (t, $J=8.1$ Hz, 1H), 2.65-2.58 (m, 1H), 2.47-2.37 (m, 3H); MS-ESI (m/z) 357 $[\text{M} + \text{H}]^+$.

20 **4-Phenyl-4-(1-(pyridin-3-yl)-1H-indol-3-yl)butanoic acid [Compound 22]:** ^1H NMR (CDCl_3 , 500 MHz): δ 8.84 (d, $J=2.2$ Hz, 1H), 8.58 (d, $J=4.6$ Hz, 1H), 7.87-7.85 (m, 1H), 7.51-7.46 (m, 3H), 7.36-7.34 (m, 2H), 7.30 (m, $J=7.5$ Hz, 2H), 7.23-7.20 (m, 3H), 7.10 (t, $J=7.7$ Hz, 1H), 4.27 (t, $J=8.1$ Hz, 1H), 2.65-2.59 (m, 1H), 2.46-2.35 (m, 3H); MS-ESI (m/z) 357 $[\text{M} + \text{H}]^+$.

25 **4-Phenyl-4-(1-(pyridin-4-yl)-1H-indol-3-yl)butanoic acid [Compound 23]:** ^1H NMR (CDCl_3 , 500 MHz): δ 8.69 (d, $J=5.6$ Hz, 2H), 7.69 (d, $J=8.5$ Hz, 1H), 7.50-7.47 (m, 3H), 7.35-7.30 (m, 5H), 7.24-7.20 (m, 1H), 7.13 (t, $J=7.6$ Hz, 1H), 4.26 (t, $J=8.31$ Hz, 1H), 2.65-2.59 (m, 1H), 2.45-2.34 (m, 3H); MS-ESI (m/z) 357 $[\text{M} + \text{H}]^+$.

4-Phenyl-4-(1-(thiophen-3-yl)-1H-indol-3-yl)butanoic acid [Compound 24]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.52 (d, $J=8.3$ Hz, 1H), 7.47 (d, $J=7.8$ Hz, 1H), 7.44 (dd, $J=5.2, 3.6$ Hz, 1H), 7.34 (d,

$J=7.63$ Hz, 2H), 7.31-7.27 (m, 4H), 7.21-7.19 (m, 3H), 7.07 (t, $J=7.6$ Hz, 1H), 4.25 (t, $J=8.3$ Hz, 1H), 2.57-2.63 (m, 1H), 2.45-2.34 (m, 3H); MS-ESI (m/z) 362 $[M + H]^+$.

4-phenyl-4-(1-(thiophen-2-yl)-1H-indol-3-yl)butanoic acid [Compound 25]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.54 (d, $J=6.4$ Hz, 2H), 7.31-7.27 (m, 3H), 7.23-7.19 (m, 2H), 7.17-7.16 (m, 1H), 7.09-7.03 (m, 3H), 4.24 (t, $J=7.38$ Hz, 1H), 2.60-2.55 (m, 1H), 2.44-2.32 (m, 3H); MS-ESI (m/z) 362 $[M + H]^+$.

4-(1-(5-bromothiophen-2-yl)-1H-indol-3-yl)-4-phenylbutanoic acid [Compound 26]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.51 (d, $J=7.7$ Hz, 1H), 7.46 (d, $J=8.8$ Hz, 1H), 7.35-7.30 (m, 4H), 7.24-7.21 (m, 2H), 7.12-7.09 (m, 2H), 7.03 (d, $J=4.7$ Hz, 1H), 6.83 (d, $J=4.13$ Hz, 1H), 4.23 (t, $J=8.3$ Hz, 1H), 2.62-2.55 (m, 1H), 2.44-2.41 (m, 2H), 2.38-2.33 (m, 1H). MS-ESI (m/z) 441 $[M + H]^+$.

4-(1H-Indol-3-yl)-4-phenylbutanoic acid [Compound 28]: ^1H NMR (CDCl_3 , 500 MHz): δ 8.01 (bs, 1H), 7.43 (d, $J=7.9$ Hz, 1H), 7.35-7.27 (m, 5H), 7.19-7.13 (m, 2H), 7.08 (s, 1H), 7.02 (t, $J=8.1$ Hz, 1H), 4.22 (t, $J=7.9$ Hz, 1H), 2.60-2.53 (m, 1H), 2.43-2.33 (m, 3H); MS-ESI (m/z) 280 $[M + H]^+$.

4-(1-Penzoyl-1H-indol-3-yl)-4-phenylbutanoic acid [Compound 29]: ^1H NMR (CDCl_3 , 500 MHz): δ 8.28 (d, $J=8.1$ Hz, 1H), 7.75 (d, $J=6.9$ Hz, 2H), 7.62 (d, $J=7.4$ Hz, 1H), 7.55 (t, $J=7.8$ Hz, 2H), 7.35 (d, $J=7.8$ Hz, 1H), 7.33-7.27 (m, 5H), 7.24 (s, 1H), 7.22-7.17 (m, 2H), 4.13 (dd, $J=8.8, 6.6$ Hz, 1H), 2.49-2.42 (m, 1H), 2.38-2.34 (m, 2H), 2.28-2.22 (m, 1H); MS-ESI (m/z) 384 $[M + H]^+$.

Phenyl(1-phenyl-1H-indol-3-yl)methanol [Compound 30]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.67-7.65 (m, 1H), 7.55-7.52 (m, 3H), 7.49-7.43 (m, 4H), 7.38-7.31 (m, 4H), 7.29-7.25 (m, 1H), 7.17-7.12 (m, 1H), 7.1 (d, $J=1.0$ Hz, 1H), 6.21 (d, $J=2.6$ Hz, 1H), 2.34 (d, $J=3.4$ Hz, 1H); MS-ESI (m/z) 300 $[M + H]^+$.

2-Phenyl-2-(1-phenyl-1H-indol-3-yl)ethan-1-ol [Compound 31]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.54 (d, $J=8.2$ Hz, 1H), 7.56-7.54 (m, 5H), 7.45-7.36 (m, 4H), 7.30-7.23 (m, 3H), 7.10-7.07 (m, 1H), 4.52 (t, $J=7.0$ Hz, 1H), 4.27 (dd, $J=10.7, 6.27$ Hz, 1H), 4.19 (dd, $J=10.7, 7.3$ Hz, 1H); MS-ESI (m/z) 314 $[M + H]^+$.

