Title: SUBSTITUTED 2,3,7,8,9,10,11,12-OCTAHYDROAZEPINO[4,5-b]PYRANO[3,2-c]INDOLES

Abstract: Disclosed are compounds of general structural formula (I), and use of the compounds, salts and solvates thereof, and pharmaceutical compositions containing the same in the treatment of a disease, disorder, and/or condition in a mammal wherein a 5-HT receptor is implicated and modulation of a 5-HT function is desired.
SUBSTITUTED
2,3,7,8,9,10,11,12-OCTAHYDROAZEPINO[4,5-b]
PYRANO[3,2-e]INDOLES

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention generally relates to a series of compounds, to pharmaceutical compositions containing the compounds, and to use of the compounds and compositions as therapeutic agents. More specifically, compounds of the present invention are pyrano azipinoindole compounds. These compounds are serotonin receptor (5-HT) ligands and are useful for treating diseases, disorders, and conditions wherein modulation of the activity of serotonin receptors (5-HT) is desired.

Brief Description of Related Technology

Serotonin has been implicated in a number of diseases, disorders, and conditions that originate in the central nervous system, including diseases, disorders, and conditions related to, for example, sleeping, eating, perceiving pain, controlling body temperature, controlling blood pressure, depression, anxiety, and schizophrenia. Serotonin also plays an important role in peripheral systems, such as the gastrointestinal system, where it has been found to mediate a variety of contractile, secretory, and electrophysiologic effects.

Because of the broad distribution of serotonin within the body, a heightened interest exists for drugs that affect serotonergic systems. In particular, agonists, partial agonists, and antagonists of serotonergic systems are of interest for the treatment of a wide range of disorders, including anxiety, depression, hypertension, migraine, obesity, compulsive disorders,
schizophrenia, autism, neurodegenerative disorders (e.g., Alzheimer's disease, Parkinsonism, and Huntington's chorea), and chemotherapy-induced vomiting.

The major classes of serotonin receptors (5-HT₁₇) contain fourteen to eighteen separate receptors that have been formally classified. See Glennon, et al., *Neuroscience and Behavioral Reviews*, 1990, 14, 35; and D. Hoyer, et al. *Pharmacol. Rev.* 1994, 46, 157-203.

For example, the 5-HT₂ family of receptors contains 5-HT₂A, 5-HT₂B, and 5-HT₂C subtypes, which have been grouped together on the basis of primary structure, secondary messenger system, and operational profile. All three 5-HT₂ subtypes are G-protein coupled, activate phospholipase C as a principal transduction mechanism, and contain a seven-transmembrane domain structure. There are distinct differences in the distribution of the three 5-HT₂ subtypes in a mammal. The 5-HT₂B and 5-HT₂A receptors are widely distributed in the peripheral nervous system, while the 5-HT₂C receptor has been found only in the central nervous system, being highly expressed in many regions of the human brain. See G. Baxter, et al. *Trends in Pharmacol. Sci.* 1995, 16, 105-110.


Additionally, U.S. Patent Nos. 3,553,232 and 3,622,673 disclose 4-(1,4,5,6-tetrahydroazepine[4,5-b]indole-3(2H)-yl) butyrophenones
useful in the treatment of mental or emotional disorders. U.S. Patent Nos. 3,652,588, 3,676,558, and 3,839,357 disclose 6-alkyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles and anorexigenic compounds thereof that are useful to tranquilize and otherwise sedate mammals or suppress hunger in mammals. The disclosure of each of the above-cited foreign and U.S. patents is incorporated herein by reference.

Despite the teachings in the above-cited publications, there remains a need for pharmaceutical agents that are useful in treating a variety of diseases, disorders, and conditions that are associated with serotonin (5-HT) receptors.
SUMMARY OF THE INVENTION

Generally, the present invention is directed to methods and compositions useful in treating a disease, disorder, and/or condition in a mammal wherein a 5-HT receptor is implicated, and modulation of a 5-HT function is desired, by using a novel compound disclosed herein.

In accordance with the present invention, novel compounds which demonstrate useful biological activity, and particularly activity as 5-HT receptor ligands, are provided. More specifically, the present compounds have the general structural Formula (I):

![Structural Formula (I)]

wherein \( R^1 \) is selected from the group consisting of H, C\(_{1-6}\) alkyl, and C\(_{1-6}\) alkenylenearyl;

\( R^2 \), independently, is selected from the group consisting of H, C\(_{1-6}\) alkyl, and OH;

\( R^3 \) is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, C(=O)R\(^a\), C(=O)OR\(^a\), C(=O)NR\(^a\)R\(^b\), C(=O)SR\(^a\), C(=S)NR\(^a\)R\(^b\), SO\(_2\)R\(^a\), SO\(_2\)NR\(^a\)R\(^b\), S(=O)R\(^a\), S(=O)NR\(^a\)R\(^b\), C(=O)NR\(^a\)C\(_{1-6}\)alkyleneOR\(^a\), C(=O)NR\(^a\)C\(_{1-6}\)alkyleneHet, C(=O)C\(_{1-6}\)alkylenearyl, C(=O)C\(_{1-6}\)alkyleneheteroaryl, C\(_{1-6}\)alkylenearyl, C\(_{1-6}\)alkyleneheteroaryl,
C_{1-4}alkyleneHet, C_{1-4}alkyleneC(=O)C_{1-4}alkylenearyl,
C_{1-4}alkyleneC(=O)C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneC(=O)Het,
C_{1-4}alkyleneC(=O)NR^aR^b, C_{1-4}alkyleneOR^a, C_{1-4}alkyleneNR^aC(=O)R^2,
C_{1-4}alkyleneOC_{1-4}alkyleneOR^a, C_{1-4}alkyleneNR^aR^b, C_{1-4}alkyleneC(=O)OR^a, and
C_{1-4}alkyleneOC_{1-4}alkyleneC(=O)OR^a;

R^1 is selected from the group consisting of H, halo, OH, CN, NO_2, CF_3,
CF_3O, NR^aR^b, aryl, and heteroaryl; and,

R^a and R^b, independently, are selected from the group consisting of
hydrogen, C_{1-4}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl, arylC_{1-3}alkyl, heteroaryl-
C_{1-3}alkyl, C_{1-3}alkylenearyl, C_{1-3}alkyleneheteroaryl, and Het; and,

Another embodiment of the present invention provides a
pharmaceutical composition comprising a compound of Formula (I), or a
pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable
carrier.

Still another embodiment of the present invention provides a
method of treating a disease, disorder, and/or condition in a mammal (e.g.,
animal or human), wherein a 5-HT receptor is implicated and modulation of a
5-HT function is desired. The method comprises administering a
therapeutically effective amount of a compound of Formula (I), or a
pharmaceutically acceptable salt thereof, to the mammal.

Yet another embodiment of the present invention comprises a
method of modulating 5-HT receptor function with an effective amount of a
compound of Formula (I), or a pharmaceutically acceptable salt thereof.

A further embodiment of the present invention provides a
method of treating or preventing diseases, disorders, and/or conditions of the
central nervous system. The method comprises administering a therapeutically
effective amount of a compound of Formula (I), or a pharmaceutically
acceptable salt thereof, to the mammal.
Specific diseases, disorders, and/or conditions for which the compound of Formula (I) has activity include, but are not limited to, obesity, depression, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, a stress related disease (e.g., general anxiety disorder), panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the urinary, gastrointestinal or cardiovascular system (e.g., stress incontinence), neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal (e.g., a human), addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, behavioral disturbance (including agitation in conditions associated with diminished cognition, e.g., dementia, mental retardation or delirium), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, movement disorder (e.g., Huntington’s disease or Tardive Dyskinesia), oppositional defiant disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder (brief and long duration disorders and psychotic disorder due to medical condition), mood disorder (major depressive or bipolar disorder with psychotic features) seasonal affective disorder, a sleep disorder, a specific developmental disorder, agitation disorder, selective serotonin reuptake inhibition (SSRI) “poop out” syndrome or a Tic disorder (e.g., Tourette’s syndrome).

Yet another embodiment of the present invention comprises the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating or preventing diseases, disorders, and conditions of the central nervous system.
Further aspects and embodiments of the invention may become apparent to those skilled in the art from a review of the following detailed description, taken in conjunction with the examples and the appended claims. While the invention is susceptible of embodiments in various forms, described hereafter are specific embodiments of the invention with the understanding that the present disclosure is intended as illustrative, and is not intended to limit the invention to the specific embodiments described herein.

**Detailed Description of the Preferred Embodiments**

In describing the preferred embodiments, certain terminology has been utilized for the sake of clarity. Such terminology is intended to encompass the recited embodiments as well as all technical equivalents which operate in a similar manner for a similar purpose to achieve a similar result.

