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(54) Title: RADIOLABELED COMPOUNDS AND USES THEREOF

(57) Abstract: The present invention relates to Radiolabeled Compounds and methods of use thereof for treating or preventing a psychiatric disorder in a subject, for stabilizing the mood of a subject having a mood disorder, or as an imaging agents for a serotonin receptor. Compositions comprising an imaging-effective amount of a Radiolabeled Compound are also disclosed.

RADIOLABELED COMPOUNDS AND USES THEREOF

[0001] This application claims the benefit of the filing date of U.S. Patent Application No. 11/823,641, filed June 28, 2007, the contents of which is incorporated by reference herein in its entirety.

[0002] All patents, patent applications and publications cited herein are hereby incorporated by reference in their entirety. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein.

[0003] This patent disclosure contains material that is subject to copyright protection. The copyright owner has no objection to the facsimile reproduction by anyone of the patent document or the patent disclosure as it appears in the U.S. Patent and Trademark Office patent file or records, but otherwise reserves any and all copyright rights.

FIELD OF THE INVENTION

[0004] The present invention relates to Radiolabeled Compounds and methods of use thereof for treating or preventing a psychiatric disorder in a subject, for stabilizing the mood of a subject having a mood disorder, or as as imaging agents for a serotonin receptor. Compositions comprising an imaging-effective amount of a Radiolabeled Compound are also disclosed.

BACKGROUND OF THE INVENTION

[0005] Powerful imaging methods currently exist which enable one to assess the living brain and body *in vivo* and thereby monitor the effectiveness of treatments that affect brain chemistry and function. Positron emission tomography (PET) is a dynamic, non-invasive imaging technique used in nuclear medicine to study various biochemical and biological process *in vivo*. In PET, labeled compounds may be administered in nanomolar or picomolar concentrations, allowing imaging studies to be performed without perturbing the biological system being studied. These labeled compounds may generally be radioisotopes that give off positrons. The emitted positrons may then collide with electrons, which generates gamma rays. The emitted gamma rays may then be detected by scanners and be processed to obtain images of the living brain and body. Like other dynamic imaging protocols, PET has the

ability collect images repeatedly over time and provide information about regional distribution of the tracer as well as the change in compartmental distribution as a function of time. As such, PET lends itself directly to measuring kinetic processes, such as rate of tracer uptake by cells, substrate metabolic rates, receptor density/affinity, and regional blood flow.

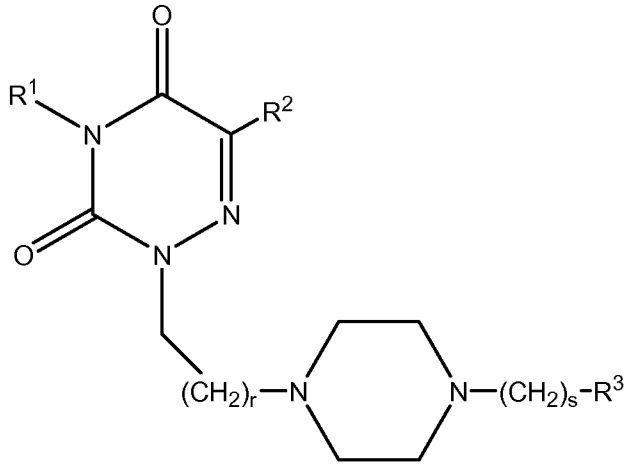
[0006] Serotonin system in the brain is an important neurotransmission network regulating various physiological functions and behavior including anxiety and mood states. Serotonin (5-hydroxytryptamine; 5-HT) has been linked with major depression, bipolar disorder, eating disorders, alcoholism, pain, anxiety, obsessive-compulsive disorders, Alzheimer's Disease, Parkinson's disease and other psychiatric maladies. It is also involved in mediating the action of many psychotropic drugs including antidepressants, antianxiety drugs and antipsychotics. There are more than a dozen known subtypes of serotonin receptors. Among these serotonin receptors, 5-HT_{1A} receptors play a role as a presynaptic autoreceptor in the dorsal raphe nucleus and as a postsynaptic receptor for serotonin in terminal field areas.

[0007] Several radioligands for 5-HT_{1A} receptors have been prepared and evaluated. The most successful radioligands studied so far for 5-HT_{1A} receptors are antagonist tracers which bind with both the G-protein-coupled high affinity (HA) state and uncoupled low affinity (LA) state of 5-HT_{1A} receptors. In contrast, agonists bind preferentially to the HA state of the 5-HT_{1A} receptor. Therefore, having a radioligand agonist tracer may provide a more meaningful functional measure of 5-HT_{1A} receptors. To date there are no successful 5-HT_{1A} agonist radiotracers available for studies in a living brain.

[0008] Thus, there is still a need in the art for radiolabeled serotonin agonist modulators that are highly selective for imaging 5-HT_{1A} receptors. Moreover, there remains a need in the art for selective radioactive tracers, which are useful for imaging 5-HT_{1A} receptors *in vivo*. The present invention addresses these needs.

SUMMARY OF THE INVENTION

[0009] In one aspect, the present invention provides Radiolabeled Compounds having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

r and s are each independently an integer ranging from 0 to 6;

R^1 is H, aryl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, 3- to 7-membered heterocycle, ^{11}C-labeled C_1-C_6 alkylene, ^{11}C-labeled C_2-C_6 alkenylene, ^{11}C-labeled C_2-C_6 alkynylene, ^{18}F-labeled C_1-C_6 alkylene, ^{18}F-labeled C_2-C_6 alkenylene, or ^{18}F-labeled C_2-C_6 alkynylene alkyne;

R^2 is H, aryl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, 3- to 7-membered heterocycle, halo, CF_3, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $N(R^4)_2$, CN, OR^4 or SR^4;

R^3 is aryl or 5- to 7-membered aromatic heterocycle, each of which is substituted with one R^6 group and optionally substituted with one or more of the following groups: C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl or 3- to 7-membered heterocycle, halo, CF_3, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_1-C_6 alkylene)-aryl, $N(R^4)_2$, CN, OR^4, SR^4, S(O)-R^4, SO_2-R^4, SO_2NH-R^4, SO_3H, NH-SO_2-R^4, C(O)R^5 or NHC(O)R^5;

each occurrence of R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, (C_1-C_6 alkylene)-aryl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl or 3- to 7-membered heterocycle;

R^5 is R^4, $N(R^4)_2$ or OR^4;

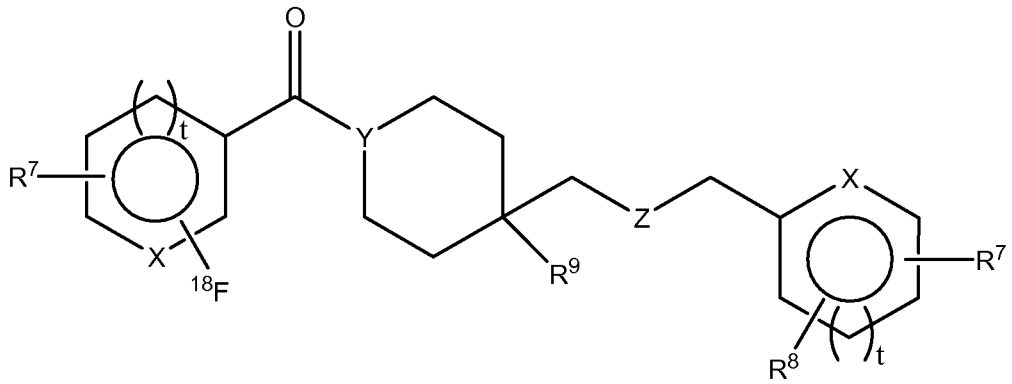
R^6 is L-M-Q;

L is a single bond, O, S, NH, F, ^{18}F, CF_3, ^{18}F-labeled CF_3, CF_2H, ^{18}F-labeled CF_2H, or ^{11}C-labeled CN;

M is ^{11}C-labeled C_1-C_6 alkylene, ^{11}C-labeled C_2-C_6 alkenylene, ^{11}C-labeled C_2-C_6 alkynylene, ^{18}F-labeled C_1-C_6 alkylene, ^{18}F-labeled C_2-C_6 alkenylene, or ^{18}F-labeled C_2-C_6 alkynylene; and

Q is H or aryl.

[0010] In another aspect, the present invention provides Radiolabeled Compounds having the Formula (II):



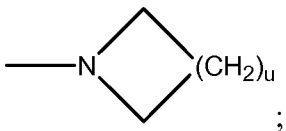
(II)

or a pharmaceutically acceptable salt thereof,

wherein:

each R^7 is independently -H, -halo, -C_1-C_6 alkyl, -C_1-C_6 fluoroalkyl, -C_3-C_7 cycloalkyl,

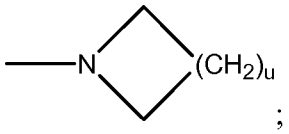
-C_3-C_7 cycloalkenyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -$N(R^{10})_2$, -CN, -OR^{10}, -SR^{10}, -S(O)-R^{10}, -SO_2-R^{10}, -SO_2NH-R^{10}, -SO_3H, -NH-SO_2-R^{10}, -$C(O)R^{11}$, -$NHC(O)R^{11}$, -aryl, -3- to 7-membered heterocycle, -alkoxycarbonyl, or



;

R^8 is -Z^a-R^{12}, -H, -halo, -C_1-C_6 alkyl, -fluoroalkyl, -C_3-C_7 cycloalkyl, -C_3-C_7 cycloalkenyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -$N(R^{10})_2$, -CN, -OR^{10}, -SR^4, -S(O)-R^{10}, -SO_2-R^{10},

-SO_2NH-R^{10}, -SO_3H, -NH-SO_2-R^{10}, -$C(O)R^{11}$, -$NHC(O)R^{11}$, -aryl, -3- to 7-membered heterocycle, -alkoxycarbonyl, or



;

R^9 is -H or -halo;

each R^{10} is independently -H, -C_1-C_6 alkyl, -C_1-C_6 fluoroalkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -aryl, -(C_1-C_6 alkylene)-aryl, -C_3-C_7 cycloalkyl, -C_3-C_7 cycloalkenyl or -3- to 7-membered heterocycle;

R^{11} is -R^4, -$N(R^4)_2$ or -OR^4;

R^{12} is -^{11}C-labeled C_1-C_6 alkyl, -^{11}C-labeled C_2-C_6 alkenyl, -^{11}C-labeled C_2-C_6 alkynyl,

-(^{11}C-labeled C_1-C_6 alkylene)-aryl, -(^{11}C-labeled C_2-C_6 alkenylene)-aryl, or

-(^{11}C-labeled C_2-C_6 alkynylene)-aryl;

each X is independently –CH-, -N-, -S-, or –O-;

Y is –CH- or –N-;

Z is -CH_2-, -NH, -S-, or –O-

Z^a is –O-, -S-, or –NH-;

t is 0 or 1, such that t is zero when X is –S-; and

u is 1 or 2.

[0011] The Compounds of Formula (I) and Formula (II) (the "Radiolabeled Compounds") are useful for: (i) detecting *in vivo* 5-HT_{1A} receptors in a subject; (ii) treating or preventing a psychiatric disorder in a subject, or (iii) stabilizing the mood of a subject having a mood disorder.

[0012] In yet another aspect, the present invention provides a method for detecting *in vivo* 5-HT_{1A} receptors in a subject, the method comprising:

(a) administering to the subject an imaging-effective amount of a Radiolabeled Compound or a pharmaceutically acceptable salt thereof, and

(b) detecting the radioactive emission of the compound or salt thereof administered to the subject.

[0013] In yet another aspect, the present invention provides a method for detecting *in vivo* 5-HT_{1A} receptors in a subject, the method comprising:

(a) administering to the subject an imaging-effective amount of a Radiolabeled Compound or a pharmaceutically acceptable salt thereof, and

(b) detecting the radioactive emission of the compound or salt thereof administered to the subject.

[0014] In the present methods, the radioactive emissions from the ^{11}C- and/or ^{18}F- atom of a Radiolabeled Compound can be detected using PET for imaging one or more 5-HT_{1A} serotonin receptors in a subject. The radioactive emission can be detected anywhere in the body of the subject. In one embodiment, the radioactive emission is detected in the brain of the subject. In a further embodiment, the subject can be known or suspected to have a psychiatric or neurological disorder.

[0015] The invention also relates to compositions comprising a physiologically acceptable carrier or vehicle and an amount of a Radiolabeled Compound that is effective to: (i) treat or prevent a psychiatric disorder in a subject; or (ii) stabilize the mood of a subject having a mood disorder. The compositions are useful for treating or preventing a psychiatric disorder in a subject, or for stabilizing the mood of a subject having a mood disorder.

[0016] The present invention may be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Abbreviations

[0017] The terms used herein having following meanings:

[0018] The term "alkyl" as used herein, refers to a straight chain or branched non-cyclic hydrocarbon, wherein one of the hydrocarbon's hydrogen atoms has been replaced with a single bond. Hence, the term "C_1-C_6 alkyl" as used herein, refers to a straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms, wherein one of the hydrocarbon's hydrogen atoms has been replaced with a single bond. Representative straight chain C_1-C_6 alkyls include methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, and *n*-hexyl. Representative branched C_1-C_6 alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, isopropyl,

sec-butyl, isobutyl, neohexyl, isohexyl, and the like. In certain embodiments, the C_1-C_6 alkyl may be substituted with one or more of the following groups: halo, O-(C_1-C_6 alkyl), OH, CN, COOR', OC(O)R', N(R')$_2$, NHC(O)R' or C(O)NHR' groups wherein each R' is independently H or unsubstituted C_1-C_6 alkyl.

[0019] The term "fluoroalkyl" as used herein, refers to a C_1-C_6 alkyl group wherein one or more of the C_1-C_6 alkyl group's hydrogen atoms have been replaced with a fluorine atom. Representative fluoroalkyls include monofluoromethyl -CHF_2, -CH_2F, -CF_3, -$CH(F)CH_3$, or -CF_2CH_3. In certain embodiments, the fluoroalkyl may be substituted with one or more of the following groups: halo, O-(C_1-C_6 alkyl), OH, CN, COOR', OC(O)R', N(R')$_2$, NHC(O)R' or C(O)NHR' groups wherein each R' is independently H or unsubstituted C_1-C_6 alkyl.

[0020] The term "alkenyl" as used herein, refers to a straight chain or branched non-cyclic hydrocarbon including at least one carbon-carbon double bond, wherein one of the hydrocarbon's hydrogen atoms has been replaced with a single bond. Hence, the term "C_2-C_6 alkenyl" as used herein, refers to a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon double bond, wherein one of the hydrocarbon's hydrogen atoms has been replaced with a single bond. Representative straight chain and branched C_2-C_6 alkenyls include vinyl, allyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, and the like. In certain embodiments, the C_2-C_6 alkenyl may be substituted with one or more of the following groups: halo, O-(C_1-C_6 alkyl), OH, CN, COOR', OC(O)R', N(R')$_2$, NHC(O)R' or C(O)NHR' groups wherein each R' is independently H or unsubstituted C_1-C_6 alkyl.

