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(71) Applicant: THE UNITED STATES OF AMERICA,  
 AS REPRESENTED BY THE SECRETARY, DE-  
 PARTMENT OF HEALTH AND HUMAN SERVICES  
 [US/US]; Office of Technology Transfer, National Insti-

tutes of Health, 6701 Rockledge Drive, Suite 700, MSC  
 7788, Bethesda, Maryland 20892-7788 (US).

(72) Inventors: JACOBSON, Kenneth A.; NIDDK, NIH,  
 Laboratory of Bioorganic Chemistry, Bldg. 8A, Bethes-  
 da, Maryland 20892-0810 (US). TOSH, Dilip K.; NID-  
 DK, NIH, Laboratory of Bioorganic Chemistry, Bldg. 8A,  
 Bethesda, Maryland 20892-0810 (US).

(74) Agent: PILLAI, Xavier et al.; Leydig, Voit & Mayer, Ltd.,  
 Two Prudential Plaza, Suite 4900, 180 North Stetson Av-  
 enue, Chicago, Illinois 60601 (US).

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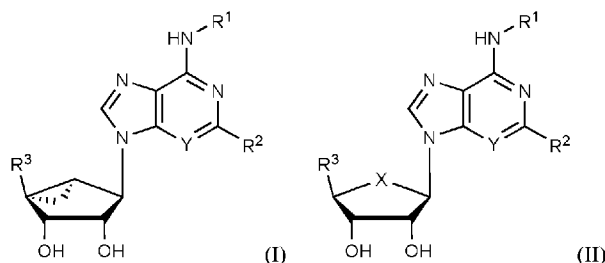
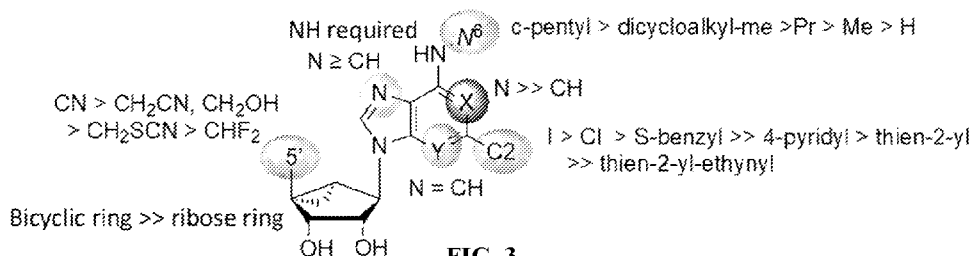
Nucleoside SAR at 5-HT<sub>2B</sub>R

FIG. 3

(57) Abstract: Disclosed are compounds of formulas (I) and (II), a salt thereof, or an optical isomer thereof, wherein R<sup>1</sup>-R<sup>3</sup>, X, and Y are as defined herein, which are 5-HT<sub>2B</sub> serotonin receptor selective antagonists, pharmaceutical compositions comprising such compounds, and methods of treating various diseases and conditions in an animal including fibrosis of the lung, skin, coronary, and liver, pulmonary arterial hypertension, valvular heart disease, pain, and cancer by the use of these compounds.

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5-HT<sub>2B</sub> SEROTONIN RECEPTOR ANTAGONISTS, PHARMACEUTICAL  
COMPOSITIONS THEREOF, AND METHODS OF USE THEREOF

CROSS-REFERENCE TO A RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/527,244, filed July 17, 2023.

STATEMENT REGARDING  
FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with Government support under Grant Number ZIADK03117 awarded by the National Institute of Diabetes & Digestive & Kidney Diseases, Division of Intramural Research. The Government has certain rights in this invention.

BACKGROUND OF THE INVENTION

[0003] Serotonin (or 5-hydroxytryptamine, 5-HT) is a neurotransmitter of the peripheral and central nervous systems (PNS and CNS). 5-HT is associated with mood disorders such as depression and schizophrenia as well as in controlling food intake, gastrointestinal function, cardiovascular function, cell development, drug seeking behavior, and pain.

[0004] The serotonin receptor 2 (5-HT<sub>2</sub>) subfamily consists of three subtypes: 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>2C</sub>. The 5-HT<sub>2B</sub> receptor is found in both the peripheral and central nervous system. The 5-HT<sub>2B</sub> receptor binds the neurotransmitter serotonin and mediates many of the central and peripheral physiologic functions of serotonin. 5-HT<sub>2B</sub> receptors regulate serotonin release via the serotonin transporter, and are important both to normal physiological regulation of serotonin levels in blood plasma, and with the abnormal acute serotonin release produced by drugs such as MDMA. Some of the effects of serotonin on the CNS include presynaptic inhibition, neuronal sensitization to tactile stimuli, mediation of some of the effects of hallucinogenic substituted amphetamines, and behavioral modifications. It has been contemplated that 5-HT<sub>2B</sub> receptor antagonists would be useful in cardioprotection, liver protection, and central nervous system activity.

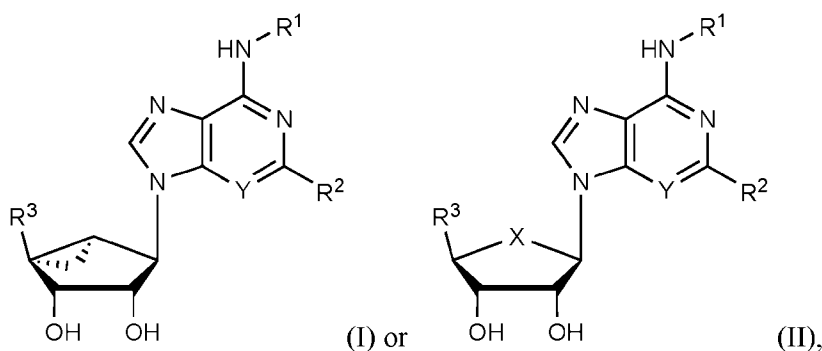
[0005] There is an unmet need for compounds and compositions for treating various disease conditions, including fibrosis of the lung, liver, skin, and coronary, pulmonary arterial

hypertension, valvular heart disease, pain, cancer, autoimmune diseases, and neuropathic pain of diverse states by selectively antagonizing 5-HT<sub>2B</sub> receptors relative to 5-HT<sub>2C</sub> receptors.

### BRIEF SUMMARY OF THE INVENTION

[0006] The invention provides compounds and compositions for treating various disease conditions, including fibrosis of the lung, liver, skin, and coronary, pulmonary arterial hypertension, valvular heart disease, pain, cancer, autoimmune diseases, and neuropathic pain of diverse states by selectively antagonizing 5-HT<sub>2B</sub> receptors relative to 5-HT<sub>2C</sub> receptors. In an aspect, the compounds of the invention, advantageously, do not reduce body core temperature. The invention also provides methods of treating such diseases by the use of these compounds and compositions.

[0007] Thus, the present invention provides a compound of formula (I) or formula (II), a salt thereof, or an optical isomer thereof,



wherein,

in the compound of formula (I),

R<sup>1</sup> is selected from the group consisting of aryl, arylalkyl, cycloalkyl, cycloalkyl alkyl, di-cycloalkylalkyl, di-bicycloalkyl, tricycloalkyl, alkyl, (cycloalkyl)(alkyl)alkylenyl, and H, wherein the aryl, alkyl, and cycloalkyl moieties can be optionally substituted with one or more of alkyl, halo, and cyano groups;

R<sup>2</sup> is selected from the group consisting of H, halo, alkylthio, arylalkylthio, heteroaryl, tetrahydropyrrolyl, cyano, and thienylalkynyl, wherein each of said moieties, other than H and halo, can be optionally substituted with one or more of alkyl, halo, and cyano groups; and

R<sup>3</sup> is selected from the group consisting of optionally substituted 5-membered aromatic heterocyclyl, 3-alkyl-1,2,4-oxadiazol-5-yl, triazolylalkyl, cyano,

alkylaminocarbonyl, alkylaminothiocarbonyl, alkyloxycarbonyl, alkyloxythiocarbonyl, hydroxyalkyl, monohaloalkyl, dihaloalkyl, cyanoalkyl, and cyanothioalkyl; and

Y = N or CH; and

in the compound of formula (II),

R<sup>1</sup> is cycloalkyl or di-cycloalkylalkyl;

R<sup>2</sup> is halo;

X is NH, O, S, Se or CH<sub>2</sub>, and

R<sup>3</sup> is COXR<sup>4</sup> or CSXR<sup>4</sup>, and R<sup>4</sup> is H, alkyl, or alkyloxy; and

Y = N or CH; and with the provisos:

- (i) in formula (II), when R<sup>3</sup> is CH<sub>2</sub>OH and R<sup>1</sup> is H, alkyl, di-cycloalkyl alkyl, or (cycloalkyl)(alkyl)alkylenyl, then R<sup>2</sup> is not chloro or H;
- (ii) in formula (I), when R<sup>3</sup> is alkylaminocarbonyl and R<sup>1</sup> is di-cycloalkyl alkyl, or (chloro substituted aryl) alkyl, then R<sup>2</sup> is not chloro; and
- (iii) in formula (I), when R<sup>3</sup> is alkylaminocarbonyl and R<sup>1</sup> is (chloro substituted aryl) alkyl, then R<sup>2</sup> is not (halo substituted thienyl)alkynyl.

#### BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0008] Figures 1A-1B depict reaction schemes to produce compounds in accordance with an aspect of the invention.

[0009] Figures 2A-2J depict calcium efflux values for certain compounds in accordance with an aspect of the invention.

[0010] Figure 3 depicts preferred substituents for providing affinity to 5-HT<sub>2B</sub> receptors in accordance with an aspect of the invention.

[0011] Figure 4 depicts a reaction scheme to prepare compounds **47**, **48**, **94**, and **95** in accordance with an aspect of the invention.

[0012] Figure 5 depicts a reaction scheme to prepare compounds **49** and **50** in accordance with an aspect of the invention.

[0013] Figure 6A depicts a reaction scheme to prepare compounds **51** and **54** in accordance with an aspect of the invention.

[0014] Figure 6B depicts a reaction scheme to prepare compounds **87** and **103** in accordance with an aspect of the invention.

[0015] Figure 7 depicts a reaction scheme to prepare compound **40**, which is a compound of formula (I) and depicted as MRS8209.

[0016] Figure 8 depicts a reaction scheme for the synthesis of 4'-cyano and difluoromethyl (N)-methanocarba adenosine derivatives in accordance with an aspect of the invention.

[0017] Figure 9 depicts a reaction scheme for the synthesis of 4'-aryl modified (N)-methanocarba adenosine derivatives in accordance with an aspect of the invention.

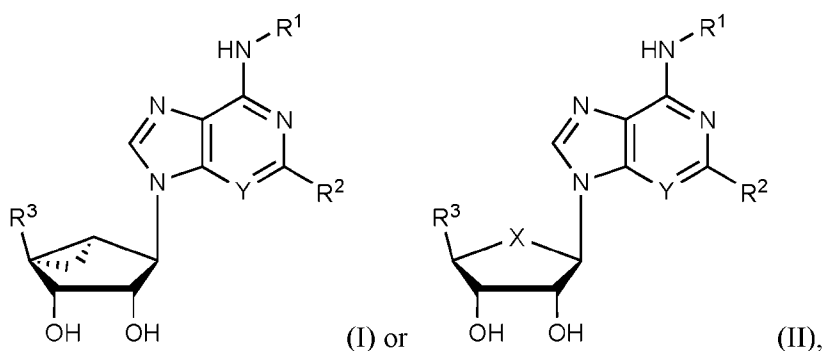
[0018] Figure 10A depicts that compound **40** (MRS8209) in accordance with an aspect of the invention advantageously does not reduce core body temperature or locomotor activity in wild type male mice at a dose of 1 mg/kg ip. Figure 10B depicts that compound **40** (MRS8209) in accordance with an aspect of the invention advantageously failed to reduce core body temperature or locomotor activity in wild type male mice at a dose of 3 mg/kg ip.

[0019] Figure 11, in parts A-D, respectively, depicts the binding affinities of compounds **18**, **29**, **32**, and **27** relative to SB 206553 as a function of concentration.

[0020] Figure 12 depicts a scheme for molecular interactions of an antagonist of the invention with the 5-hydroxytryptamine receptor 2A.

#### DETAILED DESCRIPTION OF THE INVENTION

[0021] In an aspect, the present invention provides a compound of formula (I) or formula (II), a salt thereof, or an optical isomer thereof,



wherein,

in the compound of formula (I),

$R^1$  is selected from the group consisting of aryl, arylalkyl, cycloalkyl, cycloalkyl alkyl, di-cycloalkylalkyl, di-bicycloalkyl, tricycloalkyl, alkyl, (cycloalkyl)(alkyl)alkylenyl,

and H, wherein the aryl, alkyl, and cycloalkyl moieties can be optionally substituted with one or more of alkyl, halo, and cyano groups;

$R^2$  is selected from the group consisting of H, halo, alkylthio, arylalkylthio, heteroaryl, tetrahydropyrrolyl, cyano, and thienylalkynyl, wherein each of said moieties, other than H and halo, can be optionally substituted with one or more of alkyl, halo, and cyano groups; and

$R^3$  is selected from the group consisting of optionally substituted 5-membered aromatic heterocyclyl, 3-alkyl-1,2,4-oxadiazol-5-yl, triazolylalkyl, cyano, alkylaminocarbonyl, alkylaminothiocarbonyl, alkylloxycarbonyl, alkyloxythiocarbonyl, hydroxyalkyl, monohaloalkyl, dihaloalkyl, cyanoalkyl, and cyanothioalkyl; and

Y = N or CH; and

in the compound of formula (II),

$R^1$  is cycloalkyl or di-cycloalkylalkyl;

$R^2$  is halo;

X is NH, O, S, Se or  $CH_2$ , and

$R^3$  is  $COXR^4$  or  $CSXR^4$ , and  $R^4$  is H, alkyl, or alkyloxy; and

Y = N or CH; and with the provisos:

(i) in formula (II), when  $R^3$  is  $CH_2OH$  and  $R^1$  is H, alkyl, di-cycloalkyl alkyl, or (cycloalkyl)(alkyl)alkylenyl, then  $R^2$  is not chloro or H;

(ii) in formula (I), when  $R^3$  is alkylaminocarbonyl and  $R^1$  is di-cycloalkyl alkyl, or (chloro substituted aryl)alkyl, then  $R^2$  is not chloro; and

(iii) in formula (I), when  $R^3$  is alkylaminocarbonyl and  $R^1$  is (chloro substituted aryl) alkyl, then  $R^2$  is not (halo substituted thienyl)alkynyl.

**[0022]** In an aspect, the invention provides a compound, a salt, or an optical isomer according to formula (I), wherein the aryl moiety of aryl and arylalkyl in  $R^1$  is phenyl, biphenyl, naphthyl, anthracenyl, or pyrenyl. In a particular aspect,  $R^1$  is phenyl optionally substituted with one or more of alkyl, halo, and cyano groups. In an additional aspect, the invention provides a compound, salt, or optical isomer according to formula (I) as described above, wherein  $R^3$  is an optionally substituted 5-membered aromatic heterocyclyl. In an aspect,  $R^3$  is selected from the group consisting of thienyl, furyl, oxadiazolyl, diazolyl, thiazolyl, triazolyl, pyrazolyl, and pyrrolyl, each of which is optionally substituted with halo,

C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, or aryl C<sub>1</sub>-C<sub>6</sub> alkylthio. For example, R<sup>3</sup> can be 3-alkyl-1,2,4-oxadiazol-5-yl or triazolylalkyl.

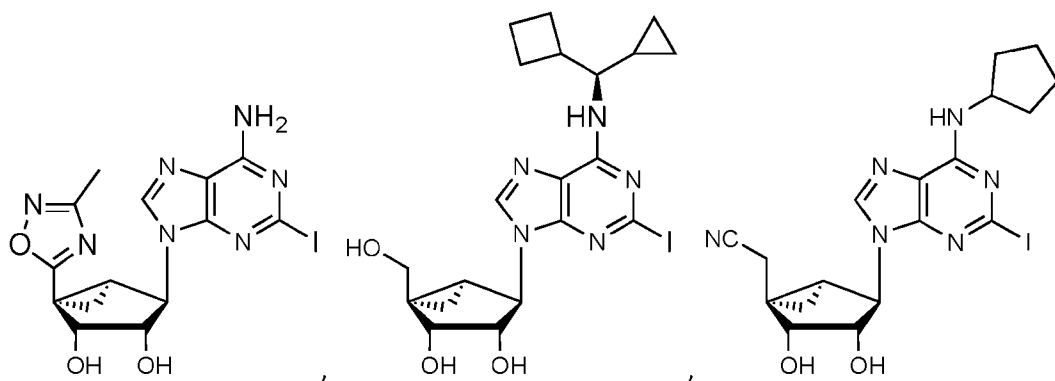
[0023] In an aspect, the invention provides a compound, a salt, or an optical isomer according to formula (I), wherein R<sup>1</sup> is selected from the group consisting of phenyl, phenylalkyl, halophenyl, dihalophenyl, halobenzyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, di-C<sub>3</sub>-C<sub>8</sub> cycloalkyl C<sub>3</sub>-C<sub>8</sub> alkyl, and C<sub>3</sub>-C<sub>8</sub> alkyl; R<sup>2</sup> is selected from the group consisting of chloro, bromo, iodo, C<sub>1</sub>-C<sub>8</sub> alkylthio, aryl C<sub>1</sub>-C<sub>8</sub> alkylthio, heteroaryl, thienylalkynyl, pyrrolidinyl, and halothienylalkynyl; and R<sup>3</sup> is selected from the group consisting of 3-methyl-1,2,4-oxadiazol-5-yl, cyano, hydroxy C<sub>1</sub>-C<sub>8</sub> alkyl, cyano C<sub>1</sub>-C<sub>8</sub> alkyl, and cyanothio C<sub>1</sub>-C<sub>8</sub> alkyl.

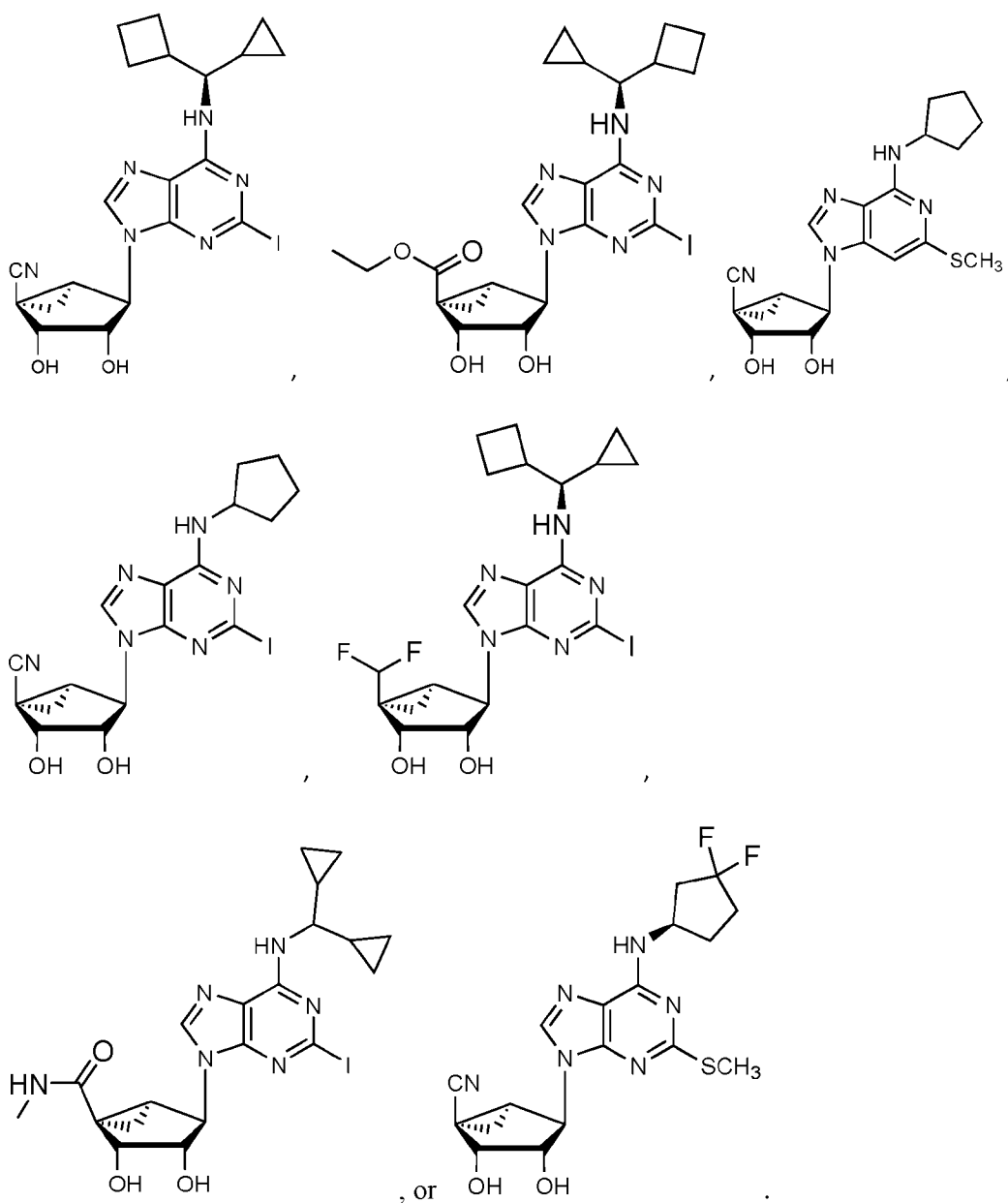
[0024] In aspect, the invention provides a compound, salt, or optical isomer according to formula (I), wherein R<sup>1</sup> is selected from the group consisting of di-cyclopropylmethyl, di-bicyclobutylmethyl, di-bicyclopentylmethyl, di-bicyclohexylmethyl, (isopropyl)(cyclopropyl)methyl, (cyclopropyl)(cyclobutyl)methyl, and dicyclopentylmethyl.