The following definitions are used, unless otherwise described:

As used herein, the term “alkyl” includes straight chained and branched hydrocarbon groups containing the indicated number of carbon atoms, typically methyl, ethyl, and straight chain and branched propyl, and butyl groups. The term “alkyl” also encompasses cycloalkyl, *i.e.*, a cyclic C₃-C₇ hydrocarbon group such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Reference to an individual group or moiety, such as “propyl,” embraces only the straight chain group or moiety. A branched chain isomer, such as “isopropyl,” is specifically referred to. When an alkyl group can be partially unsaturated, the alkyl chain may contain one or more (e.g., 1, 2, 3, or 4) double or triple bonds in the chain. Accordingly, the terms “alkenyl” and “alkynyl” are defined identically as “alkyl,” except for containing a carbon-carbon double bond or carbon-carbon triple bond, respectively.

The term “alkoxy” is defined as -OR, wherein R is alkyl.
The term “halo” is defined herein to include fluoro, chloro, bromo, or iodo. Similarly, the term “halogen” is defined herein to include fluorine, chlorine, bromine, and iodine.

The term “haloalkyl” is defined herein as an alkyl group substituted with one or more halo substituents, either fluoro, chloro, bromo, iodo, or combinations thereof. Similarly, “halocycloalkyl” is defined as a cycloalkyl group having one or more halo substituents.

The term “aryl,” alone or in combination, is defined herein as a monocyclic or bicyclic aromatic group (e.g., phenyl or naphthyl) that can be unsubstituted or substituted, for example, with one or more, and in particular one to three of the following substituents selected from the group consisting of H, halo, CN, NO₂, CF₃, N₃, C₁₋₄ alkyl, OH, NR₂, OR, C(=O)NR₂, NR₂, tetrazoyl, triazoil, amidinyl, guanidinyl, thioguanidinyl, cyanoguanidinyl, and aryl. Generally, “aryl” denotes a phenyl group, or an ortho-fused bicyclic carbocyclic group having nine to ten ring atoms in which at least one ring is aromatic.

The term “heteroaryl” is defined herein as a monocyclic or bicyclic ring system containing one or two aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring, and which can be unsubstituted or substituted, for example, with one or more, and in particular one to three, substituents, like halo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, nitro, amino, alkylamino, acylamino, alkylthio, alkylsulfinyl, and alkylsulfonyl. Examples of heteroaryl groups include thienyl, furyl, pyridyl, oxazolyl, quinolyl, isoquinolyl, indolyl, triazolyl, isothiazolyl, isoxazolyl, imidazolyl, benzothiazolyl, pyrazinyl, pyrimidinyl, thiazolyl, and thiadiazolyl. Generally, the term “heteroaryl” denotes a monocyclic or polycyclic aromatic ring containing five or six ring atoms containing carbon and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of non-peroxide oxygen, sulfur, and N(Z) wherein Z is absent or is H, O, C₁₋₄ alkyl, phenyl or benzyl.
The term "Het" generally represents a heterocyclic group, saturated or partially unsaturated, containing at least one heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur, and optionally substituted with C₁₋₄alkyl or C(=O)OR⁵. Typically "Het" is a monocyclic, bicyclic, or tricyclic group containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. A "Het" group also can contain an oxo group (=O) attached to the ring. Nonlimiting examples of Het groups include 1,3-dioxolane, 2-pyrazoline, pyrazolidine, pyrrolidine, a pyrrole, 2H-pyran, 4H-pyran, morpholine, thiomorpholine, piperidine, 1,4-dithiane, and 1,4-dioxane.

The term "alkanoyl" is defined as C(=O)R, wherein R is an alkyl group as previously defined.

The term "alkoxycarbonyl" is defined as C(=O)OR, wherein R is an alkyl group as previously defined.

The term "alkylene" refers to an alkyl group having a substituent. For example, the term "C₁₋₄alkylenearyl" refers to an alkyl group containing one to three carbon atoms, and substituted with an aryl group. The term "alkenylene" as used herein is similarly defined, and contains the indicated number of carbon atoms and a carbon-carbon double bond, and includes straight chained and branched alkenylene groups, like ethylenylene.

The term "amino" is defined as -NH₂, and the term "alkylamino" is defined as -NR₂, wherein at least one R is alkyl and the second R is alkyl or hydrogen. The term "acylamino" is defined as RC(=O)N, wherein R is alkyl or aryl.

The term "nitro" is defined as -NO₂.

The term "trifluoromethyl" is defined as -CF₃.
The term "trifluoromethoxy" is defined as -OCF₃.
The term "cyano" is defined as -CN.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum
number of carbon atoms in the moiety, i.e., the prefix $C_{ij}$ indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, "$C_{1,6}$ alkyl" refers to alkyls having one to six carbon atoms, inclusive.

Abbreviations which are well known to one of ordinary skill in the art also are used, e.g., "Bz" for benzoyl, "Bn" for benzyl, and "Ph" for phenyl.

Specific and preferred values listed below for groups or moieties, substituents, and ranges, are for purposes of illustration only and do not exclude other defined values or other values within the defined ranges.

One embodiment of the present invention comprises compounds of Formula (I):

![Chemical Structure](image)

**Formula (I)**

wherein $R^1$ is selected from the group consisting of $H$, $C_{1,6}$ alkyl, and $C_{1,6}$ alkenyl;

$R^2$, independently, is selected from the group consisting of $H$, $C_{1,4}$ alkyl, and OH;

$R^3$ is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(=O)R^4$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)SR^5$, $C(=S)NR^5R^6$, $C(=S)NR^5R^6$. 

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SO₂R₁, SO₂NR₂R₃, S(=O)R₁, S(=O)NR₂R₃, C(=O)NR₂C₆₋₁₂alkyleneOR₄,
C(=O)NR₂C₆₋₁₂alkyleneHet, C(=O)C₆₋₁₂alkylnearyl,
C(=O)C₆₋₁₂alkylneheteroaryl, Cₛ₋₁₂alkylnearyl, Cₛ₋₁₂alkylneheteroaryl,
C₆₋₁₂alkylneHet, C₆₋₁₂alkylneC(=O)C₆₋₁₂alkylnearyl,
C₆₋₁₂alkylneC(=O)C₆₋₁₂alkylneheteroaryl, Cₛ₋₁₂alkylneC(=O)Het,
Cₛ₋₁₂alkylneC(=O)NR₂R₅, Cₛ₋₁₂alkylneOR₄, Cₛ₋₁₂alkylneNR₂C(=O)R₄,
Cₛ₋₁₂alkylneOC₆₋₁₂alkylneOR₄, Cₛ₋₁₂alkylneNR₂R₅, Cₛ₋₁₂alkylneC(=O)OR₄, and
Cₛ₋₁₂alkylneOC₆₋₁₂alkylneC(=O)OR₄;

R₄ is selected from the group consisting of H, halo, OH, CN, NO₂, CF₃,
CF₃O, NR₂R₅, aryl, and heteroaryl; and,

R₅ and R₆, independently, are selected from the group consisting of
hydrogen, Cₛ₋₁₂alkyl, C₆₋₁₂cycloalkyl, aryl, heteroaryl, arylCₛ₋₁₂alkyl, heteroaryl-
Cₛ₋₁₂alkyl, Cₛ₋₁₂alkylnearyl, Cₛ₋₁₂alkylneheteroaryl, and Het; and,
pharmaceutically acceptable salts thereof.

Compounds of Formula (I) are serotonin (5-HT) receptor
ligands, and as such are useful in treating animals (including humans, farm
animals, pets, and other animals) against diseases, disorders, and conditions of
the central nervous system.

In preferred embodiments, R¹ is selected from the group
consisting of hydrogen, Cₛ₋₁₂alkylneOR₄, Cₛ₋₁₂alkylneC(=O)OR₄,
Cₛ₋₁₂alkylneC(=O)NR₂R₅.

In more preferred embodiments, R¹ is selected from the group
consisting of hydrogen, benzyl, and benzoxy; R² and R³ are hydrogen; and R¹ is
selected from the group consisting of hydrogen, alkyl, Cₛ₋₁₂alkylnearyl,
Cₛ₋₁₂alkylneOR₄, carboxylic acid, Cₛ₋₁₂alkylneC(=O)OR₄, and
Cₛ₋₁₂alkylneC(=O)NR₂R₅.

Specific compounds falling within the scope of the present
invention include, but are not limited to, the following compounds, the
preparation of each of which is described below under the heading
"Examples":

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(1). 10-benzyl-7,8,9,10,11,12-hexahydro-3H-azepino[4,5-b]pyrano[3,2-e]indole;

(2). 10-benzyl-7-methyl-7,8,9,10,11,12-hexahydro-3H-azepino[4,5-b]pyrano[3,2-e]indole;

(3). 2,3,7,8,9,10,11,12-octahydro-1H-azepino[4,5-b]pyrano[3,2-e]indole;

(4). 2,3,7,8,9,10,11,12-octahydro-7-methyl-1H-azepino[4,5-b]pyrano[3,2-e]indole;

(5). 10-benzyl-7-(4-phenoxybutyl)-7,8,9,10,11,12-hexahydro-3H-azepino[4,5-b]pyrano[3,2-e]indole;

(6). 7-(4-phenoxybutyl)-7,8,9,10,11,12-octahydro-1H-azepino[4,5-b]pyrano[3,2-e]indole;

(7). ethyl(10-benzyl-3,8,9,10,11,12-hexahydro-7H-azepino[4,5-b]pyrano[3,2-e]indol-7-yl)acetate;

(8). (10-benzyl-3,8,9,10,11,12-hexahydro-7H-azepino[4,5-b]pyrano[3,2-e]indol-7-yl)acetic acid;

(9). 2-(10-benzyl-3,8,9,10,11,12-hexahydro-7H-azepino[4,5-b]pyrano[3,2-e]indol-7-yl)-N-phenylacetamide; and,

(10). 2-(1,2,3,8,9,10,11,12-octahydro-7H-azepino[4,5-b]pyrano[3,2-e]indol-7-yl)-N-phenylacetamide.