3-Phenyl-3-(1-phenyl-1H-indol-3-yl)propan-1-ol [Compound 32]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.54-7.49 (m, 6H), 7.37 (d, $J=7.6$, 2H), 7.35-7.32 (m, 1H), 7.29 (t, $J=7.6$ Hz, 1H), 7.22 (s, 1H), 7.20-7.16 (m, 2H), 7.07 (t, $J=8.1$ Hz, 1H), 4.45 (t, $J=7.8$ Hz, 1H), 3.75-3.66 (m, 2H), 2.51 (sext, $J=6.8$ Hz, 1H), 2.34-2.23 (m, 1H), 1.46 (s, 1H); MS-ESI (m/z) 328 $[\text{M} + \text{H}]^+$.

5 **2-(Phenyl(1-phenyl-1H-indol-3-yl)methyl)propane-1,3-diol [Compound 33]:** ^1H NMR (CDCl_3 , 500 MHz): δ 7.65 (d, $J=7.6$ Hz, 1H), 7.53-7.48 (m, 5H), 7.42 (d, $J=7.2$ Hz, 2H), 7.36-7.35 (m, 1H), 7.29-7.26 (m, 3H), 7.20-7.17 (m, 2H), 7.13-7.10 (m, 1H), 4.37 (d, $J=11.2$ Hz, 1H), 4.02 (d, $J=9.8$ Hz, 1H), 3.92-3.90 (m, 1H), 3.82 (d, $J=9.8$ Hz, 1H), 3.66-3.63 (m, 1H), 2.68-2.63 (m, 1H), 2.16-2.13 (m, 2H); MS-ESI (m/z) 358 $[\text{M} + \text{H}]^+$.

10 **4-Phenyl-4-(1-phenyl-1H-indol-3-yl)butan-1-ol [Compound 34]:** ^1H NMR (CDCl_3 , 500 MHz): δ 7.54-7.48 (m, 6H), 7.36-7.24 (m, 5H), 7.22 (s, 1H), 7.19-7.15 (m, 2H), 7.06 (t, $J=7.34$ Hz, 1H), 4.26 (t, $J=7.7$ Hz, 1H), 3.67 (t, $J=6.4$ Hz, 2H), 2.36-2.29 (m, 1H), 2.15-2.11 (m, 1H), 1.73-1.56 (m, 2H), 1.23 (s, 1H); MS-ESI (m/z) 342 $[\text{M} + \text{H}]^+$.

15 **2-(5-Chloro-1-phenyl-1H-indol-3-yl)-2-phenylethan-1-ol [Compound 35]:** ^1H NMR (CDCl_3 , 500 MHz): δ 7.51-7.42 (m, 6H), 7.36-7.30 (m, 6H), 7.25 (t, $J=7.0$ Hz, 1H), 7.12 (d, $J=9.3$ Hz, 1H), 6.43 (t, $J=6.5$ Hz, 1H), 4.24-4.15 (m, 2H), 1.67 (bs, 1H); MS-ESI (m/z) 349 $[\text{M} + \text{H}]^+$.

-Phenyl-2-(1-phenyl-1H-indol-3-yl)acetonitrile [Compound 36]: ^1H NMR (CDCl_3 , 500 MHz): δ 7.54-7.45 (m, 8H), 7.39-7.29 (m, 4H), 7.24 (dt, $J=7.3$, 1.0 Hz, 1H), 7.15 (dt, $J=6.9$, 1.0 Hz, 1H), 5.43 (s, 1H); MS-ESI (m/z) 309 $[\text{M} + \text{H}]^+$.

20 **3-Phenyl-3-(1-phenyl-1H-indol-3-yl)propanenitrile [Compound 37]:** ^1H NMR (CDCl_3 , 500 MHz): δ 7.54-7.50 (m, 5H), 7.39-7.34 (m, 6H), 7.29-7.27 (m, 1H), 7.22-7.19 (m, 1H), 7.08 (t, $J=7.4$ Hz, 1H), 4.68 (t, $J=7.2$ Hz, 1H), 3.17 (dd, $J=17.0$, 7.2 Hz, 1H), 3.07 (dd, $J=16.5$, 7.2 Hz, 1H); MS-ESI (m/z) 323 $[\text{M} + \text{H}]^+$.

25 **3-Phenyl-3-(1-phenyl-1H-indol-3-yl)propanamide [Compound 38]:** ^1H NMR (CDCl_3 , 500 MHz): δ 7.53-7.46 (m, 6H), 7.38-7.2 (m, 5H), 7.21-7.16 (m, 3H), 7.07-7.04 (m, 1H), 5.43 (bs, 1H), 5.33 (bs, 1H), 4.82 (t, $J=7.3$ Hz, 1H), 3.13 (dd, $J=14.6$, 7.3 Hz, 1H), 2.93 (dd, $J=14.2$, 8.2 Hz, 1H); MS-ESI (m/z) 341 $[\text{M} + \text{H}]^+$.

1-Phenyl-3-(1-phenyl-2-(1H-tetrazol-5-yl)ethyl)-1H-indole [Compound 39]: ¹H NMR (CDCl₃, 500 MHz): δ 7.54-7.48 (m, 3H), 7.45-7.43 (m, 3H), 7.36-7.30 (m, 5H), 7.25-7.19 (m, 3H), 7.08 (t, *J*=7.5 Hz, 1H), 4.78 (t, *J*= 8.1 Hz, 1H), 3.95 (dd, *J*=15.1, 7.3 Hz, 1H), 3.73 (dd, *J*= 15.0, 7.8 Hz, 1H); MS-ESI (*m/z*) 366 [M + H]⁺.

5 **Phenyl(1-phenyl-1H-indol-3-yl)methanone [Compound 40]:** ¹H NMR (CDCl₃, 500 MHz): δ 8.51 (d, *J*= 8.3 Hz, 1H), 7.88-7.87 (m, 2H), 7.77 (s, 1H), 7.57-7.49 (m, 8H), 7.47-7.44 (m, 1H), 7.40-7.33 (m, 2H); MS-ESI (*m/z*) 298 [M + H]⁺.

10 **4-Methyl-5-phenyl-5-(1-phenyl-1H-indol-3-yl)pentan-2-one [Compound 41]:** ¹H NMR (CDCl₃, 500 MHz): δ 7.62 (d, *J*= 7.7 Hz, 1H), 7.53-7.46 (m, 5H), 7.38-7.37 (m, 2H), 7.35-7.32 (m, 1H), 7.30 (s, 1H), 7.28-7.25 (m, 2H), 7.20-7.10 (m, 3H), 3.97 (d, *J*= 10.3 Hz, 1H), 3.04-2.99 (m, 1H), 2.77 (dd, *J*= 16.7, 2.6 Hz, 1H), 2.36 (dd, *J*= 16.9, 9.1 Hz, 1H), 2.03 (s, 3H), 0.88 (d, *J*= 6.7 Hz, 3H); MS-ESI (*m/z*) 368 [M + H]⁺.