[0025] In any of the above aspects, R<sup>2</sup> is selected from the group consisting of methylthio, chloro, and iodo.

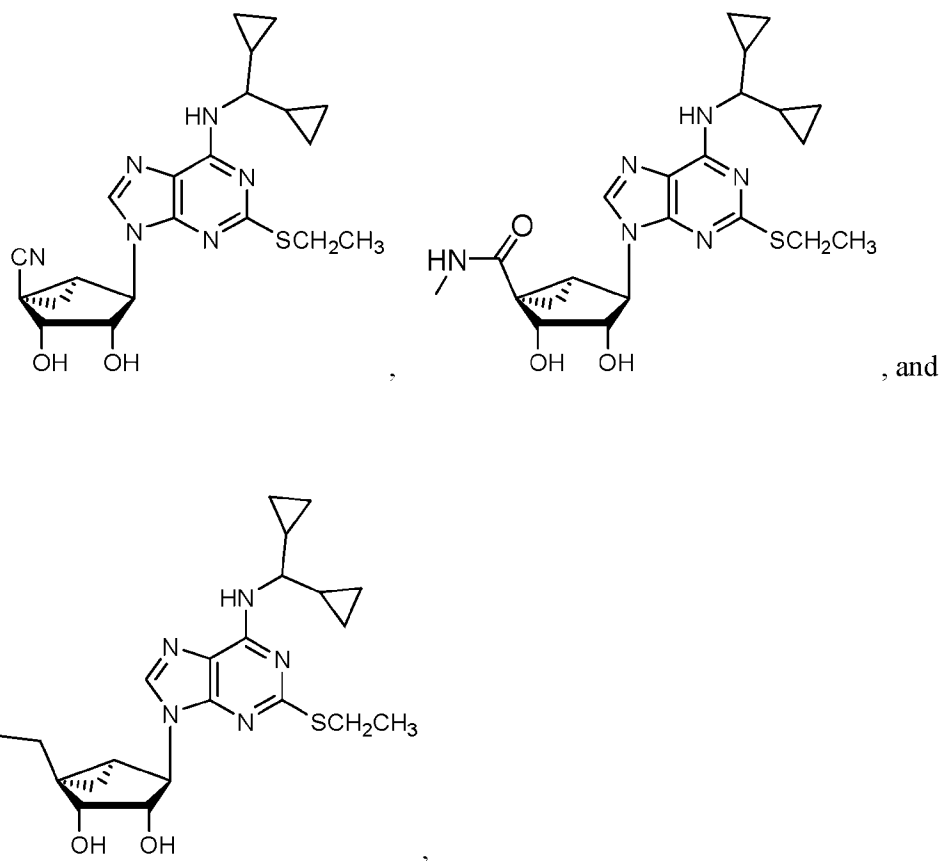
[0026] In any of the above aspects, the invention provides a compound, salt, or optical isomer according to formula (I), wherein R<sup>3</sup> is selected from the group consisting of 3-methyl-1,2,4-oxadiazol-5-yl, cyano, dihalomethyl, hydroxymethyl, cyanomethyl, methylaminocarbonyl, triazolylmethyl, and cyanothiomethyl.

[0027] In accordance with any one of the above aspects of compound, salt, or optical isomer of formula (I), wherein the compound is:





[0028] In an aspect, the invention provides compounds of formula (I) with the following structures:



and pharmaceutically acceptable salts thereof or optical isomers thereof.

[0029] In particular, the invention provides a compound, salt, or optical isomer wherein:

$R^1$  is ,  $R^2$  is Cl, and  $R^3$  is  $CH_2OH$ ;

$R^1$  is ,  $R^2$  is H, and  $R^3$  is  $CH_2OH$ ;

$R^1$  is di(cyclopropyl)methyl,  $R^2$  is Cl, and  $R^3$  is  $CHF_2$ ;

$R^1$  is isopropyl(cyclopropyl)methyl (*R*),  $R^2$  is Cl, and  $R^3$  is  $CHF_2$ ;

$R^1$  is (cyclopropyl)(cyclobutyl)methyl (*R*),  $R^2$  is I, and  $R^3$  is  $CHF_2$ ;

$R^1$  is (cyclopropyl)(cyclobutyl)methyl (*S*),  $R^2$  is I, and  $R^3$  is  $CHF_2$ ;

R<sup>1</sup> is m-chlorobenzyl, R<sup>2</sup> is I, and R<sup>3</sup> is CHF<sub>2</sub>;

R<sup>1</sup> is H, R<sup>2</sup> is Cl, and R<sup>3</sup> is CN;

R<sup>1</sup> is methyl, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is n-propyl, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is isopropyl(cyclopropyl)methyl (*R*), R<sup>2</sup> is Cl, and R<sup>3</sup> is CN;

R<sup>1</sup> is isopropyl(cyclopropyl)methyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

35: R<sup>1</sup> is (cyclobutyl)(cyclopropyl)methyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (cyclobutyl)(cyclopropyl)methyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>SCN;

R<sup>1</sup> is (cyclobutyl)(cyclopropyl)methyl (*S*), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (cyclobutyl)(cyclopropyl)methyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is (cyclopropyl)(cyclobutyl)methyl (*S*), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is cyclopentyl, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is cyclopentyl, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is 3-difluorocyclopentyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is 3-difluorocyclopentyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is 3-difluorocyclopentyl (*S*), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is 3-difluorocyclopentyl (*S*), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is , R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is bicyclo [1.1.2] butyl, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is m-chlorobenzyl, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is m-chlorobenzyl, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is Me, R<sup>2</sup> is 5-Cl-thien-2-yl, and R<sup>3</sup> is CN;

R<sup>1</sup> is nPr, R<sup>2</sup> is 5-Cl-thien-2-yl, and R<sup>3</sup> is CN;

R<sup>1</sup> is Me, R<sup>2</sup> is 5-Cl-thien-2-yl -ethynyl, and R<sup>3</sup> is CN;

R<sup>1</sup> is H, R<sup>2</sup> is S-CH<sub>2</sub>Ph, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is Me, R<sup>2</sup> is S-CH<sub>2</sub>Ph, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is Me, R<sup>2</sup> is S-CH<sub>2</sub>Ph, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is (cyclopropyl)(cyclobutyl)methyl, R<sup>2</sup> is Cl, and R<sup>3</sup> is COOCH<sub>2</sub>CH<sub>3</sub>;

R<sup>1</sup> is H, R<sup>2</sup> is I, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is Me, R<sup>2</sup> is I, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is phenylethyl, R<sup>2</sup> is I, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is Me, R<sup>2</sup> is 5-Cl-thien-2-yl, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is nPr, R<sup>2</sup> is 5-Cl-thien-2-yl, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is Me, R<sup>2</sup> is 5-Cl-thien-2-yl-ethynyl, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is nPr, R<sup>2</sup> is 4-pyridyl, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is Me, R<sup>2</sup> is I, and R<sup>3</sup> is COOCH<sub>2</sub>CH<sub>3</sub>; or

R<sup>1</sup> is (cyclopropyl)(isopropyl)methyl, R<sup>2</sup> is 5-Cl-thien-2-yl-ethynyl, and R<sup>3</sup> is CONHCH<sub>3</sub>; or

R<sup>1</sup> is Me, R<sup>2</sup> is H (Z=C-I), and R<sup>3</sup> is COOCH<sub>2</sub>CH<sub>3</sub>.

**[0030]** In accordance with a further aspect, the invention provides a compound, salt, or optical isomer according to formula (I), wherein:

R<sup>1</sup> is Me, R<sup>2</sup> is Cl-thienyl-ethynyl, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is c-Bu, R<sup>2</sup> is I; and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is c-Bu, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is c-Hex, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is c-Hex, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>Cl;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CO<sub>2</sub>Et;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>SH;

R<sup>1</sup> is Ph, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is Ph, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is Ph, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is Ph, R<sup>2</sup> is I, and R<sup>3</sup> is CO<sub>2</sub>Et;

R<sup>1</sup> is Ph, R<sup>2</sup> is Cl-thienyl-ethynyl, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is (cyclobutyl)(cyclopropyl)methyl, R<sup>2</sup> is Cl-thienyl-ethynyl, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>5</sub>Ph, R<sup>2</sup> is Cl-thienyl-ethynyl, and R<sup>3</sup> is CO<sub>2</sub>Et;

R<sup>1</sup> is (3-F-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is (3-F-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (3,5-diCl-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is (3,5-F-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is NH-(3,4-diCl-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

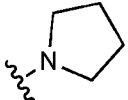
R<sup>1</sup> is (3,4-diCl-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (3-Cl-Bn), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (3-Cl-Bn), R<sup>2</sup> is I, and R<sup>3</sup> is CO<sub>2</sub>Et;

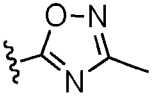
R<sup>1</sup> is (3-Cl-Bn), R<sup>2</sup> is Cl-thienyl-ethynyl, and R<sup>3</sup> is CH<sub>2</sub>CN;

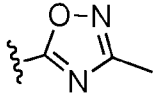
R<sup>1</sup> is pyrrolyl, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

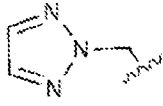
R<sup>1</sup> tetrahydropyrrolyl, R<sup>2</sup> is , and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is tetrahydropyrrolyl, R<sup>2</sup> is 2-H, Z=C-CN, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is tetrahydropyrrolyl, R<sup>2</sup> is 2-H, Z=C-CN, and R<sup>3</sup> is CN;

R<sup>1</sup> is H, R<sup>2</sup> is I, and R<sup>3</sup> is ;

R<sup>1</sup> is tetrahydropyrrolyl, R<sup>2</sup> is I, and R<sup>3</sup> is ; or

R<sup>1</sup> is (cyclopropyl)(cyclobutyl) (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is .

**[0031]** The present invention also provides a compound, salt, or optical isomer according to formula (II), wherein R<sup>1</sup> is selected from the group consisting of cycloalkyl or di-cycloalkylalkyl; R<sup>2</sup> is halo; and R<sup>3</sup> is CH<sub>2</sub>OH or COOR<sup>4</sup>, wherein R<sup>4</sup> is alkyl, more particularly, a compound of formula The compound, salt, or optical isomer according to formula (II), wherein R<sup>1</sup> is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; R<sup>2</sup> is chloro, iodo, or methylthio; and R<sup>3</sup> is COOR<sup>4</sup>, or CONHR<sup>4</sup>, wherein R<sup>4</sup> is C<sub>1</sub>-C<sub>3</sub> alkyl.

**[0032]** Referring now to terminology used generically herein, the term “alkyl” means a straight-chain or branched alkyl substituent containing from, for example, 1 to about 6 carbon atoms, preferably from 1 to about 4 carbon atoms, more preferably from 1 to 2 carbon atoms. Examples of such substituents include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl, isoamyl, hexyl, and the like.

**[0033]** The term “cycloalkyl,” as used herein, means a cyclic alkyl substituent containing from, for example, about 3 to about 8 carbon atoms, preferably from about 4 to about 7 carbon atoms, and more preferably from about 4 to about 6 carbon atoms. Examples

of such substituents include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. The cyclic alkyl groups may be unsubstituted or further substituted with alkyl groups such as methyl groups, ethyl groups, and the like.

[0034] The term “alkylcarbonyl,” as used herein, refers to an alkyl group linked to a carbonyl group and further linked to a molecule via the carbonyl group, e.g., alkyl C(=O) . The term “alkoxycarbonyl,” as used herein, refers to an alkoxy group linked to a carbonyl group and further linked to a molecule via the carbonyl group, e.g., alkyl O C(=O) .

[0035] The term “halo” or “halogen,” as used herein, means a substituent selected from Group VIIA, such as, for example, fluorine, bromine, chlorine, and iodine.

[0036] Whenever a range of the number of atoms in a structure is indicated (e.g., a C<sub>1</sub>-C<sub>12</sub>, C<sub>1</sub>-C<sub>8</sub>, C<sub>1</sub>-C<sub>6</sub>, C<sub>1</sub>-C<sub>4</sub>, or C<sub>2</sub>-C<sub>12</sub>, C<sub>2</sub>-C<sub>8</sub>, C<sub>2</sub>-C<sub>6</sub>, C<sub>2</sub>-C<sub>4</sub> alkyl, alkenyl, or alkynyl), it is specifically contemplated that any sub-range or individual number of carbon atoms falling within the indicated range also can be used. Thus, for instance, the recitation of a range of 1-8 carbon atoms (e.g., C<sub>1</sub>-C<sub>8</sub>), 1-6 carbon atoms (e.g., C<sub>1</sub>-C<sub>6</sub>), 1-4 carbon atoms (e.g., C<sub>1</sub>-C<sub>4</sub>), 1-3 carbon atoms (e.g., C<sub>1</sub>-C<sub>3</sub>), or 2-8 carbon atoms (e.g., C<sub>2</sub>-C<sub>8</sub>) as used with respect to any chemical group (e.g., alkyl, alkylamino, etc.) referenced herein encompasses and specifically describes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and/or 12 carbon atoms, as appropriate, as well as any sub-range thereof (e.g., 1-2 carbon atoms, 1-3 carbon atoms, 1-4 carbon atoms, 1-5 carbon atoms, 1-6 carbon atoms, 1-7 carbon atoms, 1-8 carbon atoms, 1-9 carbon atoms, 1-10 carbon atoms, 1-11 carbon atoms, 1-12 carbon atoms, 2-3 carbon atoms, 2-4 carbon atoms, 2-5 carbon atoms, 2-6 carbon atoms, 2-7 carbon atoms, 2-8 carbon atoms, 2-9 carbon atoms, 2-10 carbon atoms, 2-11 carbon atoms, 2-12 carbon atoms, 3-4 carbon atoms, 3-5 carbon atoms, 3-6 carbon atoms, 3-7 carbon atoms, 3-8 carbon atoms, 3-9 carbon atoms, 3-10 carbon atoms, 3-11 carbon atoms, 3-12 carbon atoms, 4-5 carbon atoms, 4-6 carbon atoms, 4-7 carbon atoms, 4-8 carbon atoms, 4-9 carbon atoms, 4-10 carbon atoms, 4-11 carbon atoms, and/or 4-12 carbon atoms, etc., as appropriate). Similarly, the recitation of a range of 6-10 carbon atoms (e.g., C<sub>6</sub>-C<sub>10</sub>) as used with respect to any chemical group (e.g., aryl) referenced herein encompasses and specifically describes 6, 7, 8, 9, and/or 10 carbon atoms, as appropriate, as well as any sub-range thereof (e.g., 6-10 carbon atoms, 6-9 carbon atoms, 6-8 carbon atoms, 6-7 carbon atoms, 7-10 carbon atoms, 7-9 carbon atoms, 7-8 carbon atoms, 8-10 carbon atoms, and/or 8-9 carbon atoms, etc., as appropriate).

[0037] In any of the above aspects, the compound or salt of formula (I) or formula (II) can have at least one asymmetric carbon atom. When the compound or salt has at least one asymmetric carbon atom, the compound or salt can exist in the racemic form, in the form of its pure optical isomers, or in the form of a mixture wherein one isomer is enriched relative to the other. In particular, in accordance with the present invention, when the inventive compounds have a single asymmetric carbon atom, the inventive compounds may exist as racemates, i.e., as mixtures of equal amounts of optical isomers, i.e., equal amounts of two enantiomers, or in the form of a single enantiomer. As used herein, "single enantiomer" is intended to include a compound that comprises more than 50% of a single enantiomer (i.e., enantiomeric excess more than 60%, more than 70%, more than 80%, more than 90%, or up to 100% pure enantiomer).

[0038] When the compound or salt has more than one chiral center, the compound or salt can therefore exist as a mixture of diastereomers or in the form of a single diastereomer. As used herein, "single diastereomer" is intended to mean a compound that comprises more than 50% of a single diastereomer (i.e., diastereomeric excess more than 60%, more than 70%, more than 80%, more than 90%, or up to 100% pure diastereomer).

[0039] In a particular aspect, the optical isomers of the compounds of the invention, in particular those of formula (I), have optical isomerism at the N<sup>6</sup> group, not the entire molecule. Thus, *R* and *S* in this disclosure refer to the optical isomerism at the N<sup>6</sup> group.

[0040] The phrase "pharmaceutically acceptable salt" is intended to include nontoxic salts synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Generally, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445, and Berge, S. M., et al., *Journal of Pharmaceutical Science*, 66, 1-19 (1977).

[0041] Suitable bases include inorganic bases such as alkali and alkaline earth metal bases, e.g., those containing metallic cations such as sodium, potassium, magnesium, calcium and the like. Non-limiting examples of suitable bases include sodium hydroxide, potassium hydroxide, sodium carbonate, and potassium carbonate. Suitable acids include inorganic

acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic, methanesulfonic acid, benzene sulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, maleic acid, tartaric acid, fatty acids, long chain fatty acids, and the like. Preferred pharmaceutically acceptable salts of inventive compounds having an acidic moiety include sodium and potassium salts. Preferred pharmaceutically acceptable salts of inventive compounds having a basic moiety (e.g., a dimethylaminoalkyl group) include hydrochloride and hydrobromide salts. The compounds of the present invention containing an acidic or basic moiety are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof.

[0042] It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

[0043] It is further understood that the above compounds and salts may form solvates, or exist in a substantially uncomplexed form, such as the anhydrous form. As used herein, the term "solvate" refers to a molecular complex wherein the solvent molecule, such as the crystallizing solvent, is incorporated into the crystal lattice. When the solvent incorporated in the solvate is water, the molecular complex is called a hydrate. Pharmaceutically acceptable solvates include hydrates, alcoholates such as methanolates and ethanolates, acetonitrilates and the like. These compounds can also exist in polymorphic forms.

[0044] The present invention further provides a pharmaceutical composition comprising a compound of formula (I) or (II), salt, or optical isomer thereof, as described above and a pharmaceutically acceptable carrier. The present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount, e.g., a therapeutically effective amount, including a prophylactically effective amount, of one or more of the aforesaid compounds, or salts thereof, of the present invention.

[0045] The pharmaceutically acceptable carrier can be any of those conventionally used and is limited only by chemico-physical considerations, such as solubility and lack of reactivity with the compound, and by the route of administration. It will be appreciated by one of skill in the art that, in addition to the following described pharmaceutical

compositions; the compounds of the present invention can be formulated as inclusion complexes, such as cyclodextrin inclusion complexes, or liposomes.

[0046] The pharmaceutically acceptable carriers described herein, for example, vehicles, adjuvants, excipients, or diluents, are well known to those who are skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one which is chemically inert to the active compounds and one which has no detrimental side effects or toxicity under the conditions of use.

[0047] The choice of carrier will be determined in part by the particular active agent, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present invention. The following formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intraarterial, intramuscular, intraperitoneal, intrathecal, rectal, and vaginal administration are merely exemplary and are in no way limiting.

[0048] Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and cornstarch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such carriers as are known in the art.

[0049] The compounds of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer.

[0050] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The compound can be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol, or hexadecyl alcohol, glycols, such as propylene glycol or polyethylene glycol, glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, such as poly(ethyleneglycol) 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

[0051] Oils, which can be used in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters. Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylene-polypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-beta-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (3) mixtures thereof.

[0052] The parenteral formulations will typically contain from about 0.5 to about 25% by weight of the active ingredient in solution. Suitable preservatives and buffers can be used in such formulations. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations ranges from about 5 to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0053] The compounds of the present invention may be made into injectable formulations. The requirements for effective pharmaceutical carriers for injectable compositions are well known to those of ordinary skill in the art. See *Pharmaceutics and Pharmacy Practice*, J. B. Lippincott Co., Philadelphia, Pa., Banker and Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., pages 622-630 (1986).