[0021] The term "alkynyl" as used herein, refers to a straight chain or branched non-cyclic hydrocarbon including at lease one carbon-carbon triple bond, wherein one of the hydrocarbon's hydrogen atoms has been replaced with a single bond. Hence, the term "C_2-C_6 alkynyl" as used herein, refers to a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at lease one carbon-carbon triple bond, wherein one of the hydrocarbon's hydrogen atoms has been replaced with a single bond. Representative straight chain and branched C_2-C_6 alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-butynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 5-hexynyl, and the like. In certain embodiments, the C_2-C_6 alkynyl may be substituted with one or more of the following groups: halo, O-(C_1-C_6 alkyl), OH, CN, COOR', OC(O)R',

$N(R')_2$, NHC(O)R' or C(O)NHR' groups wherein each R' is independently H or unsubstituted C_1-C_6 alkyl.

[0022] The term "alkylene" as used herein, refers to a straight chain or branched non-cyclic hydrocarbon, wherein two of the hydrocarbon's hydrogen atoms have been replaced with a single bond. Hence, the term "C_1-C_6 alkylene" as used herein, refers to a straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms, wherein two of the hydrocarbon's hydrogen atoms have been replaced with a single bond.

[0023] A "^{11}C-labeled C_1-C_6 alkylene group" is a C_1-C_6 alkylene group, as defined above, wherein one of the C_1-C_6 alkylene group's carbon atoms has been replaced with a ^{11}C isotope. A "^{11}C-labeled C_1-C_6 alkyl group" is a C_1-C_6 alkyl group, as defined above, wherein one of the C_1-C_6 alkyl group's carbon atoms has been replaced with a ^{11}C isotope. Representative ^{11}C-labeled C_1-C_6 alkylene groups include, but are not limited to $^{11}CH_2$, $CH_2{}^{11}CH_2$, $CH_2CH_2{}^{11}CH_2$, $CH_2CH_2CH_2{}^{11}CH_2$, $CH_2CH_2CH_2CH_2{}^{11}CH_2$, and $CH_2CH_2CH_2CH_2CH_2{}^{11}CH_2$.

[0024] A "^{18}F-labeled C_1-C_6 alkylene group" is a C_1-C_6 alkyl group, as defined above, wherein one of the C_1-C_6 alkyl group's hydrogen atoms has been replaced with a ^{18}F isotope.

[0025] The term "alkenylene" as used herein, refers to a straight chain or branched non-cyclic hydrocarbon including at least one carbon-carbon double bond, wherein two of the hydrocarbon's hydrogen atoms have been replaced with a single bond. Hence, the term "C_2-C_6 alkenylene" as used herein, refers to a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon double bond, wherein two of the hydrocarbon's hydrogen atoms have been replaced with a single bond.

[0026] A "^{11}C-labeled C_2-C_6 alkenylene group" is a C_2-C_6 alkenylene group, as defined above, wherein one of the C_2-C_6 alkenylene group's carbon atoms has been replaced with a ^{11}C isotope.

[0027] A "^{18}F-labeled C_2-C_6 alkenylene group" is a C_2-C_6 alkenylene group, as defined above, wherein one of the C_2-C_6 alkenylene group's hydrogen atoms has been replaced with a ^{18}F isotope.

[0028] The term "alkynylene" as used herein, refers to a straight chain or branched non-cyclic hydrocarbon including at lease one carbon-carbon triple bond, wherein two of the hydrocarbon's hydrogen atoms have been replaced with a single bond. Hence, the term "C_2-C_6 alkynylene" as used herein, refers to a straight chain or branched non-cyclic

hydrocarbon having from 2 to 6 carbon atoms and including at lease one carbon-carbon triple bond, wherein two of the hydrocarbon's hydrogen atoms have been replaced with a single bond.

[0029] A "^{11}C-labeled C_2-C_6 alkynylene group" is a C_2-C_6 alkynylene group, as defined above, wherein one of the C_2-C_6 alkynylene group's carbon atoms has been replaced with a ^{11}C isotope.

[0030] A "^{18}F-labeled C_2-C_6 alkynylene group" is a C_2-C_6 alkynylene group, as defined above, wherein one of the C_2-C_6 alkynylene group's hydrogen atoms has been replaced with a ^{18}F isotope.

[0031] The term "alkoxycarbonyl" means a moiety of the formula —COOR', where R' is independently H or unsubstituted C_1-C_6 alkyl. Examples of such alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, and the like.

[0032] The term "aryl" as used herein refers to a phenyl group, a biphenyl group, biphenylene group, anthracene group, fulvene group, phenanthrene group, or a naphthyl group. In certain embodiments, the aryl group may be substituted with one or more of the following groups: halo, O-C_1-C_6 alkyl, O-C_2-C_6 alkenyl, O-C_2-C_6 alkynyl, OH, CN, COOR', OC(O)R', N(R')$_2$, NHC(O)R', S-(C_1-C_6 alkyl or alkenyl or alkynyl), S-(O)-C_1-C_6 alkyl, S(O)-C_2-C_6 alkenyl, S(O)-C_2-C_6 alkynyl, S-(O_2)-C_1-C_6 alkyl, S(O_2)-C_2-C_6 alkenyl, S(O_2)-C_2-C_6 alkynyl, or C(O)NHR' groups wherein each R' is independently -H or unsubstituted -C_1-C_6 alkyl.

[0033] The term "cycloalkyl" as used herein refers to a saturated non-aromatic monocyclic cycloalkyl ring. Hence, the term "C_3-C_7 cycloalkyl" as used herein refers to a 3-, 4-, 5-, 6- or 7- membered saturated non-aromatic monocyclic cycloalkyl ring. Representative C_3-C_7 monocyclic cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. In certain embodiments, the aryl group may be substituted with one or more of the following groups: halo, O-C_1-C_6 alkyl, O-C_2-C_6 alkenyl, O-C_2-C_6 alkynyl, OH, CN, COOR', OC(O)R', N(R')$_2$, NHC(O)R', S-(C_1-C_6 alkyl or alkenyl or alkynyl), S-(O)-C_1-C_6 alkyl, S(O)-C_2-C_6 alkenyl, S(O)-C_2-C_6 alkynyl, S-(O_2)-C_1-C_6 alkyl, S(O_2)-C_2-C_6 alkenyl, S(O_2)-C_2-C_6 alkynyl, or C(O)NHR' groups wherein each R' is independently H or unsubstituted C_1-C_6 alkyl.

[0034] The term "cycloalkenyl" as used herein refers to non-aromatic monocyclic carbocyclic ring having at least one endocyclic double bond. Hence, the term "C_3-C_7 cycloalkenyl" as used herein refers to a 3-, 4-, 5-, 6- or 7- membered non-aromatic

monocyclic carbocyclic ring having at least one endocyclic double bond, but which is not aromatic. It is to be understood that when any two groups, together with the carbon atom to which they are attached form a C_3-C_7 monocyclic cycloalkenyl group, the carbon atom to which the two groups are attached remain tetravalent. Representative C_3-C_7 monocyclic cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, 1,3-cyclobutadienyl, cyclopentenyl, 1,3-cyclopentadienyl, cyclohexenyl, 1,3-cyclohexadienyl, cycloheptenyl, 1,3-cycloheptadienyl, 1,4-cycloheptadienyl and -1,3,5-cycloheptatrienyl. In one embodiment, the aryl group is substituted with one or more of the following groups: halo, O-C_1-C_6 alkyl, O-C_2-C_6 alkenyl, O-C_2-C_6 alkynyl, OH, CN, COOR', OC(O)R', N(R')$_2$, NHC(O)R', S-(C_1-C_6 alkyl or alkenyl or alkynyl), S-(O)-C_1-C_6 alkyl, S(O)-C_2-C_6 alkenyl, S(O)-C_2-C_6 alkynyl, S-(O_2)-C_1-C_6 alkyl, S(O_2)-C_2-C_6 alkenyl, S(O_2)-C_2-C_6 alkynyl, or C(O)NHR' groups wherein each R' is independently H or unsubstituted C_1-C_6 alkyl.

[0035] The term "halo" as used herein, refers to F, Cl, Br, or I.

[0036] The term "3- to 7-membered heterocycle" refers to: (i) a 3- or 4-membered non-aromatic monocyclic cycloalkyl in which 1 of the ring carbon atoms has been replaced with a N, O or S atom; (ii) a 5-, 6-, or 7-membered aromatic or non-aromatic monocyclic cycloalkyl in which 1-4 of the ring carbon atoms have been independently replaced with a N, O or S atom. The term 3- to 7-membered heterocycle also encompasses any heterocycles described by (i) or (ii) which are fused to a benzene ring, or in which any one of the ring carbon atoms comprises a carbonyl group, such as in lactam and lactone ring systems. The non-aromatic 3- to 7-membered heterocycles can be attached via a ring nitrogen, sulfur, or carbon atom. The aromatic 3- to 7-membered heterocycles are attached via a ring carbon atom. Representative examples of a 3- to 7-membered heterocycle group include, but are not limited to, dihydrofuran-2-one, dihydrofuranyl, furanyl, benzofuranyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, benzimidazolyl, indazolyl, indolinlyl, indolyl, indolizinyl, isoindolinyl, isothiazolyl, isoxazolyl, benzisoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, benzoxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, piperazinyl, piperidinyl, pyranyl, benzopyranyl,pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, quinolinyl, isoquinolinyl, quinoxalinyl, phthalazinyl, cinnolinyl, quinolizinyl, quinazolinyl, quinuclidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, benzthiazolyl, thienyl, thienothiazolyl, thienooxazolyl,

thienoimidazolyl, thiomorpholinyl, thiophenyl, benzothiphenyl, triazinyl, and triazolyl. In one embodiment, the 3- to 7-membered heterocycle group is substituted with one or more of the following groups: halo, O-(C_1-C_6 alkyl), OH, CN, COOR', OC(O)R', N(R')$_2$, NHC(O)R' or C(O)NHR' groups wherein each R' is independently H or unsubstituted C_1-C_6 alkyl.

[0037] The term "5- to 7-membered aromatic heterocycle" refers to a 5-, 6-, or 7-membered aromatic monocyclic cycloalkyl in which 1-4 of the ring carbon atoms have been independently replaced with a N, O or S atom. The term 5- to 7-membered aromatic heterocycle also encompasses any heterocycles described which are fused to a benzene ring, or in which any one of the ring carbon atoms comprises a carbonyl group, such as in lactam and lactone ring systems. The 5- to 7-membered aromatic heterocycles are attached via a ring carbon atom. Representative examples of a 5- to 7-membered aryl heterocycle group include, but are not limited to, furanyl, benzofuranyl, furazanyl, imidazolyl, benzimidazolyl, indazolyl, indolyl, indolizinyl, isoindolinyl, isothiazolyl, isoxazolyl, benzisoxazolyl, oxadiazolyl, oxazolidinyl, oxazolyl, benzoxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, pyranyl, benzopyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, quinoxalinyl, phthalazinyl, cinnolinyl, quinolizinyl, quinazolinyl, thiadiazinyl, thiadiazolyl, thiazolyl, benzthiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, and benzothiphenyl. In certain embodiments, the 5- to 7-membered aromatic heterocycle group may be substituted with one or more of the following groups: halo, O-(C_1-C_6 alkyl), OH, CN, COOR', OC(O)R', N(R')$_2$, NHC(O)R' or C(O)NHR' groups wherein each R' is independently H or unsubstituted C_1-C_6 alkyl.

[0038] The term "imaging-effective amount" when used in connection with a Radiolabeled Compound of the present invention or pharmaceutically acceptable salt thereof, is an amount of the compound that is sufficient to produce a visible image when the compound is administered to a subject and the radiation emitted by the compound is detected using positron-emission tomography ("PET") or autoradiography.

[0039] The term "isolated" as used herein means separate from other components of a reaction mixture or natural source. In certain embodiments, the isolate contains at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% of a Radiolabeled Compound of the present invention by weight of the isolate. In one

embodiment, the isolate contains at least 95% of a Radiolabeled Compound of the present invention by weight of the isolate.

[0040] The phrase "pharmaceutically acceptable salt," as used herein, is a salt of an acid and a basic nitrogen group of a Radiolabeled Compound of the present invention. Illustrative salts include, but are not limited to, sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3- naphthoate)) salts. The term "pharmaceutically acceptable salt" also refers to a salt of a Radiolabeled Compound of the present invention having an acidic functional group, such as a carboxylic acid functional group, and a base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or tri-alkylamines, dicyclohexylamine; tributyl amine; pyridine; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-OH-lower alkylamines), such as mono-; bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-*tert*-butylamine, or tris-(hydroxymethyl)methylamine, N,N-di-lower alkyl-N-(hydroxyl-lower alkyl)-amines, such as tri-(2-hydroxyethyl)amine or N,N-dimethyl-N-(2-hydroxyethyl)amine; N-methyl-D-glucamine; or amino acids such as arginine, lysine, and the like. The term "pharmaceutically acceptable salt" also includes a hydrate of a Radiolabeled Compound of the present invention.

[0041] As used herein, a "5-HT_{1A} selective agent" refers to a compound that can selectively interact with the 5-HT_{1A} receptor relative to the other known transporters, receptors, enzymes and proteins. 5-HT_{1A} selective agents include agonists and antagonists that specifically bind to 5-HT_{1A} receptors.

[0042] The term "subject," as used herein, includes, but is not limited to, a non-human animal, such as a cow, monkey, chimpanzee, baboon, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, or guinea pig; and a human. In one embodiment, a monkey is a rhesus. In another embodiment, a subject is a human.

[0043] The term "therapeutically effective amount" when used in connection with a Radiolabeled Compound of the present invention or a pharmaceutically acceptable salt

thereof is an amount that is effective to (i) treat or prevent a psychiatric disorder in a subject, or (ii) stabilize the mood of a subject having a mood disorder.

[0044] The following abbreviations are used herein and have the indicated definitions: n-BuOH is n-butyl alcohol; DMSO is *N*,*N*-dimethylsulfoxide; EtOH is ethanol; Et_3N is triethylamine; Kryptofix® 222 is 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane (Acros Organics, Belgium); mCPBA is m-chloroperbenzoic acid; $MeNH_2$ is methylamine; Ms or mesyl is methanesulfonyl; MS is mass spectrometry; NMR is nuclear magnetic resonance; PEG is polyethylene glycol; py is pyridine; TBAH is tetrabutylammonium hydroxide; Ts or tosyl is -p-toluenesulfonyl; TsCl is p-toluenesulfonyl chloride; Tf or triflyl is trifluoromethanesulfonate; and TMSCN is trimethylsilylcyanide.

The Radiolabeled Compounds

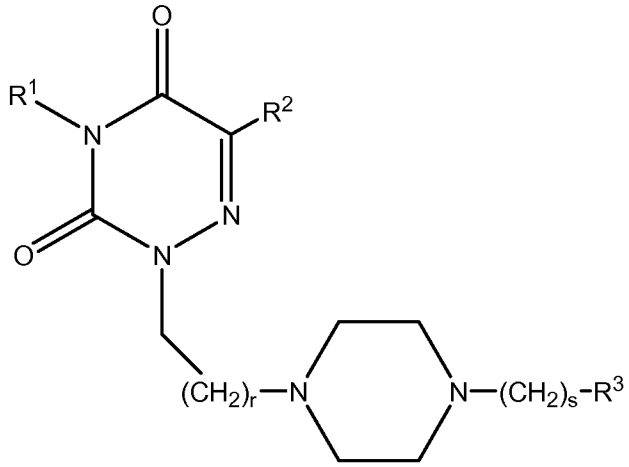
[0045] The Radiolabeled Compounds of the present invention may be useful as imaging agents for one or more 5-HT_{1A} receptors.