15 **4-Methyl-5-phenyl-5-(1-phenyl-1H-indol-3-yl)pentan-2-one [Compound 42]:** ¹H NMR (CDCl₃, 500 MHz): δ 7.57 (d, *J*= 7.8 Hz, 1H), 7.53-7.50 (m, 5H), 7.37-7.32 (m, 4H), 7.27-7.24 (m, 2H), 7.16 (q, *J*=7.5, 2H), 7.09 (t, *J*=7.7 Hz, 1H), 4.02 (d, *J*= 10.0 Hz, 1H), 3.04-2.95 (m, 1H), 2.47 (dd, *J*= 16.4, 3.0 Hz, 1H), 2.24 (dd, *J*= 17.1, 9.6 Hz, 1H), 2.00 (s, 3H), 0.88 (d, *J*= 6.3 Hz, 3H); MS-ESI (*m/z*) 368 [M + H]⁺.

Example 3: Functional evaluation of GAT 1102 analogs

20 GAT1102 analogs were functionally evaluated using the procedures described below. Results obtained are shown in the Table 1 that follows the procedures.

25 *PathHunter CB1 β-Arrestin Assay:* Chinese hamster ovary K1 (CHO-K1)-PathHunter hCB1 β-arrestin cells (DiscoverX, Fremont, CA) were seeded at 5000 cells/well in 384-well plates 24 h before use and incubated at 37 °C, 5% CO₂. Compounds were dissolved in dimethyl sulfoxide (DMSO) and diluted in optimized cell culture (OCC) media. Agonist EC80 was determined directly from an agonist dose-response curve (data not shown). The CP55,940 EC80 was 31.1 ± 0.47 nM (mean ± SEM, n = 3 independent experiments). Five microliters of allosteric modulator or vehicle solution was added to each well at the appropriate concentrations and incubated for 30 min. Five microliters of agonist was then added to each well followed by a 90 min incubation. Fifteen microliters of detection reagent was then added followed by further 60 min incubation at

room temperature. Chemiluminescence was measured on a standard luminescence plate reader as relative light units (RLU). Basal RLU was defined as zero. Results were calculated as the percentage inhibition of CP55,940 maximal effect. Data were analyzed using the fourparameter variable-slope and allosteric EC50 shift nonlinear regression equations in Prism 5.0 (GraphPad, San Diego, CA). The results of this analysis are presented as Emax ± SEM, and EC50 (nM) with 95% CI.

HitHunter cAMP assay: Inhibition of forskolin-stimulated cAMP was determined using the DiscoverX HitHunter assay in hCB1R CHO-K1 cells. Cells (20,000 cells/well in low-volume 96 well plates) were incubated overnight in Opti-MEM (Invitrogen) containing 1% FBS at 37°C and 5% CO₂. Following this, Opti-MEM media was removed and replaced with cell assay buffer (DiscoverX) and cells were co-treated at 37°C with 10 μM forskolin and hCB1R ligands (0.10 nM – 10 μM) for 30 min or 90 min cAMP antibody solution and cAMP working detection solutions were then added to cells according to the manufacturer's directions (DiscoverX®) and cells were incubated for 60 min at room temperature. cAMP solution A was added according to the manufacturer's directions (DiscoverX®) and cells were incubated for an additional 60 min at room temperature before chemiluminescence was measured on a Cytation 5 plate reader (top read, gain 200, integration time 10,000 ms). Results are shown in Figure 4.

Table 1

Compound	CB1				CB2	
	PAM mode		Agonist mode		Agonist mode	
	cAMP	β-Arrestin	cAMP	β-Arrestin	cAMP	β-Arrestin
	EC ₅₀ (μM) [E _{max} (%)]	EC ₅₀ (μM) [E _{max} (%)]	EC ₅₀ (μM) [E _{max} (%)]	EC ₅₀ (μM) [E _{max} (%)]	EC ₅₀ (μM) [E _{max} (%)]	EC ₅₀ (μM) [E _{max} (%)]
GAT211 (reference)	0.318 (73)	0.313 (59)	0.361 (94)	>10 (14)	>10 (0)	>10 (0)
Compound 7	4.18 (78.89)	>10 (0)	NA	NA	NA	NA
Compound 8	0.509 (144)	>10 (0)	NA	NA	NA	NA
Compound 9	1.28 (158)	>10 (0)	NA	NA	NA	NA

Compound 10	>10 (6.98)	>10 (4.59)	NA	NA	NA	NA
GAT1102	0.419 (101)	>10 (0)	0.356 (89)	>10 (0)	0.271 (81)	>10 (0)
Compound 11	1.89 (100)	>10 (0)	1.26 (62)	>10 (0)	NA	NA
Compound 12	0.704 (101)	>10 (0)	1.06 (60)	>10 (0)	NA	NA
Compound 13	>10 (0)	>10 (0)	NA	NA	NA	NA
Compound 14	NA	NA	NA	NA	NA	NA
Compound 15	0.639 (84)	>10 (0)	0.506 (86)	>10 (0)	1.05 (81)	>10 (0)
Compound 16	0.934 (104)	>10 (0)	0.689 (94)	>10 (0)	0.359 (80)	>10 (0)
Compound 17	1.44 (93)	>10 (0)	1.25 (73)	>10 (0)	1.00 (74)	>10 (0)
Compound 18	0.61 (97)	>10 (0)	1.036 (87)	>10 (0)	0.407 (64)	>10 (0)
Compound 19	1.42 (98)	>10 (0)	0.827 (98)	>10 (0)	0.654 (95)	>10 (0)
Compound 20	1.09 (96)	>10 (0)	0.355 (96)	>10 (0)	0.505 (98)	>10 (0)
Compound 21	0.869 (96)	>10 (0)	0.457 (95)	>10 (0)	1.11 (85)	>10 (0)
Compound 22	1.00 (109)	>10 (0)	0.831 (87)	>10 (0)	0.731 (68)	>10 (0)
Compound 23	1.063 (104)	>10 (0)	0.357 (83)	>10 (0)	0.570 (78)	>10 (0)
(+)-GAT1102	NA	NA	NA	NA	NA	NA
(-)-GAT1102	NA	NA	NA	NA	NA	NA
Compound 24	NA	NA	NA	NA	NA	NA
Compound 25	NA	NA	NA	NA	NA	NA
Compound 26	NA	NA	NA	NA	NA	NA
Compound 27	NA	NA	NA	NA	NA	NA