[0054] Topical formulations, including those that are useful for transdermal drug release, are well-known to those of skill in the art and are suitable in the context of the invention for application to skin. Topically applied compositions are generally in the form of liquids, creams, pastes, lotions and gels. Topical administration includes application to the oral mucosa, which includes the oral cavity, oral epithelium, palate, gingival, and the nasal mucosa. In some aspects, the composition contains at least one active component and a suitable vehicle or carrier. It may also contain other components, such as an anti-irritant. The carrier can be a liquid, solid or semi-solid. In aspects, the composition is an aqueous solution. Alternatively, the composition can be a dispersion, emulsion, gel, lotion or cream vehicle for the various components. In one aspect, the primary vehicle is water or a biocompatible solvent that is substantially neutral or that has been rendered substantially neutral. The liquid vehicle can include other materials, such as buffers, alcohols, glycerin,

and mineral oils with various emulsifiers or dispersing agents as known in the art to obtain the desired pH, consistency and viscosity. It is possible that the compositions can be produced as solids, such as powders or granules. The solids can be applied directly or dissolved in water or a biocompatible solvent prior to use to form a solution that is substantially neutral or that has been rendered substantially neutral and that can then be applied to the target site. In aspects of the invention, the vehicle for topical application to the skin can include water, buffered solutions, various alcohols, glycols such as glycerin, lipid materials such as fatty acids, mineral oils, phosphoglycerides, collagen, gelatin and silicone based materials.

[0055] Additionally, the compounds of the present invention may be made into suppositories by mixing with a variety of bases, such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

[0056] The dose administered to a mammal, particularly, a human, in accordance with the present invention should be sufficient to effect the desired response. Such responses include reversal or prevention of the adverse effects of the disease for which treatment is desired or to elicit the desired benefit. One skilled in the art will recognize that dosage will depend upon a variety of factors, including the age, condition, and body weight of the human, as well as the source, particular type of the disease, and extent of the disease in the human. The size of the dose will also be determined by the route, timing and frequency of administration as well as the existence, nature, and extent of any adverse side-effects that might accompany the administration of a particular compound and the desired physiological effect. It will be appreciated by one of skill in the art that various conditions or disease states may require prolonged treatment involving multiple administrations.

[0057] Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is initiated with smaller dosages that are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. The present inventive method typically will involve the administration of about 0.1 to about 300 mg of one or more of the compounds described above per kg body weight of the animal or mammal.

[0058] The therapeutically effective amount of the compound or compounds administered can vary depending upon the desired effects and the factors noted above. Typically, dosages will be between 0.01 mg/kg and 250 mg/kg of the subject's body weight, and more typically between about 0.05 mg/kg and 100 mg/kg, such as from about 0.2 to about 80 mg/kg, from about 5 to about 40 mg/kg or from about 10 to about 30 mg/kg of the subject's body weight. Thus, unit dosage forms can be formulated based upon the suitable ranges recited above and the subject's body weight. The term "unit dosage form" as used herein refers to a physically discrete unit of therapeutic agent appropriate for the subject to be treated.

[0059] Alternatively, dosages are calculated based on body surface area and from about 1 mg/m<sup>2</sup> to about 200 mg/m<sup>2</sup>, such as from about 5 mg/m<sup>2</sup> to about 100 mg/m<sup>2</sup> will be administered to the subject per day. In particular aspects, administration of the therapeutically effective amount of the compound or compounds involves administering to the subject from about 5 mg/m<sup>2</sup> to about 50 mg/m<sup>2</sup>, such as from about 10 mg/m<sup>2</sup> to about 40 mg/m<sup>2</sup> per day. It is currently believed that a single dosage of the compound or compounds is suitable, however a therapeutically effective dosage can be supplied over an extended period of time or in multiple doses per day. Thus, unit dosage forms also can be calculated using a subject's body surface area based on the suitable ranges recited above and the desired dosing schedule.

[0060] The present invention provides a method of antagonizing a 5-HT<sub>2B</sub> serotonin receptor in an animal in need thereof comprising administering a compound, salt, or isomer or a pharmaceutical composition as described above.

[0061] The present invention further provides a method of treating fibrosis of the lung, skin, coronary and or liver fibrosis, pulmonary arterial hypertension, valvular heart disease, pain, or cancer in an animal in need thereof, comprising administering a compound, salt, or isomer or a pharmaceutical composition as described above.

[0062] The present invention discloses use of a compound of formula (I) or (II), salt, or optical isomer as described above, or a pharmaceutical composition thereof, for antagonizing a 5-HT<sub>2B</sub> serotonin receptor in an animal in need thereof, in particular, for treating fibrosis of the lung, skin, coronary and or liver fibrosis, pulmonary arterial hypertension, valvular heart disease, pain, or cancer in an animal in need thereof.

[0063] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

#### EXAMPLE 1

[0064] This example illustrates a method of synthesis of certain compounds of the present invention, as illustrated in FIG. 1. The protected 6-chloro nucleoside precursors **57** and **58** were synthesized by a Mitsunobu reaction from methanocarba sugar **56**. Amination of the nucleobase 6 position with either ammonia or various dicycloalkyl-methylamines in the presence of DIPEA in isopropanol provided 2-Cl and 2-I intermediates **59** – **64**. Silyl deprotection at the 5'-position of the nucleoside precursor with TBAF gave the isopropylidene-protected intermediates **65** – **68**. The 5'-hydroxymethyl group was modified with different functional groups to give chloro derivatives (**72**, **73**, using thionyl chloride), fluoro derivative (**75**, using DAST) or mesylated compounds **69** – **71** (using mesyl chloride). 5'-Chloro-5'-deoxy nucleosides (**72**, **73**) were further transformed to various thioalkyl derivatives by a SN2 reaction with the appropriate sodium alkylthioate in DMF. In the direct fluorination reaction by DAST, some unwanted impurities often contaminated the desired product. In order to avoid this problem, an indirect method was used where the mesylated compounds (**69** – **71**) were converted to 4'-fluoromethyl derivatives **74**, **76** in the presence of tetrabutylammonium fluoride (TBAF) in THF under reflux condition. The silyl and isopropylidene group together (**59** – **62**) or only isopropylidene group (**72** – **87**) was hydrolyzed in the presence of DOWEX50 in aqueous methanol or with aqueous TFA in MeOH to afford the final compounds (**9b**, **11**, **12**, **15**, **16**, **19**, **23**, **24**, and **26** – **36**). A 3-deaza methanocarba nucleoside **25** was prepared by a similar route. The *N*<sup>6</sup> amination of compound **88** to obtain **89** with dicylopentylmethylamine was performed at 140 °C under microwave condition for 25 h to give **89** in only moderate yield (22%), which upon subsequent acid hydrolysis afforded compound **25**.

[0065] Reagents and Conditions: (i) 6-Cl-purine derivative, Ph<sub>3</sub>P, DIAD, THF, rt; (ii) NH<sub>3</sub>/2-propanol, 80°C; (iii) R<sup>1</sup>NH<sub>2</sub>, DIPEA, 2-propanol, rt; (iv) TBAF, THF, rt; (v) MsCl, pyridine, rt; (vi) SOCl<sub>2</sub>, pyridine, CH<sub>3</sub>CN, -5 °C to rt; (vii) TBAF, THF, reflux, (viii) DAST, CH<sub>2</sub>Cl<sub>2</sub>, rt; (ix) R<sup>4</sup>SNa, DMF, rt; (x) 10% TFA, MeOH, 70°C; (xi) DOWEX50, MeOH-H<sub>2</sub>O, rt.

[0066] Materials and instrumentation: Dimethyl sulfoxide (DMSO), and other reagents were obtained from Sigma-Aldrich (St. Louis, MO). <sup>1</sup>H NMR spectra were obtained with a

Bruker 400 spectrometer using CDCl<sub>3</sub>, CD<sub>3</sub>OD and DMSO as solvents. Chemical shifts are expressed in  $\delta$  values (ppm) with tetramethylsilane ( $\delta$  0.00) for CDCl<sub>3</sub> and water ( $\delta$  3.30) for CD<sub>3</sub>OD. NMR spectra were collected with a Bruker AV spectrometer equipped with a z-gradient [<sup>1</sup>H, <sup>13</sup>C, <sup>15</sup>N]-cryoprobe. TLC analysis was carried out on glass sheets precoated with silica gel F254 (0.2 mm) from Sigma- Aldrich. The purity of final nucleoside derivatives was checked using a Hewlett–Packard 1100 HPLC equipped with a Zorbax SB-Aq 5  $\mu$ m analytical column (50  $\times$  4.6 mm; Agilent Technologies Inc., Palo Alto, CA, USA). Mobile phase: linear gradient solvent system, 5 mM TBAP (tetrabutylammonium dihydrogen phosphate); CH<sub>3</sub>CN from 80:20 to 0:100 in 13 min; the flow rate was 0.5 mL/min. Peaks were detected by UV absorption with a diode array detector at 230, 254, and 280 nm. All derivatives tested for biological activity showed >95% purity by HPLC analysis (detection at 254 nm). Low-resolution mass spectrometry was performed with a JEOL SX102 spectrometer with 6-kV Xe atoms following desorption from a glycerol matrix or on an Agilent LC/MS 1100 MSD, with a Waters (Milford, MA, USA) Atlantis C18 column.

[0067] High resolution mass spectroscopic (HRMS) measurements were performed on a proteomics optimized Q-TOF-2 (Micromass-Waters) using external calibration with polyalanine, unless noted. Observed mass accuracies are those expected based on known performance of the instrument as well as trends in masses of standard compounds observed at intervals during the series of measurements. Reported masses are observed masses uncorrected for this time- dependent drift in mass accuracy.

[0068] **(1R,2R,3S,4R,5S)-4-(6-((Dicyclopropylmethyl)amino)-2-iodo-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (11)**: DOWEX 50 (50 mg) was added to a solution of compound **68** (99 mg, 0.18 mmol) in MeOH (3 mL) and water (2 mL), and the mixture was stirred for 6 h at room temperature. After completion of stirring material, the reaction mixture was filtered, and the filtrate was evaporated under vacuum. The crude mixture was purified on flash silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 20:1) to give compound **11** (78 mg, 86%) as a colorless powder. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.38 (s, 1H), 4.81 (s, 1H), 4.78 (d, J = 6.0 Hz, 1H), 4.28 (d, J = 11.6 Hz, 1H), 3.87 (d, J = 6.8 Hz, 1H), 3.39 (br s, 1H), 3.37 (d, J = 11.6 Hz, 1H), 1.61-1.58 (m, 1H), 1.54 (d, J = 4.8 Hz, 1H), 1.16-1.07 (m, 2H), 0.78-0.74 (m, 1H), 0.59-0.54 (m, 2H), 0.47-0.37 (m, 6H). HRMS calculated for C<sub>19</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub>I (M + H)<sup>+</sup>: 498.1002; found 498.1007.

[0069] **(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclopropylmethyl)amino)-9*H*-purin-9-yl)-1- (fluoromethyl)bicyclo[3.1.0]hexane-2,3-diol (12)**. Compound **12** (83%) was prepared from compound **74** following the same method as for compound **11**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.13 (s, 1H), 5.09 (dd, *J*<sub>1</sub> = 10.0 Hz, *J*<sub>2</sub> = 50.2 Hz, 1H), 4.84 (s, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 4.38 (dd, *J*<sub>1</sub> = 10.0 Hz, *J*<sub>2</sub> = 50.2 Hz, 1H), 3.90 (d, *J* = 6.4 Hz, 1H), 3.46 (br s, 1H), 1.83-1.80 (m, 1H), 1.73-1.69 (m, 1H), 1.18-1.10 (m, 2H), 0.90-0.87 (m, 1H), 0.60-0.55 (m, 2H), 0.47-0.39 (m, 6H). HRMS calculated for C<sub>19</sub>H<sub>24</sub>N<sub>5</sub>O<sub>2</sub>FCl (M+H)<sup>+</sup>: 408.1603; found 408.1609.

[0070] **(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclopropylmethyl)amino)-9*H*-purin-9-yl)-1- ((methylthio)methyl)bicyclo[3.1.0]hexane-2,3-diol (15)**: Compound **15** (84%) was prepared from compound **85** following the same method as for compound **11**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.34 (s, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.76 (s, 1H), 3.98 (d, *J* = 6.8 Hz, 1H), 3.46 (br s, 1H), 3.25 (d, *J* = 13.6 Hz, 1H), 2.76 (d, *J* = 13.6 Hz, 1H), 2.21 (s, 3H), 1.65-1.62 (m, 1H), 1.57 (t, *J* = 4.8 Hz, 1H), 1.18-1.10 (m, 2H), 0.84-0.81 (m, 1H), 0.60-0.55 (m, 2H), 0.47-0.40 (m, 6H). HRMS calculated for C<sub>20</sub>H<sub>27</sub>N<sub>5</sub>O<sub>2</sub>SCl (M + H)<sup>+</sup>: 436.1574; found 436.1580.

[0071] **(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(6-((Dicyclopropylmethyl)amino)-2-iodo-9*H*-purin-9-yl)-1- ((methylthio)methyl)bicyclo[3.1.0]hexane-2,3-diol (16)**. Compound **16** (84%) was prepared from compound **86** following the same method as for compound **11**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.24 (s, 1H), 4.82 (d, *J* = 7.2 Hz, 1H), 4.76 (s, 1H), 3.97 (d, *J* = 6.8 Hz, 1H), 3.48 (br s, 1H), 3.24 (d, *J* = 11.6 Hz, 1H), 2.82 (d, *J* = 11.6 Hz, 1H), 2.20 (s, 3H), 1.61-1.58 (m, 1H), 1.53 (d, *J* = 4.8 Hz, 1H), 1.17-1.08 (m, 2H), 0.84-0.81 (m, 1H), 0.61-0.54 (m, 2H), 0.47-0.37 (m, 6H). HRMS calculated for C<sub>20</sub>H<sub>27</sub>N<sub>5</sub>O<sub>2</sub>SI (M + H)<sup>+</sup>: 528.0930; found 528.0929.

[0072] **(1*R*,2*R*,3*S*,4*R*,5*S*)-4-(6-((Dicyclobutylmethyl)amino)-2-iodo-9*H*-purin-9-yl)-1- (hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (19)**. Compound **19** (90%) was prepared from compound **62** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.38 (s, 1H), 4.81 (s, 1H), 4.79 (d, *J* = 6.0 Hz, 1H), 4.35-4.31 (m, 1H), 4.28 (d, *J* = 11.6 Hz, 1H), 3.89 (d, *J* = 6.8 Hz, 1H), 3.38 (d, *J* = 11.6 Hz, 1H), 2.51-2.47 (m, 2H), 1.99-1.83 (m, 10H), 1.79-1.76 (m, 2H), 1.62-1.59 (m, 1H), 1.55 (t, *J* = 4.8 Hz, 1H), 0.78-0.74 (m, 1H). HRMS calculated for C<sub>21</sub>H<sub>29</sub>N<sub>5</sub>O<sub>3</sub>I (M + H)<sup>+</sup>: 526.1315; found 526.1321.

[0073] (1*R*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclopentylmethyl)amino)-9*H*-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**24**). Compound **24** (91%) was prepared from compound **63** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.44 (s, 1H), 4.81 (s, 1H), 4.79 (d, *J* = 6.4 Hz, 1H), 4.40 (t, *J* = 6.8 Hz, 1H), 4.29 (d, *J* = 11.6 Hz, 1H), 4.14-4.08 (m, 1H), 3.91 (d, *J* = 6.8 Hz, 1H), 2.22-2.14 (m, 2H), 1.81-1.71 (m, 5H), 1.62-1.54 (m, 7H), 1.30-1.23 (m, 5H), 1.13-1.05 (m, 1H), 0.76-0.75 (m, 1H). HRMS calculated for C<sub>23</sub>H<sub>33</sub>N<sub>5</sub>O<sub>3</sub>Cl (M + H)<sup>+</sup>: 462.2272; found 462.2274.

[0074] (1*R*,2*R*,3*S*,4*R*,5*S*)-4-(6-Chloro-4-((dicyclopentylmethyl)amino)-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**25**). Compound **25** (90%) was prepared from compound **89** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.53 (s, 1H), 6.88 (s, 1H), 4.68 (d, *J* = 6.4 Hz, 1H), 4.59 (s, 1H), 4.36 (br s, 1H), 4.30 (d, *J* = 11.6 Hz, 1H), 3.86 (d, *J* = 5.6 Hz, 1H), 2.20-2.14 (m, 2H), 1.76-1.71 (m, 5H), 1.60-1.53 (m, 9H), 1.45-1.31 (m, 4H), 0.80-0.77 (m, 1H). HRMS calculated for C<sub>24</sub>H<sub>34</sub>N<sub>4</sub>O<sub>3</sub>Cl (M + H)<sup>+</sup>: 461.2319; found 461.2316.

[0075] (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclopentylmethyl)amino)-9*H*-purin-9-yl)-1-(fluoromethyl)bicyclo[3.1.0]hexane-2,3-diol (**26**). Compound **26** (89%) was prepared from compound **75** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.16 (s, 1H), 5.08 (dd, *J*<sub>1</sub> = 10.0 Hz; *J*<sub>2</sub> = 50.2 Hz, 1H), 4.85 (s, 1H), 4.74 (d, *J* = 6.4 Hz, 1H), 4.41-4.27 (m, 2H), 3.93 (d, *J* = 6.8 Hz, 1H), 2.28-2.15 (m, 2H), 1.83-1.69 (m, 4H), 1.62-1.55 (m, 9H), 1.44-1.25 (m, 5H), 0.93-0.88 (m, 1H). HRMS calculated for C<sub>23</sub>H<sub>32</sub>N<sub>5</sub>O<sub>2</sub>ClF (M + H)<sup>+</sup>: 464.2229; found 464.2220.

[0076] (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclopentylmethyl)amino)-9*H*-purin-9-yl)-1-(chloromethyl)bicyclo[3.1.0]hexane-2,3-diol (**27**). Compound **27** (88%) was prepared from compound **72** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.29 (s, 1H), 4.82-4.79 (m, 2H), 4.40 (t, *J* = 6.8 Hz, 1H), 4.30 (d, *J* = 12.0 Hz, 1H), 4.00 (d, *J* = 6.8 Hz, 1H), 3.69 (d, *J* = 11.6 Hz, 1H), 2.25-2.14 (m, 2H), 1.83-1.73 (m, 5H), 1.65-1.52 (m, 8H), 1.44-1.28 (m, 5H), 0.98-0.95 (m, 1H). HRMS calculated for C<sub>23</sub>H<sub>32</sub>N<sub>5</sub>O<sub>2</sub>Cl<sub>2</sub> (M + H)<sup>+</sup>: 480.1933; found 480.1937.

[0077] (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclopentylmethyl)amino)-9*H*-purin-9-yl)-1-((methylthio)methyl)bicyclo[3.1.0]hexane-2,3-diol (**28**). Compound **28** (90%) was prepared from compound **77** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.35 (s, 1H), 4.80-4.76 (m, 2H), 4.40 (t, *J* = 6.8 Hz, 1H), 4.00 (d, *J* =

6.4 Hz, 1H), 3.24 (d,  $J = 13.6$  Hz, 1H), 2.77 (d,  $J = 13.6$  Hz, 1H), 2.24-2.14 (m, 5H), 1.84-1.71 (m, 4H), 1.65-1.50 (m, 9H), 1.44-1.28 (m, 5H), 0.84-0.81 (m, 1H). HRMS calculated for  $C_{24}H_{35}N_5O_2ClS$  ( $M+H$ ) $^+$ : 492.2200; found 492.2203.

**[0078] (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclopentylmethyl)amino)-9*H*-purin-9-yl)-1-((ethylthio)methyl)bicyclo[3.1.0]hexane-2,3-diol (29).** Compound **29** (93%) was prepared from compound **78** following the same method as for compound **9b**.  $^1H$  NMR ( $CD_3OD$ , 400 MHz)  $\delta$  8.33 (s, 1H), 4.80-4.77 (m, 2H), 4.40 (t,  $J = 6.8$  Hz, 1H), 3.99 (d,  $J = 6.4$  Hz, 1H), 3.30 (d,  $J = 13.6$  Hz, 1H), 2.73 (d,  $J = 13.6$  Hz, 1H), 2.68-2.65 (m, 2H), 2.25-2.14 (m, 2H), 1.81-1.76 (m, 5H), 1.65-1.55 (m, 9H), 1.44-1.25 (m, 7H), 0.84-0.81 (m, 1H). HRMS calculated for  $C_{25}H_{37}N_5O_2ClS$  ( $M + H$ ) $^+$ : 506.2357; found 506.2354.

**[0079] (1*S*,2*R*,3*S*,4*R*,5*S*)-1-((Butylthio)methyl)-4-(2-chloro-6-((dicyclopentylmethyl)amino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexane-2,3-diol (30).** Compound **30** (90%) was prepared from compound **79** following the same method as for compound **9b**.  $^1H$  NMR ( $CD_3OD$ , 400 MHz)  $\delta$  8.40 (s, 1H), 4.83 (d,  $J = 7.2$  Hz, 1H), 4.77 (s, 1H), 4.40 (t,  $J = 6.8$  Hz, 1H), 4.01 (d,  $J = 6.4$  Hz, 1H), 3.29 (d,  $J = 13.6$  Hz, 1H), 2.75 (d,  $J = 13.6$  Hz, 1H), 2.62-2.58 (m, 2H), 2.25-2.15 (m, 2H), 1.81-1.78 (m, 5H), 1.63-1.51 (m, 9H), 1.45-1.27 (m, 8H), 0.92 (t,  $J = 7.2$  Hz, 3H), 0.83-0.80. HRMS calculated for  $C_{27}H_{41}N_5O_2ClS$  ( $M + H$ ) $^+$ : 534.2670; found 534.2665.