[0046] In certain embodiments, the Radiolabeled Compounds of the present invention may have one or more of the following characteristics: (i) high affinity and selectivity for the 5-HT_{1A} receptor compared to the other known transporters, receptors, enzymes and proteins; (ii) sufficient lipophilicity to allow rapid blood-brain-barrier penetration and generation of polar metabolites that do not cross the blood-brain-barrier; and (iii) high specific activity of the radiolabeled groups of the compounds of the present invention.

[0047] It is possible for the Radiolabeled Compounds of the present invention to have one or more chiral centers, and, as such, the Radiolabeled Compounds can exist in various stereoisomeric forms. Accordingly, Formula (I) and Formula (II), although not depicting specific stereoisomers of the Radiolabeled Compounds, are understood to encompass all possible stereoisomers.

The Radiolabeled Compounds of Formula (I)

[0048] As stated above, the present invention encompasses Radiolabeled Compounds having the Formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein R^1, R^2 and R^3 are as defined above for the Radiolabeled Compounds of Formula (I).

[0049] In one embodiment, R^1 is C_1-C_6 alkyl.

[0050] In another embodiment, R^1 is methyl.

[0051] In one embodiment, R^2 is H.

[0052] In another embodiment, R^2 is H, and R^1 is methyl.

[0053] In one embodiment, R^3 is aryl.

[0054] In another embodiment, R^3 is naphthyl.

[0055] In still another embodiment, R^3 is naphthyl substituted with $-O^{11}CH_3$.

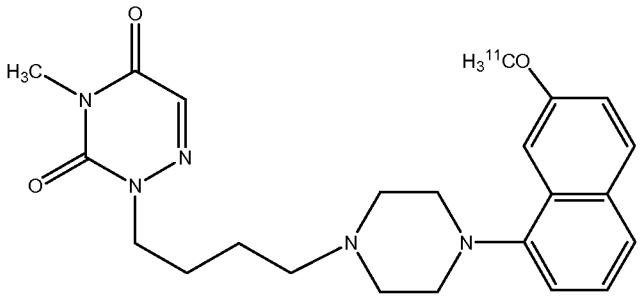
[0056] In one embodiment, r is 3.

[0057] In another embodiment, s is 0.

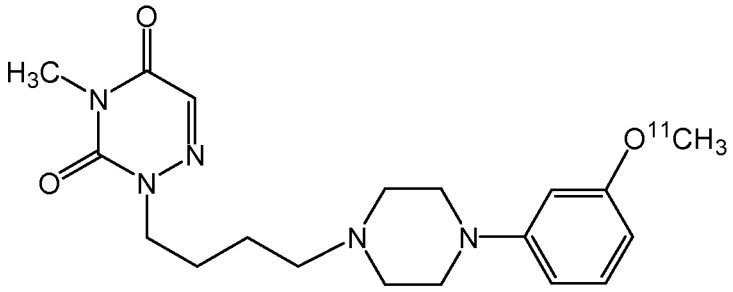
[0058] In still another embodiment, r is 3 and s is 0.

[0059] In yet another embodiment, R^3 is naphthyl substituted with $-O^{11}CH_3$, r is 3, and s is 0.

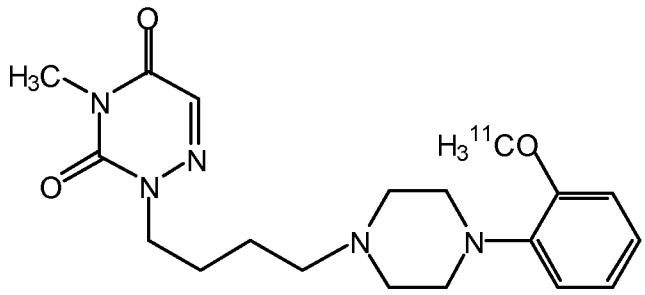
[0060] Illustrative Radiolabeled Compounds of Formula (I)) include the compounds having the structure:



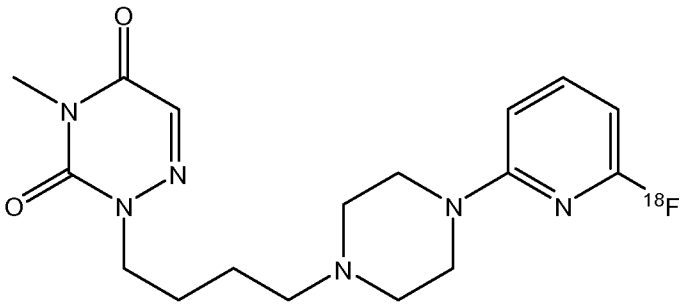
A;



B;



C;



D;

and pharmaceutically acceptable salts thereof.

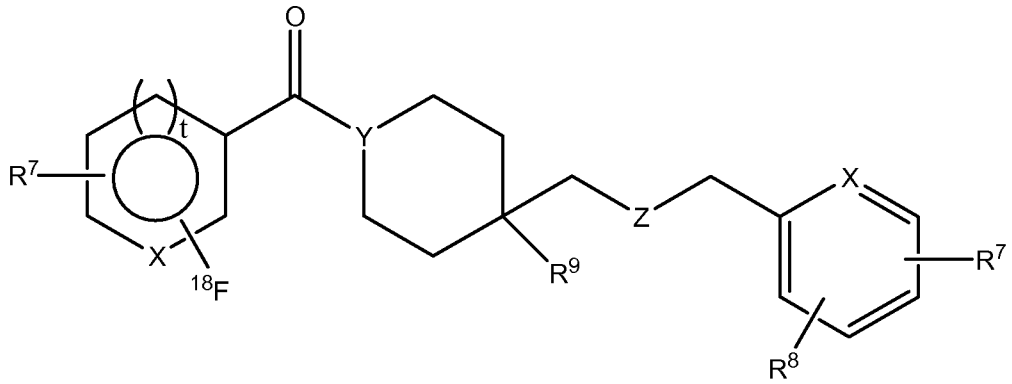
[0061] The Radiolabeled Compounds of Formula (I) can act as agonists or antagonists of the 5-HT_{1A} receptor.

[0062] In one embodiment, a Radiolabeled Compound of Formula (I) is an antagonist of the 5-HT_{1A} receptor.

[0063] In another embodiment, a Radiolabeled Compound of Formula (I) is an agonist of the 5-HT_{1A} receptor.

The Radiolabeled Compounds of Formula (II)

[0064] As stated above, the present invention encompasses Radiolabeled Compounds having the Formula (II):



(II)

or pharmaceutically acceptable salts thereof, wherein X, Y, Z, R^7, R^8, R^9 and t are as defined above for the Radiolabeled Compounds of Formula (II).

[0065] In one embodiments, each R^7 is independently –H, -F, -Cl, a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 5 carbon atoms such as methyl, ethyl, propyl, butyl, pentyl, isopropyl, 1-methyl-ethyl, 1-methyl-propyl, 1-methyl-butyl, 2-methyl-propyl, 2-methyl-butyl, 3-methyl-butyl, 1-ethyl-propyl, or 2-ethyl-propyl; a fluoroalkyl radical such as fluoromethyl, difluoromethyl, trifluoromethyl, $-CH(F)CH_3$ or $-CF_2CH_3$; a cyclopropyl, cyclobutyl, or cyclopentyl radical; a substituted or unsubstituted 5-membered aromatic heterocyclic group containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, such that the heterocycle cannot have more than one sulfur ring atom and one oxygen ring atom; $-OR^{10}$ or $-SR^{10}$ where R^{10} is independently a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 5 carbon atoms, a monofluoromethyl or trifluoromethyl radical, a cyclopropyl radical, a cyclobutyl radical, or a cyclopentyl radical; or an alkoxycarbonyl group such as $–OC(O)CH_3$ or $–OC(O)-CH_2CH_3$.

[0066] In another embodiments, R^8 is $-Z^a-R^{12}$, -H, -F, -Cl, a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 5 carbon atoms such as methyl, ethyl, propyl, butyl, pentyl, isopropyl, 1-methyl-ethyl, 1-methyl-propyl, 1-methyl-butyl, 2-methyl-propyl, 2-methyl-butyl, 3-methyl-butyl, 1-ethyl-propyl, or 2-ethyl-propyl; a fluoroalkyl radical such as fluoromethyl, difluoromethyl, trifluoromethy, $-CH(F)CH_3$ or $-CF_2CH_3$; a cyclopropyl, cyclobutyl, or cyclopentyl radical; a substituted or unsubstituted 5-membered aromatic heterocyclic group containing 1 to 3 heteroatoms selected from

nitrogen, oxygen, and sulfur, such that the heterocycle cannot have more than one sulfur ring atom and one oxygen ring atom; -OR^{10} or –SR^{10} where R^{10} is independently a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 5 carbon atoms, a monofluoromethyl or trifluoromethyl radical, a cyclopropyl radical, a cyclobutyl radical, or a cyclopentyl radical; or an alkoxycarbonyl group such as $OC(O)CH_3$ or $–OC(O)-CH_2CH_3$.

[0067] In still another embodiment, R^{12} is -(^{11}C-labeled C_1-C_6 alkyl, -(^{11}C-labeled C_2-C_6 alkenyl, -(^{11}C-labeled C_2-C_6 alkynyl, -(^{11}C-labeled C_1-C_6 alkylene)-aryl, -(^{11}C-labeled C_2-C_6 alkenylene)-aryl, or -(^{11}C-labeled C_2-C_6 alkynylene)-aryl.

[0068] In a further embodiment, Z^a is –O-, -S-, or –NH-.

[0069] In another embodiment, R^9 is -H or -F.

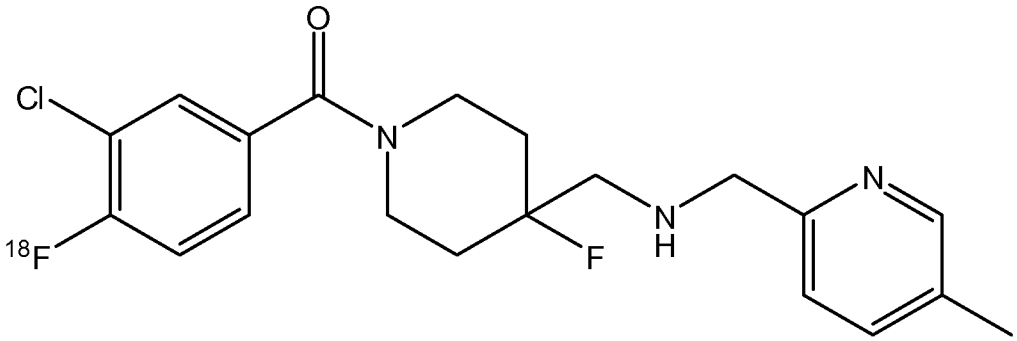
[0070] In still another embodiment X is –N-.

[0071] In yet another embodiment Y is -N-.

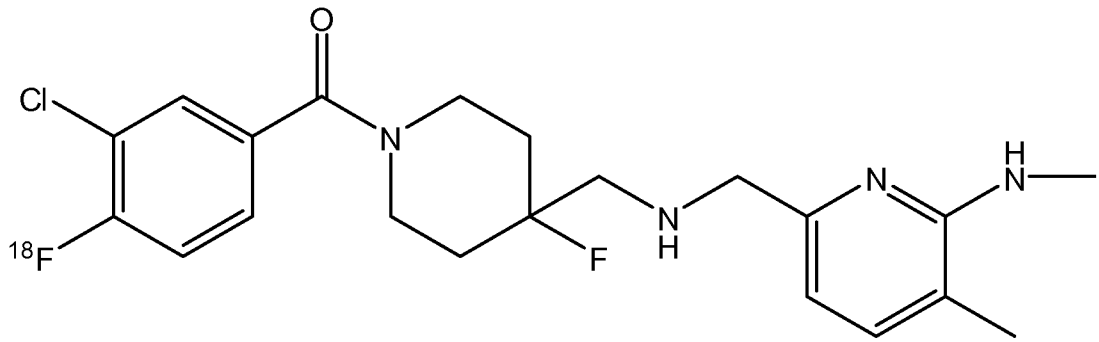
[0072] In a further embodiment Z is –NH-.

[0073] In another embodiment t is 1.

[0074] Illustrative Radiolabeled Compounds of Formula (II) include the compounds having the structure:



E; and



F;

and pharmaceutically acceptable salts thereof.

[0075] The Radiolabeled Compounds of Formula (II) can act as agonists or antagonists of the 5-HT_{1A} receptor.

[0076] In one embodiment, a Radiolabeled Compound of Formula (II) is an antagonist of the 5-HT_{1A} receptor.

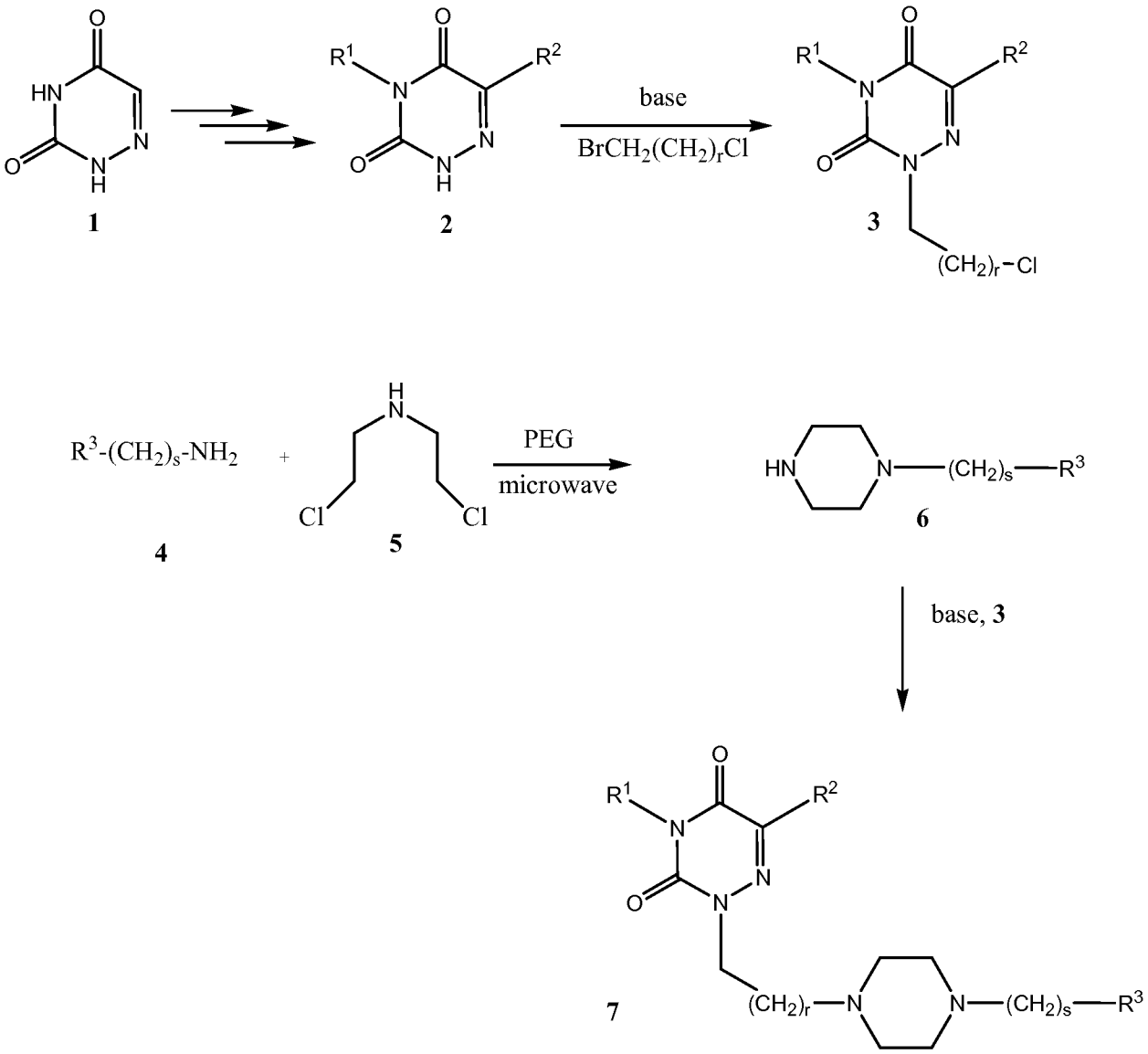
[0077] In another embodiment, a Radiolabeled Compound of Formula (II) is an agonist of the 5-HT_{1A} receptor.