Compounds of Formula (I) can be prepared by any suitable method known in the art, or by the following reaction sequence which forms part of the present invention. All of the starting materials are commercially available, or are prepared by procedures described herein or by procedures that would be well known to one of ordinary skill in organic and/or pharmaceutical chemistry. In the methods below, R¹, R², R³, R⁴, R⁵, and R⁶ are as defined in structural Formula (I) above.

It should be understood that protecting groups can be utilized in accordance with general principles of organic synthetic chemistry to provide compounds of structural Formula (I). Protecting compounds and protecting
groups are well known to persons skilled in the art. See e.g., T.W. Greene et al., “Protective Groups in Organic Synthesis, Second Edition,” John Wiley and Sons, Inc., NY, NY (1991). These protecting groups are removed when necessary by appropriate basic, acidic, or hydrogenolytic conditions known to persons skilled in the art. Accordingly, compounds of structural Formula (I) not specifically exemplified herein can be prepared by persons skilled in the art.

Compounds of the general structural Formula (I) can be prepared by a number of methods as described hereinafter. For example, one method of synthesizing the compounds of Formula (I) includes demethylation of an azepinoindole of the Structure (1), below, with boron tribromide. (Bz=benzoyl or C(=O)phenyl):

![Structure (1)](image_url)

The azepinoindole can be obtained by following the procedures set forth in J. Org. Chem., 1968, 33, 3187-95. Demethylation of the azepinoindole provides Structure (2).
The demethylated Structure (2) is then alkylated with propargyl bromide to form Structure (3).

Structure (3) is subjected to Claisen rearrangement conditions known to persons skilled in the art to provide the pyrano Structure (4).
The pyrano Structure (4) then is treated with lithium aluminum hydride, followed by hydrogenation in the presence of palladium-on-carbon, to yield the compound of the general structural Formula (I).

Alternatively, compounds of general structural Formula (I) can be prepared by the foregoing reactions wherein the azepinoindole of Structure (1), above, is first reacted with sodium hydride and methyl iodide to result in a methylated compound of Structure (1), shown below.

Compounds of Formula (I) can be converted to other compounds of Formula (I). Thus, for example, a particular substituent can be
interconverted to prepare another suitably substituted compound of Formula (I). Examples of appropriate interconversions include, but are not limited to, nitro to amino, OR to hydroxy by suitable reducing means (e.g., using a reducing agent such as SnCl₂ or a palladium catalyst, such as palladium-on-carbon) or amino to substituted amino, such as acylamino or sulphonylamino, using standard acylating or sulfonylating conditions.

The phrases “pharmaceutically acceptable salts” or “a pharmaceutically acceptable salt thereof” refer to salts prepared from pharmaceutically acceptable acids or bases, including organic and inorganic acids and bases. Salts can be prepared from pharmaceutically acceptable acids. Pharmaceutically acceptable salts can be obtained using standard procedures known by those skilled in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Suitable pharmaceutically acceptable acids include acetic, benzenesulfonic (besylate), benzoic, p-bromophenylsulfonic, camphorsulfonic, carbonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, hydroiodic, isethionic, lactic, maleic, malic, mandelic, methanesulfonic (mesylate), mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluene sulfonic, and the like. Examples of such pharmaceutically acceptable salts, thus, include, but are not limited to, acetate, benzoate, β-hydroxybutyrate, bisulfate, bisulfite, bromide, butyne-1,4-dioate, carpoate, chloride, chlorobenzoate, citrate, dihydrogenphosphate, dinitrobenzoate, fumarate, glycollate, heptanoate, hexyne-1,6-dioate, hydroxybenzoate, iodide, lactate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, oxalate, phenylbutyrate, phenylproionate, phosphate, phthalate, phylacetate, propanesulfonate, propiolate, propionate, pyrophosphate, pyrosulfate, sebacate, suberate, succinate, sulfate, sulfite, sulfonate, tartrate, xylene sulfonate, and the like. The compounds of the
Formula (I) also can provide pharmaceutically acceptable metal salts, in particular alkali metal (e.g., sodium, potassium, magnesium, or lithium) salts and alkaline earth metal (e.g., calcium) salts, with bases.

Compounds of Formula (I) are useful in treating diseases, disorders, and conditions of the central nervous system occurring in mammals. Typically, the mammal is a human being, but the inventive compounds can be used to treat other animals such as livestock, pets, or other animals.

It is to be understood that "a compound of Formula (I)," or a pharmaceutically acceptable (acidic or basic) salt or solvate (i.e., hydrate) thereof, can be administered as the neat compound, or as a pharmaceutical composition containing the compound in combination with a suitable excipient. Such pharmaceutical compositions can be prepared by methods and contain excipients which are known by those skilled in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975), the disclosure of which is incorporated herein by reference. In cases where a compound is sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be preferred.

The compounds of this invention can be administered in oral unit dosage forms, such as aerosol sprays, buccal tablets, capsules, elixirs, pills, sachets, suspensions, syrups, tablets, troches, wafers, and the like. The compounds also can be administered parenterally, (e.g., subcutaneously, intravenously, intramuscularly, or by intraperitoneal injection), using forms known in the pharmaceutical art. The compounds further can be administered rectally or vaginally, in such forms as suppositories or bougies, transdermally, such as with a "patch" containing active ingredient, or nasally (i.e., by inhalation).

In general, the preferred route of administration of a present compound is oral. For oral administration, the active compound can be combined with one or more excipients and used in the form of ingestible
aerosol sprays, buccal tablets, capsules, elixirs, pills, sachets, suspensions, syrups, tablets, troches, wafers, and the like. Such compositions and preparations typically contain at least 0.1% of active compound. The percentage of the compounds in these preparations can be varied, e.g., about 0.01 to about 60% of the weight of a given unit dosage form. The amount of active compound in such orally administered compositions is sufficient to provide an effective dosage level.

The aerosol sprays, buccal tablets, capsules, elixirs, pills, sachets, suspensions, syrups, tablets, troches, wafers, and the like also can contain one or more binders, diluents disintegrating agents, excipients, lubricants, sweetening agents, or flavoring agents. Suitable binders include, for example, gum arabic, tragacanth, acacia, polyvinylpyrrolidone, corn starch, methylcellulose, or gelatin. Suitable diluents include, for example, lactose, dextrose, sucrose, mannitol, sorbitol, and cellulose. Suitable disintegrating agents include, for example, starches, alginic acid, and alginates. Suitable excipients include dicalcium phosphate. Suitable lubricants include, for example, silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols. Suitable wetting agents include, for example, lecithin, polysorbates, and laurylsulfates. Generally, any effervescent agents, dyestuffs, and/or sweeteners known by those of ordinary skill in the art can be used in the preparation of a pharmaceutical composition. For example, suitable sweetening agents include sucrose, fructose, lactose or aspartame, and suitable flavoring agents include peppermint, oil of wintergreen, or cherry flavoring. The aforementioned ingredients are merely representative and one skilled in the art could envision other binders, excipients, sweetening agents, and the like.

When the unit dosage form is a capsule, it can contain, in addition to ingredients of the above type, a liquid carrier (e.g., vegetable oil or a polyethylene glycol). Various other ingredients can be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For
instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar, and the like. A syrup or elixir can contain the active compound, sucrose or fructose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and flavoring, such as cherry or orange flavor. Any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound can be incorporated into sustained-release preparations and devices including, but not limited to, those relying on osmotic pressures to obtain a desired release profile (e.g., the OROS drug delivery devices as designed and developed by Alza Corporation, Mountain View, California).

Orally administered compositions can be prepared by any method that includes the step of bringing the active compound into intimate association with a carrier, which constitutes one or more necessary or desirable ingredients. Generally, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers, finely divided solid carriers, or both, and then, if necessary, shaping the product into a desired form.

For example, a tablet can be prepared by compression or molding techniques, optionally, using one or more accessory ingredients. Compressed tablets can be prepared by compressing the active ingredient in a suitable machine into a free-flowing form, such as a powder or granules. Thereafter, the compressed, free-flowing form optionally can be mixed with binders, diluents, lubricants, disintegrating agents, effervescing agents, dyestuffs, sweeteners, wetting agents, and non-toxic and pharmacologically inactive substances typically present in pharmaceutical compositions. The pharmaceutical composition can contain about 5 to about 95% compound of the present invention, and preferably from about 25 to about 90% compound of the present invention. Molded tablets can be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine.
Oral administration is the most convenient route of administration and avoids the disadvantages associated with other routes of administration. For patients suffering from a swallowing disorder or from impairment of drug absorption after oral administration, the drug can be administered by other methods, such as parenterally, rectally or vaginally, transdermally, and nasally.