**[0080] (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(6-((Dicyclopentylmethyl)amino)-2-(methylthio)-9*H*-purin-9-yl)-1-((methylthio)methyl)bicyclo[3.1.0]hexane-2,3-diol (31).**  $CH_3SNa$  (27 mg, 0.38 mmol) was added to a solution of compound **28** (19 mg, 0.03 mmol) in dry DMF (1 mL) and heated at 90 °C under microwave condition for 1 h. Solvent was evaporated under vacuum, and the residue was purified on flash silica gel column chromatography (hexane: ethylacetate = 1:1) to give compound **31** (11 mg, 57%) as a colorless syrup.  $^1H$  NMR ( $CD_3OD$ , 400 MHz)  $\delta$  8.24 (s, 1H), 4.81-4.78 (m, 2H), 4.50 (t,  $J = 6.8$  Hz, 1H), 4.01 (d,  $J = 6.8$  Hz, 1H), 3.23 (d,  $J = 13.6$  Hz, 1H), 2.73 (d,  $J = 13.6$  Hz, 1H), 2.56 (s, 3H), 2.22-2.16 (m, 5H), 1.77-1.75 (m, 5H), 1.64-1.52 (m, 9H), 1.45-1.31 (m, 4H), 0.82-0.79 (m, 1H). HRMS calculated for  $C_{25}H_{38}N_5O_2S_2$  ( $M + H$ ) $^+$ : 504.2467; found 504.2458.

**[0081] (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclopentylmethyl)amino)-9*H*-purin-9-yl)-1-(((2- fluorophenyl)thio)methyl)bicyclo[3.1.0]hexane-2,3-diol (32).** Compound **32** (88%) was prepared from compound **81** following the same method as for compound **9b**.  $^1H$  NMR ( $CD_3OD$ , 400 MHz)  $\delta$  8.13 (s, 1H), 7.49-7.45 (m, 1H), 7.20-7.14 (m, 1H), 7.07-7.01

(m, 2H), 4.84 (d,  $J = 6.8$  Hz, 1H), 4.71 (s, 1H), 4.40 (t,  $J = 6.8$  Hz, 1H), 4.05 (d,  $J = 6.4$  Hz, 1H), 3.69 (d,  $J = 14.0$  Hz, 1H), 3.82 (d,  $J = 14.0$  Hz, 1H), 2.25-2.15 (m, 2H), 1.85-1.72 (m, 4H), 1.62-1.55 (m, 9H), 1.45-1.27 (m, 5H), 0.91-0.89 (m, 1H). HRMS calculated for  $C_{29}H_{36}N_5O_2ClSF$  (M + H)<sup>+</sup>: 572.2262; found 572.2273.

**[0082] (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclopentylmethyl)amino)-9H-purin-9-yl)-1-(((3,4-dimethoxyphenyl)thio)methyl)bicyclo[3.1.0]hexane-2,3-diol (33).** Compound **33** (87%) was prepared from compound **84** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.11 (s, 1H), 7.06 (s, 1H), 6.98 (d,  $J = 8.0$  Hz, 1H), 6.83 (d,  $J = 8.0$  Hz, 1H), 4.79 (d,  $J = 6.0$  Hz, 1H), 4.70 (s, 1H), 4.40 (d,  $J = 6.8$  Hz, 1H), 4.00 (d,  $J = 6.8$  Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.67 (d,  $J = 14.4$  Hz, 1H), 3.21 (d,  $J = 14.4$  Hz, 1H), 2.23-2.15 (m, 2H), 1.87-1.71 (m, 4H), 1.61-1.56 (m, 9H), 1.40-1.29 (m, 5H), 0.91-0.87 (m, 1H). HRMS calculated for  $C_{31}H_{41}N_5O_4ClS$  (M + H)<sup>+</sup>: 614.2568; found 614.2565.

**[0083] (1*R*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclohexylmethyl)amino)-9H-purin-9-yl)-1-(hydroxymethyl) bicyclo[3.1.0]hexane-2,3-diol (34).** Compound **34** (88%) was prepared from compound **64** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.45 (s, 1H), 4.81-4.78 (m, 2H), 4.29 (d,  $J = 11.6$  Hz, 1H), 4.17 (t,  $J = 6.4$  Hz, 1H), 3.90 (d,  $J = 6.8$  Hz, 1H), 3.36 (d,  $J = 11.6$  Hz, 1H), 1.77-1.62 (m, 15H), 1.54 (t,  $J = 4.8$  Hz, 1H), 1.37-1.05 (m, 8H), 0.78-0.75 (m, 1H). HRMS calculated for  $C_{25}H_{37}N_5O_3Cl$  (M + H)<sup>+</sup>: 490.2585; found 490.2579.

**[0084] (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclohexylmethyl)amino)-9H-purin-9-yl)-1-(fluoromethyl)bicyclo[3.1.0]hexane-2,3-diol (35).** Compound **35** (91%) was prepared from compound **76** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.14 (s, 1H), 5.08 (dd,  $J_1 = 11.2$  Hz,  $J_2 = 49.8$  Hz, 1H), 4.84 (s, 1H), 4.74 (d,  $J = 6.8$  Hz, 1H), 4.38 (dd,  $J_1 = 11.2$  Hz,  $J_2 = 49.8$  Hz, 1H), 4.17 (t,  $J = 6.4$  Hz, 1H), 3.92 (d,  $J = 6.4$  Hz, 1H), 1.83-1.65 (m, 15H), 1.33-1.04 (m, 9H), 0.91-0.87 (m, 1H). HRMS calculated for  $C_{25}H_{36}N_5O_2F$  (M + H)<sup>+</sup>: 492.2542; found 492.2543.

**[0085] (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclohexylmethyl)amino)-9H-purin-9-yl)-1-(chloromethyl)bicyclo[3.1.0]hexane-2,3-diol (36).** Compound **36** (89%) was prepared from compound **73** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.29 (s, 1H), 4.83-4.79 (m, 2H), 4.31 (d,  $J = 11.6$  Hz, 1H), 4.17 (t,  $J = 6.4$  Hz, 1H), 4.00 (d,  $J = 6.8$  Hz, 1H), 3.69 (d,  $J = 11.6$  Hz, 1H), 1.84-1.65 (m, 15H), 1.36-1.04 (m, 9H), 0.98-0.95 (m, 1H). HRMS calculated for  $C_{25}H_{36}N_5O_2Cl_2$  (M + H)<sup>+</sup>: 508.2246; found 508.2244.

[0086] **(1*R*,2*R*,3*S*,4*R*,5*S*)-4-(6-(((*R*)-Cyclobutyl(cyclopropyl)methyl)amino)-2-iodo-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (43).** A solution of compound **90** (108 mg, 0.13 mmol) in methanol (2 mL) and 10% TFA was heated at 70 °C overnight. Solvent was evaporated under reduced pressure and the residue was purified on flash silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 15:1) to provide compound **43** (56 mg, 81%) as colorless syrup. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.37 (s, 1H), 4.81 (s, 1H), 4.78 (d, *J* = 6.8 Hz, 1H), 4.28 (d, *J* = 10.6 Hz, 1H), 3.88 (d, *J* = 6.4 Hz, 1H), 3.79 (br s, 1H), 3.38 (d, *J* = 10.6 Hz, 1H), 2.70-2.66 (m, 1H), 2.18-2.09 (m, 1H), 2.02-1.87 (m, 4H), 1.82-1.80 (m, 1H), 1.60-1.58 (m, 1H), 1.55-1.53 (m, 1H), 0.94-0.90 (m, 1H), 0.78-0.75 (m, 1H), 0.55 (t, *J* = 8.0 Hz, 1H), 0.41-0.39 (m, 3H). HRMS calculated for C<sub>20</sub>H<sub>27</sub>N<sub>5</sub>O<sub>3</sub>I (M + H)<sup>+</sup>: 512.1159; found 512.1165.

[0087] **(1*R*,2*R*,3*S*,4*R*,5*S*)-4-(6-(((*S*)-Cyclobutyl(cyclopropyl)methyl)amino)-2-iodo-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (45).** Compound **45** (85%) was prepared from compound **91** following the same method for compound **43**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.37 (s, 1H), 4.81 (s, 1H), 4.78 (d, *J* = 6.8 Hz, 1H), 4.28 (d, *J* = 10.6 Hz, 1H), 3.88 (d, *J* = 6.4 Hz, 1H), 3.78 (br s, 1H), 3.38 (d, *J* = 10.6 Hz, 1H), 2.69-2.65 (m, 1H), 2.18-2.07 (m, 1H), 1.97-1.86 (m, 4H), 1.82-1.80 (m, 1H), 1.60-1.58 (m, 1H), 1.55-1.52 (m, 1H), 0.93-0.91 (m, 1H), 0.77-0.74 (m, 1H), 0.54 (t, *J* = 8.0 Hz, 1H), 0.42-0.38 (m, 3H). HRMS calculated for C<sub>20</sub>H<sub>27</sub>N<sub>5</sub>O<sub>3</sub>I (M + H)<sup>+</sup>: 512.1159; found 512.1166.

[0088] **Ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclopentylmethyl)amino)-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carboxylate (47).** Compound **47** (91%) was prepared from compound **94** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.98 (s, 1H), 5.24 (d, *J* = 6.8 Hz, 1H), 4.77 (s, 1H), 4.39 (t, *J* = 6.8 Hz, 1H), 4.28-4.23 (m, 2H), 4.12 (d, *J* = 6.4 Hz, 1H), 2.24-2.14 (m, 3H), 1.88-1.86 (m, 1H), 1.81-1.76 (m, 4H), 1.63-1.50 (m, 9H), 1.44-1.34 (m, 2H), 1.33-1.28 (m, 5H). HRMS calculated for C<sub>25</sub>H<sub>35</sub>N<sub>5</sub>O<sub>4</sub>Cl (M + H)<sup>+</sup>: 504.2378; found 504.2381.

[0089] **Ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-(((*S*)-cyclobutyl(cyclopropyl)methyl)amino)-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carboxylate (48).** Compound **48** (88%) was prepared from compound **95** following the same method as for compound **9b**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.89 (s, 1H), 5.24 (d, *J* = 6.4 Hz, 1H), 4.76 (s, 1H), 4.30-4.25 (m, 2H), 4.11 (d, *J* = 6.4 Hz, 1H), 3.78 (br s, 1H), 2.69-2.63 (m, 1H), 2.17-2.14 (m, 1H), 2.11-2.06 (m, 1H), 2.02-

1.89 (m, 4H), 1.86-1.79 (m, 1H), 1.62-1.59 (m, 1H), 1.35-1.31 (m, 4H), 0.94-0.90 (m, 1H), 0.54 (t,  $J = 8.0$  Hz, 1H), 0.37 (br s, 3H). HRMS calculated for  $C_{22}H_{29}N_5O_4$ l (M + H)  $^+$ : 554.1264; found 554.1263.

[0090] **(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(6-Amino-2-chloro-9H-purin-9-yl)-2,3-dihydroxy-N,N-bis(2-methoxyethyl)bicyclo[3.1.0]hexane-1-carboxamide (49) and (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-Chloro-6-((dicyclopropylmethyl)amino)-9H-purin-9-yl)-2,3-dihydroxy-N,N-bis(2-methoxyethyl)bicyclo[3.1.0]hexane-1-carboxamide (50).** Dowex50 (75 mg) was added to a solution of compound 99 (55 mg, 0.10 mmol) in MeOH (1 mL) - water (1 mL) and the mixture was stirred overnight at room temperature. After completion of starting material, the reaction mixture was filtered, and evaporated under vacuum. The crude mixture was purified on flash silica gel column chromatography ( $CH_2Cl_2$ : MeOH = 20:1) to give the desired compound **50** (28 mg, 56%) as a colorless syrup. Further elution with ( $CH_2Cl_2$ :MeOH = 15:1) gave a N<sup>6</sup> truncated derivative **49** (11 mg, 26%) as a colorless syrup.  $^1H$  NMR ( $CD_3OD$ , 400 MHz)  $\delta$  8.93 (s, 1H), 4.82 (s, 1H), 4.66 (d,  $J = 6.4$  Hz, 1H), 4.25-4.21 (m, 1H), 3.94 (d,  $J = 6.4$  Hz, 1H), 3.66-3.48 (m, 8H), 3.38 (s, 3H), 3.36 (s, 3H), 2.02-1.96 (m, 2H), 1.39-1.37 (m, 1H), 1.16-1.10 (m, 2H), 0.60-0.56 (m, 2H), 0.48-0.40 (m, 6H). HRMS calculated for  $C_{25}H_{36}N_6O_5Cl$  (M + H)  $^+$ : 535.2436; found 535.2438.

[0091] **(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(6-amino-2-chloro-9H-purin-9-yl)-2,3-dihydroxy-N,N-bis(2-methoxyethyl)bicyclo[3.1.0]hexane-1-carboxamide (49):**  $^1H$  NMR ( $CD_3OD$ , 400 MHz)  $\delta$  8.98 (s, 1H), 4.83 (s, 1H), 4.66 (d,  $J = 6.4$  Hz, 1H), 4.25-4.21 (m, 1H), 3.97 (d,  $J = 6.6$  Hz, 1H), 3.86-3.59 (m, 8H), 3.38 (s, 3H), 3.36 (s, 3H), 2.01-1.96 (m, 2H), 1.39-1.36 (m, 1H). HRMS calculated for  $C_{18}H_{26}N_6O_5Cl$  (M + H)  $^+$ : 441.1653; found 441.1648.

[0092] **(2*R*,3*R*,4*S*,5*R*)-2-(6-(((*S*)-Cyclobutyl(cyclopropyl)methyl)amino)-2-iodo-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (51) and (*S*)-N-(Cyclobutyl(cyclopropyl)methyl)-2-iodo-9H-purin-6-amine (54).** A solution of compound 101 (20 mg, 0.03 mmol) in methanol (2 mL) and 10% TFA (2 mL) was heated at 70 °C for 2 h. After completion of starting material, solvent was evaporated under reduced pressure and the residue was purified on flash silica gel column chromatography ( $CH_2Cl_2$ :MeOH = 40:1) to give a compound **54** (2.4 mg, 18%) as colorless syrup, which was found to be fragmented base moiety. Further elution with ( $CH_2Cl_2$ : MeOH = 20:1) gave the desired compound **51** (10 mg, 52%) as syrup. Data for compound **54**:  $^1H$  NMR ( $CD_3OD$ , 400 MHz)  $\delta$  7.96 (s, 1H), 3.79 (br s, 1H), 2.72-2.64 (m, 1H), 2.15-2.05 (m, 1H), 2.02-1.84 (m, 4H), 1.84-1.79 (m, 1H),

0.97-0.88 (m, 1H), 0.57-0.53 (m, 1H), 0.39-0.37 (m, 3H). HRMS calculated for  $C_{13}H_{17}N_5I$  (M + H)<sup>+</sup>: 370.0529; found 370.0526. Data for compound **51**: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.16 (s, 1H), 5.91 (d, J = 5.2 Hz, 1H), 4.68 (d, J = 9.2 Hz, 1H), 4.32-4.31 (m, 1H), 4.16 (s, 1H), 3.91-3.74 (m, 3H), 2.70-2.66 (m, 1H), 2.10-2.09 (m, 1H), 2.03-1.89 (m, 4H), 1.86-1.76 (m, 1H), 0.94-0.92 (m, 1H), 0.55-0.53 (m, 1H), 0.37 (br s, 3H). HRMS calculated for  $C_{18}H_{25}N_5O_4I$  (M + H)<sup>+</sup>: 502.0951; found 502.0951.

**[0093] (S)-N-(Cyclobutyl(cyclopropyl)methyl)-2-iodo-9H-purin-6-amine (55).**

Compound **55** (84%) was prepared from compound **102** following the same method as for compound **61**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.23 (s, 1H), 2.62 (br s, 2H), 0.37-0.35 (m, 1H), 0.21-0.23 (m, 2H), 0.44-0.46 (m, 2H). HRMS calculated for  $C_9H_{11}N_5Cl$  (M + H)<sup>+</sup>: 224.0703; found 224.0702.

**[0094] 9-((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-3*b*-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-5-yl)-2,6-dichloro-9H-purine (57).** Compound **57** was synthesized as reported (compound **54** in Tosh et al.<sup>9</sup>).

**[0095] 9-((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-3*b*-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-5-yl)-6-chloro-2-iodo-9H-purine (58).** Compound **58** was synthesized as reported (compound **11** in Tosh et al.<sup>40</sup>).

**[0096] 9-((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-3*b*-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-5-yl)-2-iodo-N-(dicyclopropylmethyl)-9H-purin-6-amine (61).** Compound **61** (83%) was prepared from compound **58** following the same method as for compound **62**; see below. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.12 (s, 1H), 7.66-7.62 (m, 4H), 7.43-7.27 (m, 6H), 5.30 (d, J = 6.8 Hz, 1H), 4.90 (s, 1H), 4.71 (d, J = 6.8 Hz, 1H), 4.23 (d, J = 10.4 Hz, 1H), 3.88 (d, J = 10.4 Hz, 1H), 3.42 (br s, 1H), 1.58-1.52 (m, 4H), 1.32-1.25 (m, 4H), 1.17-1.11 (m, 2H), 1.07 (s, 9H), 1.01-0.98 (m, 1H), 0.60-0.54 (m, 2H), 0.49-0.39 (m, 6H). HRMS calculated for  $C_{38}H_{47}N_5O_3SiI$  (M + H)<sup>+</sup>: 776.2490; found 776.2493.

**[0097] 9-((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-3*b*-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-5-yl)-N-(dicyclobutylmethyl)-2-iodo-9H-purin-6-amine (62).** Dicyclobutylmethanamine hydrochloride (99 mg, 0.71 mmol) and DIPEA (0.24 mL, 1.42 mmol) was added to a solution of compound **58** (100 mg, 0.14 mmol) in isopropanol (1.5 mL) stirred at room temperature overnight. Solvent was evaporated under vacuum, and the residue was purified on flash silica

gel column chromatography (hexane: ethyl acetate = 2:1) to give compound **62** (94 mg, 82%) as colorless foamy solid.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  7.89 (s, 1H), 7.65-7.62 (m, 4H), 7.43-7.29 (m, 6H), 5.64 (d,  $J$  = 6.8 Hz, 1H), 5.29 (d,  $J$  = 6.8 Hz, 1H), 4.95 (s, 1H), 4.61 (d,  $J$  = 6.8 Hz, 1H), 4.40-4.34 (m, 1H), 4.30 (d,  $J$  = 10.8 Hz, 1H), 3.73 (d,  $J$  = 10.8 Hz, 1H), 2.46-2.41 (m, 2H), 1.97-1.79 (m, 12H), 1.56-1.54 (m, 4H), 1.25 (s, 3H), 1.08 (s, 9H), 1.01-1.00 (m, 1H). HRMS calculated for  $\text{C}_{40}\text{H}_{51}\text{N}_5\text{O}_3\text{SiI}$  ( $\text{M} + \text{H}$ ) $^+$ : 804.2806; found 804.2814.

**[0098]** **9-((3a*R*,3b*R*,4a*S*,5*R*,5a*S*)-3b-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydro cyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-2-chloro-*N*-(dicyclopentylmethyl)-9*H*- purin-6-amine (63).** Compound **63** (79%) was prepared from compound **57** following the same method as for compound **61**.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.26 (s, 1H), 7.66-7.43 (m, 4H), 7.43-7.30 (m, 6H), 5.35 (d,  $J$  = 7.2 Hz, 1H), 4.95 (s, 1H), 4.72 (d,  $J$  = 6.8 Hz, 1H), 4.42 (t,  $J$  = 7.2 Hz, 1H), 4.24 (d,  $J$  = 10.8 Hz, 1H), 3.75 (d,  $J$  = 10.8 Hz, 1H), 2.20-2.14 (m, 2H), 1.81-1.77 (m, 4H), 1.64-1.53 (m, 9H), 1.52 (s, 3H), 1.45-1.33 (m, 4H), 1.25 (s, 3H), 1.14-1.12 (m, 1H), 1.08 (s, 9H), 0.98-0.92 (m, 1H). HRMS calculated for  $\text{C}_{42}\text{H}_{55}\text{N}_5\text{O}_3\text{SiCl}$  ( $\text{M} + \text{H}$ ) $^+$ : 740.3763; found 740.3753.

**[0099]** **9-((3a*R*,3b*R*,4a*S*,5*R*,5a*S*)-3b-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydro cyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-2-chloro-*N*-(dicyclohexylmethyl)-9*H*-purin-6-amine (64).** Compound **64** (84%) was prepared from compound **57** following the same method as for compound **61**.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.28 (s, 1H), 7.66-7.64 (m, 4H), 7.43-7.31 (m, 6H), 5.35 (d,  $J$  = 7.2 Hz, 1H), 4.96 (s, 1H), 4.73 (d,  $J$  = 6.8 Hz, 1H), 4.29-4.15 (m, 2H), 3.75 (d,  $J$  = 6.8 Hz, 1H), 1.77-1.69 (m, 12H), 1.65-1.61 (m, 7H), 1.52 (s, 3H), 1.38-1.22 (m, 5H), 1.14-1.12 (m, 3H), 1.07 (s, 9H), 0.99-0.95 (m, 1H). HRMS calculated for  $\text{C}_{44}\text{H}_{59}\text{N}_5\text{O}_3\text{SiCl}$  ( $\text{M} + \text{H}$ ) $^+$ : 768.4076; found 768.4087.