Methods for Making the Radiolabeled Compounds of Formula (I)

[0078] The Radiolabeled Compounds of Formula (I) can be made using the synthetic procedures outlined below in Schemes 1-3.

[0079] Scheme 1 shows methods for making the Radiolabeled Compounds of Formula (I).

Scheme 1



wherein r, s, R^1, R^2 and R^3 are defined above for the Compounds of Formula (I).

The heterocyclic compound **1** can be used as is or can be derivatized using methods well-known to one of ordinary skill in the art of organic synthesis to prepare compounds of formula **2** wherein one or both of R^1 and R^2 are other than hydrogen. The compounds of Formula **2** are then alkylated using an alkylating agent of Formula $BrCH_2(CH_2)_rCl$ in the presence of a base to provide the synthetic intermediates of Formula **3**.

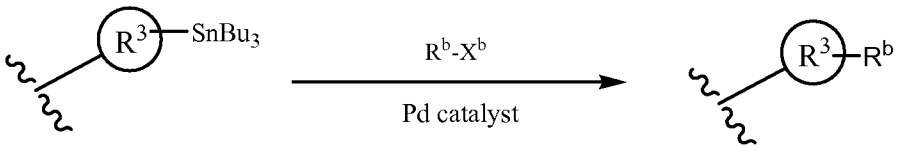
An amine of Formula **4** can be reacted with di-(2-chloroethyl)amine using microwave irradiation to provide the piperazine intermediates of formula **6**. Finally, a compound of Formula **6** is coupled with a compound of Formula **3** in the presence of a base to provide the Compounds of Formula **7**.

It will be apparent to one of ordinary skill in the art that radiolabeled group R^6, which is a substituent on group R^3 in the compounds of Formula (I) may be present in the compounds of Formula **4** or alternatively may be absent from the compounds of Formula **4**. In the latter case, the radiolabeled group R^6 may be attached to group R^3 in any step of the synthesis, or alternatively, may be attached to an intact compound of Formula **7**.

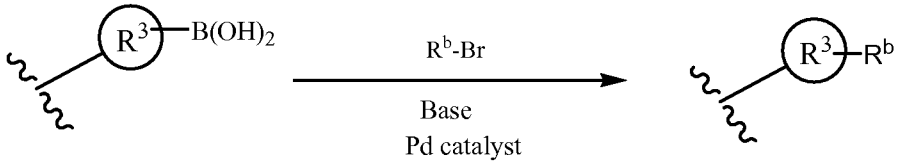
[0080] Scheme 2 shows methods for attaching the following radiolabeled groups to the R^3 group of a precursor to a Radiolabeled Compound of Formula (I): ^{11}C-labeled C_1-C_6 alkyl, ^{11}C-labeled C_2-C_6 alkenyl, ^{11}C-labeled C_2-C_6 alkynyl, (^{11}C-labeled C_1-C_6 alkylene)-aryl, (^{11}C-labeled C_2-C_6 alkenylene)-aryl, (^{11}C-labeled C_2-C_6 alkynylene)-aryl, ^{18}F-labeled C_1-C_6 alkyl, ^{18}F-labeled C_2-C_6 alkenyl, ^{18}F-labeled C_2-C_6 alkynyl, (^{18}F-labeled C_1-C_6 alkylene)-aryl, (^{18}F-labeled C_2-C_6 alkenylene)-aryl, or (^{18}F-labeled C_2-C_6 alkynylene)-aryl.

Scheme 2

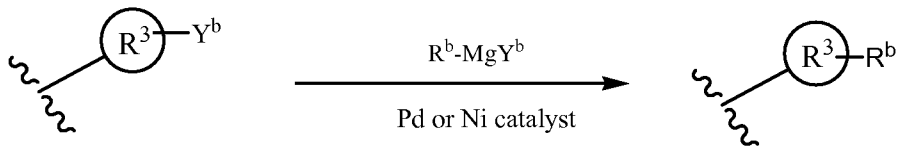
Stille-Type Coupling



Suzuki-Type Coupling



Kumada-Type Coupling



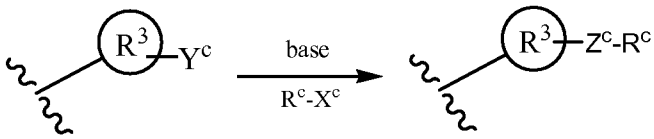
wherein R^3 is defined above for the Radiolabeled Compounds of Formula (I); X^b is Cl, Br, I, or OTf; Ra is ^{11}C-labeled C_1-C_6 alkyl, ^{11}C-labeled C_2-C_6 alkenyl, ^{11}C-labeled C_2-C_6 alkynyl, (^{11}C-labeled C_1-C_6 alkylene)-aryl, (^{11}C-labeled C_2-C_6 alkenylene)-aryl,

(^{11}C-labeled C_2-C_6 alkynylene)-aryl, ^{18}F-labeled C_1-C_6 alkyl, ^{18}F-labeled C_2-C_6 alkenyl, ^{18}F-labeled C_2-C_6 alkynyl, (^{18}F-labeled C_1-C_6 alkylene)-aryl, (^{18}F-labeled C_2-C_6 alkenylene)-aryl, or (^{18}F-labeled C_2-C_6 alkynylene)-aryl; and each occurrence of Y^b is independently Cl, Br, or I.

[0081] An R^3 group of a precursor to a Radiolabeled Piperazine Compound of formula (I) can be substituted with a radiolabeled group at any point during the synthetic route outlined in Scheme 1. As outlined in Scheme 2, the unlabeled R^3 group of a Compound of formula **4**, **6** or **7** as shown in Scheme 1 can be subjected to a palladium- or nickel-catalyzed coupling process including, but not limited to a Suzuki coupling (A. Suzuki, *Pure Appl. Chem.* 1991, 63:419-422), a Kumada coupling (M. Kumada, *Pure Appl. Chem.* 1980, 52:669), or a Stille coupling (J.K. Stille, *Angew. Chem. Int. Ed.* 1986, 25:508-524) process to provide a product which contains an R^3 group that is substituted with any of the following radiolabeled groups: -^{11}C-labeled C_1-C_6 alkyl, -^{11}C-labeled C_2-C_6 alkenyl, -^{11}C-labeled C_2-C_6 alkynyl, -(^{11}C-labeled C_1-C_6 alkylene)-aryl, -(^{11}C-labeled C_2-C_6 alkenylene)-aryl, -(^{11}C-labeled C_2-C_6 alkynylene)-aryl, -^{18}F-labeled C_1-C_6 alkyl, -^{18}F-labeled C_2-C_6 alkenyl, -^{18}F-labeled C_2-C_6 alkynyl, -(^{18}F-labeled C_1-C_6 alkylene)-aryl, -(^{18}F-labeled C_2-C_6 alkenylene)-aryl, or -(^{18}F-labeled C_2-C_6 alkynylene)-aryl.

[0082] Scheme 3 shows methods for attaching radiolabeled groups of formula Z^c-R^c to an R^3 group of a precursor to a Radiolabeled Compound of Formula (I), wherein Z^c is O, S, or NH; and R^c is ^{11}C-labeled C_1-C_6 alkyl, ^{11}C-labeled C_2-C_6 alkenyl, ^{11}C-labeled C_2-C_6 alkynyl, (^{11}C-labeled C_1-C_6 alkylene)-aryl, (^{11}C-labeled C_2-C_6 alkenylene)-aryl, (^{11}C-labeled C_2-C_6 alkynylene)-aryl, ^{18}F-labeled C_1-C_6 alkyl, ^{18}F-labeled C_2-C_6 alkenyl, ^{18}F-labeled C_2-C_6 alkynyl, (^{18}F-labeled C_1-C_6 alkylene)-aryl, (^{18}F-labeled C_2-C_6 alkenylene)-aryl, or (^{18}F-labeled C_2-C_6 alkynylene)-aryl.

Scheme 3



wherein R^3 is defined above for the Radiolabeled Compounds of Formula (I); R^c is ^{11}C-labeled C_1-C_6 alkyl, ^{11}C-labeled C_2-C_6 alkenyl, ^{11}C-labeled C_2-C_6 alkynyl,

(^{11}C-labeled C_1-C_6 alkylene)-aryl, (^{11}C-labeled C_2-C_6 alkenylene)-aryl, (^{11}C-labeled C_2-C_6 alkynylene)-aryl,), ^{18}F-labeled C_1-C_6 alkyl, ^{18}F-labeled C_2-C_6 alkenyl, ^{18}F-labeled C_2-C_6 alkynyl, (^{18}F-labeled C_1-C_6 alkylene)-aryl, (^{18}F-labeled C_2-C_6 alkenylene)-aryl, or (^{18}F-labeled C_2-C_6 alkynylene)-aryl; X^c is Cl, Br, I, OMs, OTs, or OTf; Y^c is OH, SH, or NH_2; and Z^c is O, S, or NH.

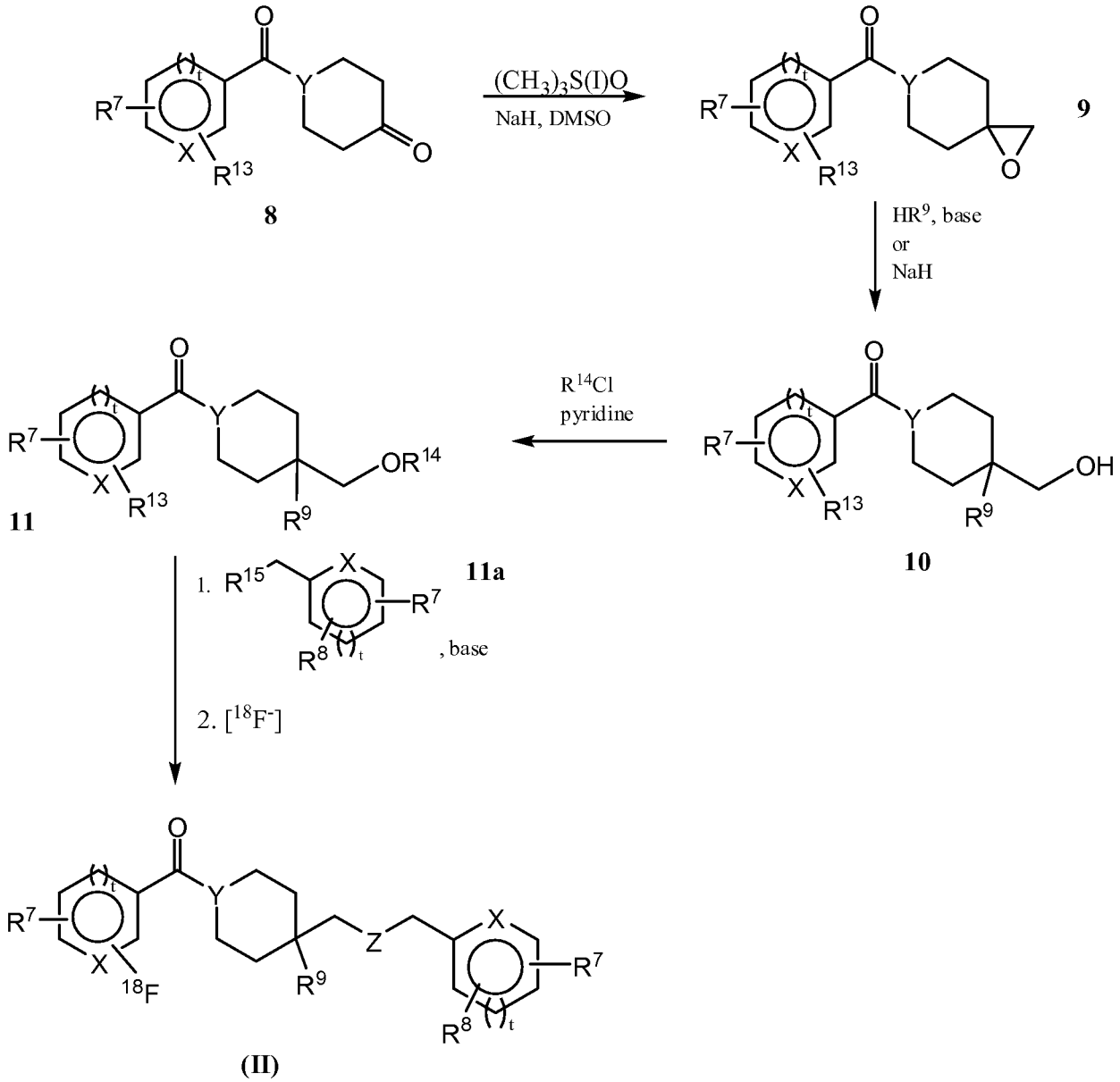
[0083] An OH, NH_2, or SH group attached to an R^3 group of a compound of Formula **4**, **6** or **7** as shown in Scheme 1 can be treated with base and the resulting oxygen, sulfur, or nitrogen anion can be reacted with a group having the formula R^c-X^c, wherein X^c is Cl, Br, I, OMs, OTs, or OTf, to provide a product which contains an R^3 group that is substituted with a radiolabeled group of formula Z^c-R^c, wherein Z^c is O, S, or NH; and R^c is ^{11}C-labeled C_1-C_6 alkyl, ^{11}C-labeled C_2-C_6 alkenyl, ^{11}C-labeled C_2-C_6 alkynyl, (^{11}C-labeled C_1-C_6 alkylene)-aryl, (^{11}C-labeled C_2-C_6 alkenylene)-aryl, (^{11}C-labeled C_2-C_6 alkynylene)-aryl, ^{18}F-labeled C_1-C_6 alkyl, ^{18}F-labeled C_2-C_6 alkenyl, ^{18}F-labeled C_2-C_6 alkynyl, (^{18}F-labeled C_1-C_6 alkylene)-aryl, (^{18}F-labeled C_2-C_6 alkenylene)-aryl, or (^{18}F-labeled C_2-C_6 alkynylene)-aryl.