Parenteral administration is performed by preparing the composition containing the active compound. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Pharmaceutical dosage forms suitable for parenteral administration (e.g., subcutaneously, intravenously, intramuscularly, or by intraperitoneal injection or infusion) can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid, and stable under the conditions of manufacture and storage.

The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (e.g., glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many
cases, it is preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be achieved by use of agents that delay absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions. Sterilization of the powders also can be accomplished through irradiation and aseptic crystallization methods known to persons skilled in the art.

For parenteral administration, the active compounds are presented in aqueous solution in a concentration of about 0.1 to about 10%, more preferably about 0.1 to about 7%, by weight. The solution can contain other ingredients, such as emulsifiers, antioxidants, or buffers.

For topical administration, the present compounds can be applied in neat form, e.g., when the compound is a liquid. However, it is desirable to administer the compounds to the skin as compositions in combination with a dermatologically acceptable carrier, which can be a solid, semi-solid, or a liquid. Useful solid carriers include, but are not limited to, finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina, and the like. Useful liquid carriers include, but are not limited to, water, alcohols, glycols, and water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of a surfactant. Adjuvants, such as fragrances and additional antimicrobial agents, can be added to optimize the properties for a given use.

The resultant liquid compositions can be applied topically by absorbent pads,
used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

For administration by inhalation, compounds of the present invention can be delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin, for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Compounds of the present invention also can be formulated in rectal compositions, such as suppositories or retention enemas, e.g., containing conventional suppository bases. In addition to the formulations described previously, the compounds also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Generally, compounds of the invention are serotonin receptor (5-HT) ligands. The ability of a compound of the invention to act as a 5-HT receptor agonist, partial agonist, or antagonist can be determined using in vitro and in vivo assays that are known in the art. The invention provides compounds of Formula (I) that act as either agonists, partial agonists, or as antagonists of one or more 5-HT receptor subtypes.

The inventive compounds of the present invention can be useful as modulators of 5-HT receptor function. Thus, the compounds are useful for treating diseases, disorders, and conditions where modulation of 5-HT receptor function is desired. Such diseases, disorders, and conditions include, but are not limited to the following: obesity, depression,
schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, a stress related disease (e.g., general anxiety disorder), panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the urinary, gastrointestinal or cardiovascular system (e.g., stress incontinence), neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal (e.g., a human), addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, behavioral disturbance (including agitation in conditions associated with diminished cognition (e.g., dementia, mental retardation or delirium)), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthmic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, movement disorder (e.g., Huntington's disorder or Tardive Dyskinesia), oppositional defiant disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder (brief and long duration disorders and psychotic disorder due to medical condition), mood disorder (major depressive or bipolar disorder with psychotic features) seasonal affective disorder, a sleep disorder, a specific developmental disorder, agitation disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome or a Tic disorder (e.g., Tourette's syndrome). Treatment of the above diseases, disorders, and conditions is accomplished by delivering a therapeutically effective amount of the compound of Formula (I) to the mammal.

As used herein, the terms "treat," "treatment," and "treating," extend to prophylaxis, in other words "prevent," "prevention," and "preventing," lowering, stopping, or reversing the progression or severity of the condition or symptoms being treated. As such, the term "treatment"
includes both medical therapeutic and/or prophylactic administration, as appropriate. The terms “prevent,” “prevention,” and “preventing” refer to an administration of the pharmaceutical composition to a person who has in the past suffered from the aforementioned diseases, disorders, or conditions, such as, for example, migraine headaches, but is not suffering from the diseases, disorders, or conditions at the time of the composition’s administration.

Compounds and pharmaceutical compositions suitable for use in the present invention include those wherein the active ingredient is administered in an effective amount to achieve its intended purpose. More specifically, a “therapeutically effective amount” means an amount effective to treat the disease, disorder, and/or condition. Determination of a therapeutically effective amounts is well within the capability of persons skilled in the art, especially in light of the detailed disclosure provided herein.

A “therapeutically effective dose” refers to that amount of the compound that results in achieving the desired treatment (or effect). Therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized.

The dosage regimen and amount for treating patients with the compounds of this invention is selected in accordance with a variety of factors including, for example, the type, age, weight, sex, and medical condition of the patient, the severity of the condition, and the route of administration. An ordinarily skilled physician or psychiatrist can readily determine and prescribe an effective amount of the compound to prevent or arrest the progress of the condition. In so proceeding, the physician or psychiatrist can employ relatively low initial dosages and subsequently increasing the dose until a maximum response is obtained.
The compound is administered in unit dosage form, for example, containing about 0.05 mg to about 500 mg, preferably about 0.1 mg to about 250 mg, and more preferably about 1 mg to about 150 mg, of active ingredient per unit dosage form. The desired dose can be presented in a single dose, or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself can be further divided, e.g., into a number of discrete loosely spaced administrations.

The compositions can be administered orally, sublingually, transdermally, or parenterally at dose levels of about 0.01 to about 150 mg/kg, preferably about 0.1 to about 50 mg/kg, and more preferably about 0.1 to about 10 mg/kg of mammal body weight.

The exact regimen for administration of the compounds and compositions disclosed herein necessarily depends upon the needs of the individual subject being treated, the patient type (i.e., human or animal), the type of treatment and, of course, the judgment of the attending practitioner or physician. In practice, the physician determines the actual dosing regimen which is most suitable for an individual patient, and the dosage varies with the age, weight, and response of the particular patient. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this invention.

Specifically, for administration to a human in the curative or prophylactic treatment of the diseases, disorders, and conditions identified above, oral dosages of a compound of Formula (I) generally are about 0.5 to about 1000 mg daily for an average adult patient (70 kg). Thus, for a typical adult patient, individual tablets or capsules contain 0.2 to 500 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal, or sublingual administration typically are 0.1 to 500 mg per single dose as required.
For veterinary use, a compound of Formula (I), or a nontoxic salt thereof, is administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

In a particular embodiment, the invention includes a pharmaceutical composition for the curative or prophylactic treatment of diseases, disorders, and conditions, where modulation of 5-HT receptor function is desired, the composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier. Such diseases and disorders include, but are not limited to the following: obesity, depression, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, a stress related disease (e.g., general anxiety disorder), panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the urinary, gastrointestinal or cardiovascular system (e.g., stress incontinence), neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal (e.g., a human), addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, behavioral disturbance (including agitation in conditions associated with diminished cognition (e.g., dementia, mental retardation or delirium)), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthmic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, movement disorder (e.g., Huntington’s disorder or Tardive Dyskinesia), oppositional defiant disorder, peripheral neuropathy, post-traumatic stress -26-
disorder, premenstrual dysphoric disorder, a psychotic disorder (brief and long duration disorders and psychotic disorder due to medical condition), mood disorder (major depressive or bipolar disorder with psychotic features) seasonal affective disorder, a sleep disorder, a specific developmental disorder, agitation disorder, selective serotonin reuptake inhibition (SSRI) “poop out” syndrome or a Tic disorder (e.g., Tourette's syndrome). Treatment of the above diseases, disorders, and conditions is accomplished by delivering a therapeutically effective amount of the compound of Formula (I) to the mammal.

Another embodiment of the present invention provides a method of treating the above-noted diseases, disorders, and conditions in a human or mammal body which comprises administering to said body a therapeutically effective amount of a compound of Formula (I).

According to another embodiment of the present invention, there is provided the use of a compound of Formula (I) for the manufacture of a medicament for the treatment of the above-noted diseases, conditions, and disorders.

**Examples**

The following examples and preparations are provided to illustrate the invention but are not intended to limit the scope of the invention.

The following abbreviations are used hereafter in the accompanying examples: μM (micromole), Bn (benzyl), Bz (benzyol), cm (centimeter), DMSO (dimethyl sulfoxide), Et₂N (triethylamine), EtOAc (ethyl acetate), g. (gram), IR (infrared), KBr (potassium bromide), m.p. (melting point), MeOH (methanol), MgSO₄ (magnesium sulfate), MHz (megahertz), min. (minute), mL (milliliter), mmol (millimole), NMR (nuclear magnetic resonance), and psi (pounds per square inch).
Preparation of Structure (1):

3-benzoyl-9-methoxy-6-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole 
Methylated (Structure (1)).