Compound 28	4.35 (71)	>10 (0)	9.81 (60)	>10 (0)	>10 (29)	>10 (0)
Compound 29	0.709 (114)	>10 (0)	0.596 (92)	>10 (0)	0.419 (76)	>10 (0)
Compound 30	>10 (0)	>10 (0)	NA	NA	NA	NA
Compound 31	>10 (1.311)	>10 (0)	NA	NA	NA	NA
Compound 32	>10 (27.14)	>10 (0)	NA	NA	NA	NA
Compound 33	NA	NA	NA	NA	NA	NA
Compound 34	>10 (0)	>10 (5)	NA	NA	NA	NA
Compound 35	>10 (2.814)	>10 (0)	NA	NA	NA	NA
Compound 38	>10(27.1)	>10 (0)	NA	NA	NA	NA
Compound 39	0.423 (94)	>10 (0)	NA	NA	NA	NA
Compound 40	>10 (11.67)	>10 (0.273)	NA	NA	NA	NA
Compound 41	>10 (0)	>10 (0)	>10 (0)	>10 (0)	>10 (34)	>10 (0)
Compound 42	>10 (0)	>10 (0)	>10 (0)	>10 (0)	>10 (0)	>10 (0)

NA: Not Available

Example 4: Electrophysiological characterization of GAT1102

- 5 The compound GAT1102 exhibited agonist properties in some cells. Averaged direct inhibition of excitatory postsynaptic currents (EPSCs) upon applying 1 μ M GAT1102 can be seen in Figure 2A. There was some evidence of a modest GAT1102 PAM effect in the form of a slowing recovery for depolarization-induced suppression of excitation (DSE) but in most cases this was occluded by the direct inhibition (agonism). Depolarization response curves before and after
- 10 GAT1102 treatment are shown in Figure 2B. Figure 2C shows sample DSE time course from a cell showing an enhanced DSE inhibition after GAT1102 treatment, which is consistent with a PAM-like response.

Example 5: *In vivo* Evaluation of GAT1102 in IOP Studies

Animals

Normotensive C57Bl/6J mice and *Sh3pxd2b* mice were obtained from Jackson Laboratory (Bar Harbor, Maine). The *Sh3pxd2b* mice were bred in house, and their progenies with abnormal phenotypical morphology, identified as a nee mice, were used for experiments.

Drugs

5 GAT1102 was dissolved in a standard vehicle containing 2% DMSO (Sigma Aldrich, Oakville, ON, Canada) and 4% Tween-20 (Sigma-Aldrich) in Tocrisolve (Bio-Techne, Minneapolis, MN). In normotensive C57Bl/6J animals WIN55,212-2 (0.25%) was dissolved together with GAT1102 (0.2%). In the ocular hypertensive nee mice GAT 1102 was administered alone at 0.2%. Drug was administered topically (5 µl/eye) to the right eyes, while the left eyes
10 received vehicle control (2% DMSO + 4% Tween-20 in Tocrisolve; 5 µl).

IOP Measurements

Mice were anesthetized with the isoflurane (3% induction, 1.5% maintenance). The intraocular pressure (IOP) was measured with a handheld rebound tonometer (Tonolab, Icare, Finland), calibrated to mouse. Ten recordings were taken for each eye and then averaged. The
15 IOP readings were taken at time 0 (baseline), 1, 6 and 12 hrs after the drug/vehicle administration. All the measurements were taken at the same time of the day, in order to minimize variability related to diurnal changes in IOP. See Figure 3A-3B

Data was analyzed by GraphPad version 6.0 (GraphPad Software, Inc., La Jolla, CA). Paired t-tests were used to compare between eyes of the same animal. A *P* value of < 0.05 was
20 considered significant. The IOP-lowering effect of subthreshold WIN55,212-2 (WIN) was found to be potentiated by the GAT1102 in normotensive C57Bl/6J mice. IOP was significantly lower in eyes receiving 0.2% GAT1102 combined with subthreshold 0.25% WIN at 6 and 12 hrs after topical administration compared to vehicle (n=5) See Figure 3A. GAT1102 (0.2%) significantly decreased IOP in ocular hypertensive nee mice at 1 and 12 hrs after topical administration (n=6).
25 Values are represented as a change in IOP from the baseline (time 0). See Figure 3B

The animal data make a compelling case for the utility of GAT1102 for reduced increased intraocular pressure associated with glaucoma. Based on our previous findings with GAT211, a CB1 PAM, we strongly believe that the class of compounds disclosed in this patent application will be useful for treating several other disorders mediated through CB1 receptor.

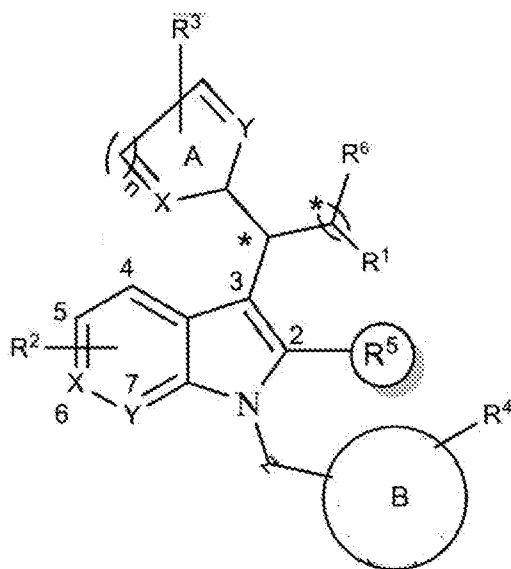
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CLAIMS

What is claimed is:

1. A compound having a structure according to Formula I



I

wherein

- X and Y are independently N or C at any of positions 4, 5, 6, and/or 7;

Z is an alkyl spacer, $(CH_2)_k$, optionally substituted and optionally including N, O, S, or a carbonyl group in the chain, and k is 0 to 4;

- A is a saturated or unsaturated carbocyclic or heterocyclic ring, the heteroatom(s) being N, S, or O in any combination, and n is 1 or 2; A also can be a 5 or 6 membered substituted or unsubstituted hetero(aromatic) ring;