**[0100]** **((3a*R*,3b*R*,4a*S*,5*R*,5a*S*)-5-(2-chloro-6-((dicyclopentylmethyl)amino)-9*H*-purin-9-yl)-2,2- dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-3b(3a*H*)-yl)methanol (66).** TBAF (0.6 mL, 1M solution in THF) was added to a solution of compound **62** (296 mg, 0.4 mmol) in dry THF (5 mL) and stirred for 1 h until completion of starting material. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (hexane: ethylacetate = 1:2) to give the alcohol **66** (182 mg, 91%) as a colorless syrup.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.22 (s, 1H), 5.39 (d,  $J$  = 6.8 Hz, 1H), 4.95 (s, 1H), 4.71 (d,  $J$  = 7.2 Hz, 1H), 4.39 (t,  $J$  = 6.8 Hz, 1H), 4.01 (d,  $J$  = 11.6 Hz, 1H), 3.62 (d,  $J$  = 11.6 Hz, 1H), 2.24-2.14 (m, 2H), 1.81-1.69 (m, 5H), 1.63-1.54 (m, 7H), 1.52

(s, 3H), 1.43-1.30 (m, 5H), 1.28 (s, 3H), 1.14 (d,  $J = 5.2$  Hz, 1H), 0.99-0.95 (m, 1H). HRMS calculated for  $C_{26}H_{37}N_5O_3Cl$  ( $M + H$ )<sup>+</sup>: 502.2585; found 502.2587.

**[0101] ((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-5-(2-Chloro-6-((dicyclohexylmethyl)amino)-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-3*b*(3*aH*)-yl)methanol (67).** Compound **67** (90%) was prepared from compound **64** following the same method as for compound **66**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.22 (s, 1H), 5.39 (d,  $J = 7.2$  Hz, 1H), 4.95 (s, 1H), 4.71 (d,  $J = 7.2$  Hz, 1H), 4.17 (t,  $J = 6.4$  Hz, 1H), 4.01 (d,  $J = 11.6$  Hz, 1H), 3.62 (d,  $J = 11.6$  Hz, 1H), 1.77-1.66 (m, 16H), 1.52 (s, 3H), 1.33-1.24 (m, 5H), 1.21-1.02 (m, 6H), 0.99-0.96 (m, 1H). HRMS calculated for  $C_{28}H_{41}N_5O_3Cl$  ( $M + H$ )<sup>+</sup>: 530.2898; found 530.2900.

**[0102] ((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-5-(6-((Dicyclopropylmethyl)amino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-3*b*(3*aH*)-yl)methanol (68).** Compound **68** (91%) was prepared from compound **61** following the same method as for compound **66**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.12 (s, 1H), 5.35 (d,  $J = 7.2$  Hz, 1H), 4.93 (s, 1H), 4.71 (d,  $J = 6.4$  Hz, 1H), 3.94 (d,  $J = 11.2$  Hz, 1H), 3.76 (d,  $J = 11.2$  Hz, 1H), 3.4 (br s, 1H), 1.66-1.62 (m, 1H), 1.52 (s, 3H), 1.26 (s, 3H), 1.16-1.07 (m, 3H), 0.99-0.96 (m, 1H), 0.59-0.54 (m, 2H), 0.47-0.37 (m, 6H). HRMS calculated for  $C_{22}H_{29}N_5O_3I$  ( $M + H$ )<sup>+</sup>: 538.1315; found 538.1314.

**[0103] ((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-5-(2-Chloro-6-((dicyclopropylmethyl)amino)-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-3*b*(3*aH*)-yl)methyl methanesulfonate (69).** Methanesulfonyl chloride (30  $\mu$ L, 0.37 mmol) was added to a solution of compound **65** (84 mg, 0.18 mmol) in dry pyridine (1 mL) and the mixture was stirred for 30 min at room temperature. Saturated NaHCO<sub>3</sub> solution was added to quench the reaction, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 times), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 1:2) to give the mesylated derivative **69** (64 mg, 65%) as a colorless syrup. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.09 (s, 1H), 5.40 (d,  $J = 7.2$  Hz, 1H), 4.97 (s, 1H), 4.80 (d,  $J = 11.2$  Hz, 1H), 4.28 (d,  $J = 6.8$  Hz, 1H), 3.50 (br s, 1H), 3.16 (s, 3H), 1.85-1.80 (m, 1H), 1.72-1.66 (m, 1H), 1.54 (s, 3H), 1.32-1.30 (m, 1H), 1.27 (s, 3H), 1.21-1.12 (m, 2H), 0.60-0.55 (m, 2H), 0.46-0.39 (m, 6H). HRMS calculated for  $C_{23}H_{31}N_5O_5ClS$  ( $M + H$ )<sup>+</sup>: 524.1734; found 524.1734.

**[0104] ((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-5-(2-Chloro-6-((dicyclohexylmethyl)amino)-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-3*b*(3*aH*)-yl)methyl methanesulfonate (71).** Compound **71** (70%) was prepared from compound **67** following the same method as for compound **69**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.11 (s, 1H), 5.44 (d, J = 6.8 Hz, 1H), 4.97 (s, 1H), 4.87 (d, J = 11.2 Hz, 1H), 4.81 (d, J = 7.2 Hz, 1H), 4.27 (d, J = 11.2 Hz, 1H), 4.17 (t, J = 6.4 Hz, 1H), 3.17 (s, 3H), 1.85-1.82 (m, 1H), 1.77-1.66 (m, 14H), 1.33-1.30 (m, 2H), 1.27 (s, 3H), 1.21-1.04 (m, 8H). HRMS calculated for C<sub>29</sub>H<sub>43</sub>N<sub>5</sub>O<sub>5</sub>ClS (M + H)<sup>+</sup>: 608.2673; found 608.2684.

**[0105] 2-Chloro-9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-3*b*-(chloromethyl)-2,2-dimethylhexahydrocyclopropa [3,4]cyclopenta[1,2-d][1,3]dioxol-5-yl)-N-(dicyclopentylmethyl)-9H-purin-6-amine (72).** SOCl<sub>2</sub> (57 μL, 0.78 mmol) was added dropwise to a solution of compound **66** (131 mg, 0.26 mmol) in dry CH<sub>3</sub>CN (4 mL) followed by pyridine (42 μL, 0.52 mmol) at -5 °C, and the resulting mixture was stirred for 30 min under the same conditions. After 30 min the reaction mixture was brought to room temperature and stirred for 6 hrs. The reaction mixture was quenched with water and neutralized with 1M NaHCO<sub>3</sub> solution. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 times), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 2:1) to afford the chloro derivative **72** (101 mg, 75%) as a colorless syrup. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.22 (s, 1H), 5.37 (d, J = 7.2 Hz, 1H), 4.94 (s, 1H), 4.78 (d, J = 7.2 Hz, 1H), 4.39 (t, J = 6.8 Hz, 1H), 4.16 (d, J = 11.6 Hz, 1H), 3.78 (d, J = 11.6 Hz, 1H), 2.22-2.14 (m, 2H), 1.82-1.74 (m, 5H), 1.62-1.56 (m, 7H), 1.53 (s, 3H), 1.43- 1.28 (m, 6H), 1.26 (s, 3H), 1.13-1.09 (m, 1H). HRMS calculated for C<sub>26</sub>H<sub>35</sub>N<sub>5</sub>O<sub>2</sub>Cl<sub>2</sub> (M + H)<sup>+</sup>: 520.2246; found 520.2244.

**[0106] 2-Chloro-9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-3*b*-(chloromethyl)-2,2-dimethylhexahydrocyclopropa [3,4]cyclopenta[1,2-d][1,3]dioxol-5-yl)-N-(dicyclohexylmethyl)-9H-purin-6-amine (73).** Compound **73** (73%) was prepared from compound **67** following the same method as for compound **72**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.15 (s, 1H), 5.37 (d, J = 6.8 Hz, 1H), 4.94 (s, 1H), 4.78 (d, J = 7.2 Hz, 1H), 4.16-4.13 (m, 2H), 3.78 (d, J = 11.6 Hz, 1H), 1.83-1.65 (m, 16H), 1.53 (s, 3H), 1.33-1.21 (m, 5H), 1.21-1.04 (m, 7H). HRMS calculated for C<sub>28</sub>H<sub>40</sub>N<sub>5</sub>O<sub>2</sub>Cl<sub>2</sub> (M + H)<sup>+</sup>: 548.2559; found 548.2552.

**[0107] 2-Chloro-N-(dicyclopropylmethyl)-9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-3*b*-(fluoromethyl)-2,2- dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-5-**

**yl)-9H-purin-6-amine (74).** TBAF (0.12 mL, 1M solution in THF) was added to a solution of compound **69** (21 mg, 0.04 mmol) in dry THF and the mixture heated at 70 °C for two h. Solvent was evaporated, and the residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 1:1) to provide the fluoro derivative **74** (15 mg, 83%) as a colorless syrup. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.07 (s, 1H), 5.38 (d, J = 6.8 Hz, 1H), 4.98 (d, J = 2.0 Hz, 1H), 4.76-4.72 (m, 1H), 4.58 (dd, J<sub>1</sub> = 10.0 Hz, J<sub>2</sub> = 48.2 Hz, 1H), 3.46 (br s, 1H), 3.27-3.23 (m, 1H), 1.80-1.77 (m, 1H), 1.72-1.64 (m, 1H), 1.53 (s, 3H), 1.48-1.39 (m, 1H), 1.27 (s, 3H), 1.16-1.08 (m, 2H), 0.60-0.55 (m, 2H), 0.46-0.39 (m, 6H). HRMS calculated for C<sub>22</sub>H<sub>28</sub>N<sub>5</sub>O<sub>2</sub>ClF (M + H)<sup>+</sup>: 448.1916; found 448.1924.

**[0108] 2-Chloro-N-(dicyclopentylmethyl)-9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-3*b*-(fluoromethyl)-2,2- dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-9H-purin-6-amine (75).** DAST (17 μL, 0.13 mmol) was added dropwise to a solution of compound **66** (44 mg, 0.08 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at 0 °C and stirred for 30 min at the same condition. After completion of the starting material solvent was evaporated under vacuum, and the residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 2:1) to give fluoro derivative **75** (24 mg, 55%) as a colorless syrup. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.16 (s, 1H), 5.39 (d, J = 6.8 Hz, 1H), 4.93 (s, 1H), 4.81-4.74 (m, 2H), 4.76 (d, J = 7.2 Hz, 1H), 4.37 (t, J = 6.8 Hz, 1H), 2.22-2.16 (m, 2H), 1.86-1.71 (m, 5H), 1.63-1.61 (m, 9H), 1.53 (s, 3H), 1.38-1.31 (m, 4H), 1.27 (s, 3H), 1.12-1.06 (m, 1H). HRMS calculated for C<sub>26</sub>H<sub>36</sub>N<sub>5</sub>O<sub>2</sub>ClF (M + H)<sup>+</sup>: 504.2542; found 504.2545.

**[0109] 2-Chloro-N-(dicyclohexylmethyl)-9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-3*b*-(fluoromethyl)-2,2- dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-9H-purin-6-amine (76).** Compound **76** (85%) was prepared from compound **71** following the same method as for compound **74**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.09 (s, 1H), 5.38 (d, J = 6.8 Hz, 1H), 4.97 (s, 1H), 4.86-4.74 (m, 2H), 4.57 (dd, J<sub>1</sub> = 10 Hz, J<sub>2</sub> = 48.6 Hz, 1H), 1.17 (t, J = 6.4 Hz, 1H), 1.76-1.65 (m, 15H), 1.53 (s, 3H), 1.33-1.24 (m, 5H), 1.20-1.04 (m, 8H). HRMS calculated for C<sub>28</sub>H<sub>40</sub>N<sub>5</sub>O<sub>2</sub>ClF (M + H)<sup>+</sup>: 532.2855; found 532.2857.

**[0110] 2-Chloro-N-(dicyclopentylmethyl)-9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-2,2-dimethyl-3*b*-(methylthio)methyl)hexahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-9H-purin- 6-amine (77).** Compound **77** (65%) was prepared from compound **72** following the same method as for compound **87**, as described later herein. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.15 (s, 1H), 5.33 (d, J = 7.2 Hz, 1H), 4.90 (s, 1H), 4.77 (d, J = 7.2 Hz, 1H), 4.40 (t, J

= 6.8 Hz, 1H), 3.24 (d, J = 13.6 Hz, 1H), 2.75 (d, J = 13.6 Hz, 1H), 2.22-2.14 (m, 5H), 1.81-1.74 (m, 4H), 1.66-1.54 (m, 9H), 1.53 (s, 3H), 1.44-1.28 (m, 4H), 1.26 (s, 3H), 1.19 (t, J = 4.8 Hz, 1H), 1.00-0.97 (m, 1H). HRMS calculated for C<sub>27</sub>H<sub>39</sub>N<sub>5</sub>O<sub>2</sub>ClS (M + H)<sup>+</sup>: 532.2513; found 532.2513.

**[0111] 2-Chloro-N-(dicyclopentylmethyl)-9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-3*b*-((ethylthio)methyl)-2,2-dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-9H-purin-6-amine (78).** Compound **78** (70%) was prepared from compound **72** following the same method as for compound **87**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.17 (s, 1H), 5.33 (d, J = 6.8 Hz, 1H), 4.90 (s, 1H), 4.77 (d, J = 7.2 Hz, 1H), 4.40 (t, J = 6.8 Hz, 1H), 3.22 (d, J = 13.4 Hz, 1H), 2.85 (d, J = 13.4 Hz, 1H), 2.64-2.59 (m, 2H), 2.24-2.14 (m, 2H), 1.81-1.63 (m, 4H), 1.63-1.54 (m, 9H), 1.52 (s, 3H), 1.44-1.22 (m, 10H), 1.17 (t, J = 4.8 Hz, 1H), 1.00-0.96 (m, 1H). HRMS calculated for C<sub>28</sub>H<sub>41</sub>N<sub>5</sub>O<sub>2</sub>ClS (M + H)<sup>+</sup>: 546.2670; found 546.2667.

**[0112] 9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-3*b*-((butylthio)methyl)-2,2-dimethylhexahydrocyclopropa[3,4] cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-2-chloro-N-(dicyclopentylmethyl)-9H-purin-6-amine (79).** Compound **79** (73%) was prepared from compound **72** following the same method as for compound **87**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.16 (s, 1H), 5.33 (d, J = 7.2 Hz, 1H), 4.90 (s, 1H), 4.79 (d, J = 7.2 Hz, 1H), 4.40 (t, J = 6.8 Hz, 1H), 3.19 (d, J = 13.2 Hz, 1H), 2.87 (d, J = 13.2 Hz, 1H), 2.56 (t, J = 7.2 Hz, 2H), 2.22-2.14 (m, 2H), 1.78-1.74 (m, 5H), 1.65-1.55 (m, 8H), 1.52 (s, 3H), 1.41-1.29 (m, 8H), 1.27 (s, 3H), 1.15 (t, J = 4.8 Hz, 1H), 1.00-0.94 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H). HRMS calculated for C<sub>30</sub>H<sub>45</sub>N<sub>5</sub>O<sub>2</sub>ClS (M + H)<sup>+</sup>: 574.2983; found 574.2988.

**[0113] 2-Chloro-N-(dicyclopentylmethyl)-9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-3*b*-(((2-fluorophenyl)thio) methyl)-2,2-dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-9H-purin-6-amine (81).** Compound **81** (74%) was prepared from compound **72** following the same method as for compound **87**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.06 (s, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.20-7.15 (m, 1H), 7.05-6.98 (m, 2H), 5.35 (d, J = 6.8 Hz, 1H), 4.85 (s, 1H), 4.79 (d, J = 7.2 Hz, 1H), 4.40 (t, J = 6.8 Hz, 1H), 3.65 (d, J = 13.2 Hz, 1H), 3.29 (d, J = 13.2 Hz, 1H), 2.22-2.16 (m, 2H), 1.83-1.73 (m, 4H), 1.68-1.53 (m, 9H), 1.51 (s, 3H), 1.40-1.33 (m, 4H), 1.25 (s, 3H), 1.09 (t, J = 4.8 Hz, 1H), 0.96-0.93 (m, 1H). HRMS calculated for C<sub>32</sub>H<sub>40</sub>N<sub>5</sub>O<sub>2</sub>ClSF (M + H)<sup>+</sup>: 612.2575; found 612.2567.

[0114] **2-Chloro-N-(dicyclopentylmethyl)-9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-3*b*-(((3,4-dimethoxyphenyl) thio)methyl)-2,2-dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-5-yl)-9H-purin-6-amine (84).** Compound **84** (72%) was prepared from compound **72** following the same method as for compound **87**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.05 (s, 1H), 7.08-7.04 (m, 2H), 6.84-6.82 (m, 1H), 5.34 (d, J = 6.8 Hz, 1H), 4.88 (s, 1H), 4.76 (d, J = 6.4 Hz, 1H), 4.39 (t, J = 7.2 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.60 (d, J = 13.4 Hz, 1H), 3.21 (d, J = 13.4 Hz, 1H), 2.24-2.16 (m, 2H), 1.84-1.69 (m, 4H), 1.68-1.56 (m, 8H), 1.54 (s, 3H), 1.45-1.30 (m, 5H), 1.26 (s, 3H), 1.14-1.08 (m, 1H), 0.94-0.87 (m, 1H). HRMS calculated for C<sub>34</sub>H<sub>45</sub>N<sub>5</sub>O<sub>4</sub>SCl (M + H)<sup>+</sup>: 654.2881; found 654.2883.

[0115] **2-Chloro-N-(dicyclopropylmethyl)-9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-2,2-dimethyl-3*b*-((methylthio) methyl)hexahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-5-yl)-9H-purin-6-amine (85).** Sodium thiomethoxide (17 mg, 0.24 mmol) was added to a solution of compound **69** (25 mg, 0.047 mmol) in dry DMF (1 mL) at 0 °C and stirred for 1 h. The reaction mixture was quenched with water, and the aqueous layer was extracted with ethyl acetate (3 times), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated. The residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 2:1) to give compound **85** (15 mg, 66%) as a colorless syrup. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.14 (s, 1H), 5.32 (d, J = 6.8 Hz, 1H), 4.90 (s, 1H), 4.75 (d, J = 6.8 Hz, 1H), 3.47 (br s, 1H), 3.21 (d, J = 13.6 Hz, 1H), 2.75 (d, J = 13.6 Hz, 1H), 2.16 (s, 3H), 1.59-1.55 (m, 1H), 1.52 (s, 3H), 1.26 (s, 3H), 1.19-1.09 (m, 3H), 0.99-0.96 (m, 1H), 0.60-0.55 (m, 2H), 0.47-0.43 (m, 6H). HRMS calculated for C<sub>23</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>ClS (M + H)<sup>+</sup>: 477.0360; found 477.0364.

[0116] **N-(Dicyclopropylmethyl)-9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-2,2-dimethyl-3*b*-((methylthio)methyl) hexahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-5-yl)-2-iodo-9H-purin-6-amine (86).** Compound **86** (85%) was prepared from compound **70** following the same method as for compound **85**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.03 (s, 1H), 5.31 (d, J = 6.8 Hz, 1H), 4.91 (s, 1H), 4.76 (d, J = 6.8 Hz, 1H), 4.12 (d, J = 13.6 Hz, 1H), 2.71 (d, J = 13.6 Hz, 1H), 2.17 (s, 3H), 1.52-1.50 (m, 4H), 1.26 (s, 3H), 1.17-1.07 (m, 3H), 0.99-0.95 (m, 1H), 0.60-0.54 (m, 2H), 0.47-0.37 (m, 6H). HRMS calculated for C<sub>23</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>IS (M + H)<sup>+</sup>: 568.1243; found 568.1249.

[0117] **9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-2,2-dimethyl-3*b*-((methylthio)methyl)hexahydrocyclopropa[3,4] cyclopenta[1,2-d][1,3]dioxol-5-yl)-2-iodo-9H-purin-6-amine (87).** Sodium thiomethoxide (29 mg, 0.41 mmol) was added to a

solution of compound **104** (38 mg, 0.082 mmol) in dry DMF (1 mL) stirred at room temperature for 1 h. The reaction mixture was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (EtOAc: MeOH = 100:0.5) to give compound **87** (15 mg, 39%) as a colorless syrup. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.08 (s, 1H), 5.32 (d, J = 7.2 Hz, 1H), 4.89 (s, 1H), 4.77 (d, J = 7.2 Hz, 1H), 2.72 (d, J = 13.6 Hz, 1H), 2.17-2.14 (m, 4H), 1.53-1.51 (m, 4H), 1.27 (s, 3H), 1.17 (d, J = 4.8 Hz, 1H), 1.00-0.96 (m, 1H). HRMS calculated for C<sub>16</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>IS (M + H)<sup>+</sup>: 474.0461; found 474.0461.