Methylated Structure (1)

To a solution of 3-benzoyl-9-methoxy-1,2,3,4,5,6-
hexahydroazepino[4,5-b]indole (U.S. Patent No. 3,839, 357) (10.90 g., 34.01 
mmol) in N,N-dimethylformamide (340.0 mL) was added sodium hydride 
(1.50 g., 60% in oil, 37.41 mmol) at 0°C. The mixture was stirred at room 
temperature for 20 min. and cooled to 0°C. After the addition of methyl iodide 
(2.54 mL, 5.79 g., 40.81 mmol), the resulting mixture was stirred at room 
temperature for 16 hours. Water (400.0 mL) and ethyl acetate (400.0 mL) then 
were added, and the organic and aqueous phases separated. The aqueous layer 
was extracted with ethyl acetate (2X). The combined ethyl acetate solution 
was dried (MgSO₄) and filtered. The filtrate was concentrated *in vacuo*. The 
residue was subjected to column chromatography (silica gel, 50%
EtOAc/hexane) to yield 9.96 g. (87%) of a yellowish oil as Structure (1). IR 
(liq.) 2937, 2906, 1629, 1601, 1579, 1486, 1462, 1445, 1424, 1381, 1375, 
1347, 1299, 1288, 1271, 1246, 1229, 1156, 1143, 1047, 1035, 1031, 789, 727, 
707 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.43-7.39, 7.17-7.12, 6.97-6.82, 
4.09-4.00, 3.93-3.88, 3.76-3.57, 3.21-3.11, 2.92-2.87; MS (ESI⁺) m/z 335 
(M⁺+H); HRMS (FAB) calcd for C₂₁H₂₂N₂O₂ + H: 335.1759, found: 335.1754.
Preparation of Structure (2):

3-benzoyl-9-hydroxy-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (Structure (2)).

![Structure (2)](image)

To a solution of Structure (1) (3-benzoyl-9-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole) (8.43 g., 26.3 mmol) in dichloromethane (260 mL) was added boron tribromide (2.61 mL, 6.93 g., 27.6 mmol) at 0°C. The resulting mixture was stirred at room temperature for 16 hours. Water (300 mL) then was added. The resulting solid was filtered and collected to yield a light grey solid as Structure (2). M.p. 194-195°C; IR (KBr) 3381,3325, 3261, 3252, 3085, 3061, 3025, 2997, 2975, 2934, 2903, 2873, 2843, 1627, 1595, 1496, 1493, 1468, 1372, 1294, 1286, 1277, 1244, 1222, 1196, 1157, 850, 838, 809, 786, 744, 705 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 10.51-10.42, 8.31, 7.47-7.39, 7.04, 6.73-6.62, 6.53-6.50, 3.85, 3.51, 3.02, 2.87, 2.78, 2.64; MS (ESI⁺) m/z 307 (M⁺+H). HRMS cacld for C₁₉H₁₈N₂O₂ + H: 307.1446, found: 307.1455; Anal. Calcd. for C₁₉H₁₈N₂O₂ + H₂O: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.13; H, 5.70; N, 8.45.
Preparation of a Methylated Structure (2):
3-benzoyl-9-hydroxy-6-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole
(Methylated Structure (2)).

Methylated Structure (2)

To a solution of Structure (1) (13.0 g., 38.9 mmol) in dichloromethane (400 mL) was added boron tribromide (7.35 mL, 19.5 g., 77.8 mmol) at 0°C. The resulting mixture was stirred at room temperature for 36 hours. Ammonium chloride solution (10.0 mL) and water (400 mL) then were added sequentially. After separation of the organic and liquid phases, the aqueous layer was extracted with dichloromethane (2X). The combined dichloromethane solution was dried (MgSO₄) and filtered. The filtrate was concentrated in vacuo and the residue was subjected to column chromatography (silica gel, 70% EtOAc/hexane) to yield a yellowish solid as the methylated Structure (2). M.p. 138-141°C; IR (KBr) 3491, 3358, 3270, 3070, 3067, 2982, 2951, 2936, 2886, 2837, 1626, 1588, 1501, 1467, 1372, 1349, 1343, 1289, 1278, 1245, 1212, 1158, 1145, 840, 748, 708, 701 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 7.43-7.39, 7.05, 6.85-6.67, 4.06-3.90, 3.71-3.55, 3.16-3.03, 2.86-2.81; MS m/z 320 (M⁺); HRMS (FAB) calcd for C₂₀H₂₀N₂O₂ + H: 321.1603, found: 321.1614; Anal. Calcd. for C₂₀H₂₀N₂O₂: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.79; H, 6.33; N, 8.66.
Preparation of Structure (3):

3-benzoyl-9-(2-propynyl)oxy)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole

(Structure (3)).

A mixture of Structure (2) (8.00 g., 26.0 mmol), propargyl bromide (3.48 mL, 3.71 g., 80%, 31.2 mmol), and cesium carbonate (33.9 g., 104 mmol) in acetone (260 mL) was stirred at room temperature for 48 hours. After filtration through a pad of celite, the filtrate was concentrated in vacuo to dryness and the residue was subjected to column chromatography (silica gel, 60% EtOAc/hexane) to yield 6.34 g. (71%) of a colorless solid as Structure (3). M.p. 167-168°C; IR (KBr) 3262, 3222, 3062, 3045, 2950, 2909, 2886, 2841, 2113, 1609, 1583, 1577, 1495, 1467, 1456, 1443, 1286, 1268, 1248, 830, 811, 788, 740, 706, 699, 684, 674, 632 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.89-7.70, 7.42, 7.19-7.16, 7.06-6.84, 4.74-4.69, 4.14-3.98, 3.70-3.62, 3.20-3.05, 2.88-2.76, 2.52-2.48. MS (ESI+) m/z 345 (M⁺+H); HRMS calcd for C₂₁H₁₈N₂O₂ + H: 345.1603, found: 345.1605; Anal. Calcd. for C₂₁H₁₈N₂O₂: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.17; H, 5.83; N, 7.93.
Preparation of a Methylated Structure (3):

3-benzoyl-6-methyl-9-(2-propynylxy)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (Methylated Structure (3)).

A mixture of Structure (2) (3.78 g., 11.8 mmol), propargyl bromide (1.58 mL, 2.10 g., 80%, 14.1 mmol), and cesium carbonate (11.5 g., 35.4 mmol) in acetone (118 mL) was stirred at room temperature for 48 hours. After filtration through a pad of celite, the filtrate was concentrated in vacuo and the residue was subjected to column chromatography (silica gel, 50% EtOAc/hexane) to yield 3.06 g. (72%) of a light yellow foam as the methylated Structure (3). IR (KBr) 3282, 3228, 3100, 3079, 3058, 3026, 2974, 2932, 2839, 2575, 2478, 2337, 2116, 1625, 1601, 1577, 1511, 1484, 1464, 1445, 1424, 1383, 1375, 1348, 1299, 1290, 1271, 1246, 1220, 1213, 1155, 1145, 1046, 1027, 928, 790, 708, 630 cm^-1; ^1H NMR (300 MHz, CDCl₃) δ 7.48-7.41, 7.18-7.14, 7.07-6.88, 4.74-4.68, 4.11-4.00, 3.72-3.57, 3.21-3.12, 2.91-2.87, 2.52-2.48.
Preparation of Structure (4):

10-benzoyl-7,8,9,10,11,12-hexahydro-3H-azepino[4,5-b]pyrano[3,2-c]indole
(Structure (4)).

A solution of Structure (3) (5.51 g., 16.0 mmol) in bromobenzene (160 mL) was refluxed for 24 hours. After cooling to room temperature, the bromobenzene was removed in vacuo. The residue was subjected to column chromatography (silica gel, 70%EtOAC/Hex) to yield 5.50 g. (99%) of a yellowish solid as Structure (4). M.p. 241-243°C; IR (KBr) 3265, 3064, 3050, 2975, 2951, 2928, 2898, 2840, 1615, 1602, 1579, 1493, 1465, 1273, 1246, 1220, 1100, 788, 738, 704, 697 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.88-7.62, 7.42, 7.17-6.91, 6.70, 5.91-5.74, 4.72-4.63, 4.08-3.96, 3.82-3.73, 3.42-2.80. MS(ESI+) m/z 345 (M⁺+H); HRMS (FAB) calcd for C₂₂H₂₀N₂O₃ + H: 345.1603, found: 345.1611; Anal. Calcd. for C₂₂H₂₀N₂O₃: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.31; H, 6.02; N, 7.98.
Preparation of a Methylated Structure (4):

10-benzoyl-7-methyl-7,8,9,10,11,12-hexahydro-3H-azepino[4,5-b]pyrano[3,2-c]indole (Methylated Structure (4)).