[0084] Radiolabeled compounds of Formula (I) that can be made using the methods of the invention include the compound having the Formula (A), (B), and pharmaceutically acceptable salts thereof.

Methods for Making the Radiolabeled Compounds of Formula (II)

[0085] The Radiolabeled Compounds of Formula (II) can be made using the synthetic procedures outlined in Scheme 4 below.

Scheme 4


(CH3)3S(I)O
NaH, DMSO
HR9, base
or
NaH
R14Cl
pyridine
1. R15
, base
2. [18F-]
8
9
10
11
11a
(II)

wherein R^7, R^8, R^9, X, Y, Z, and t are defined above for the Radiolabeled Compounds of Formula (II); R^{13} is -F or $-NO_2$; R^{14} is –mesyl, -tosyl or –triflyl; and R^{15} is –OH, –SH, or $–NH_2$.

[0086] A compound of Formula **8** can be reacted with trimethylsulfoxonium iodide in the presence of NaH to provide an epoxide compound of formula **9**. The epoxide ring of Formula **9** can then be reacted with: (1) a compound of formula HR^9 in the presence of a base, where R^9 is -halo to provide a compound of Formula **10** wherein R^9 is –halo; or (2) NaH to provide a compound of Formula **10** wherein R^9 is –H. The hydroxyl group of a compound of Formula **10** can be converted to a leaving group by reacting with a compound of formula $R^{14}Cl$ in the presence of a non-nucleophilic base, such as pyridine to provide a compound of Formula **11**. Finally, a compound of Formula **11** can be coupled with a compound of Formula **11a** in the presence of base and the resultant adduct can then be reacted with Kryptofix 222/[^{18}F] and potassium carbonate as described in de Vries *et al.*, *Journal of Nuclear Medicine* 2003, 44:1700-1706, to provide the Radiolabeled Compounds of Formula (II).

Uses of the Radiolabeled Compounds as Radiological Imaging Agents

[0087] The Radiolabeled Compounds can be used as imaging agents to image one or more 5-HT_{1A} receptors in a subject.

[0088] In one embodiment, the present invention relates to the use of a Radiolabeled Compound for detecting one or more 5-HT_{1A} receptors *in vivo*. In particular, the present methods for detecting 5-HT_{1A} receptors *in vivo* contemplate the use of PET, where the imaging probe is a Radiolabeled Compound of the present invention.

[0089] In another embodiment, the invention provides a method for imaging one or more 5-HT_{1A} receptors in a subject comprising the steps: (a) administering to the subject an imaging-effective amount of a Radiolabeled Compound or pharmaceutically acceptable salt thereof, and (b) detecting the radioactive emission of the compound or salt thereof administered in step (a).

[0090] In one embodiment, the detecting of step (b) is carried out using PET.

[0091] In another embodiment, the 5-HT_{1A} receptors being imaged are in the brain of the subject.

[0092] Methods for imaging, and thereby detecting, 5-HT_{1A} receptors *in vivo* are desirable in order to screen individuals for psychiatric neurological disorders or for diseases,

disorders, states or conditions that are related to the binding of serotonin to 5-HT_{1A} receptors. For example, the following list of processes, diseases or disorders may involve alterations in normal binding of serotonin to 5-HT_{1A} receptors: mood disorders, such as a major depressive disorder or bipolar disorder; an eating disorder, such as anorexia nervosa or bulemia; an addictive disorder, such as drug addiction, alcoholism, or sexual addiction; a sleep disorder, such as insomnia or narcolepsy; a disease associated with cognitive dysfunction, such as Alzheimer's disease; a neurodegenerative disease, such as stroke; a pain disorder, including neuropathic pain or cancer pain; psychotic disorders such as schizophrenia; a movement disorder, such as Parkinson's disease; an anxiety disorder such as panic disorder, or obsessive-compulsive disorder or social phobia; a seizure disorder, such as temporal lobe epilepsy. Further, Radiolabeled Compounds of the present invention which are selective for the 5-HT_{1A} receptor can be used to screen for individuals who are more likely to respond to drugs that act on these receptors or susceptible to side effects of drugs which bind to the 5-HT_{1A} receptor, as manifested by an increased detection of radiolabeled 5-HT_{1A} selective agents in specified tissue compartments. These compounds can used to identify the dose range of drugs to treat illnesses and disorders that work by binding to this receptor.

[0093] In one embodiment, the Radiolabeled Compounds have high specific activity. In one embodiment, the invention provides Radiolabeled Compounds having a specific activity that is greater than about 1000 Ci/micromole.

[0094] Further, the Radiolabeled Compounds may have a high affinity and specificity to the 5-HT_{1A} receptor. In one embodiment, the Radiolabeled Compounds have a 5-HT_{1A} receptor binding affinity that is from about 20 to about 100,000 greater than the binding affinity for any of the other known transporters, receptors, enzymes, and peptides.

[0095] The Radiolabeled Compounds of the present invention can be used to detect and/or quantitatively measure 5-HT_{1A} receptor levels in subjects, including humans. The Radiolabeled Compounds of the present invention can also be used to measure and/or detect 5-HT_{1A} receptors in 5-HT_{1A} receptor related diseases, conditions and disorders, including but not limited to, mood disorders, such as a major depressive disorder or bipolar disorder; an eating disorder, such as anorexia nervosa or bulemia; an addictive disorder, such as drug addiction, alcoholism, or sexual addiction; a sleep disorder, such as insomnia or narcolepsy; a disease associated with cognitive dysfunction, such as Alzheimer's disease; a neurodegenerative disease, such as stroke; a pain disorder, including neuropathic pain or cancer pain; psychotic disorders such as schizophrenia; a movement disorder, such as

Parkinson's disease; an anxiety disorder such as panic disorder, or obsessive-compulsive disorder or social phobia; a seizure disorder, such as temporal lobe epilepsy.

[0096] The ability to quantitatively measure 5-HT_{1A} receptor levels in a subject is useful for pre-screening subjects and in one embodiment, a Radiolabeled Compound of the present invention can be administered to a subject to help determine whether the subject is likely to be a responder or non-responder to medicinal agents which bind 5-HT_{1A} receptors. The ability to quantitatively measure 5-HT_{1A} receptor levels in a subject is useful for pre-screening clinical trial patient populations.

[0097] The Radiolabeled Compounds of the present invention can be used to detect or monitor processes, diseases or disorders that may involve the binding of serotonin to 5-HT_{1A} receptors, including but not limited to, a mood disorder, such as a major depressive disorder or bipolar disorder; an eating disorder, such as anorexia nervosa or bulemia; an addictive disorder, such as drug addiction, alcoholism, or sexual addiction; a sleep disorder, such as insomnia or narcolepsy; a disease associated with cognitive dysfunction, such as Alzheimer's disease; a neurodegenerative disease, such as stroke; a pain disorder, including neuropathic pain or cancer pain; a psychotic disorder, such as schizophrenia; a movement disorder, such as Parkinson's disease; an anxiety disorder such as panic disorder, or obsessive-compulsive disorder or social phobia; a seizure disorder, such as temporal lobe epilepsy.

[0098] The Radiolabeled Compounds of the present invention can also be used to help determine the capacity that one or more 5-HT_{1A} receptors have for signaling. In this embodiment, the present methods for imaging 5-HT_{1A} receptors can be used to determine the percentage of 5-HT_{1A} receptors that are at high affinity state. In a specific embodiment, the Radiolabeled Compound of the present invention being administered for imaging one or more 5-HT_{1A} receptors, is an agonist of the 5-HT_{1A} receptor.

[0099] Further, the Radiolabeled Compounds of the present invention can be used to screen for individuals who are more susceptible to side effects of agents which bind to 5-HT_{1A} receptors, as manifested by an increased detection of the Radiolabeled Compounds of the present invention in specified tissue compartments.

[0100] Additionally, the Radiolabeled Compounds of the present invention are useful in drug discovery programs and in one embodiment, can be used to determine the efficacy of agents that bind to 5-HT_{1A} receptors when such agents are administered to a subject to treat a disorder whose etiology involves the binding of serotonin to one or more 5-HT_{1A} receptors. In another embodiment, the Radiolabeled Compounds of the present invention can be used to

monitor the occupancy rate of 5-HT_{1A} receptors in a subject after the subject has been administered an agent which binds to 5-HT_{1A} receptors. In one embodiment, the occupancy rate of 5-HT_{1A} receptors for experimental drugs can be used to help determine optimal dosage levels of such drugs. In so far as the Radiolabeled Compound of the present invention is an agonist, it has special advantages in quantifying the receptor occupancy of potential new therapeutic agents that are also agonists and therefore in determining the optimal dose to use for those agents as part of an Investigational New Drug (IND) application process and thereby shorten the time period to acquire data for regulatory approval for marketing and general use in treatment. When the Radiolabeled Compound of the present invention is an agonist it will also aid the study and diagnosis of disease by being more sensitive to the quantification of serotonin release and depletion.

[0101] Alternatively, the methods for detection can be used to monitor the course of a 5-HT_{1A} receptor related disease in an individual. Thus, whether a particular therapeutic regimen aimed at ameliorating the cause of the disease, or the disease process itself, is effective, can be determined by measuring the decrease of 5-HT_{1A} receptors at suspected sites of disease.

[0102] In a further embodiment, the present methods for imaging one or more 5-HT_{1A} receptors can provide images of the location of 5-HT_{1A} receptors and serve as a guide to surgeons who are operating in the area of such receptors. In one embodiment, the surgeon is a neurosurgeon operating on the brain of a subject.

Uses of the Radiolabeled Compounds to Treat or Prevent a Psychiatric Disorder

[0103] A psychiatric disorder can be treated or prevented by administration of a therapeutically effective amount of a Radiolabeled Compound of the present invention.

[0104] Psychiatric disorders that can be treated or prevented by administering a therapeutically effective amount of a Radiolabeled Compound of the present invention include, but are not limited to, a mood disorder, such as a major depressive disorder, bipolar disorder, manic depression, depression, cyclothymia, dysthymia, or borderline personality disorder; an eating disorder, such as anorexia nervosa or bulemia; an addictive disorder, such as drug addiction, alcoholism, or sexual addiction; a sleep disorder, such as insomnia or narcolepsy; a disease associated with cognitive dysfunction, such as Alzheimer's disease; a neurodegenerative disease, such as stroke; a pain disorder, including neuropathic pain or cancer pain; psychotic disorders such as schizophrenia; a movement disorder, such as

Parkinson's disease; an anxiety disorder such as panic disorder, or obsessive-compulsive disorder or social phobia; a seizure disorder, such as temporal lobe epilepsy.

[0105] In one embodiment, the psychiatric disorder is a mood disorder.

[0106] In another embodiment, the psychiatric disorder is an eating disorder.

[0107] In another embodiment, the psychiatric disorder is an addictive disorder.

[0108] In another embodiment, the psychiatric disorder is a disease associated with cognitive dysfunction.

[0109] In a specific embodiment, the psychiatric disorder is Alzheimer's disease.

[0110] In still another embodiment, the psychiatric disorder is a neurodegenerative disease.

[0111] In yet another embodiment, the psychiatric disorder is a pain disorder.

[0112] In another embodiment, the psychiatric disorder is a psychotic disorder.

[0113] In one embodiment, the psychiatric disorder is a movement disorder.

[0114] In another embodiment, the psychiatric disorder is an anxiety disorder.

[0115] In still another embodiment, the psychiatric disorder is a seizure disorder.

[0116] In yet another embodiment, the psychiatric disorder is an obsessive-compulsive disorder.

Uses of the Radiolabeled Compounds to Stabilize the Mood of a Subject Having a Mood Disorder

[0117] The mood of a subject having a mood disorder can be stabilized by administration of a therapeutically effective amount of a Radiolabeled Compound of the present invention.

[0118] Mood disorders in which the Radiolabeled Compounds of the present invention are useful for stabilizing the mood include, but are not limited to, a major depressive disorder, bipolar disorder, manic depression, depression, cyclothymia, dysthymia, and borderline personality disorder.

[0119] In one embodiment, the mood disorder is a major depressive disorder.

[0120] In another embodiment, the mood disorder is bipolar disorder.

[0121] Examples of conditions treatable or preventable using the Radiolabeled Compounds of the present invention include, but are not limited to, an eating disorder, such as anorexia nervosa or bulemia; drug addiction, alcoholism, or sexual addiction; a sleep disorder, such as insomnia or narcolepsy; a disease associated with cognitive dysfunction, such as Alzheimer's disease; a neurodegenerative disease, such as stroke; a pain disorder,

including neuropathic pain or cancer pain; psychotic disorders such as schizophrenia; a movement disorder, such as Parkinson's disease; an anxiety disorder such as panic disorder, or obsessive-compulsive disorder or social phobia; or a seizure disorder, such as temporal lobe epilepsy.

Therapeutic/Diagnostic Administration of the Radiolabeled Compounds

[0122] The Radiolabeled Compounds of the present invention are advantageously useful in veterinary and human medicine. As described above, the Radiolabeled Compounds of the present invention are useful for imaging 5-HT_{1A} receptors in a subject.

[0123] When administered to a subject, the Radiolabeled Compounds of the present invention can be administered as a component of a composition that comprises a physiologically acceptable carrier or vehicle. The present compositions, which comprise a Radiolabeled Compound of the present invention, can be administered orally or by any other convenient route, for example, by infusion or bolus injection, or by absorption through epithelial or mucocutaneous linings (*e.g.*, oral, rectal, and intestinal mucosa, *etc.*) and can be administered together with another biologically active agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.*, and can be administered.

[0124] Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. In some instances, administration will result in the release of the Radiolabeled Compounds of the present invention into the bloodstream. The mode of administration is left to the discretion of the practitioner.

[0125] In one embodiment, the Radiolabeled Compounds of the present invention are administered orally.

[0126] In another embodiment, the Radiolabeled Compounds of the present invention are administered intravenously.

[0127] In another embodiment, the Radiolabeled Compounds of the present invention are administered transdermally.

[0128] In other embodiments, it can be desirable to administer the Radiolabeled Compounds of the present invention locally. This can be achieved, for example, and not by way of limitation, by local infusion during surgery, by injection, by means of a catheter, by

means of a suppository or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

[0129] In certain embodiments, it can be desirable to introduce the Radiolabeled Compounds of the present invention into the central nervous system or gastrointestinal tract by any suitable route, including intraventricular, intrathecal, and epidural injection, and enema. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

[0130] Pulmonary administration can also be employed, *e.g.*, by use of an inhaler of nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or a synthetic pulmonary surfactant.

[0131] In another embodiment the Radiolabeled Compounds of the present invention can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science* 249:1527-1533 (1990) and *Liposomes in the Therapy of Infectious Disease and Cancer, pp.* 317-327 and 353-365 (1989)).