[0118] **1-((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-3*b*-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydro cyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-4,6-dichloro-1*H*-imidazo[4,5-*c*]pyridine (**88**)**. Diisopropyl azodicarboxylate (DIAD) (0.22 mL, 1.16 mmol) was added to a solution of triphenylphosphine (306 mg, 1.16 mmol) and 3-deaza-2,6-dichloro-purine (220 mg, 1.16 mmol) in dry THF (5 mL) at 0 °C and stirred at room temperature for 10 min. A solution of compound 56 (256 mg, 0.58 mmol) in THF (2 mL) was added to the reaction mixture and stirred overnight at room temperature. Solvent was evaporated, and the residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 3:1) to give compound **88** (209 mg, 59%) as a colorless foamy solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.88 (s, 1H), 7.72-7.67 (m 5H), 7.46-7.36 (m, 6H), 5.68 (s, 1H), 5.37 (d, J = 6.8 Hz, 1H), 4.79 (d, J = 7.2 Hz, 1H), 4.29 (d, J = 11.2 Hz, 1H), 3.47 (d, J = 11.2 Hz, 1H), 1.94-1.91 (m, 1H), 1.52 (s, 3H), 1.29 (s, 3H), 1.25 (t, J = 4.8 Hz, 1H), 1.14 (s, 9H), 0.93-0.90 (m, 1H). HRMS calculated for C<sub>32</sub>H<sub>36</sub>N<sub>3</sub>O<sub>3</sub>Cl<sub>2</sub>Si (M + H)<sup>+</sup>: 608.1903; found 608.1904.

[0119] **1-((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-3*b*-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-6-chloro-*N*-(dicyclopentylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine (**89**)**.

Dicyclopentylmethanamine (178 mg, 0.87 mmol) and DIPEA (0.38 mL, 2.18 mmol) was added to a solution of compound **88** (133 mg, 0.21 mmol) in isopropanol (2 mL) and heated at 140 °C under microwave condition for 25 h. Solvent was evaporated under vacuum, and the residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 4:1) to give compound **89** (36 mg, 22%) as colorless foamy solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.33 (s, 1H), 7.72-7.65 (m 4H), 7.46-7.35 (m, 6H), 6.73 (s, 1H), 5.36 (d, J = 7.2 Hz, 1H), 4.82 (s, 1H), 4.63 (d, J = 6.8 Hz, 1H), 4.38 (br s, 1H), 4.25 (d, J = 11.2 Hz, 1H), 3.48 (d, J = 11.2 Hz, 1H), 2.19-2.13 (m, 2H), 1.79-1.73 (m, 5H), 1.60-1.52 (m, 11H), 1.42-1.32 (m,

4H), 1.27 (s, 3H), 1.19 (t, J = 4.8 Hz, 1H), 1.14 (s, 9H), 0.91-0.87 (m, 1H). HRMS calculated for C<sub>43</sub>H<sub>56</sub>N<sub>4</sub>O<sub>3</sub>ClSi (M + H)<sup>+</sup>: 739.3810; found 739.3822.

**[0120] 9-(((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-3*b*-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydro cyclopropa [3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-N-((*R*)-cyclobutyl(cyclopropyl)methyl)-2-iodo-9H-purin-6-amine (90).** (*R*)-

cyclobutyl(cyclopropyl)methanamine hydrochloride (115 mg, 0.71 mmol) and DIPEA (0.24 mL, 1.42 mmol) was added to a solution of compound **58** (100 mg, 0.14 mmol) in isopropanol (1.5 mL) stirred at room temperature overnight. Solvent was evaporated under vacuum, and the residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 2:1) to give compound **90** (108 mg, 96%) as colorless foamy solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.12 (s, 1H), 7.66-7.62 (m, 4H), 7.41-7.27 (m, 6H), 5.30 (d, J = 6.8 Hz, 1H), 4.90 (s, 1H), 4.71 (d, J = 6.8 Hz, 1H), 4.23 (d, J = 10.8 Hz, 1H), 3.88 (d, J = 10.8 Hz, 1H), 3.80 (br s, 1H), 2.70-2.66 (m, 1H), 2.11-2.09 (m, 1H), 1.98-1.87 (m, 4H), 1.82-1.79 (m, 1H), 1.59-1.52 (m, 4H), 1.25 (s, 3H), 1.11 (s, 9H), 1.01-0.91 (m, 3H), 0.56-0.54 (m, 1H), 0.48-0.37 (m, 3H). HRMS calculated for C<sub>39</sub>H<sub>49</sub>N<sub>5</sub>O<sub>3</sub>SiI (M + H)<sup>+</sup>: 790.2649; found 790.2642.

**[0121] 9-(((3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-3*b*-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-N-((*S*)-**

**cyclobutyl(cyclopropyl)methyl)-2-iodo-9H-purin-6-amine (91).** Compound **91** (89%) was prepared from compound **58** following the same method for compound **90**. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.12 (s, 1H), 7.67-7.62 (m, 4H), 7.41-7.26 (m, 6H), 5.30 (d, J = 6.8 Hz, 1H), 4.90 (s, 1H), 4.71 (d, J = 6.8 Hz, 1H), 4.23 (d, J = 10.4 Hz, 1H), 3.88 (d, J = 10.8 Hz, 1H), 3.81 (br s, 1H), 2.72-2.70 (m, 1H), 2.12-2.09 (m, 1H), 2.01-1.89 (m, 4H), 1.85-1.79 (m, 1H), 1.59-1.52 (m, 4H), 1.25 (s, 3H), 1.07 (s, 9H), 1.01-0.92 (m, 3H), 0.57-0.53 (m, 1H), 0.47-0.37 (m, 3H). HRMS calculated for C<sub>39</sub>H<sub>49</sub>N<sub>5</sub>O<sub>3</sub>SiI (M + H)<sup>+</sup>: 790.2649; found 790.2646.

**[0122] Ethyl (3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-5-(2-chloro-6-((dicyclopentylmethyl)amino)-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-**

**3*b*(3*aH*)-carboxylate (94).** Compound **94** (84%) was prepared from compound **93a** following the same method as for compound **90** (see Fig. 4; Reagents and Conditions: (i) R<sup>1</sup>NH<sub>2</sub>.HCl, DIPEA, 2-propanol, rt; (ii) 10% TFA, MeOH, 70 °C). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.05 (s, 1H), 5.86 (d, J = 7.2 Hz, 1H), 4.97 (s, 1H), 4.81 (d, J = 6.8 Hz, 1H), 4.38 (d,

$J = 7.2$  Hz, 1H), 4.28-4.20 (m, 2H), 2.28-2.23 (m, 1H), 2.21-2.13 (m, 2H), 1.84-1.71 (m, 5H), 1.67-1.52 (m, 9H), 1.51 (s, 3H), 1.43-1.38 (m, 2H), 1.35-1.31 (m, 5H), 1.26 (s, 3H). HRMS calculated for  $C_{28}H_{39}N_5O_4Cl$  ( $M + H$ )<sup>+</sup>: 544.2691; found 544.2689.

**[0123] Ethyl (3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-5-(2-iodo-6-(((*S*)-cyclobutyl(cyclopropyl)methyl)amino)-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3*b*(3*aH*)-carboxylate (95).** Compound **95** (86%) was prepared from compound **93b** following the same method as for compound **90** (Reagents and Conditions: (i) TEMPO, BAIB,  $CH_3CN-H_2O$ , rt; (ii) Deoxo-Fluor,  $CH_2Cl_2$ , rt; (iii) Dowex50,  $MeOH-H_2O$ ).  $^1H$  NMR ( $CD_3OD$ , 400 MHz)  $\delta$  7.95 (s, 1H), 5.82 (d,  $J = 6.8$  Hz, 1H), 4.93 (s, 1H), 4.81 (d,  $J = 6.8$  Hz, 1H), 4.33-4.24 (m, 2H), 3.77 (br s, 1H), 2.71-2.65 (m, 1H), 2.26-2.22 (m, 1H), 2.10-2.06 (m, 1H), 1.99-1.82 (m, 4H), 1.82-1.79 (m, 1H), 1.64-1.60 (m, 1H), 1.53-1.49 (m, 4H), 1.34 (t,  $J = 7.2$  Hz, 3H), 1.28 (s, 3H), 0.93-0.87 (m, 1H), 0.56 (t,  $J = 7.2$  Hz, 1H), 0.35 (br s, 3H). HRMS calculated for  $C_{25}H_{33}N_5O_4I$  ( $M + H$ )<sup>+</sup>: 594.1577; found 594.1578.

**[0124] (3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-5-(2-chloro-6-((dicyclopropylmethyl)amino)-9H-purin-9-yl)-*N,N*-bis(2-methoxyethyl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3*b*(3*aH*)-carboxamide (99).** Deoxo-Fluor (0.21 mL, 45% solution in THF, 0.32 mmol) was added to a solution of compound **97** (prepared as reported, 975 mg, 0.16 mmol) in dry  $CH_2Cl_2$  and stirred overnight at room temperature (Reagents and Conditions: (i) TEMPO, BAIB,  $CH_3CN-H_2O$ , rt; (ii) Deoxo-Fluor,  $CH_2Cl_2$ , rt; (iii) Dowex50,  $MeOH-H_2O$ ). Solvent was evaporated and the residue was purified on flash silica gel column chromatography (hexane:ethyl acetate = 1:2) to give a product **99** (56 mg, 60%) as colorless syrup instead of desired product **98**.  $^1H$  NMR ( $CD_3OD$ , 400 MHz)  $\delta$  8.48 (s, 1H), 5.30 (d,  $J = 7.2$  Hz, 1H), 5.02 (s, 1H), 4.74 (d,  $J = 7.2$  Hz, 1H), 4.08-4.05 (m, 1H), 3.71-3.48 (m, 14H), 2.26-2.22 (m, 1H), 1.60-1.57 (m, 4H), 1.44-1.40 (m, 1H), 1.27 (s, 3H), 1.18-1.09 (m, 2H), 0.60-0.55 (m, 2H), 0.44-0.42 (m, 6H). HRMS calculated for  $C_{28}H_{40}N_6O_5Cl$  ( $M + H$ )<sup>+</sup>: 575.2745; found 575.2748.

**[0125] ((3*aR*,4*R*,6*R*,6*aR*)-6-(6-(((*S*)-cyclobutyl(cyclopropyl)methyl)amino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol (101).** Compound **101** (82%) was prepared from compound **100** (see Fig. 6A; Reagents and Conditions: A. (i) (*S*)-(c-Bu)(c-Pr)CHNH<sub>2</sub>.HCl, DIPEA, 2-propanol, rt; (iii) 10% TFA, MeOH, 70 °C. B. (i) c-Pr(CH<sub>2</sub>)NH<sub>2</sub>, DIPEA, 2-propanol, rt.) following the same method as

for compound **62**.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.15 (s, 1H), 6.11 (d,  $J = 7.2$  Hz, 1H), 5.25-5.23 (m, 1H), 5.03-5.01 (m, 1H), 4.36-4.33 (m, 1H), 3.82-3.72 (m, 3H), 2.70-2.64 (m, 1H), 2.11-2.06 (m, 1H), 1.99-1.88 (m, 4H), 1.84-1.79 (m, 1H), 1.62 (s, 3H), 1.39 (s, 3H), 0.94-0.89 (m, 1H), 0.55 (t,  $J = 7.6$  Hz, 1H), 0.37 (br s, 3H). HRMS calculated for  $\text{C}_{21}\text{H}_{29}\text{N}_5\text{O}_4\text{I}$  ( $\text{M} + \text{H}$ ) $^+$ : 541.1264; found 541.1264.

**[0126] 9-((3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-3*b*-(chloromethyl)-2,2-dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxol-5-yl)-2-iodo-9H-purin-6-amine (104).**  $\text{SOCl}_2$  (62  $\mu\text{L}$ , 0.78 mmol) was added dropwise to a solution of compound **68** (152 mg, 0.28 mmol) in dry  $\text{CH}_3\text{CN}$  (3 mL) followed by pyridine (46  $\mu\text{L}$ , 0.56 mmol) at  $-5^\circ\text{C}$ , and the resulting mixture was stirred for 30 min under the same conditions (see FIG. 6B; Reagents and Conditions: (i)  $\text{SOCl}_2$ , pyridine,  $\text{CH}_3\text{CN}$ ,  $-5^\circ\text{C}$  to rt; (iii) 10% TFA, MeOH,  $70^\circ\text{C}$ ; (iii)  $\text{CH}_3\text{SNa}$ , DMF, rt.). After 30 min the reaction mixture was brought to room temperature and stirred overnight. The reaction mixture was quenched with water and neutralized with 1M  $\text{NaHCO}_3$  solution. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 times), dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated. The residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 1:2) to afford the chloro derivative **104** (90 mg, 69%) as a colorless syrup.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.09 (s, 1H), 5.36 (d,  $J = 6.8$  Hz, 1H), 4.93 (s, 1H), 4.79 (d,  $J = 7.2$  Hz, 1H), 4.26 (d,  $J = 11.6$  Hz, 1H), 3.73 (d,  $J = 11.6$  Hz, 1H), 1.79-1.75 (m, 1H), 1.53 (s, 3H), 1.30-1.25 (m, 4H), 1.13-1.09 (m, 1H). HRMS calculated for  $\text{C}_{15}\text{H}_{18}\text{N}_5\text{O}_2\text{ClI}$  ( $\text{M} + \text{H}$ ) $^+$ : 462.0194; found 462.0200.

**[0127] (3*aR*,3*bR*,4*aS*,5*R*,5*aS*)-5-(6-(cyclopentylamino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3*b*(3*aH*)-carbonitrile.** This compound is an intermediate in the synthesis of MRS8209 (see below). As shown in Fig. 7, TEMPO (8.5 mg, 0.05 mmol) and iodine (201 mg, 1.68 mmol) were added to a solution of 4'-hydroxymethyl derivative (291 mg, 0.56 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) and stirred for 2 h at room temperature. After 2 h, iodine (201 mg, 1.68 mmol) was again added followed by ammonium hydroxide solution (5 mL) and heated the reaction mixture at  $60^\circ\text{C}$  overnight. Saturated solution of  $\text{Na}_2\text{S}_2\text{O}_3$  (10 mL) was added into the reaction mixture to quench the reaction and aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 times), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated under vacuum. The crude reaction mixture was purified on flash silica gel column chromatography (hexane:ethyl acetate = 1:2) to give the 4'-cyano derivative as a colorless powder (245 mg, 85%).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  7.93 (s, 1H), 5.61 (d,  $J = 7.2$  Hz,

1H), 4.99 (s, 1H), 4.87 (d,  $J = 7.2$  Hz, 1H), 4.51 (br s, 1H), 2.44-2.40 (m, 1H), 2.12-2.06 (m, 2H), 1.84-1.80 (m, 2H), 1.77-1.67 (m, 2H), 1.64-1.58 (m, 4H), 1.55 (s, 3H), 1.28 (s, 3H). HRMS calculated for  $C_{20}H_{24}N_6O_2I$  ( $M + H$ )<sup>+</sup>: 507.1005; found 507.1010.

**[0128] (1R,2R,3S,4R,5S)-4-(6-(cyclopentylamino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carbonitrile (MRS8209) (40).** As shown in Fig. 7, a solution of 245 mg (0.48 mmol) of the 4'-cyano derivative, as described in the preceding paragraph, in methanol (5 mL) and 10% TFA (aqueous, 5 mL) was heated at 70°C for 3 h. Solvent was evaporated under reduced pressure and the residue was purified on flash silica gel column chromatography ( $CH_2Cl_2$ :MeOH = 20:1) to provide compound MRS8209 (205 mg, 91%) as colorless powder. <sup>1</sup>H NMR ( $CD_3OD$ , 400 MHz)  $\delta$  7.97 (s, 1H), 5.13 (d,  $J = 7.2$  Hz, 1H), 4.79 (s, 1H), 4.51 (br s, 1H), 4.08 (d,  $J = 6.8$  Hz, 1H), 2.38-2.34 (m, 1H), 2.14-2.06 (m, 2H), 1.94 (t,  $J = 5.2$  Hz, 1H), 1.84-1.80 (m, 2H), 1.77-1.67 (m, 2H), 1.66-1.55 (m, 2H), 1.47-1.43 (m, 1H). HRMS calculated for  $C_{17}H_{20}N_6O_2I$  ( $M + H$ )<sup>+</sup>: 467.0692; found 467.0697.

**[0129] 2-((1S,2R,3S,4R,5S)-4-(6-(cyclopentylamino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexan-1-yl)acetonitrile (41).** Compound **41** was prepared following the same method as per above method for compound **40**. <sup>1</sup>H NMR ( $CD_3OD$ , 400 MHz)  $\delta$  8.02 (s, 1H), 4.77 (s, 1H), 4.74 (d,  $J = 6.4$  Hz, 1H), 4.50 (br s, 1H), 3.94 (d,  $J = 6.8$  Hz, 1H), 3.19-3.01 (m, 2H), 2.13-2.06 (m, 2H), 1.83-1.77 (m, 2H), 1.71-1.65 (m, 3H), 1.62-1.55 (m, 3H), 0.92-0.88 (m, 1H). HRMS calculated for  $C_{18}H_{22}N_6O_2I$  ( $M + H$ )<sup>+</sup>: 481.0849; found 481.0850.

**[0130] (1R,2R,3S,4R,5S)-4-(6-(((R)-3,3-difluorocyclopentyl)amino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carbonitrile (42).** <sup>1</sup>H NMR ( $CD_3OD$ , 400 MHz)  $\delta$  8.00 (s, 1H), 5.13 (d,  $J = 6.8$  Hz, 1H), 4.80 (s, 1H), 4.70 (br s, 1H), 4.08 (d,  $J = 6.4$  Hz, 1H), 2.72-2.60 (m, 1H), 2.38-2.29 (m, 3H), 2.20-2.08 (m, 2H), 1.94 (t,  $J = 4.8$  Hz, 1H), 1.91-1.83 (m, 1H), 1.48-1.44 (m, 1H). HRMS calculated for  $C_{17}H_{18}N_6O_2IF_2$  ( $M + H$ )<sup>+</sup>: 503.0504; found 503.0509.

**[0131] 2-((1S,2R,3S,4R,5S)-4-(6-(((R)-3,3-difluorocyclopentyl)amino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexan-1-yl)acetonitrile (43).** <sup>1</sup>H NMR ( $CD_3OD$ , 400 MHz)  $\delta$  8.02 (s, 1H), 4.78 (s, 1H), 4.74-4.71 (m, 2H), 3.94 (d,  $J = 6.8$  Hz, 1H), 3.19-3.05 (m, 2H), 2.72-2.60 (m, 1H), 2.39-2.29 (m, 2H), 2.23-2.08 (m, 2H), 1.94-1.83 (m, 1H), 1.68-1.65 (m, 1H), 1.56 (t,  $J = 5.2$  Hz, 1H), 0.92-0.88 (m, 1H). HRMS calculated for  $C_{18}H_{20}N_6O_2IF_2$  ( $M + H$ )<sup>+</sup>: 517.0660; found 517.0659.

[0132] (1R,2R,3S,4R,5S)-4-(6-(((S)-3,3-difluorocyclopentyl)amino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carbonitrile (44). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.99 (s, 1H), 5.13 (d, *J* = 6.8 Hz, 1H), 4.80 (s, 1H), 4.70 (br s, 1H), 4.08 (d, *J* = 6.4 Hz, 1H), 2.72-2.60 (m, 1H), 2.38-2.29 (m, 3H), 2.21-2.08 (m, 2H), 1.94 (t, *J* = 4.8 Hz, 1H), 1.91-1.84 (m, 1H), 1.48-1.44 (m, 1H). HRMS calculated for C<sub>17</sub>H<sub>18</sub>N<sub>6</sub>O<sub>2</sub>IF<sub>2</sub> (M + H)<sup>+</sup>: 503.0504; found 503.0509.

[0133] 2-((1S,2R,3S,4R,5S)-4-(6-(((S)-3,3-difluorocyclopentyl)amino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexan-1-yl)acetonitrile (45). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.01 (s, 1H), 4.78 (s, 1H), 4.74-4.71 (m, 2H), 3.94 (d, *J* = 6.8 Hz, 1H), 3.19-3.05 (m, 2H), 2.72-2.60 (m, 1H), 2.39-2.29 (m, 2H), 2.23-2.08 (m, 2H), 1.93-1.83 (m, 1H), 1.68-1.65 (m, 1H), 1.56 (t, *J* = 5.2 Hz, 1H), 0.92-0.88 (m, 1H). HRMS calculated for C<sub>18</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>IF<sub>2</sub> (M + H)<sup>+</sup>: 517.0660; found 517.0654.