A solution of the methylated Structure (3) (0.23 g., 0.65 mmol) in bromobenzene (7.0 mL) was refluxed for 24 hours. After cooling to room temperature, bromobenzene was removed in vacuo. The residue was subjected to column chromatography (silica gel, 60% EtOAc/hexane) to yield a yellowish solid as the methylated Structure (4). M.p. >177°C; ¹H NMR (300 MHz, CDCl₃) δ 7.42, 7.05-6.97, 6.74, 5.93-5.74, 4.69-4.65, 4.12-4.05, 3.80-2.92. MS (ESI+) m/z 381 (M⁺+Na). Anal. Calcd. for C₂₂H₂₂N₂O₂.H₂O: C, 73.38; H, 6.43; N, 7.44. Found: C, 72.92; H, 6.03; N, 7.35.
Example 1:

**Preparation of 10-benzyl-7,8,9,10,11,12-hexahydro-3H-azepino[4,5-b]pyrano[3,2-e]indole.**

To a solution of Structure (4) (0.82 g., 5.88 mmol) in tetrahydrofuran (25.0 mL) was added lithium aluminum hydride (0.91 g., 23.8 mmol). The resulting mixture was stirred at room temperature for 16 hours. Water (0.91 mL), 15% sodium hydroxide solution (0.91 mL), and water (2.70 mL) then were added to the mixture sequentially. The resulting mixture was filtered through a pad of celite, and the filtrate was concentrated in vacuo. The residue was subjected to column chromatography (silica gel, 50% EtOAc/hexane, 1% Et₃N) to yield 0.64 g. (81%) of a colorless solid as the title compound. M.p. 157-160°C (CH₂Cl₂/hexane); 'H NMR (300 MHz, CDCl₃) δ 7.78, 7.45, 7.39-7.30, 7.08-7.01, 6.67, 5.81, 4.67, 3.88, 3.22-3.11, 3.11-2.93; HRMS (FAB) calcd for C₂₂H₂₂N₂O⁺H: 331.1810, found 331.1817; Anal. Calcd. for C₂₂H₂₂N₂O: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.49; H, 6.77; N, 8.37.
Example 2:

Preparation of 10-benzyl-7-methyl-7,8,9,10,11,12-hexahydro-

To a solution of the methylated Structure (4) (1.79 g., 4.98
mmol) in tetrahydrofuran (50.0 mL) was added lithium aluminum hydride
(1.89 g., 49.8 mmol). The resulting mixture was stirred at room temperature
for 16 hours. Water (1.89 mL), 15% sodium hydroxide solution (1.89 mL),
and water (5.00 mL) then were added to the mixture sequentially. The
resulting mixture was filtered through a pad of celite, and the filtrate was
concentrated *in vacuo*. The residue was subjected to column chromatography
(silica gel, 50% EtOAc/hexane, 1% Et3N) to yield 0.87 g. (51%) of a colorless
solid as the title compound. M.p. 112-114°C(EtOAc/hexane); IR (KBr) 3081,
3058, 3029, 3022, 1634, 1593, 1576, 1550, 1494, 1467, 1454, 1368, 1230, 1108
\( \text{cm}^{-1} \); \(^1\)H NMR (400 MHz, CDCl<sub>3</sub>) \& 7.42-7.40, 7.36-7.33, 7.29-7.25, 7.12,
6.99, 6.71, 5.81, 4.67-4.65, 3.80, 3.57, 3.17-3.14, 3.00-2.95, 2.84-2.81, 2.78-
2.75, 2.65-2.62; \(^{13}\)C NMR (DMSO-\(\text{d}_6\)) \& 148.5, 139.7, 137.2, 132.4, 129.0,
128.3, 127.0, 123.5, 123.1, 119.3, 114.1, 112.8, 110.1, 109.2, 64.6, 61.4, 55.2,
53.1, 29.5, 25.3, 25.0; HRMS (FAB) cacl for C\(_{23}\)H\(_{24}\)N\(_2\)O + H: 345.1967,
found: 345.1976.
Example 3:

Preparation of 2,3,7,8,9,10,11,12-octahydro-1\(H\)-azepino[4,5-b]pyrano[3,2-e]indole hydrochloride.

A solution containing the compound of Example 1 (0.38 g., 1.17 mmol) in ethanol (20.0 mL) was hydrogenated in the presence of palladium-on-carbon (0.20 g.) and 2 N hydrochloric acid (0.58 mL, 1.17 mmol) at 55 psi for 24 hours. After filtration through a pad of celite, the filtrate was concentrated \textit{in vacuo}. The residue was recrystallized from EtOAc/MeOH to yield 0.31 g. (94%) of a light yellow solid as the compound of Example 3. M.p. >283°C (dec.); IR (KBr) 3235, 3229, 2983, 2957, 2946, 2926, 2877, 2855, 2817, 2752, 2738, 2717, 2681, 2639, 2600, 2540, 1585, 1497, 1454, 1435, 1430, 1225, 1186, 1089, 805 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 10.82, 9.55, 6.95, 6.48, 4.04-4.02, 3.30-3.23, 3.13-3.10, 3.07-3.04, 1.99-1.93; \(^13\)C NMR (DMSO-\(d_6\)) \(\delta\) 147.7, 135.1, 129.4, 125.9, 111.6, 111.5, 110.2, 109.6, 64.8, 46.3, 44.4, 24.3, 22.7, 22.5, 22.2; MS (ESI\(^{+}\)) \textit{m/z}\n
243 (M\(^{+}\)+H); HRMS (FAB) calcd for C\(_{15}\)H\(_{18}\)N\(_2\)O + H: 243.1497, found: 243.1500; Anal. Calcd. for C\(_{15}\)H\(_{18}\)N\(_2\)O.HCl: C, 64.63; H, 6.87; N, 10.05. Found: C, 64.23; H, 6.95; N, 9.87.
Example 4:

Preparation of 7-methyl-2,3,7,8,9,10,11,12-octahydro-1H-azepino[4,5-b]pyrano[3,2-e]indole hydrochloride.

A solution containing the compound of Example 2 (0.18 g., 0.51 mmol) in ethanol (20.0 mL) was hydrogenated in the presence of palladium-on-carbon (0.07 g.) and 2 N hydrochloric acid (0.51 mL, 0.51 mmol) at 50 psi for 48 hours. After filtration through a pad of celite, the filtrate was concentrated in vacuo. The residue was recrystallized from EtOAc/MeOH to yield 0.13 g. (84%) of a light yellow solid as the compound of Example 4. M.p. >217°C (dec.); IR (KBr) 2946, 2877, 2844, 2809, 1609, 1585, 1551, 1467, 1447, 1280, 1267, 1255, 1238, 1109, 787 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 7.07, 6.52, 4.04-4.01, 3.57, 3.31-3.28, 3.19-3.12, 3.07-3.03, 1.96-1.92; ¹³C NMR (DMSO-d₆) δ 148.5, 136.8, 131.2, 125.2, 112.3, 112.1, 110.9, 108.8, 65.4, 46.3, 44.2, 29.7, 23.1, 22.6, 22.4; MS (ESI⁺) m/z 257 (M⁺+H); HRMS cacld for C₁₉H₂₉N₂O + H: 257.1654, found: 257.1646; Anal. Calcd. for C₁₉H₂₉N₂O.HCl.H₂O: C, 61.83; H, 7.46; N, 9.01. Found: C, 62.07; H, 7.41; N, 9.01.
Example 5:

Preparation of 10-benzyl-7-(4-phenoxybutyl)-7,8,9,10,11,12-hexahydro-3H-azepino[4,5-b]pyrano[3,2-e]indole.

To a solution containing the compound of Example 1 (0.08 g., 0.24 mmol) in N,N-dimethylformamide (5.00 mL) was added sodium hydride (0.011 g., 60% in oil, 0.29 mmol) at 0°C. The mixture was stirred at room temperature for 20 min., then down to 0°C. After 4-phenoxybutyl bromide (0.072 g., 0.32 mmol) was added to the mixture, the resulting mixture was stirred at room temperature for 16 hours. Water and ethyl acetate then were added to the mixture, and the organic and aqueous phases were separated. The aqueous layer then was extracted with ethyl acetate (2X). The combined ethyl acetate solution was dried (MgSO₄) and filtered. The filtrate was concentrated in vacuo. The residue was subjected to preparative thin layer chromatography (silica gel, 50% EtOAc/hexane) to yield 0.033 g. (29%) of a light yellow oil as the compound of Example 5. ¹H NMR (300 MHz, CDCl₃) δ 7.42, 7.13, 7.03, 6.95, 6.87, 6.71, 5.81, 4.69-4.67, 4.09, 3.93, 3.75, 3.17-3.14, 2.97-2.94, 1.87-1.76; MS (ESI+) m/z 479 (M⁺+1).
Example 6:

Preparation of 7-(4-phenoxybutyl)-2,3,7,8,9,10,11,12-octahydro-1H-azepino[4,5-b]pyrano[3,2-e]indole hydrochloride.

A solution containing the compound of Example 5 (0.085 g., 0.18 mmol) in ethanol (10.0 mL) was hydrogenated in the presence of palladium-on-carbon (0.04 g.) and 2 N hydrochloric acid (0.09 mL, 0.18 mmol) at 50 psi for 16 hours. After filtration through a pad of celite, the filtrate was concentrated in vacuo. The residue was recrystallized from EtOAc/MeOH to yield 0.075 g. (99%) of a light yellow solid as the compound of Example 6. $^1$H NMR (300 MHz, MeOH-d$_4$) δ 7.24-7.19, 7.03, 6.90-6.80, 6.57, 4.18-4.06, 3.85, 3.47-3.32, 3.28-3.17, 3.11, 2.04-1.95, 1.89-1.65, 1.40-1.25, 0.95-0.81; MS (ESI+) m/z 391 (M$^+$+H).
Example 7:

Preparation of ethyl (10-benzyl-3,8,9,10,11,12-hexahydro-7H-azepino[4,5-b]pyrano[3,2-e]indol-7-yl)acetate.