[0132] In yet another embodiment the Radiolabeled Compounds of the present invention can be delivered in a controlled-release system or sustained-release system (*see*, *e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled or sustained-release systems discussed in the review by Langer, *Science* 249:1527-1533 (1990) can be used. In one embodiment a pump can be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); and Saudek *et al.*, *N. Engl. J Med.* 321:574 (1989)). In another embodiment polymeric materials can be used (see *Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 2:61 (1983); Levy *et al.*, *Science* 228:190 (1935); During *et al.*, *Ann. Neural.* 25:351 (1989); and Howard *et al.*, *J. Neurosurg.* 71:105 (1989)).

[0133] The present compositions can optionally comprise a suitable amount of a physiologically acceptable excipient so as to provide the form for proper administration of a Radiolabeled Compound of the present invention to the subject.

[0134] Such physiologically acceptable excipients can be liquids, such as water for injection, bactereostatic water for injection, sterile water for injection, and oils, including those of petroleum, subject, vegetable, or synthetic origin, such as peanut oil, soybean oil,

mineral oil, sesame oil and the like. The pharmaceutical excipients can be saline, gum acacia; gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment the physiologically acceptable excipients are sterile when administered to a subject. Water is a particularly useful excipient when the Radiolabeled Compound of the present invention is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[0135] The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills; pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions. aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment the composition is in the form of a capsule (see *e.g.* U.S. Patent No. 5,698,155). Other examples of suitable physiologically acceptable excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro eds., 19th ed. 1995), incorporated herein by reference.

[0136] In one embodiment the Radiolabeled Compounds are formulated in accordance with routine procedures as a composition adapted for oral administration to human beings. Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment the excipients are of pharmaceutical grade.

[0137] In one embodiment, when a Radiolabeled Compound is orally administered, the Radiolabeled Compound is administered in combination with an additional therapeutic agent that can increase the oral bioavailability of the Radiolabeled Compound, as described, for example, in U.S. Patent No. 6,008,222. The additional therapeutic agent may be administered separately from the Radiolabeled Compound or the additional agent and the Radiolabeled Compound may be co-administered as part of the same composition. In a specific embodiment, the additional agent that increases the oral bioavailability of a Radiolabeled Compound is nefazodone.

[0138] In another embodiment the Radiolabeled Compounds can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lignocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized-powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the Radiolabeled Compounds are to be administered by infusion, they can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the Radiolabeled Compounds are administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

[0139] The Radiolabeled Compounds can be administered by controlled-release or sustained-release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,431,922; 5,354;556; and 5,733,556, each of which is incorporated herein by reference. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those skilled in the art, including those described herein, can be readily selected for use with the Radiolabeled Compounds of the invention. The invention

thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release. The invention also encompasses transdermal delivery devices, including but not limited to, a transdermal patch and other devices, such as those described in U.S. Patent No. 5,633,009.

[0140] In one embodiment a controlled- or sustained-release composition comprises a minimal amount of a Radiolabeled Compound to image one or more 5-HT_{1A} receptors in a subject. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased subject compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Radiolabeled Compound, and can thus reduce the occurrence of adverse side effects.

[0141] Controlled- or sustained-release compositions can initially release an amount of a Radiolabeled Compound that promptly produces the desired diagnostic effect, and gradually and continually release other amounts of the Radiolabeled Compound to maintain this level of diagnostic effect over an extended period of time. To maintain a constant level of the Radiolabeled Compound in the body, the Radiolabeled Compound can be released from the dosage form at a rate that will replace the amount of Radiolabeled Compound being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions.

[0142] The amount of the Radiolabeled Compound that is effective as an imaging agent to detect one or more 5-HT_{1A} receptors in a subject can be determined using standard clinical and nuclear medicine techniques. In addition, *in vitro* or *in vivo* testing can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on certain factors - the route of administration, the identity of the subject and the identity of the particular radionuclide being detected- and should be decided according to the judgment of the practitioner and each subject's circumstances in view of, *e.g.*, published clinical studies. Suitable imaging-effective dosage amounts, however, range from about about 0.01 mCi to about 30 mCi; about 2 mCi to about 30 mCi; about 10 to about 30mCi or preferably from about 2 mCi to about 5 mCi. The Radiolabeled Compounds will have a specific activity of >1000 Ci/micromol at the time of administration to insure a low injected

mass and adequate counts for imaging. The imaging-effective dosage amounts described herein refer to total amounts administered; that is, if more than one dose of a Radiolabeled Compound is administered, the imaging-effective dosage amounts correspond to the total amount administered.

Kits

[0143] The invention encompasses kits that can simplify the administration of a Radiolabeled Compound to a subject.

[0144] A typical kit of the invention comprises a unit dosage form of a Radiolabeled Compound.

[0145] In one embodiment the unit dosage form is within a container, which can be sterile, containing a therapeutically effective amount of a Radiolabeled Compound and a physiologically acceptable carrier or vehicle. The kit can further comprise a label or printed instructions instructing the use of the Radiolabeled Compound to (i) treat or prevent a psychiatric disorder in a subject, or (ii) stabilize the mood of a subject having a mood disorder..

[0146] In another embodiment the unit dosage form is within a container, which can be sterile, containing an imaging-effective amount of a Radiolabeled Compound and a physiologically acceptable carrier or vehicle. The kit can further comprise a label or printed instructions instructing the use of the Radiolabeled Compound as an imaging agent in order to image or detect one or more 5-HT_{1A} receptors in a subject.

[0147] Kits of the invention can further comprise a device that is useful for administering the unit dosage forms. Examples of such a device include, but are not limited to, a syringe, a drip bag, a patch, an inhaler, and an enema bag.

EXAMPLES

[0148] The following examples are set forth to assist in understanding the invention and should not, of course, be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

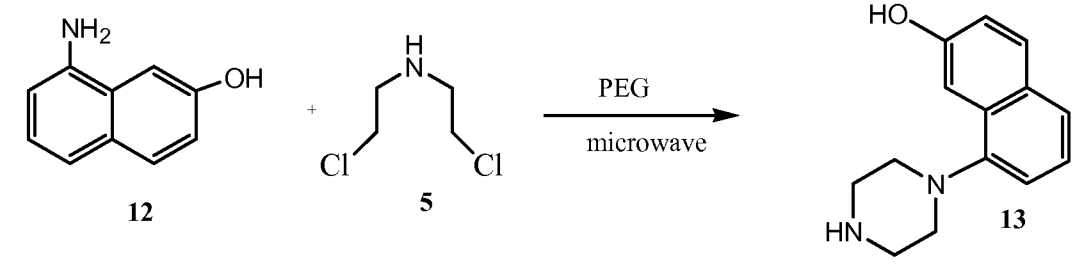
General Methods

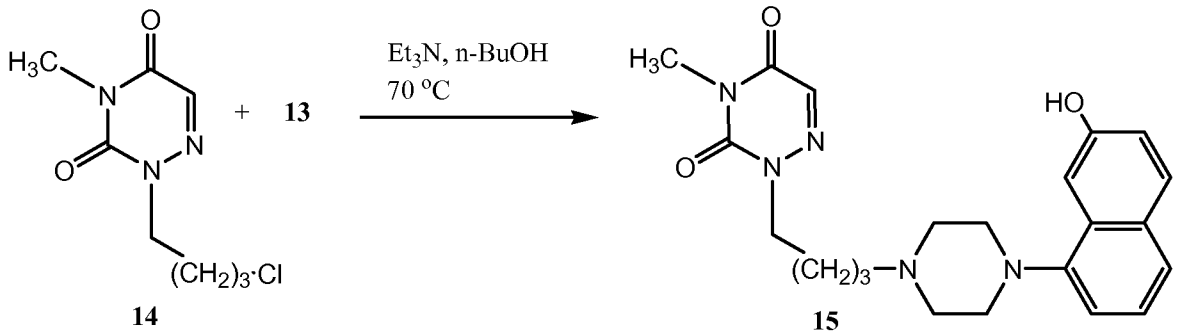
[0149] Proton nuclear magnetic resonance (NMR) spectra were obtained from Bruker PPX 300 and 400 MHz spectrophotometer. Spectra are recorded in $CDCl_3$ and the chemical shifts are reported in parts per million relative to TMS for ^1H NMR as internal standards. The mass spectra were recorded on JKS-HX 11UHF/HX110 HF Tandem Mass Spectrometer in the FAB+ mode. Flash column chromatography was performed on silica gel (Fisher 200-400 mesh) using the solvent system indicated. The radiochemical and chemical purities were analyzed by RP-HPLC with PDA and NaI detectors.

Example 1

Preparation of Compound A

*Step A: Preparation of Intermediate Compound **15***

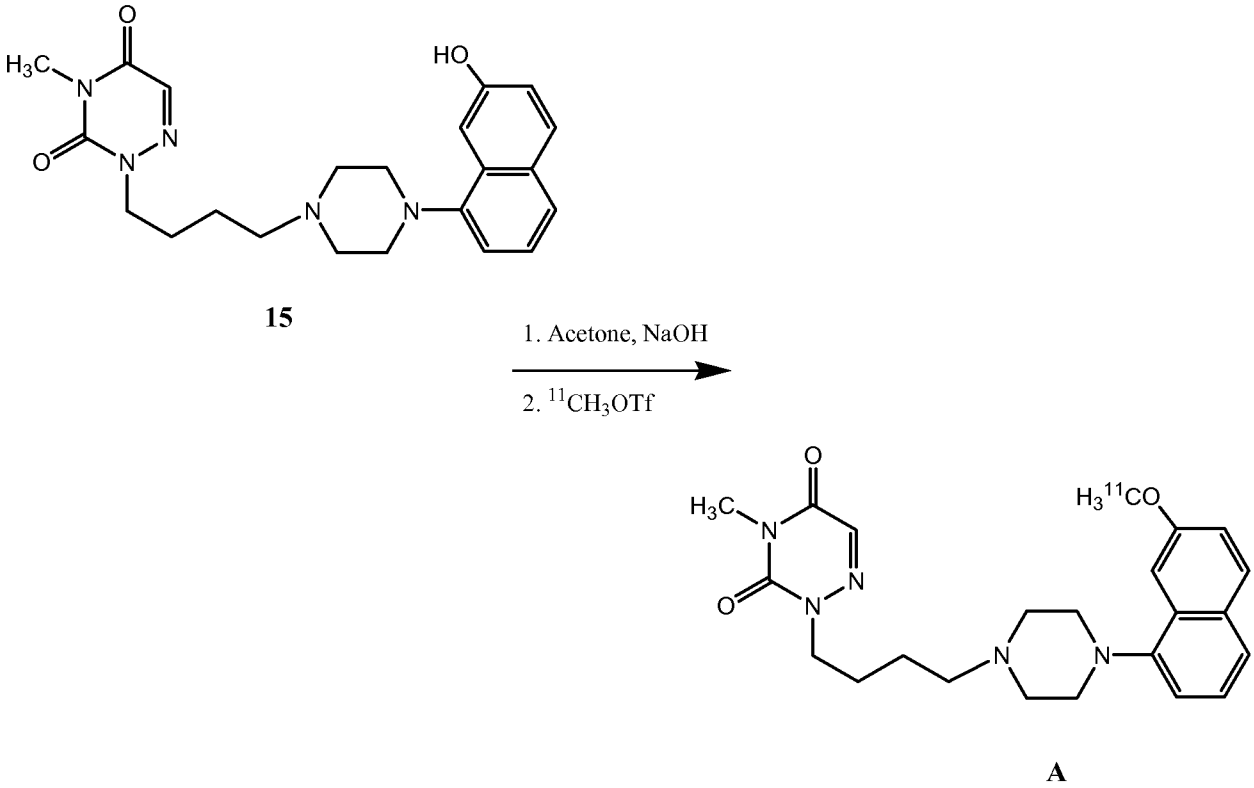




[0150] Amine **12** (796 mg, 5 mmol) was diluted with PEG-400 (2 mL) and to the resulting solution was added dichloroamine compound **5** (892 mg, 5 mmol). The resulting reaction was heated under microwave conditions for 10 seconds, then allowed to cool to room temperature. This heat/cool process was repeated two more times. It is noted that during the heating/cooling cycles, copious amounts of hydrochloric acid gas is released. After the evolution of hydrochloric acid gas subsided, the reaction mixture was triturated using chloroform to precipitate out a crude solid residue. The crude solid residue was filtered and washed with chloroform. The washed solid was then recrystallized from chloroform:methanol to provide compound **13** in 54 % yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 11.6 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.53-7.54 (m, 1H), 7.30 (m, 1H), 7.22 (s, 1H), 7.15-7.20 (m, 1H), 3.60 (t, J = 6.8 Hz, 4H), 3.39-3.41 (m, 4H).

[0151] Piperazine compound **13** (272 mg, 1.19 mmol) was diluted with n-butanol (4 mL) and to the resulting solution was added chloride compound **14** (151 mg, 0.7 mmol, commercially available), followed by dropwise addition of triethylamine (0.5 mL). The resulting reaction was heated at refluxed for about 12 hours, allowed to cool to room temperature, then concentrated *in vacuo* to provide a crude residue. The crude residue was triturated with diethyl ether and the resultant off-white solid which precipitated out was filtered, washed with diethyl ether (50 mL), then purified using flash column chromatography on silica gel (mobile phase - gradient of 5% to 10% methanol in chloroform) to provide precursor compound **15** as a colorless solid (146 mg, 51%). M.p = 205-206 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 11.7 Hz, 1H), 7.48-7.45 (m, 2H), 7.37 (s, 1H), 7.22-7.19 (m, 1H), 7.08-7.4 (m, 2H), 4.02 (t, J = 9.5 Hz, 2H), 3.33 (s, 3H), 3.19-3.08 (m, 4H), 2.85-2.70 (m, 4H), 2.54-2.49 (t, J = 10.1 Hz, 2H), 1.87-1.77 (m, 2H), 1.66-1.56 (m, 2H). HRMS calcd for $C_{22}H_{28}O_3N_5$ (MH^+): 410.2192; Found: 410.2194.

*Step B: Radiolabeling of Compound **15** to Provide Compound **A**:*

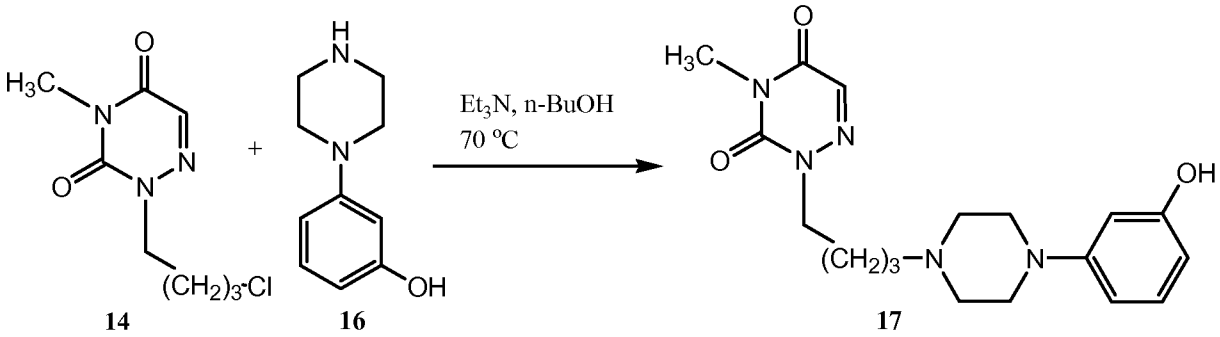


[0152] Precursor compound **15** (1.0 mg) was placed in a 1 mL vial. To the vial was added acetone (400 μL), followed by 5 M sodium hydroxide (10 μL). The resulting solution was allowed to stand for 5 minutes, then [^{11}C]-methyl triflate was transported by a stream of argon (20-30 mL/ min) into the vial over a period of 5 minutes at room temperature. The reaction mixture was removed from the vial via syringe and directly injected onto a semi preparative RP-HPLC column (Phenomenex C18, 10 mm x 250 mm) and eluted at a flow rate of 10 mL/min using a mobile phase of acetonitrile:0.1 M aqueous ammonium formate (40:60). Compound A eluted at 8-9 minutes and the fractions containing Compound **A** were collected, diluted with deionized water (100 μL added to each fraction), and combined. The combined diluted fractions were filtered through a C-18 Sep-Pak cartridge and concentrated in vacuo to provide a crude residue which was reconstituted using absolute ethanol (1 mL) to provide Compound **A** (35 % yield based on [^{11}C]CO_2 at EOS).