[0134] (1R,2R,3S,4R,5S)-4-(6-(bicyclo[1.1.1]pentan-1-ylamino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carbonitrile (46). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.97 (s, 1H), 5.13 (d, *J* = 6.4 Hz, 1H), 4.79 (s, 1H), 4.07 (d, *J* = 6.4 Hz, 1H), 2.52 (s, 1H), 2.38-2.34 (m, 1H), 2.25 (s, 6H), 1.95 (t, *J* = 4.8 Hz, 1H), 1.47-1.43 (m, 1H). HRMS calculated for C<sub>17</sub>H<sub>18</sub>N<sub>6</sub>O<sub>2</sub>I (M + H)<sup>+</sup>: 465.0536; found 465.0537.

[0135] 2-((1S,2R,3S,4R,5S)-4-(6-(bicyclo[1.1.1]pentan-1-ylamino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexan-1-yl)acetonitrile (47). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.00 (s, 1H), 4.77 (s, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 3.93 (d, *J* = 6.4 Hz, 1H), 3.19-3.04 (m, 2H), 2.52 (s, 1H), 2.48 (s, 6H), 1.68-1.65 (m, 1H), 1.56 (t, *J* = 5.2 Hz, 1H), 0.91-0.87 (m, 1H). HRMS calculated for C<sub>18</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>I (M + H)<sup>+</sup>: 479.0692; found 479.0698.

[0136] (1R,2R,3S,4R,5S)-4-(6-((3-chlorobenzyl)amino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxy bicyclo[3.1.0]hexane-1-carbonitrile (48). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.99 (s, 1H), 7.43 (s, 1H), 7.34-7.24 (m, 3H), 5.13 (d, *J* = 6.8 Hz, 1H), 4.79 (s, 1H), 4.72 (br s, 2H), 4.08 (d, *J* = 6.4 Hz, 1H), 2.39-2.35 (m, 1H), 1.94 (t, *J* = 5.2 Hz, 1H), 1.47-1.43 (m, 1H). HRMS calculated for C<sub>19</sub>H<sub>17</sub>N<sub>6</sub>O<sub>2</sub>ICl (M + H)<sup>+</sup>: 523.0146; found 523.0142.

[0137] 2-((1S,2R,3S,4R,5S)-4-(6-((3-chlorobenzyl)amino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexan-1-yl)acetonitrile (49). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.01 (s, 1H), 7.43 (s, 1H), 7.34-7.25 (m, 3H), 4.78 (s, 1H), 4.74-4.73 (m, 3H), 3.94 (d, *J* = 6.8 Hz, 1H), 3.18-3.05 (m, 2H), 1.69-1.66 (m, 1H), 1.56 (t, *J* = 5.2 Hz, 1H), 0.91-0.88 (m, 1H). HRMS calculated for C<sub>20</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>ICl (M + H)<sup>+</sup>: 537.0303; found 537.0302.

[0138] **1R,2R,3S,4R,5S)-4-(2-(5-chlorothiophen-2-yl)-6-(methylamino)-9H-purin-9-yl)-2,3-dihydroxybicyclo [3.1.0]hexane-1-carbonitrile (50).** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.02 (s, 1H), 7.88 (d, *J* = 4.0 Hz, 1H), 7.00 (d, *J* = 4.0 Hz, 1H), 5.41 (d, *J* = 6.8 Hz, 1H), 4.82 (s, 1H), 4.22 (d, *J* = 6.8 Hz, 1H), 3.17 (br s, 3H), 2.42-2.38 (m, 1H), 1.91 (t, *J* = 4.8 Hz, 1H), 1.50-1.47 (m, 1H). HRMS calculated for C<sub>17</sub>H<sub>16</sub>N<sub>6</sub>O<sub>2</sub>SCl (M + H)<sup>+</sup>: 403.0744; found 403.0744.

[0139] **(1R,2R,3S,4R,5S)-4-(2-(5-chlorothiophen-2-yl)-6-(propylamino)-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carbonitrile (51).** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.03 (s, 1H), 7.87 (d, *J* = 4.0 Hz, 1H), 6.99 (d, *J* = 4.0 Hz, 1H), 5.41 (d, *J* = 6.4 Hz, 1H), 4.82 (s, 1H), 4.22 (d, *J* = 6.8 Hz, 1H), 3.63 (br s, 2H), 2.42-2.38 (m, 1H), 1.91 (t, *J* = 4.8 Hz, 1H), 1.79-1.73 (m, 2H), 1.50-1.46 (m, 1H), 1.05 (t, *J* = 7.6 Hz, 3H). HRMS calculated for C<sub>19</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>SCl (M + H)<sup>+</sup>: 431.1057; found 431.1053.

[0140] **(1R,2R,3S,4R,5S)-4-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(methylamino)-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carbonitrile (52).** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.21 (s, 1H), 7.36 (d, *J* = 4.0 Hz, 1H), 7.03 (d, *J* = 4.0 Hz, 1H), 5.10 (d, *J* = 6.4 Hz, 1H), 4.85 (s, 1H), 4.08 (d, *J* = 6.4 Hz, 1H), 3.15 (br s, 3H), 2.47-2.43 (m, 1H), 2.01 (t, *J* = 5.2 Hz, 1H), 1.51-1.48 (m, 1H). HRMS calculated for C<sub>19</sub>H<sub>16</sub>N<sub>6</sub>O<sub>2</sub>SCl (M + H)<sup>+</sup>: 427.0744; found 427.0748.

[0141] **(1R,2R,3S,4R,5S)-4-(2-(benzylthio)-6-(methylamino)-9H-purin-9-yl)-1-(hydroxymethyl) bicyclo[3.1.0]hexane-2,3-diol (54).** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.36 (s, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.31-7.19 (m, 3H), 4.85 (s, 1H), 4.76 (d, *J* = 6.4 Hz, 1H), 4.52-4.44 (m, 2H), 4.27 (d, *J* = 12.0 Hz, 1H), 3.88 (d, *J* = 6.4 Hz, 1H), 3.22 (d, *J* = 7.2 Hz, 1H), 3.11 (br s, 3H), 1.62-1.59 (m, 1H), 1.55 (d, *J* = 4.8 Hz, 1H), 0.77-0.74 (m, 1H). HRMS calculated for C<sub>20</sub>H<sub>24</sub>N<sub>5</sub>O<sub>3</sub>S (M + H)<sup>+</sup>: 414.1600; found 414.1605.

[0142] **2-((1S,2R,3S,4R,5S)-4-(2-(benzylthio)-6-(methylamino)-9H-purin-9-yl)-2,3-dihydroxy bicyclo[3.1.0]hexan-1-yl)acetonitrile (55).** <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.05 (s, 1H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.30-7.19 (m, 3H), 4.82 (s, 1H), 4.66 (d, *J* = 6.4 Hz, 1H), 4.52-4.44 (m, 2H), 4.00 (d, *J* = 6.8 Hz, 1H), 3.13-3.09 (m, 4H), 2.86 (d, *J* = 17.2 Hz, 1H), 1.75-1.72 (m, 1H), 1.63 (d, *J* = 5.2 Hz, 1H), 0.90-0.86 (m, 1H). HRMS calculated for C<sub>21</sub>H<sub>23</sub>N<sub>6</sub>O<sub>2</sub>S (M + H)<sup>+</sup>: 423.1603; found 423.1609.

[0143] Figure 8 depicts a reaction scheme to synthesize certain 4'-modified (N)-methanocarpa-adenosine derivatives in accordance with an aspect of the invention. Reagents

and Conditions: (i)  $R^1NH_2$ , DIPEA, 2-propanol, rt-70°C; (ii) TBAF, THF, rt; (iii) TEMPO,  $I_2$ ,  $CH_2Cl_2$ ,  $NH_4OH$ , rt-60°C; (iv) (a) TEMPO, BAIB,  $CH_3CN$ , rt; (b) Deoxofluoro or DAST,  $CH_2Cl_2$ , rt; (v) acetone cyanohydrin,  $Ph_3P$ , DIAD, THF, rt; (vi) (a)  $MsCl$ , pyridine, rt; (b)  $KSCN$ , DMF, 80 °C; (vii) 2*H*-1,2,3-triazole,  $Ph_3P$ , DIAD, THF, rt; (viii) 10% TFA, MeOH, 70°C.

[0144] Figure 9 depicts a reaction scheme to synthesize certain 4'-aryl derivatives in accordance with another aspect of the invention. Reagents and Conditions: (i) TEMPO, BAIB,  $CH_3CN-H_2O$  rt; (ii) DCC, *N*'-hydroxyacetimidamide, DMF, 90°C; (iii) 10% TFA, MeOH, 70°C.

## EXAMPLE 2

[0145] This example illustrates the binding affinities of some of the compounds of the invention. The binding affinity at the three human (h) 5-HT<sub>2</sub>Rs and 2 - 3 subtypes of hARs was determined as reported in Tosh et al. 2016. The compounds showed weak binding at the 5-HT<sub>2A</sub>R. An *N*<sup>6</sup>-alkyl, cycloalkyl or dicycloalkylmethyl group was required for binding at 5-HT<sub>2</sub>Rs, as indicated by the inactivity of 6-NH<sub>2</sub> derivatives **9** and **10**, which nevertheless displayed AR affinity. In the series of *N*<sup>6</sup>-dicycloalkylmethyl 4'-CH<sub>2</sub>OH analogues with the same (Cl) substitution at the C2 position, with increasing the cycloalkyl ring size from 3 to 5 carbons, there was a progression toward lower 5-HT<sub>2B</sub>R affinity (*K*<sub>i</sub>, nM): **4** (11) > **18** (136) > **24** (797). However, the progression was opposite when comparing 5-HT<sub>2C</sub>R affinity of the series of *N*<sup>6</sup>-dicycloalkylmethyl 4'-CH<sub>2</sub>Cl analogues with the same C2-chloro substitution. Upon increasing ring size in that series from 4 to 6, 5-HT<sub>2C</sub> affinities increased with *K*<sub>i</sub> values of 908, 580 and 73.5 nM, for **21**, **27** and **36**, respectively. However, in the same series the 5-HT<sub>2B</sub> affinity trended lower (*K*<sub>i</sub>, nM): **21** (205), **27** (496), **36** (586). With asymmetric C $\alpha$  substitution, there was a small stereochemical preference. The 5-HT<sub>2B</sub>R affinity varied according to asymmetric *N*<sup>6</sup> substitution: (R)-cyclobutyl-cyclopropyl (**42**, *K*<sub>i</sub> 77 nM) > ((R)-cyclopropyl-prop-2-yl) (**37**, *K*<sub>i</sub> 163 nM) analogues (both being 2-Cl-4'-CH<sub>2</sub>OH analogues). When these two compounds were modified with 2-I, the 5-HT<sub>2B</sub>R affinity improved significantly in both cases (**43**, 17 nM; **38**, 82 nM, respectively). Among 4'-CH<sub>2</sub>OH *N*<sup>6</sup>-(cyclobutyl-cyclopropylmethyl) analogues, there was a roughly two-fold difference in 5-HT<sub>2B</sub>R affinity with a preference for the *N*<sup>6</sup>-(R)- compared to the (S)-diastereomer (**42** cf. **44**; **43** cf. **45**). However, there was no preference for the *N*<sup>6</sup>-(cyclopropyl-prop-2-ylmethyl) analogues (**39** cf. **41**). Upon examining symmetrically *N*<sup>6</sup>-substituted 2-iodo derivatives in

comparison to the corresponding 2-chloro analogues, the 5-HT<sub>2B</sub>R affinity improved ~2-fold for dicyclobutyl analogue **19** (80 nM) compared to **18** but remained the same for the dicyclopentyl **11** (11.2 nM) analogue compared to **4**. The adenine 3-deaza substitution was well tolerated at the 5-HT<sub>2B</sub>R with retention of moderate affinity in **25** compared to **24**.

[0146] 5'-Hydroxyl substitution with halo (Cl or F) when small rings were present at N<sup>6</sup> either lowered (e.g., dicyclopentylmethyl **12** cf. **4**) and or preserved (dicyclobutylmethyl **21** cf. **18**) the 5-HT<sub>2B</sub>R affinity. However, with the largest (dicyclohexyl) rings, the 5-HT<sub>2C</sub>R affinity was slightly improved with 5'-deoxy-5'-halo, e.g. compound **36** compared to **34**. The corresponding 5'-alkylthio-5'-deoxy analogues **28** and **29** displayed moderate 5-HT<sub>2B</sub>R and 5-HT<sub>2C</sub>R affinity (K<sub>i</sub> ~200 nM), while the latter disappeared with the longer thioalkyl chains.

[0147] In the dicyclopentyl series, the 4'-CH<sub>2</sub>F analogue **12** displayed moderate 5-HT<sub>2B</sub>R but not 5-HT<sub>2C</sub>R affinity, while the corresponding 4'-CH<sub>2</sub>SCH<sub>3</sub> analogue **15** displayed greater 5-HT<sub>2B</sub>R (23 nM) and 5-HT<sub>2C</sub>R affinity. However, 2-iodo substitution in **16** significantly reduced the 5-HT<sub>2B</sub>R affinity (24-fold) compared to **15** without change at the 5-HT<sub>2C</sub>R. Truncation of the 5' group combined with 2-iodo substitution greatly reduced affinity in **13** (5-HT<sub>2B</sub>R K<sub>i</sub> 1270 nM) and the corresponding 7-deaza analogue **14**. The 2-chloro equivalent of truncated derivative **13** (not shown) **9** displayed K<sub>i</sub> values of 675 and 1860 nM at the 5-HT<sub>2B</sub>R and 5-HT<sub>2C</sub>R, respectively. 5'-Phenyl-thio ethers in the N<sup>6</sup>-dicyclopentylmethyl series displayed moderate 5-HT<sub>2B</sub>R affinity, e.g., K<sub>i</sub> of 256 nM with 3,4-dimethoxy substitution in **33**. In the 5'-ester series, the rank order of 5-HT<sub>2B</sub>R affinity (K<sub>i</sub>, nM) was **5** (dicyclopentyl, 15 nM) > **7** (dicyclobutyl, 136 nM) ≥ **47** (dicyclopentyl, 239 nM). The 5-HT<sub>2B</sub>R affinity of ribosides appeared only in a 5'-CONH<sub>2</sub> derivative **52** compared to the inactive 4'-CH<sub>2</sub>OH analogue **51**. A 2-iodo-adenine nucleobase **54** displayed moderate 5-HT<sub>2B</sub>R affinity (313 nM).

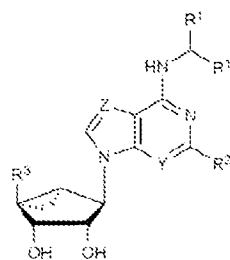
[0148] At the ARs, affinity generally varied in the order hA<sub>1A</sub>R > hA<sub>3</sub>AR > hA<sub>2A</sub>AR. A<sub>2B</sub>AR affinity was not determined, because this receptor is consistently the weakest for this series of (N)-methanocarba adenosine derivatives. Compounds **11**, **15**, **19**, **38** and **43** (2-I) had nearly balanced A<sub>1A</sub>R and 5-HT<sub>2B</sub>R affinity, and 5-HT<sub>2C</sub>R affinity was somewhat lower. Compound **43** was 3.7-, 186- and >500-fold selective in 5-HT<sub>2B</sub>R binding compared to A<sub>1A</sub>R, A<sub>2A</sub>AR and A<sub>3</sub>AR. However, ((S)-cyclobutyl-cyclopentyl)-2-iodo 4'-CH<sub>2</sub>OH analogue **44** had at least an order of magnitude 5-HT<sub>2B</sub>R selectivity compared to other 5-

HT<sub>2</sub>Rs and ARs. It is also to be noted that the mouse (m) AR affinity can vary greatly compared to the hARs, especially at the A<sub>3</sub>AR.

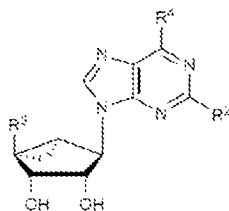
**[0149]** Substitution of the 5'-hydroxyl with halo (Cl or F) increased A<sub>1</sub>AR affinity for N<sup>6</sup>-cyclopropylmethyl analogues (cf. **12** and **4**; **39** and **37**). With larger cycloalkyl rings, the A<sub>1</sub>AR affinity either remained the same (**27**) or decreased (**20**, **21**, **26**, **35** and **36**). The 2-S-alkyl substitution (**31**) greatly decreased A<sub>1</sub>AR affinity. A 5'-deoxy-5'-methylthio substitution decreased A<sub>1</sub>AR, but not A<sub>3</sub>AR affinity, by roughly 2 – 10-fold (**10**, **15**, **16** and **28**). A 2-iodo group substantially decreased the AR affinity compared to 2-chloro. The adenine 3-deaza substitution in **25** greatly reduced A<sub>1</sub>AR and A<sub>3</sub>AR affinity. Compound **51** was selective for the A<sub>1</sub>AR and lacked 5-HT<sub>2B</sub>/CR affinity.

**[0150]** A direct comparison of analogous (N)-methanocarba analogues with the corresponding ribosides (cf. **45** and **51**; **18** and **53**) indicated a major reduction in 5-HT<sub>2B</sub>/CR affinity of roughly three orders of magnitude with a furanose ring. Thus, the (N)-methanocarba substitution is essential for 5-HT<sub>2B</sub>/CR binding in the 4'-CH<sub>2</sub>OH series. However, when a 5'-carbonyl group is present in ribose series, e.g., primary carboxamide **52** (K<sub>i</sub> 178 nM), the 5-HT<sub>2B</sub> affinity was restored. This was consistent with μM affinity of selective A<sub>3</sub>AR agonists that are ribosides having 5'-methanocarbas and N<sup>6</sup>-(3-iodobenzyl) groups. The adenine nucleobase alone **54**, with appropriate ((S)-cyclobutyl-cyclopropyl)-2-iodo substitution provided weak 5-HT<sub>2B</sub> affinity (only 9-fold weaker than the corresponding (N)-methanocarba derivative **44**) that was dependent on optimal 2- and 6-position substitutions (cf. **55**). Furthermore, the ribose equivalent of **18** was reported to have K<sub>i</sub> values of >10,000 and 1450 nM at 5-HT<sub>2B</sub>/CRs, respectively, i.e., substantially lower affinity.