To a suspension of sodium hydride (0.076 g., 60% dispersion in mineral oil) in N,N-dimethylformamide (3.00 mL) was added a solution containing the compound of Example 1 (0.57 g., 1.70 mmol) in N,N-dimethylformamide (5.00 mL) at 0 °C. The mixture was stirred at room temperature for 30 min., then ethyl bromoacetate (0.23 mL, 2.07 mmol) was added to the mixture, and stirring was continued at room temperature for 18 hours. Water then was added to the mixture, and the resulting mixture was partitioned between ethyl acetate (organic layer) and water. The organic layer was washed several times with water, then concentrated in vacuo. The residue was subjected to column chromatography (silica gel, 10-40 % EtOAc/heptane) to yield 0.34 g. (47%) of a light yellow oil as the compound of Example 7. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.42, 7.35, 7.29, 7.10, 6.93, 6.71, 5.83, 4.71, 4.67, 4.18, 3.82, 3.25-3.14, 3.11-2.84, 1.25; MS (ESI+) $m/z$ 417 (M+H), HRMS (FAB) calcd for C$_{26}$H$_{28}$N$_2$O$_5$+H: 417.2178, found 417.2183.
Example 8:

**Preparation of (10-benzyl-3,8,9,10,11,12-hexahydro-7H-azepino[4,5-b]pyrano[3,2-c]indol-7-yl)acetic acid.**

The compound of Example 7 (0.29 g., 0.70 mmol) was dissolved in ethanol (5.00 mL). Lithium hydroxide monohydrate (0.044 g., 1.00 mmol) was added to the solution, and the solution turned red in color. The solution then was stirred at room temperature for 4 hours, concentrated, and partitioned between ethyl acetate and 1 N hydrochloric acid. The organic layer was washed with water and concentrated *in vacuo* to yield 0.12 g. of a yellow solid as the compound of Example 8. M.p. 185-187°C; HPLC Ret. Time = 2.91 min.; MS (ESI+) m/z 389 (M+H); HRMS (FAB) calcd for C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>+H: 389.1865, found 389.1877.
Example 9:

Preparation of 2-((10-benzyl-3,8,9,10,11,12-hexahydro-7H-azepino[4,5-b]pyrano[3,2-e]indol-7-yl)-N-phenylacetamide.

A mixture containing the compound of Example 8 (0.12 g., 0.309 mmol), 1-(3-dimethylaminopropyl)3-ethylcarbodiimidine hydrochloride (0.071 g., 0.37 mmol), and aniline (0.035 g., 0.37 mmol) in N,N-dimethylformamide (7.00 mL) was stirred at room temperature for 18 hours. The mixture then was poured into a 1:1 solution of water/saturated sodium bicarbonate, to form a precipitate which then was filtered to provide 0.085 g. of a light brown solid as the compound of Example 9. M.p. 134-136 °C; MS (ESI+) \( m/z \) 464 (M+H); HRMS (FAB) calcd for \( C_{36}H_{29}N_2O_2\), 464.2338, found 464.2345.
Example 10:

Preparation of 2-(1,2,3,8,9,10,11,12-octahydro-7H-azepino[4,5-b]pyrano[3,2-e]indol-7-yl)-N-phenylacetamide hydrochloride.

A mixture containing the compound of Example 9 (0.078 g., 0.30 mmol), 1 N hydrochloric acid (0.17 mL, 0.17 mmol), and palladium-on-carbon (10%, 0.25 g.) in ethanol (50 mL) was placed on a Parr hydrogenator under 50 psi of hydrogen and shaken for 52 hours. The reaction mixture then was filtered through celite, and concentrated in vacuo to provide 0.025 g. (36%) of a gray solid. Crystallization from MeOH/Et₂O yielded 0.005 g. of a dark gray solid as the compound of Example 10. M.p. >250 °C (dec.); HPLC Ret. Time = 2.99 min.; HRMS (FAB) calcd for C₂₃H₂₅N₂O₂⁺H: 376.2025, found 376.2032.
Efficacy Data

All of the Example compounds provided above are believed to be 5-HT ligands, with the ability to displace >50% of a radiolabeled test ligand from one or more 5-HT receptor subtypes at a concentration of 1 μM. The procedures used for testing such displacement are well known and readily available to persons skilled in the art.

Having described the invention in detail and by reference to the preferred embodiments thereof, it will be apparent that modifications and variations are possible without departing from the scope of the appended claims.

The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art.
What is claimed is:

1. A compound having a structural formula

![Structural formula image]

wherein R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₁₋₆ alkenylenearyl;

R², independently, is selected from the group consisting of H, C₁₋₄ alkyl, and OH;

R³ is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, C(=O)R⁺, C(=O)OR⁺, C(=O)NR⁺R⁺, C(=O)SR⁺, C(=S)NR⁺R⁺, SO₂R⁺, SO₂NR⁺R⁺, S(=O)R⁺, S(=O)NR⁺R⁺, C(=O)NR⁺C₁₋₄ alkenyleneOR⁺, C(=O)NR⁺C₁₋₄ alkenyleneHet, C(=O)C₁₋₄ alkenylenearyl, C(=O)C₁₋₄ alkenyleneheteroaryl, C₁₋₄ alkenylenearyl, C₁₋₄ alkenylenehetereoaryl, C₁₋₄ alkenyleneHet, C₁₋₄ alkenyleneC(=O)C₁₋₄ alkenylenearyl, C₁₋₄ alkenyleneC(=O)C₁₋₄ alkenyleneheteroaryl, C₁₋₄ alkenyleneC(=O)Het, C₁₋₄ alkenyleneC(=O)NR⁺R⁺, C₁₋₄ alkenyleneOR⁺, C₁₋₄ alkenyleneNR⁺C(=O)R⁺, C₁₋₄ alkenyleneOC₁₋₄ alkenyleneOR⁺, C₁₋₄ alkenyleneNR⁺R⁺, C₁₋₄ alkenyleneC(=O)OR⁺, and C₁₋₄ alkenyleneOC₁₋₄ alkenyleneC(=O)OR⁺;

R⁴ is selected from the group consisting of H, halo, OH, CN, NO₂, CF₃, CF₃O, NR⁺R⁺, aryl, and heteroaryl; and,
$R^a$ and $R^b$, independently, are selected from the group consisting of hydrogen, C$_{1-6}$alkyl, C$_{3-8}$cycloalkyl, aryl, heteroaryl, arylC$_{1-3}$alkyl, heteroaryl-C$_{1-3}$alkyl, C$_{1-3}$alkylenearyl, C$_{1-3}$alkyleneheteroaryl, and Het; and, pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein $R^3$ is selected from the group consisting of hydrogen, C$_{1-6}$alkyl, C$_{1-6}$alkyleneOR$^a$, C$_{1-6}$alkyleneC(=O)OR$^3$, C$_{1-6}$alkyleneC(=O)NR$^a$R$^b$, C(=O)R$^3$, C(=S)NR$^a$R$^b$, and C(=O)C$_{1-6}$alkylenearyl.

3. The compound of claim 1 wherein $R^1$ is selected from the group consisting of hydrogen and benzyl.

4. The compound of claim 3 wherein $R^2$ and $R^4$ are hydrogen.

5. The compound of claim 4 wherein $R^3$ is selected from the group consisting of hydrogen, alkyl, C$_{1-6}$alkylenearyl, C$_{1-6}$alkyleneOR$^a$, carboxylic acid, C$_{1-6}$alkyleneC(=O)OR$^a$, and C$_{1-6}$alkyleneC(=O)NR$^a$R$^b$.

6. The compound of claim 5 wherein $R^3$ is selected from the group consisting of hydrogen, methyl, C$_4$alkylene-O-phenol, -CCOOEt, -CCOOH, and N-phenylacetamide.