Example 2

Preparation of Compound B

Step A: Preparation of Intermediate Compound 17



14 16 17

[0153] Piperazine compound **16** (150 mg, 0.84 mmol, commercially available) and chloride compound **14** (183 mg, 0.84 mmol, commercially available) were diluted with n-butanol (5 mL) and to the resulting solution was added triethylamine (0.5 mL, added drop wise). The resulting reaction was heated and refluxed for about 12 hours, allowed to cool to room temperature, then concentrated *in vacuo* to provide a crude residue. The crude residue was triturated using diethyl ether and the resultant off-white precipitate was filtered, washed with diethyl ether (50 mL) and purified using flash column chromatography on silica gel (mobile phase was gradient of 5% to 10% methanol in dichloromethane) to provide precursor compound **17** as a colorless solid (220 mg, 73%). m.p = 162-64 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (s, 1H), 7.0 (m, 1H), 6.4 (d, 1H, J = 8.16), 6.2-6.3 (2H, m), 4.0 (t, J = 7 Hz, 2H), 3.3 (s, 3H), 3.14-3.15 (m, 4H), 2.5-2.6 (m, 4H), 2.4 (t, J = 7 Hz, 2H), 1.7 (m, 2H), 1.5 (m, 2H). HRMS calcd for $C_{18}H_{26}O_3N_5$ (MH^+): 360.2036; Found: 360.2033.

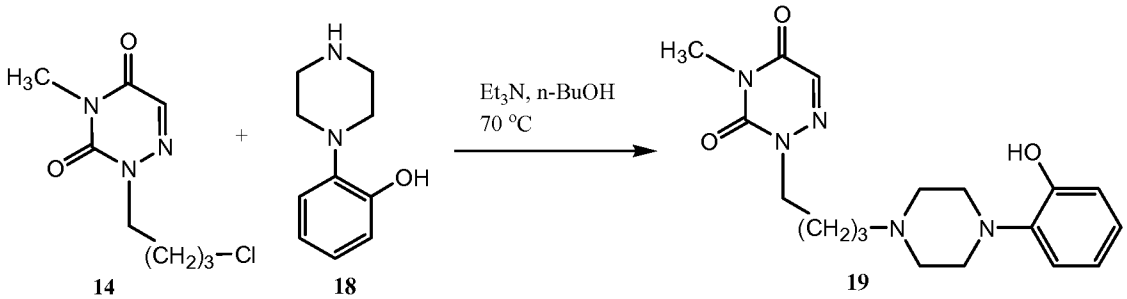
*Step B: Radiolabeling of Compound **17** to Provide Compound **B**:*

[0154] Compound **B** was made using the method described in Example 1, Step B, substituting Compound **17** for Compound **15**.

Example 3

Preparation of Compound C

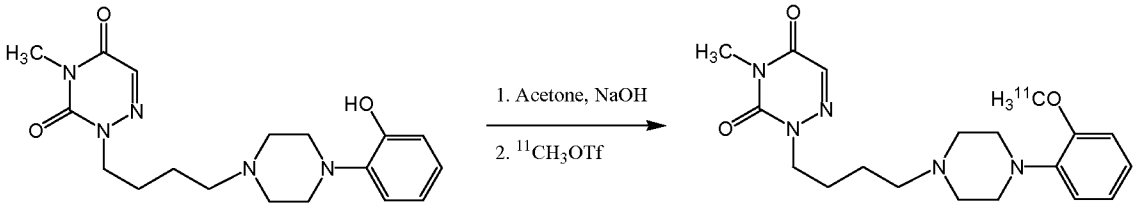
*Step A: Preparation of Intermediate Compound **19***



14 18 19

[0155] Intermediate compound **19** was made using the method described in Example 1, Step A, and substituting Compound **18** for Compound **13**. Compound **18** can be made using the method set forth in Example 5.1, Step A, and substituting 8-amino-1-naphthol for Compound **12**.

*Step B: Radiolabeling of Compound **19** to Provide Compound **C**:*



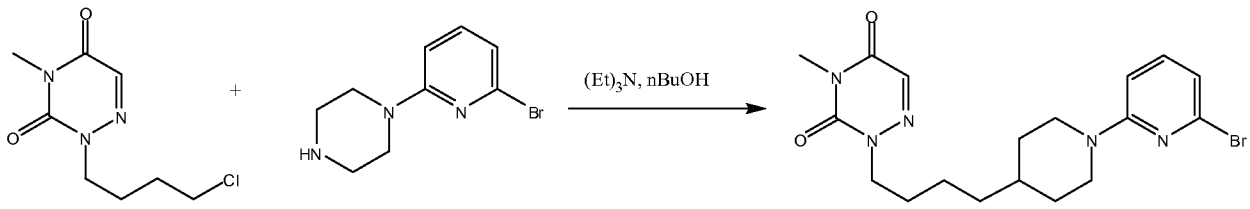
19 **C**

[0156] Compound **C** was made using the method described in Example 5.1, Step B, and substituting Compound **19** for Compound **15**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.7 (s, 1H), 7.3-6.8 (m, 4H), 4.2 (t, 2H), 3.3 (s, 3H), 2.9 (m, 4H), 2.6 (m, 4H), 2.4 (t, 2H), 1.8 (m, 2H), 1.6 (m, 2H). HRMS calcd for $C_{18}H_{26}O_3N_5$ (MH+): 360.2036; Found: 360.2032.

Example 4

Preparation of Compound D

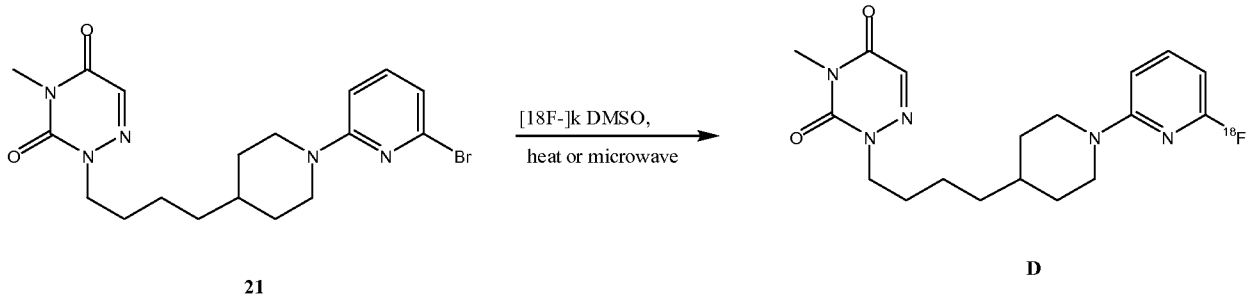
*Step A: Preparation of Intermediate Compound **21***



14 **20** **21**

[0157] Intermediate compound was made using a method identical to compound **15** described in Example 1. ^{1}H NMR (400 MHz, $CDCl_3$) *d*: 1.58-1.63 (m, 2H); 1.84 (pentet, 2H, *J* = 7.6 Hz); 2.44 (t, 2H, *J* = 7.6 Hz); 2.54 (t, 4H, *J* = 5.2 Hz); 3.37 (s, 3H); 3.56 (t, 4H, *J* = 4.8 Hz); 4.05 (t, 2H, *J* = 7.2 Hz); 6.53 (d, 1H, *J* = 8.4 Hz); 6.76 (d, 1H, *J* = 7.2 Hz); 7.33 (dd, 1H, J = 7.6, 8.0 Hz); 7.42 (s, 1H).

*Step B: Radiolabeling of Compound **21** to Provide Compound D:*



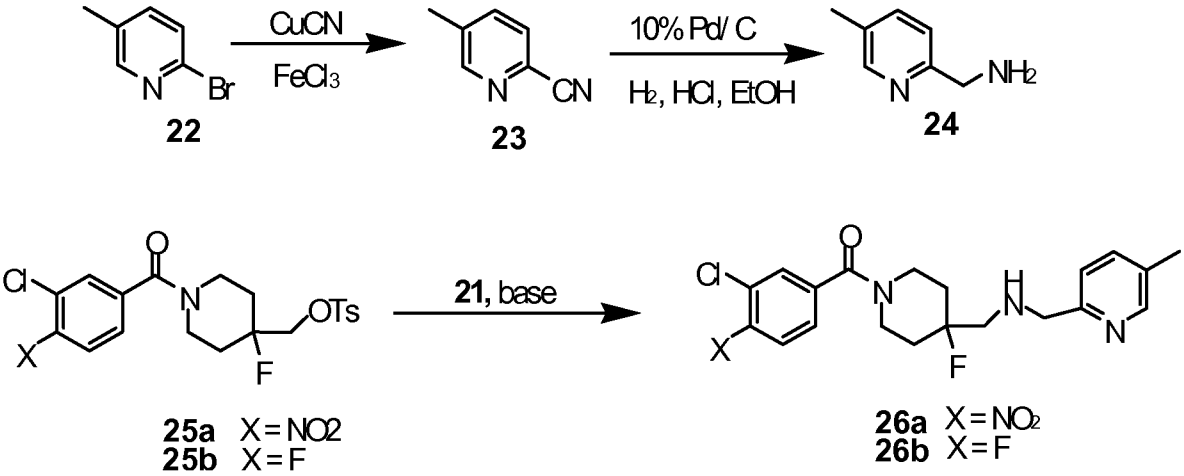
21 **D**

[0158] The precursor compound **21** (1.0 mg) may then be dissolved in 400 μL of DMSO and transferred to a reaction vessel containing azeotropically dried $[^{18}F]^-$, KRYPTOFIX, and K_2CO_3. The reaction mixture may be heated at 100 °C for 15 minutes, cooled down, and diluted with 0.5 mL of water and injected onto a semi preparative RP-HPLC (Phenomenex C18, 10 x 250 mm, 10 μ). The product fraction based on a γ-detector may be collected, diluted with 100 mL of deionized water, and passed through a classic C-18 Sep-Pak cartridge. Reconstruction of the product in 1 mL of absolute ethanol provides Compound **D**. A microwave can also be used instead of heating at 100 °C for 15 minutes.

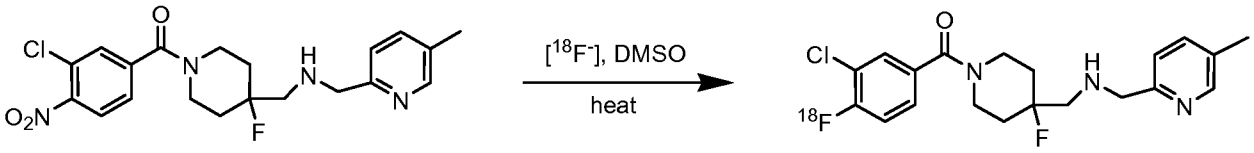
Example 5

Preparation of Compound E

*Step A: Preparation of Intermediate Compounds **26a** and **26b***



*Step B: Radiolabeling of Compound **26a** to Provide Compound **E**:*



26a E

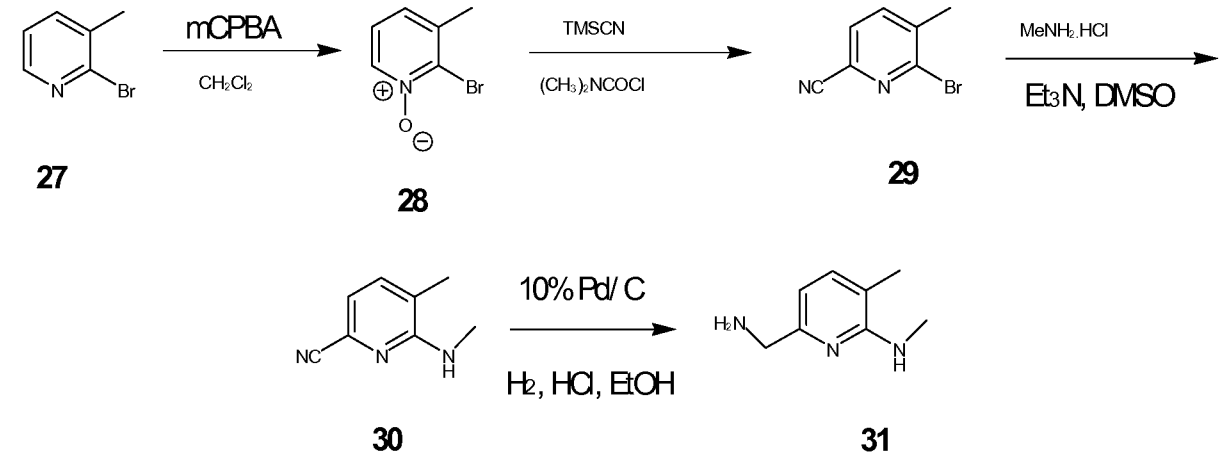
[0159] The precursor compound **26a** (1.0 mg) may then be dissolved in 400 μL of DMSO and transferred to a reaction vessel containing azeotropically dried $[^{18}F]^-$, KRYPTOFIX, and K_2CO_3. The reaction mixture may be heated at 100 °C for 15 minutes, cooled down, and diluted with 0.5 mL of water and injected onto a semi preparative RP-HPLC (Phenomenex C18, 10 x 250 mm, 10 μ). The product fraction based on a gamma(γ)-detector may be collected, diluted with 100 mL of deionized water, and passed through a classic C-18 Sep-Pak cartridge. Reconstruction of the product in 1 mL of absolute ethanol provides Compound **E**.

Example 6

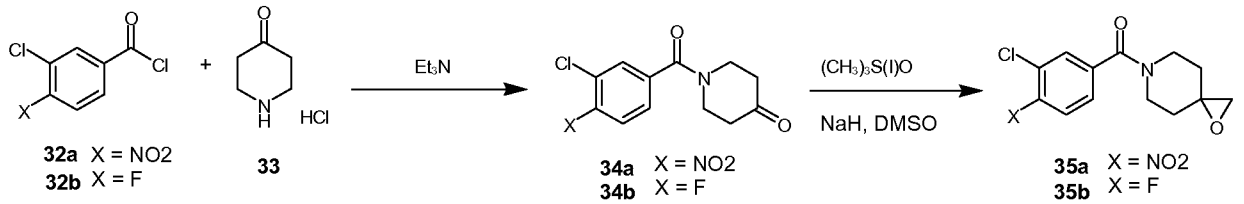
Preparation of Compound F

[0160] As shown schematically below, two different possible routes of preparing intermediate compounds **37a** and **37b** can be illustrated.