B is a substituted or unsubstituted carbocyclic, bicyclic, (hetero)aromatic, or heterocyclic ring, preferably a 3 to 10 membered ring, a 4 to 7 membered ring, or a 5 to 6 membered ring;

R^1 is H, alkyl, optionally substituted, $=CH_2$, $(CHR)_xCO_2R$, or $(CH_2)_xOH$, wherein each R is independently H or an alkyl, optionally substituted, and x is 0 to 5;

- R^2 and R^4 are independently H, halogen, alkoxy, OH, alkyl, haloalkyl, optionally substituted, alkyne, NO_2 , CN, CO_2R , NR_2 , a deuterated alkyl group, a five- or six-membered

heterocyclic ring, a (hetero)aromatic ring, or SO_2NHR , wherein R is independently H or alkyl, optionally substituted;

R^3 is independently H, halogen, alkoxy, OH, alkyl optionally substituted, alkyne, NO_2 , CN, CO_2R , a three to six membered heterocyclic ring containing N and optionally an O or S, or SO_2NHR , wherein R is independently H or alkyl, optionally substituted;

R^5 is H, halogen, alkyl, optionally substituted, or aryl;

R^6 is $(\text{CHR}^7)_p\text{CO}_2\text{R}^7$; CN; OH; CONH_2 ; alkyl, optionally substituted (e.g., CF_3), CONR^7R^8 ; aryl; heterocyclic ring; $\text{CH}=\text{CHCO}_2\text{R}^7$; or $(\text{CHR}^7)_y\text{COR}^7$; wherein R^7 and R^8 , including each of R^7 , is independently H or alkyl, optionally substituted, and p and y are each 0 to 4;

* represents a chiral center; and

m is 0 to 5.

2. The compound of claim 1, wherein R^6 is CO_2H .

3. The compound of claim 1, wherein R^6 is CO_2H and m is 1.

4. The compound of claim 1, wherein each of R^1 and R^6 is CO_2H .

5. The compound of claim 1, wherein each of R^1 and R^6 is CO_2H and m is 1.

6. The compound of claim 1, wherein R^1 is CH_2OH and m is 1.

7. The compound of claim 1, wherein each of R^1 and R^6 is CH_2OH and m is 1.

8. The compound of claim 1, wherein R^6 is a heterocyclic ring.

9. The compound of claim 8, wherein the heterocyclic ring is tetrazole.

10. The compound of claim 1, wherein R^6 is CH_2COR^7 and R^7 is alkyl and m is 1.

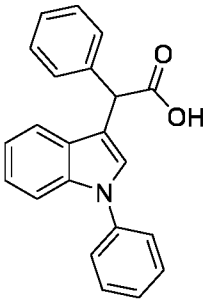
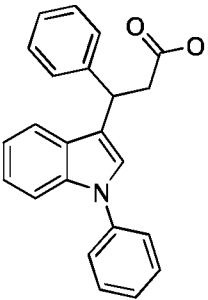
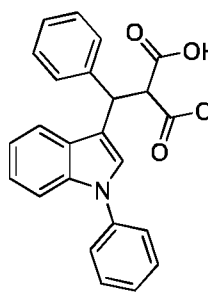
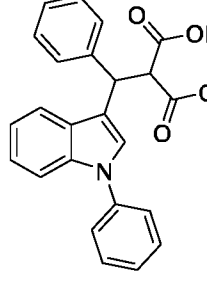
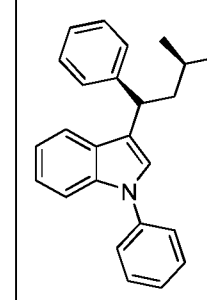
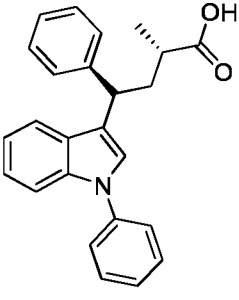
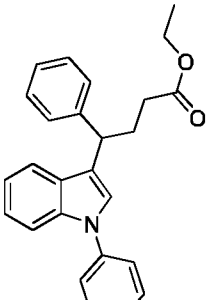
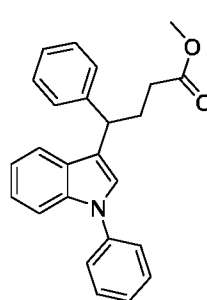
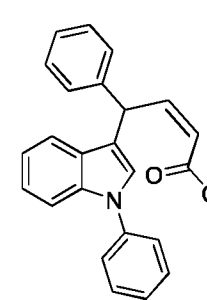
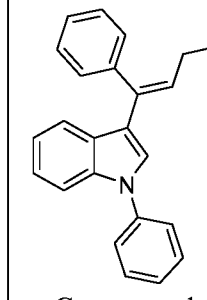
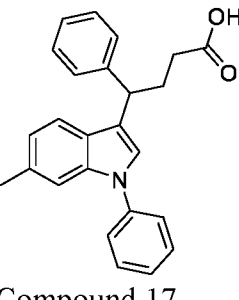
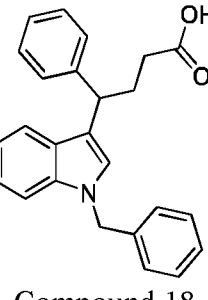
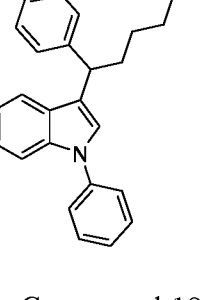
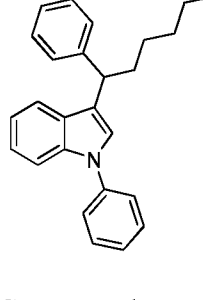
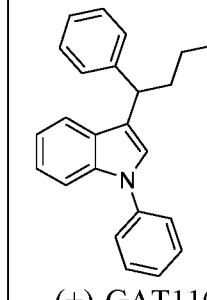
11. The compound of claim 10, wherein R^1 is H.