8. A compound selected from the group consisting of:
   10-benzyl-7,8,9,10,11,12-hexahydro-3H-azepino[4,5-b]pyrano[3,2-e]indole;
   10-benzyl-7-methyl-7,8,9,10,11,12-hexahydro-3H-azepino[4,5-b]pyrano[3,2-e]indole;
   2,3,7,8,9,10,11,12-octahydro-1H-azepino[4,5-b]pyrano[3,2-e]indole;
   2,3,7,8,9,10,11,12-octahydro-7-methyl-1H-azepino[4,5-b]pyrano[3,2-e]indole;
   10-benzyl-7-(4-phenoxybutyl)-7,8,9,10,11,12-hexahydro-3H-azepino[4,5-b]pyrano[3,2-e]indole;
   7-(4-phenoxybutyl)-7,8,9,10,11,12-octahydro-1H-azepino[4,5-b]pyrano[3,2-e]indole;
   ethyl(10-benzyl-3,8,9,10,11,12-hexahydro-7H-azepino[4,5-b]pyrano[3,2-e]indol-7-yl)acetate;
   (10-benzyl-3,8,9,10,11,12-hexahydro-7H-azepino[4,5-b]pyrano[3,2-e]indol-7-yl)acetic acid;
   2-(10-benzyl-3,8,9,10,11,12-hexahydro-7H-azepino[4,5-b]pyrano[3,2-e]indol-7-yl)-N-phenylacetamide; and,
   2-(1,2,3,8,9,10,11,12-octahydro-7H-azepino[4,5-b]pyrano[3,2-e]indol-7-yl)-N-phenylacetamide.
9. A method of treating a disease or disorder of the central nervous system in a mammal comprising administering to said mammal a pharmaceutically effective amount of a compound having the formula

\[
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{9} \\
\text{10} \\
\text{R}^2 \\
\text{R}^3 \\
\text{N} \\
\text{6} \\
\text{7} \\
\text{8} \\
\text{9} \\
\text{10} \\
\end{array}
\end{array}
\]

wherein \( R^1 \) is selected from the group consisting of \( H \), \( C_{1-6} \) alkyl, and \( C_{1-6} \) alkenylnaryl;

\( R^2 \), independently, is selected from the group consisting of \( H \), \( C_{1-6} \) alkyl, and \( \text{OH} \);

\( R^3 \) is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, \( C(=O)R^a \), \( C(=O)OR^a \), \( C(=O)NR^aR^b \), \( C(=O)SR^a \), \( C(=S)NR^aR^b \), \( \text{SO}_2R^a \), \( \text{SO}_2NR^aR^b \), \( S(=O)R^a \), \( S(=O)NR^aR^b \), \( C(=O)NR^aC_{1-6} \text{alkyleneOR}^a \), \( C(=O)NR^aC_{1-6} \text{alkyleneHet} \), \( C(=O)C_{1-6} \text{alkylenearyl} \), \( C(=O)C_{1-6} \text{alkyleneheteroaryl} \), \( C_{1-6} \text{alkyleneheteroaryl} \), \( C_{1-6} \text{alkylenec}(=O)C_{1-6} \text{alkyleneheteroaryl} \), \( C_{1-6} \text{alkylenec}(=O)C_{1-6} \text{alkylenearyl} \), \( C_{1-6} \text{alkylenec}(=O)C_{1-6} \text{alkyleneHet} \), \( C_{1-6} \text{alkylenec}(=O)C_{1-6} \text{alkyleneheteroaryl} \), \( C_{1-6} \text{alkylenec}(=O)R^a \), \( C_{1-6} \text{alkylenec}(=S)R^a \), \( C_{1-6} \text{alkylenec}NR^aC(=O)R^a \), \( C_{1-6} \text{alkylenec}OC_{1-6} \text{alkylenec}(=O)R^a \), \( C_{1-6} \text{alkylenec}NR^aR^b \), \( C_{1-6} \text{alkylenec}(=O)OR^a \), and \( C_{1-6} \text{alkylenec}OC_{1-6} \text{alkylenec}(=O)OR^a \);

\( R^4 \) is selected from the group consisting of \( H \), \( \text{Halo} \), \( \text{OH} \), \( \text{CN} \), \( \text{NO}_2 \), \( \text{CF}_3 \), \( \text{CF}_3\text{O} \), \( \text{NR}^aR^b \), aryl, and heteroaryl; and,
R¹ and R², independently, are selected from the group consisting of hydrogen, C₁₆₋₇alkyl, C₃₋₇cycloalkyl, aryl, heteroaryl, arylC₁₋₃alkyl, heteroaryl-C₁₋₇alkyl, C₁₋₃alkylenearyl, C₁₋₃alkyleneheteroaryl, and Het; and, pharmaceutically acceptable salts thereof.

10. The method of claim 9 wherein the mammal is a human, farm animal, pet, or other type of animal.

11. The method of claim 10 wherein the mammal is a human.

12. The method of claim 9 wherein said disease or disorder is selected from the group consisting of obesity, depression, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, a stress related disease, panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the urinary, gastrointestinal or cardiovascular system, neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal, addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, behavioral disturbance, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthmic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, a movement disorder, oppositional defiant disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, mood disorder, seasonal affective disorder, a sleep
disorder, a specific developmental disorder, agitation disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, and a Tic disorder.

13. The method of claim 12 wherein said compound is administered rectally, topically, nasally, orally, sublingually, transdermally or parenterally.

14. The method of claim 12 wherein said compound is administered in an amount of about 0.01 to about 150 mg/kg of body weight of the mammal per day.

15. The method of claim 14 wherein said compound is administered in an amount of about 0.1 to about 50 mg/kg of body weight of the mammal per day.

16. The method of claim 15 wherein said compound is administered in an amount of about 0.1 to about 10 mg/kg of body weight of the mammal per day.
17. A preparation of a medicament from a composition comprising a therapeutically effective amount of a compound of Formula (I):

\[
\text{Formula (I)}
\]

wherein R\(^1\) is selected from the group consisting of H, C\(_{1-6}\) alkyl, and C\(_{1-6}\) alkylenearyl;

R\(^2\), independently, is selected from the group consisting of H, C\(_{1-6}\) alkyl, and OH;

R\(^3\) is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, C(=O)R\(^a\), C(=O)OR\(^a\), C(=O)NR\(^b\)R\(^b\), C(=O)SR\(^a\), C(=S)NR\(^b\)R\(^b\), SO\(_2\)R\(^a\), SO\(_2\)NR\(^b\)R\(^b\), S(=O)R\(^a\), S(=O)NR\(^b\)R\(^b\), C(=O)NR\(^b\)C\(_{1-6}\)alkyleneOR\(^a\), C(=O)NR\(^b\)C\(_{1-6}\)alkyleneHet, C(=O)C\(_{1-6}\)alkylenearyl, C(=O)C\(_{1-6}\)alkyleneheteroaryl, C\(_{1-6}\)alkylenearyl, C\(_{1-6}\)alkyleneheteroaryl, C\(_{1-6}\)alkyleneHet, C\(_{1-6}\)alkyleneC(=O)C\(_{1-6}\)alkylenearyl, C\(_{1-6}\)alkyleneC(=O)C\(_{1-6}\)alkyleneheteroaryl, C\(_{1-6}\)alkyleneC(=O)Het, C\(_{1-6}\)alkyleneC(=O)NR\(^b\)R\(^b\), C\(_{1-6}\)alkyleneOR\(^a\), C\(_{1-6}\)alkyleneNR\(^b\)C(=O)R\(^a\), C\(_{1-6}\)alkyleneOC\(_{1-6}\)alkyleneOR\(^a\), C\(_{1-6}\)alkyleneNR\(^b\)R\(^b\), C\(_{1-6}\)alkyleneC(=O)OR\(^a\), and C\(_{1-6}\)alkyleneOC\(_{1-6}\)alkyleneC(=O)OR\(^a\);

R\(^4\) is selected from the group consisting of H, halo, OH, CN, NO\(_2\), CF\(_3\), CF\(_3\)O, NR\(^b\)R\(^b\), aryl, and heteroaryl; and,
$R^a$ and $R^b$, independently, are selected from the group consisting of hydrogen, C$_{1-3}$alkyl, C$_{3-8}$cycloalkyl, aryl, heteroaryl, arylC$_{1-3}$alkyl, heteroaryl-C$_{1-3}$alkyl, C$_{1-3}$alkylenearyl, C$_{1-3}$alkyleneheteroaryl, and Het; and, pharmaceutically acceptable salts thereof.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D49112 A61K31/55 //C07D491/12, 307:00, 223:00, 209:00

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)
IPC 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEMABS Data, EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>A, P</td>
<td>WO 00 64899 A (HESTER JACKSON B JR ; UPJOHN CO (US); ACKER BRAD A (US); JACOBSEN E) 2 November 2000 (2000-11-02) abstract; examples 16,20</td>
<td>1-17</td>
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<tr>
<td>A</td>
<td>US 3 776 922 A (EPSTEIN J ET AL) 4 December 1973 (1973-12-04) abstract; claims</td>
<td>1-17</td>
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X Further documents are listed in the continuation of box C.

X Patent family members are listed in annex.

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Date of the actual completion of the international search
5 November 2001

Date of mailing of the international search report
21/11/2001

Name and mailing address of the ISA
European Patent Office, P.B. 5018 Patentlaan 2 NL – 2280 HV Rijswijk
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Authorized officer
Frelon, D

Form PCT/ISA/010 (second sheet) (July 1992)
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<tr>
<td>A</td>
<td>EP 0 028 381 A (SANDOZ AG) 13 May 1981 (1981-05-13) abstract; example 11</td>
<td>1-17</td>
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<tr>
<td>A</td>
<td>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SWEETNAM, P. M. ET AL: &quot;Receptor binding profile suggests multiple mechanisms of action are responsible for ibogaine's putative anti-addictive activity&quot; retrieved from STN Database accession no. 123:25599 XP002182002 abstract &amp; PSYCHOPHARMACOLOGY (BERLIN) (1995), 118(4), 369-76</td>
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