*Step A: Preparation of Intermediate Compounds **37a** and **37b***



27 28 29 30 31

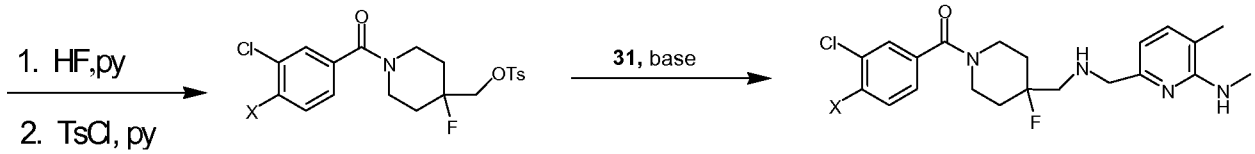


32a X = NO2
32b X = F

33

34a X = NO2
34b X = F

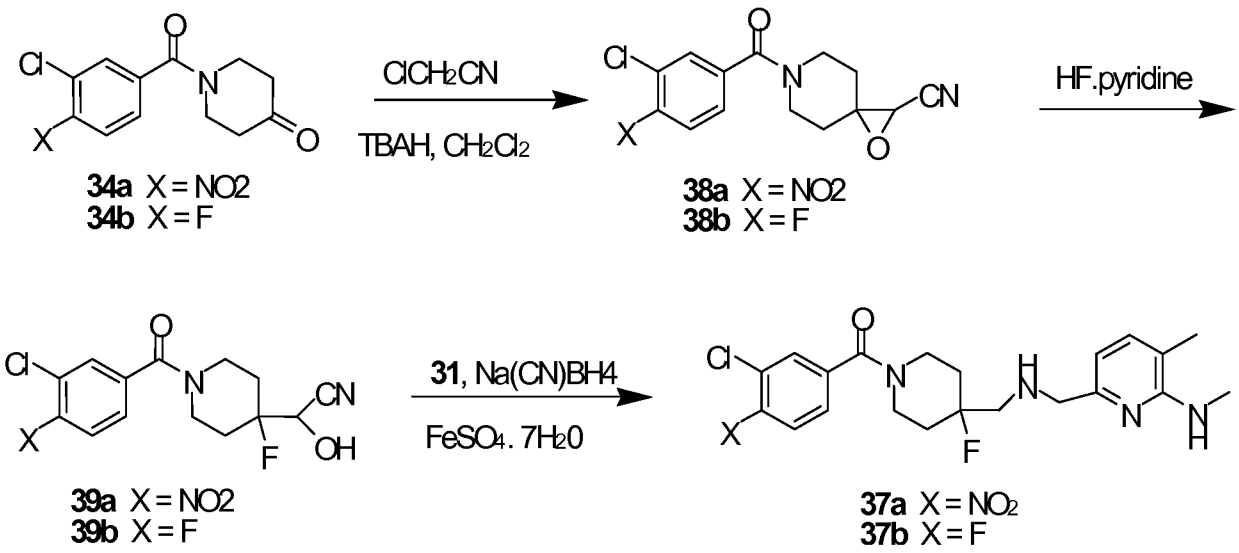
35a X = NO2
35b X = F



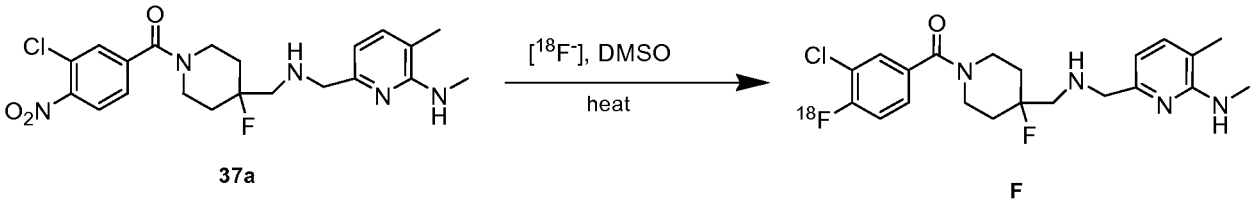
36a X = NO2
36b X = F

37a X = NO_2
37b X = F

*Step B: Alternate Preparation of Intermediate Compounds **37a** and **37b***



*Step C: Radiolabeling of Precursor Compound **37a** to Provide Compound **F**:*

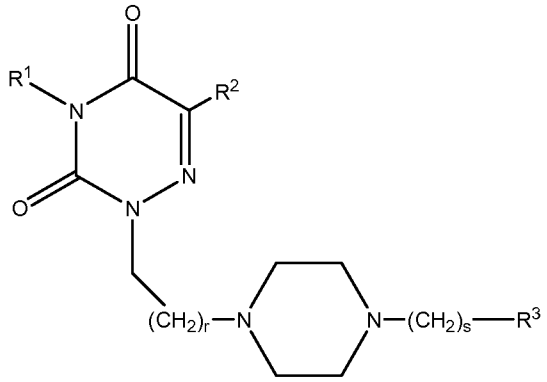


[0161] Compound **F** may be prepared using the method described in Example 5, step B, and substituting Compound **37a** for Compound **26a**.

[0162] Upon review of the description and embodiments of the present invention, those skilled in the art will understand that modifications and equivalent substitutions may be performed in carrying out the invention without departing from the essence of the invention. Thus, the invention is not meant to be limiting by the embodiments described explicitly above, and is limited only by the claims which follow.

What is claimed:

1. A compound having the formula:



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

r and s are each independently an integer ranging from 0 to 6;

R^1 is –H, –aryl, -C_1-C_6 alkyl, -C_3-C_7 cycloalkyl, -C_3-C_7 cycloalkenyl, -3- to 7-membered heterocycle, -^{11}C-labeled C_1-C_6 alkylene, -^{11}C-labeled C_2-C_6 alkenylene, -^{11}C-labeled C_2-C_6 alkynylene, -^{18}F-labeled C_1-C_6 alkylene, -^{18}F-labeled C_2-C_6 alkenylene, or -^{18}F-labeled C_2-C_6 alkynylene alkyne;

R^2 is –H, –aryl, -C_1-C_6 alkyl, -C_3-C_7 cycloalkyl, -C_3-C_7 cycloalkenyl, -3- to 7-membered heterocycle, -halo, -CF_3, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -$N(R^4)_2$, -CN, -OR^4 or -SR^4;

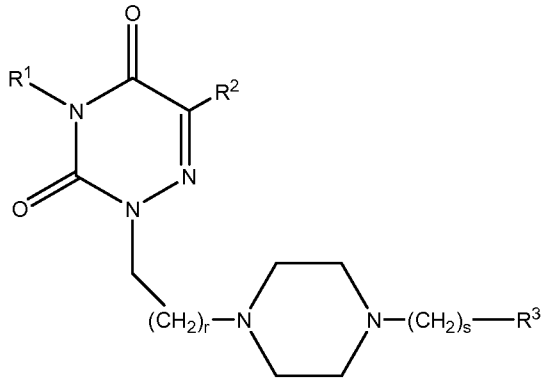
R^3 is –aryl or -5- to 7-membered aromatic heterocycle, each of which is substituted with one R^6 group and optionally substituted with one or more of the following groups: -C_1-C_6 alkyl, -C_3-C_7 cycloalkyl, -C_3-C_7 cycloalkenyl or -3- to 7-membered heterocycle, -halo, -CF_3, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkylene)-aryl, -$N(R^4)_2$, -CN, -OR^4, -SR^4, -S(O)-R^4, -SO_2-R^4, -SO_2NH-R^4, -SO_3H, -NH-SO_2-R^4, -C(O)R^5 or -NHC(O)R^5;

each occurrence of R^4 is independently –H, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -aryl, -(C_1-C_6 alkylene)-aryl, -C_3-C_7 cycloalkyl, -C_3-C_7 cycloalkenyl or -3- to 7-membered heterocycle;

R^5 is –R^4, -$N(R^4)_2$ or -OR^4;

R^6 is -F, -^{18}F, -CF_3, -^{18}F-labeled CF_3, -CF_2H, -^{18}F-labeled CF_2H, or -^{11}C-labeled CN.

2. A compound having the formula:



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

r and s are each independently an integer ranging from 0 to 6;

R^1 is -^{11}C-labeled C_1-C_6 alkylene, -^{11}C-labeled C_2-C_6 alkenylene, -^{11}C-labeled C_2-C_6 alkynylene, -^{18}F-labeled C_1-C_6 alkylene, -^{18}F-labeled C_2-C_6 alkenylene, or -^{18}F-labeled C_2-C_6 alkynylene alkyne;

R^2 is –H, –aryl, -C_1-C_6 alkyl, -C_3-C_7 cycloalkyl, -C_3-C_7 cycloalkenyl, -3- to 7-membered heterocycle, -halo, -CF_3, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -$N(R^4)_2$, -CN, -OR^4 or -SR^4;

R^3 is –aryl or -5- to 7-membered aromatic heterocycle, each of which is substituted with one R^6 group and optionally substituted with one or more of the following groups: -C_1-C_6 alkyl, -C_3-C_7 cycloalkyl, -C_3-C_7 cycloalkenyl or -3- to 7-membered heterocycle, -halo, -CF_3, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkylene)-aryl, -$N(R^4)_2$, -CN, -OR^4, -SR^4, -S(O)-R^4, -SO_2-R^4, -SO_2NH-R^4, -SO_3H, -NH-SO_2-R^4, -C(O)R^5 or -NHC(O)R^5;

each occurrence of R^4 is independently –H, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -aryl, -(C_1-C_6 alkylene)-aryl, -C_3-C_7 cycloalkyl, -C_3-C_7 cycloalkenyl or -3- to 7-membered heterocycle;

R^5 is –R^4, -$N(R^4)_2$ or -OR^4;

R^6 is –L-M-Q;

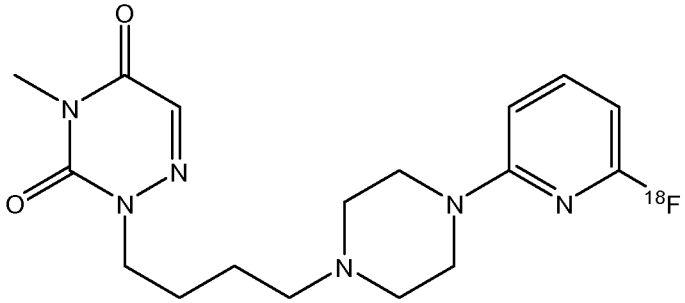
L is a single bond, -O-, -S-, -NH-, -F, -^{18}F, -CF_3, -^{18}F-labeled CF_3, -CF_2H, -^{18}F-labeled CF_2H, or -^{11}C-labeled CN;

M is -^{11}C-labeled C_1-C_6 alkylene-, -^{11}C-labeled C_2-C_6 alkenylene-, -^{11}C-labeled C_2-C_6 alkynylene-, -^{18}F-labeled C_1-C_6 alkylene-, -^{18}F-labeled C_2-C_6 alkenylene-, or -^{18}F-labeled C_2-C_6 alkynylene-;

Q is –H or -aryl.

3. The compound of claim 1, wherein R^1 is -^{11}C-labeled C_1-C_6 alkylene, -^{11}C-labeled C_2-C_6 alkenylene, -^{11}C-labeled C_2-C_6 alkynylene, -^{18}F-labeled C_1-C_6 alkylene, -^{18}F-labeled C_2-C_6 alkenylene, or -^{18}F-labeled C_2-C_6 alkynylene alkyne.

4. The compound of claim 1, having the formula:



or a pharmaceutically acceptable salt thereof.

5. A composition comprising a physiologically acceptable salt and the compound of claims 1 or 2, or a pharmaceutically acceptable salt thereof.

6. A composition comprising a therapeutically effective amount of a compound of claims 1 or 2, or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier or vehicle.

7. A composition comprising an imaging-effective amount of a compound of claims 1 or 2, or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier or vehicle.

8. A method for imaging one or more 5-HT_{1A} receptors in a subject *in vivo*, the method comprising:

(a) administering to the subject an imaging-effective amount of the compound of claims 1 or 2, or a pharmaceutically acceptable salt thereof; and

(b) detecting the radioactive emission of the compound or salt thereof administered to the subject.

9. The method of claim 8, wherein the radioactive emission is detected using positron-emission tomography.

10. The method of claim 8, wherein the radioactive emission is detected in the brain of the subject.

11. The method of claim 8, wherein the subject is known or suspected to have a neurological disorder.

12. The method of claim 11, wherein the neurological disorder is an affective disorder, an anxiety disorder, an eating disorder, an addictive disorder, a sleep disorder, a disease associated with cognitive dysfunction, a neurodegenerative disease, such as stroke; a seizure disorder, a pain disorder; a panic disorder, a disorder of movement, or an obsessive-compulsive disorder.

13. The method of claim 12, wherein the disease associated with cognitive dysfunction is Alzheimer's disease.

14. The method of claim 12, wherein the neurodegenerative disease is stroke.

15. The method of claim 12, wherein the disorder of movement is Parkinson's disease.

16. The method of claim 12, wherein the seizure disorder is epilepsy.

17. The method of claim 12, wherein the affective disorder is depression.

18. The method of claim 8, wherein the compound selectively binds to the 5-HT_{1A} receptor relative to other serotonin receptors.

19. A method for treating a psychiatric disorder in a subject, the method comprising administering to the subject a therapeutically effective amount of the compound of claims 1 or 2, or a pharmaceutically acceptable salt thereof.

20. The method of claim 19, wherein the psychiatric disorder is Alzheimer's disease.

21. A method for stabilizing the mood of a subject having a mood disorder, the method comprising administering to the subject a therapeutically effective amount of the compound of claims 1 or 2, or a pharmaceutically acceptable salt thereof.

22. The method of claim 21, wherein the mood disorder is bipolar disorder or depression.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/68408

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 51/00 (2008.04)
USPC - 424/1.89
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(8): A61K 51/00 (2008.04)
USPC: 424/1.89

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
All Prior Art Databases (text search - see terms below)
USPC: 424/1.89, 1.81; 544/182; 546/194 (text search - see terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google Scholar; Google Patents; FreePatentsOnline
Search Terms: 11C, 18F, alkenylene, alkylene, alkynylene, alzheimer$1, brain$1, depression, effective, emission, epilepsy, HT1A, imaging, label$3, method, mood, Parkinson$1, PET, positron, radio, receptor$1, stabiliz$3, therapeutically, tre

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2006/083424 A2 (MANN et al.) 10 August 2006 (10.08.2006), entire document especially pg. 3, ln. 1 - pg. 4, ln. 5	1 and 4-22 ---------- 2-3
Y	US 2005/0187226 A1 (WILSON et al.) 25 August 2005 (25.08.2005), para [0219]	2-3

☐ Further documents are listed in the continuation of Box C. ☐

* 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	Date of mailing of the international search report
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Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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