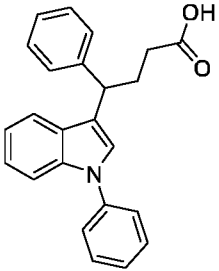
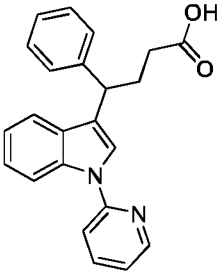
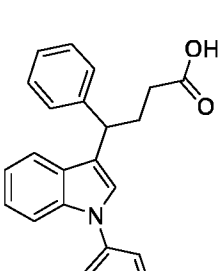
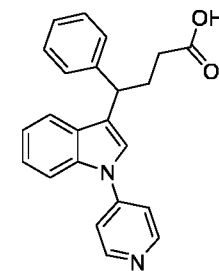
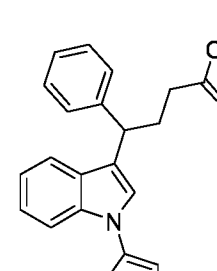
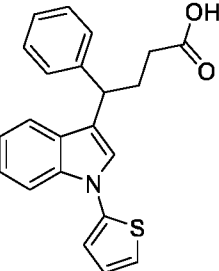
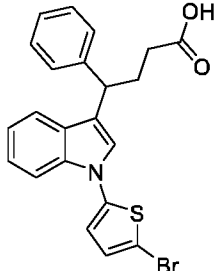
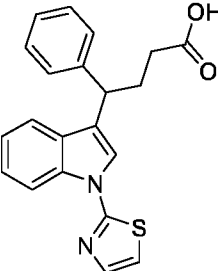
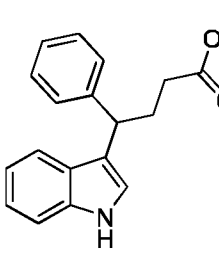
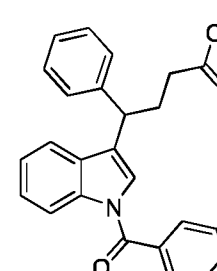
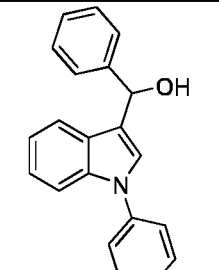
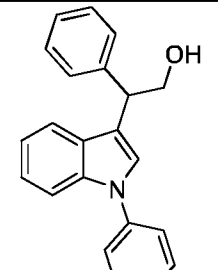
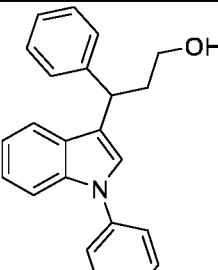
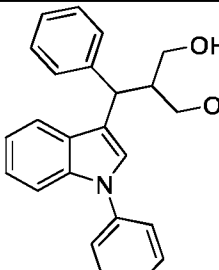
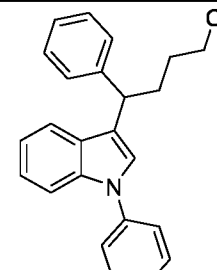
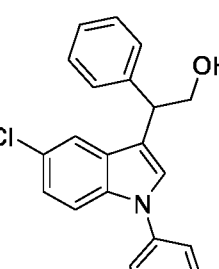
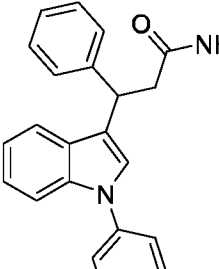
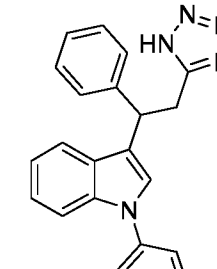
12. The compound of claim 10, wherein each of R^1 and R^7 is CH_3 .

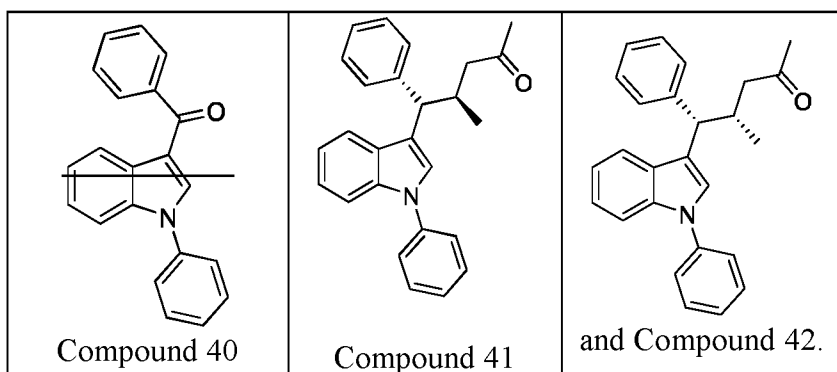
5

13. The compound of claim 1, wherein R^3 is piperidine, piperazine, or pyrrolidine.

14. The compound of claim 1 selected from the group consisting of

				
Compound 7	Compound 8	Compound 9	Compound 10	Compound 11
				
Compound 12	Compound 13	Compound 14	Compound 15	Compound 16
				
Compound 17	Compound 18	Compound 19	Compound 20	(+)-GAT1102

 (-)-GAT1102	 Compound 21	 Compound 22	 Compound 23	 Compound 24
 Compound 25	 Compound 26	 Compound 27	 Compound 28	 Compound 29
 Compound 30	 Compound 31	 Compound 32	 Compound 33	 Compound 34
 Compound 35			 Compound 38	 Compound 39



15. The compound of any of claims 1-14 that binds to a CB1 receptor.

5 16. The compound of any of claims 1-14 that binds to a CB2 receptor.

17. The compound of claims 15 or 16 that is a positive allosteric modulator.

18. A composition comprising a compound of any of claims 1-17.

10

19. A pharmaceutical composition comprising a compound of any of claims 1-17 and one or more excipients.

20. A method of treating a medical condition selected from the group consisting of glaucoma,
 15 post-traumatic stress disorder, epilepsy, pain, neuropathic pain, a neurodegenerative disease, Huntington's disease, Alzheimer's disease, or Parkinson's disease, the method comprising administering the compound of any of claims 1-17, the composition of claim 18, or the pharmaceutical composition of claim 19 to a subject in need thereof.

20 21. The method of claim 20, wherein the medical condition is glaucoma.

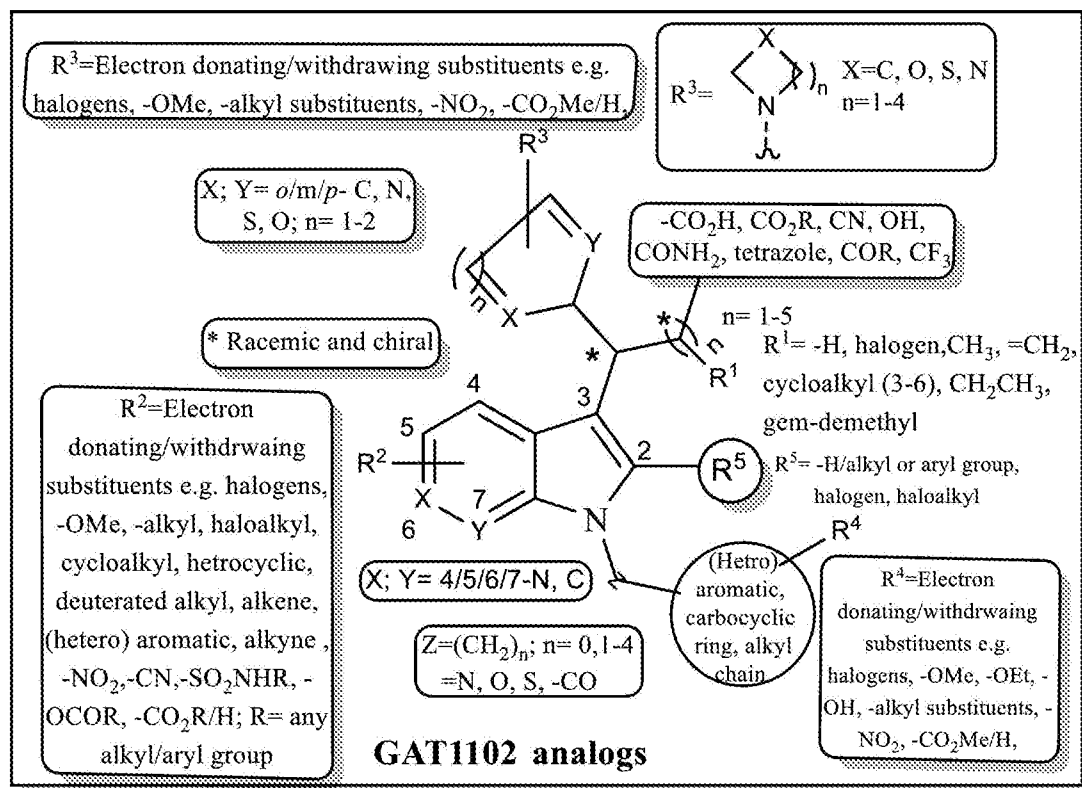
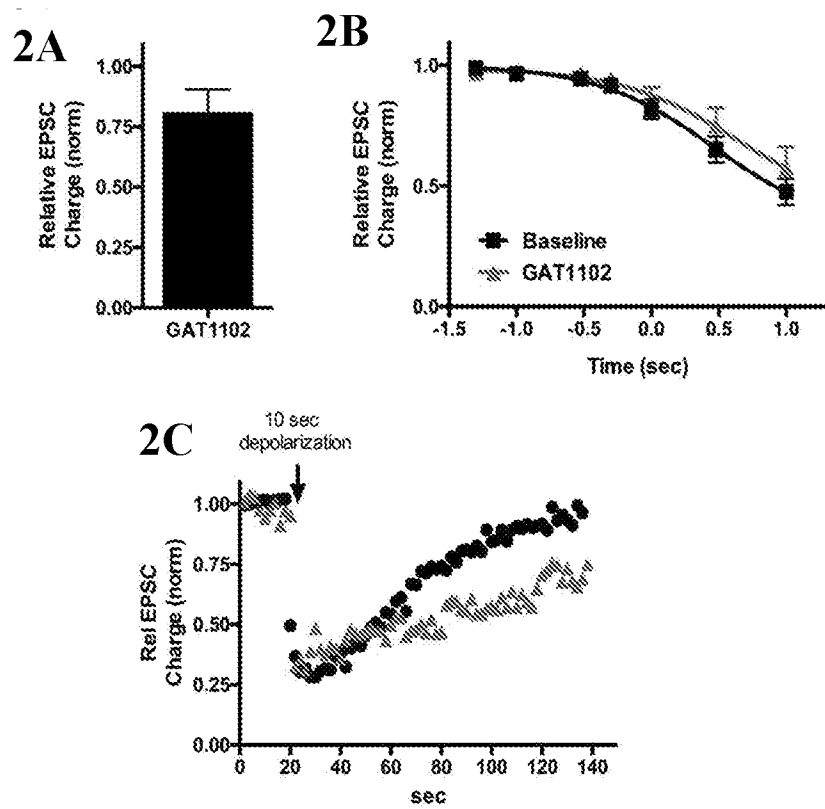
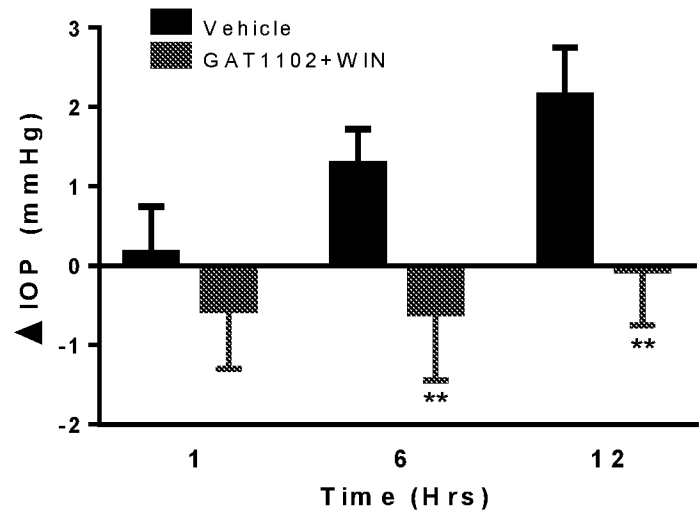


Fig. 1

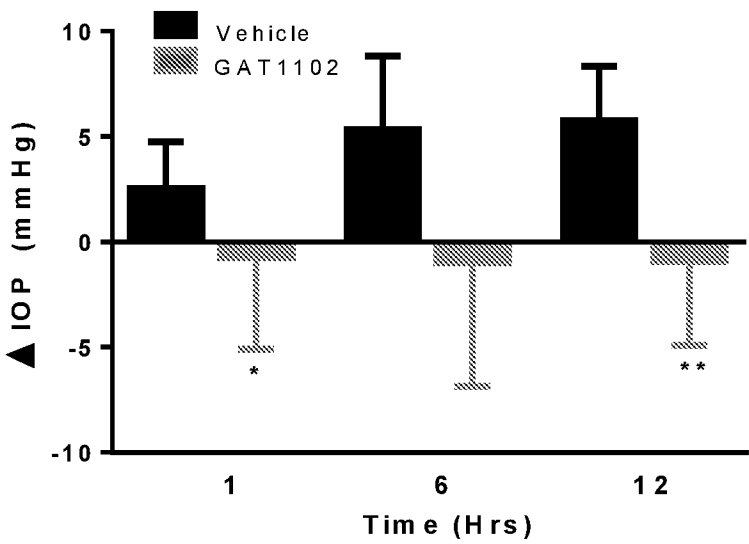


Figs. 2A-2C

3A



3B



Figs. 3A-3B

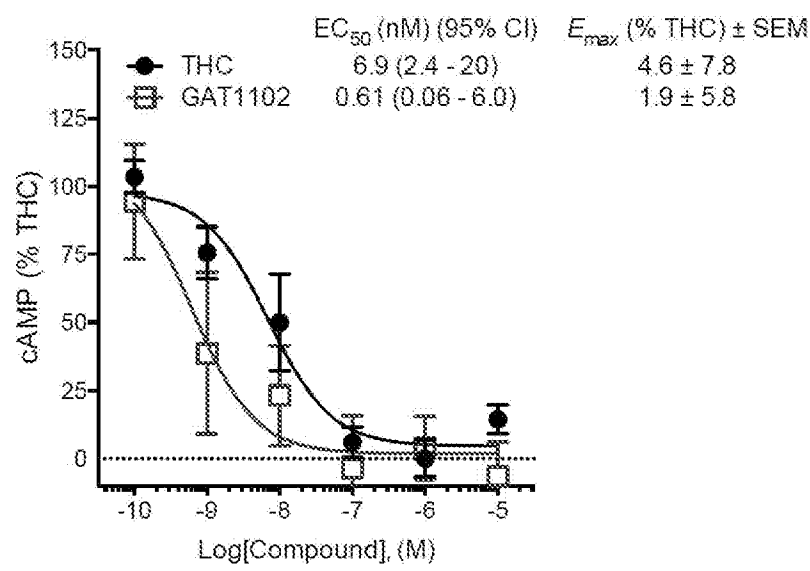


Fig.4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/39354

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/404; C07D 209/10; A61P 25/00; A61P 27/02 (2019.01)

CPC - A61K 31/404; C07D 209/10

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	PUBCHEM-CID: 42774242 Create date: 20 July 2009 (20.07.2009) pages 1-5. pg 2, structure.	1-2, (15-16)/(1-2)
A	PRICE et al. 'Allosteric Modulation of the Cannabinoid CB1 Receptor', MOLECULAR PHARMACOLOGY, 2005, Vol. 68, No. 5, pp. 1484-1495. DOI: 10.1124/mol.105.016162. abstract; pg 1486, Fig.2	1-2, (15-16)/(1-2)
A	US 2015/0005346 A1 (NORTHEASTERN UNIVERSITY) 01 January 2015 (01.01.2015) para [0002], [0054]	1-2, (15-16)/(1-2)
A	WO 2016/029310 A1 (THE GOVERNING COUNCIL OF THE UNIVERSITY OF TORONTO) 03 March 2016 (03.03.2016) para [0002], pg 111, Table 2	1-2, (15-16)/(1-2)

☐ 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 August 2019

Date of mailing of the international search report

25 OCT 2019

Name and mailing address of the ISA/US

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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/39354

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.: 17-21
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:
Please see attached sheet--

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, (15-16)/(1-2)

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/US 19/39354

Attachment to Box.No.III:

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 searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-16 directed to a compound of Formula I, as described in claim 1, and selected from the compounds specified in claim 14.

The compound will be searched to the extent that the compound encompasses the first species of claim 1 [see note below], represented by Formula I, wherein

each X is N and Y is C;

Z is (CH₂)_k, where k is 0;

n is 1;

B is a substituted 3-membered carbocyclic ring;

m is 0; R₂, R₃, R₄ and R₅ are each H;

R₆ is (CHR₇)pCO₂R₇, wherein p is 0 and R₇ is H; and * represents a chiral center.

It is believed that claims 1-2 and (15-16)/(1-2) read on this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1, described above.

Applicant is invited to elect additional compound(s) wherein each additional compound elected will require one additional invention fee.

Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass 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.

Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound represented by the first-listed compound of claim 14, represented by Formula I, wherein

each X and Y is C; n is 2;

Ring B is a 6-membered carbocyclic aromatic ring;

m is 0; R₂, R₃, R₄ and R₅ are each H;

R₆ is (CHR₇)pCO₂R₇, wherein p is 0 and R₇ is H (i.e., claims 1-2, 14 and (15-16)/(1-2,14)).

The group of inventions listed above 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:

Special Technical Features:

Group I+ includes the technical feature of a unique compound, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of a compound having the core structure of Formula I.

This shared technical feature, however, does not provide a contribution over the prior art, as being obvious over Pubchem-CID:

42774242 Create date: 20 July 2009 (hereinafter 'Pubchem') which discloses an achiral analog of the compound of Formula I, wherein each X and Y is C; n is 2;

Z is (CH₂)_k, where k is 1;

Ring B is a 6-membered carbocyclic aromatic ring;

m is 1; R₁, R₂, R₃, R₄ and R₅ are each H;

R₆ is (CHR₇)pCO₂R₇, wherein p is 0 and R₇ is H (pg 2, structure). While Pubchem does not specifically disclose * as a chiral center, based on the asymmetric nature of the carbon atom attached to the indole, phenyl and -CH₂-COOH, it would have been obvious to one of ordinary skill in the art to isolate chiral enantiomers of the compound disclosed in Pubchem, through routine experimentation, as having enhanced utility in chemical industry.

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature, that would otherwise unify the inventions of Group I+.

The inventions of Groups I+, thus lack unity under PCT Rule 13.

Note: The description of Formula I in claim 1 lacks clarity.

-Ring A is described as a saturated or unsaturated carbocyclic or heterocyclic ring in the claim, but the structure of Formula I depicts A as an unsaturated or aromatic ring.

-The description of Formula I includes the variable 'm', which is missing from the structure.

For the purposes of this LOU analysis, the carbon attached to R₁ and R₆ and enclosed in parenthesis is assumed to have the variable 'm' next to it and not the asterisk, because R₁ can be H which makes that carbon achiral. In addition, the first species of claim 1 has been defined based on the structure of ring A in Formula I, not according to the description of A laid out in the claim.

Note reg. Item 4: Claims 17-21 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).