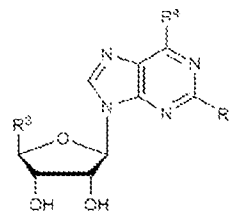
**[0151]** Table 1. Affinity at 5HT<sub>2</sub> receptors and ARs of N<sup>6</sup>-, C2-, and 5'-modified (N)-methanocarba-adenosine derivatives. Y = N, unless noted. Affinity is expressed as mean ± SEM (N = 2 – 3, unless noted).<sup>c</sup>



4, 11-36



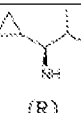
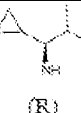
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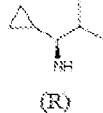
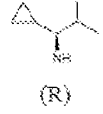
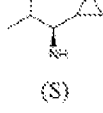
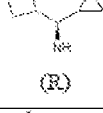
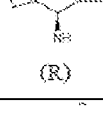


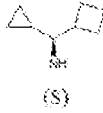
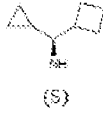
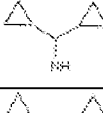
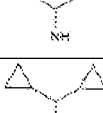
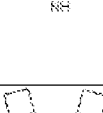
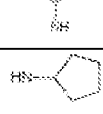
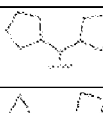
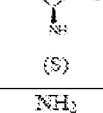
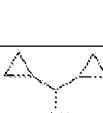
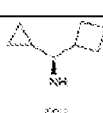
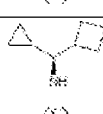
51-53

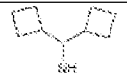
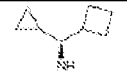
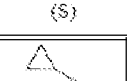
| No.                                                                               | R <sup>1</sup> or R <sup>4</sup> | R <sup>2</sup> | R <sup>3</sup> ,<br>Other changes | K <sub>i</sub> , 5HT <sub>2A</sub><br>(K <sub>i</sub> , nM, or<br>% inhib.;<br>(pK <sub>i</sub> )) <sup>c</sup> | K <sub>i</sub> , 5HT <sub>2B</sub><br>(K <sub>i</sub> , nM, or<br>% inhib.;<br>(pK <sub>i</sub> )) <sup>c</sup> | K <sub>i</sub> , 5HT <sub>2C</sub><br>(K <sub>i</sub> , nM, or<br>% inhib.;<br>(pK <sub>i</sub> )) <sup>c</sup> | K <sub>i</sub> , A <sub>1</sub> AR<br>(nM or %<br>inhib.) <sup>c</sup><br>(A <sub>2A</sub> AR) | K <sub>i</sub> , A <sub>2</sub> AR<br>(nM or %<br>inhib.) <sup>c</sup> |
|-----------------------------------------------------------------------------------|----------------------------------|----------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| <i>N<sup>6</sup> substituent with symmetric C<sub>4</sub> or 6-NH<sub>2</sub></i> |                                  |                |                                   |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                |                                                                        |
| 9a <sup>a,b</sup>                                                                 | NH <sub>2</sub>                  | Cl             | CH <sub>2</sub> OH                | 5%                                                                                                              | 50%                                                                                                             | 8%                                                                                                              | 105±63,<br>(3420±270)                                                                          | 353±54                                                                 |
| 9b                                                                                | NH <sub>2</sub>                  | I              | CH <sub>2</sub> OH                | -27%                                                                                                            | -3%                                                                                                             | -38%                                                                                                            | ND,<br>(73±6%)                                                                                 | ND                                                                     |
| 10a                                                                               | NH <sub>2</sub>                  | I              | CH <sub>2</sub> Cl                | 0%                                                                                                              | 11%                                                                                                             | 12%                                                                                                             | 147, <sup>k</sup><br>(5350 <sup>b</sup> )                                                      | 390±40                                                                 |

|                 |                                                                                     |    |                                  |      |                             |                            |                       |                   |
|-----------------|-------------------------------------------------------------------------------------|----|----------------------------------|------|-----------------------------|----------------------------|-----------------------|-------------------|
| 10b             |    | I  | CH <sub>2</sub> SCH <sub>3</sub> | 0%   | 12%                         | 12%                        | 1350±180,<br>(3120)   | 92.5±7.8          |
| 4 <sup>c</sup>  |    | Cl | CH <sub>2</sub> OH               | 0%   | 11.1<br>(7.95±0.16)         | 83.5<br>(7.06±0.15)        | 39±17,<br>(2200)      | 1600±210          |
| 11              |    | I  | CH <sub>2</sub> OH               | 35%  | 11.2<br>(7.95±0.29)         | 249<br>(6.60±0.03)         | 13.4±4.2,<br>(63%)    | 7810±2470         |
| 12              |    | Cl | CH <sub>2</sub> F                | 14%  | 82.3<br>(7.08±0.04)         | 47%                        | 5.95±0.72,<br>(55%)   | 3700±570          |
| 13 <sup>d</sup> |    | I  | H                                | 13%  | 1270<br>(5.90±0.03)         | 3390<br>(5.47±0.14)        | 23%,<br>(1 μM)        | ND                |
| 14 <sup>e</sup> |    | I  | H, Z=CH                          | 3%   | 1300<br>(5.88) <sup>b</sup> | 30%                        | ND                    | 5310±1310         |
| 15              |    | Cl | CH <sub>2</sub> SCH <sub>3</sub> | 19%  | 23.1<br>(7.64±0.12)         | 772<br>(6.11±0.32)         | 63.2±18.7             | 932±75            |
| 16              |    | I  | CH <sub>2</sub> SCH <sub>3</sub> | 24%  | 522<br>(6.28±0.06)          | 493<br>(6.31±0.09)         | 466±136,<br>(40%)     | 62%               |
| 17 <sup>b</sup> |  | H  | CH <sub>2</sub> OH               | 18%  | 186<br>(6.73±0.07)          | 1020<br>(5.99±0.15)        | 22.7±3.0,<br>(34±1%)  | 51±6%             |
| 18 <sup>b</sup> |  | Cl | CH <sub>2</sub> OH               | 8%   | 136<br>(6.87±0.06)          | 368<br>(6.43±0.19)         | 8.96±1.02,<br>(55±5%) | 25±2%             |
| 19 <sup>e</sup> |  | I  | CH <sub>2</sub> OH               | 16%  | 79.7<br>(7.10±0.01)         | 719<br>(6.14±0.05)         | 294±14,<br>(37±1%)    | 34,300<br>±7700   |
| 20 <sup>b</sup> |  | H  | CH <sub>2</sub> Cl               | 11%  | 1090<br>(5.96±0.26)         | 1230<br>(5.91±0.14)        | 32.7±12.4,<br>(38±3%) | 49±4%             |
| 21 <sup>b</sup> |  | Cl | CH <sub>2</sub> Cl               | 28%  | 205<br>(6.69±0.12)          | 906<br>(6.04±0.27)         | 120±23,<br>(17±24%)   | 3820±1820         |
| 22 <sup>b</sup> |  | Cl | CH <sub>2</sub> S-(2-F-Ph)       | 21%  | 601<br>(6.22±0.26)          | 1250<br>(5.90±0.08)        | 45±4%,<br>(22±5%)     | 9750±4030         |
| 23 <sup>c</sup> |  | Cl | H                                | 0%   | 26%                         | 2170<br>(5.66±0.18)        | 34±3%,<br>(12±3%)     | 46±2%             |
| 24              |  | Cl | CH <sub>2</sub> OH               | 22%  | 797 (6.10) <sup>b</sup>     | 536<br>(6.27) <sup>b</sup> | 436±163,<br>(24±6%)   | 4380              |
| 25              |  | Cl | CH <sub>2</sub> OH<br>(Y=CH)     | 1%   | 732<br>(6.14±0.17)          | 1270<br>(5.90±0.03)        | 11±7%,<br>(-12%)      | 35±16%            |
| 26              |  | Cl | CH <sub>2</sub> F                | 38%  | 444<br>(6.35±0.07)          | 580<br>(6.09±0.03)         | 1620±360,<br>(21%)    | 7200±1070         |
| 27              |  | Cl | CH <sub>2</sub> Cl               | 5.19 | 496<br>(6.30±0.13)          | 481<br>(6.24±0.22)         | 529±136,<br>(36%)     | 8260 <sup>e</sup> |
| 28              |  | Cl | CH <sub>2</sub> SCH <sub>3</sub> | 47%  | 202<br>(6.69±0.07)          | 481<br>(6.32±0.13)         | 50±11%,<br>(-12±8%)   | 5270 <sup>e</sup> |

|                                                                |                                                                                     |                       |                                                                  |                   |                     |                     |                      |                         |
|----------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------|------------------------------------------------------------------|-------------------|---------------------|---------------------|----------------------|-------------------------|
| 29                                                             |    | Cl                    | CH <sub>2</sub> SCH <sub>2</sub> CH <sub>3</sub>                 | 38%               | 186<br>(6.73±0.02)  | 47%                 | 54±1%,<br>(-43±21%)  | 6280 <sup>a</sup>       |
| 30                                                             |    | Cl                    | CH <sub>2</sub> S(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub> | 22%               | 549<br>(6.26±0.23)  | 27%                 | -1±11%,<br>(5±4%)    | 73% <sup>b</sup><br>33% |
| 31                                                             |    | S-<br>CH <sub>3</sub> | CH <sub>3</sub> SCH <sub>3</sub>                                 | 5.03              | 222<br>(6.65±0.09)  | 49%                 | 15±1%,<br>(-60±20%)  | 6620±180 <sup>c</sup>   |
| 32                                                             |    | Cl                    | CH <sub>2</sub> S-(2-F-Ph)                                       | 36%               | 640<br>(6.19±0.46)  | 37%                 | -6±3%,<br>(-10±12%)  | 1%                      |
| 33                                                             |    | Cl                    | CH <sub>2</sub> S-(3,4-<br>OMe <sub>2</sub> -Ph)                 | 25%               | 256<br>(6.59±0.04)  | 368<br>(6.43±0.06)  | 39±13%,<br>(19±3%)   | 76%                     |
| 34                                                             |    | Cl                    | CH <sub>2</sub> OH                                               | 47%               | 147<br>(6.83±0.06)  | 128<br>(6.89±0.06)  | 1900±180,<br>(7±16%) | 16,600±100              |
| 35 <sup>d</sup>                                                |    | Cl                    | CH <sub>2</sub> F                                                | 5.44 <sup>h</sup> | 435<br>(6.36±0.11)  | 163<br>(6.79±0.17)  | 47±3%,<br>(-27%)     | 5040±320                |
| 36                                                             |   | Cl                    | CH <sub>2</sub> Cl                                               | 21%               | 586<br>(6.23±0.20)  | 73.5<br>(7.13±0.07) | 63±5%,<br>(-9±6%)    | 9320±<br>3850           |
| <i>N<sup>o</sup> substituent with asymmetric C<sub>α</sub></i> |                                                                                     |                       |                                                                  |                   |                     |                     |                      |                         |
| 37 <sup>a</sup>                                                |  | Cl                    | CH <sub>2</sub> OH                                               | 1%                | 163<br>(6.79±0.04)  | 186<br>(6.73±0.11)  | 103±7,<br>(2200±310) | 1240±320                |
| 38                                                             |  | I                     | CH <sub>2</sub> OH                                               | 7%                | 81.9<br>(7.09±0.01) | 904<br>(6.04±0.07)  | 30.7±0.6,<br>(60±9%) | 11,700±300              |

|                 |                                                                                           |    |                                |     |                     |                     |                           |                       |
|-----------------|-------------------------------------------------------------------------------------------|----|--------------------------------|-----|---------------------|---------------------|---------------------------|-----------------------|
| 39 <sup>2</sup> | <br>(R)  | Cl | CH <sub>2</sub> F              | 11% | 934<br>(6.03±0.03)  | 45%                 | 9.84±2.15,<br>(73±2%)     | 6100±790 <sup>a</sup> |
| 40 <sup>2</sup> | <br>(R)  | Cl | CH <sub>2</sub> N <sub>3</sub> | 0%  | 380<br>(6.42±0.06)  | 2380<br>(5.62±0.00) | 28.5±5.5,<br>(61±8%)      | 2440 <sup>a,b</sup>   |
| 41 <sup>2</sup> | <br>(S)  | Cl | CH <sub>2</sub> OH             | 0%  | 163<br>(6.79±0.04)  | 672<br>(6.17±0.16)  | 104±6,<br>(1520±120)      | 3450±670              |
| 42 <sup>a</sup> | <br>(R)  | Cl | CH <sub>2</sub> OH             | 0%  | 77<br>(7.09±0.01)   | 270<br>(6.57±0.04)  | 144±32,<br>(3940±320)     | 3470±490              |
| 43              | <br>(R) | I  | CH <sub>2</sub> OH             | 26% | 17.4<br>(7.76±0.03) | 552<br>(6.26±0.05)  | 63.9±10.0,<br>(3080±1190) | 42±1%                 |

|                                                       |                                                                                            |    |                                                                          |     |                     |                    |                         |           |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------|----|--------------------------------------------------------------------------|-----|---------------------|--------------------|-------------------------|-----------|
| 44 <sup>a</sup>                                       | <br>(S)   | Cl | CH <sub>2</sub> OH                                                       | -1% | 34<br>(7.42±0.06)   | 298<br>(6.53±0.11) | 298±4,<br>(2690±370)    | 3240±460  |
| 45                                                    | <br>(S)   | I  | CH <sub>2</sub> OH                                                       | 29% | 33<br>(7.48±0.05)   | 670<br>(6.22±0.35) | 42.7±2.7,<br>(50±6%)    | 34±6%     |
| <i>5'-Esters, 5'-amides, 9- riboxides and adenine</i> |                                                                                            |    |                                                                          |     |                     |                    |                         |           |
| 5 <sup>a</sup>                                        | <br>(S)   | Cl | COOCH <sub>2</sub> CH <sub>3</sub>                                       | 19% | 15<br>(7.82±0.10)   | 30<br>(7.52±0.03)  | 360±74,<br>(1570±180)   | 236±41    |
| 6 <sup>a</sup>                                        | <br>(S)   | Cl | CONHCH <sub>3</sub>                                                      | 9%  | 23<br>(7.64±0.04)   | 269<br>(6.57±0.01) | 110±14,<br>(4320±870)   | 34±11     |
| 46 <sup>a</sup>                                       | <br>(S)  | Cl | CONH-<br>(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>                 | 0%  | 630<br>(6.20±0.11)  | 142<br>(6.85±0.00) | 2580±1220,<br>(23±5%)   | 8110±1270 |
| 7 <sup>b</sup>                                        | <br>(S) | Cl | COOCH <sub>2</sub> CH <sub>3</sub>                                       | 35% | 136<br>(6.87±0.15)  | 351<br>(6.45±0.09) | 73.8±14.2,<br>(57±12%)  | 1160±300  |
| 8 <sup>b,c</sup>                                      | <br>(S) | Cl | CONHCH <sub>3</sub>                                                      | 0%  | 78.2<br>(7.11±0.08) | 44%                | 18.3±6.3,<br>(3250±300) | 3.7±0.9   |
| 47                                                    | <br>(S) | Cl | COOCH <sub>2</sub> CH <sub>3</sub>                                       | 42% | 239<br>(6.62±0.04)  | 139<br>(6.86±0.16) | 55±7%,<br>(-22%)        | 9720±390  |
| 48                                                    | <br>(S) | I  | COOCH <sub>2</sub> CH <sub>3</sub>                                       | 13% | 33<br>(7.48±0.04)   | 331<br>(6.48±0.04) | 2180±1020,<br>(15%)     | 53%       |
| 49                                                    | NH <sub>2</sub>                                                                            | Cl | CON-<br>(CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> ) <sub>2</sub> | 3%  | 30%                 | 12%                | 998±27                  | 51±2%     |
| 50                                                    | <br>(S) | Cl | CON-<br>(CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> ) <sub>2</sub> | 0%  | 1230<br>(5.91±0.03) | 38%                | 34±6%                   | 30±2%     |
| 51                                                    | <br>(S) | I  | CH <sub>2</sub> OH                                                       | 6%  | 44%                 | -1%                | 21.3±8.4,<br>(72±3%)    | 34%       |
| 52                                                    | <br>(S) | I  | CONH <sub>2</sub>                                                        | 9%  | 178<br>(6.75±0.10)  | -1%                | 147±33,<br>(39±2%)      | 56%       |

|                 |                                                                                   |    |                    |      |                    |                             |                           |                 |
|-----------------|-----------------------------------------------------------------------------------|----|--------------------|------|--------------------|-----------------------------|---------------------------|-----------------|
| 53 <sup>b</sup> |  | Cl | CH <sub>2</sub> OH | 31%  | 47%                | 1450<br>(6.84) <sup>b</sup> | 17.8±18.7,<br>(2550±540)  | 13,200<br>±2500 |
| 54              |  | I  | NA                 | -10% | 313<br>(6.50±0.82) | 5%                          | 648±346                   | ND              |
| 55              |  | Cl | NA                 | 6%   | 29%                | 24%                         | 49%<br>(1 μM),<br>(67±3%) | ND              |

<sup>a</sup>Data from Tosh et al., 2012 and 2016. <sup>b</sup>Data from Tosh et al., 2018 and 2019.

<sup>c</sup>Radioligands (parental cells) used are: 5-HT<sub>2A</sub>, [<sup>3</sup>H]ketanserin (HEKT); 5-HT<sub>2B</sub>, [3H]LSD (stable HEK); 5-HT<sub>2C</sub>, [<sup>3</sup>H]mesulergine (Flp-IN HEK); A<sub>1</sub>, [<sup>3</sup>H]R-PIA (HEK); A<sub>2A</sub>, [<sup>3</sup>H]CGS21680 (HEK); A<sub>3</sub>, [<sup>125</sup>I]I-AB-MECA (HEK), according to published procedures<sup>c</sup>. D. K. Tosh (2021), D. K. Tosh et al. (2019); and J. Besnard et al. (2012). When a percent is given, it refers to inhibition at 10 μM (or 1 μM, as noted). For 5-HT<sub>2</sub>Rs, the pK<sub>i</sub> value as a mean ± SEM is given in parentheses. For ARs, the K<sub>i</sub> value or percent inhibition at the A<sub>2A</sub>AR is given in parentheses (under A<sub>1</sub>AR data) as a mean ± SEM. <sup>d</sup>K<sub>i</sub> at 5HT<sub>1D</sub> receptor is 1.99 μM. <sup>e</sup>Data from Jacobson et al., 2005. Synthesis reported in Tosh et al., 2020. <sup>g</sup>Pottie, 2022. <sup>h</sup>n = 1. NA, not applicable. ND, not determined.

### EXAMPLE 3

**[0152]** This example illustrates some of the pharmacological properties of compounds in accordance with an aspect of the invention. Three compounds having high affinity, **43**, **45** and **48**, were examined in functional assays in Flp-In 293 T-Rex cell lines stably-expressing 5-HT<sub>2A</sub>R, 5-HT<sub>2B</sub>R and 5-HT<sub>2C</sub>R measuring Gq protein-mediated calcium flux activity (Figure 2, Table 2). The K<sub>B</sub> values of all 3 compounds at the 5-HT<sub>2B</sub>R were in the range of 2 – 3 nM. The ratio of 5-HT<sub>2B</sub>R and 5-HT<sub>2C</sub>R functional antagonist affinities ranged from 45 (**48**) to 113-fold (**43**). Compound **43** was >500- and 32-fold fold selective in binding compared to 5-HT<sub>2A</sub>R and 5-HT<sub>2C</sub>R. Weak antagonism (>10,000 nM) with the 5-HT<sub>2A</sub>R was detected, consistent with the binding results, and all three compounds proved to be antagonists, with no agonist activity. Furthermore, compounds were tested in 5-HT<sub>2B</sub> BRET orthologous assays measuring Gq dissociation, β-arrestin1 and β-arrestin2 recruitment assays (Figure 2). Compounds again showed no agonist activity in these assays, thus demonstrating lack of agonism or functional selectivity at this receptor subtype. In fact, some compounds

displayed inverse agonist activities in Gq and  $\beta$ -arrestin2 recruitment assays further supporting lack of agonist activity.

**[0153]** Table 2 sets forth antagonist affinity ( $K_B$ ) estimates for selected analogues using 5-HT stimulated 5-HT<sub>2</sub> Gq-mediated calcium flux functional responses compared to binding assays<sup>a</sup>. 5-HT was used as a positive control for each receptor subtype ( $EC_{50}$  = 0.24, 0.70 and 0.51 nM for 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub>, respectively), and clozapine was the reference antagonist. Values represent mean  $\pm$  SEM performed in three independent experiments.

Table 2. Antagonist Affinity Estimated Values

| Compound  | 5-HT <sub>2B</sub>           |                     |                 |      | 5-HT <sub>2C</sub>           |                     |                 |      | 2B/2C selectivity | 5-HT <sub>2A</sub>  |                 |      |
|-----------|------------------------------|---------------------|-----------------|------|------------------------------|---------------------|-----------------|------|-------------------|---------------------|-----------------|------|
|           | K <sub>i</sub> (binding, nM) | K <sub>B</sub> , nM | pK <sub>B</sub> | SEM  | K <sub>i</sub> (binding, nM) | K <sub>B</sub> , nM | pK <sub>B</sub> | SEM  |                   | K <sub>B</sub> , nM | pK <sub>B</sub> | SEM  |
| Clozapine | N/A                          | 16.9                | 8.07            | 0.57 | N/A                          | 16.2                | 7.79            | 0.02 | <b>1.9</b>        | 3.4                 | 8.47            | 0.05 |
| <b>43</b> | 17.4                         | 1.8                 | 8.88            | 0.24 | 552                          | 165.9               | 6.83            | 0.15 | <b>112.6</b>      | > 10,000            | <5.00           | N/A  |
| <b>45</b> | 33                           | 3.3                 | 8.51            | 0.12 | 800                          | 327.7               | 6.54            | 0.16 | <b>93.6</b>       | > 10,000            | <5.00           | N/A  |
| <b>48</b> | 33                           | 1.9                 | 8.76            | 0.12 | 331                          | 78.6                | 7.11            | 0.04 | <b>44.7</b>       | > 10,000            | <5.00           | N/A  |

|                                           |     | EC <sub>50</sub> , nM | pEC <sub>50</sub> | SEM  |     |      | EC <sub>50</sub> , nM | pEC <sub>50</sub> | SEM |  |      | EC <sub>50</sub> , nM | pEC <sub>50</sub> | SEM |
|-------------------------------------------|-----|-----------------------|-------------------|------|-----|------|-----------------------|-------------------|-----|--|------|-----------------------|-------------------|-----|
| 5-HT EC <sub>50</sub> , pEC <sub>50</sub> | N/A | 0.70                  | 9.31              | 0.25 | N/A | 0.51 | 9.49                  | 0.28              |     |  | 0.24 | 9.68                  | 0.19              |     |

<sup>a</sup> The corresponding binding p $K_i$  values were: at 5-HT<sub>2B</sub> **43**, 7.76; **45**, 7.48; **48**, 7.48; at 5-HT<sub>2C</sub> **43**, 6.26; **45**, 6.22; **48**, 6.48.

**[0154]** Fig. 2 depicts functional assays showing antagonism of compounds **43**, **45** and **48** in Flp-In 293 T-Rex cell lines stably-expressing 5-HT<sub>2B</sub>R (A), 5-HT<sub>2C</sub>R (B) and 5-HT<sub>2A</sub>R (C) measuring Gq-mediated calcium flux activity. Clozapine was used as a reference antagonist. The absence of agonism in the nucleosides was shown in 5-HT<sub>2B</sub> BRET orthologous assays measuring Gq dissociation (D),  $\beta$ -arrestin1 (E) and  $\beta$ -arrestin2 recruitment (F) assays. Serotonin (5-HT) was used as agonist in all assays (at 10 nM in antagonist mode, A-C).

**[0155]** The off-target binding affinities at 42 diverse receptors, transporters and channels, in addition to 5-HT<sub>2A</sub>R, 5-HT<sub>2B</sub>R and 5-HT<sub>2C</sub>R affinity, were determined for all of these compounds. Most of the derivatives displayed  $\mu$ M affinity at the  $\sigma$ 1 and/or  $\sigma$ 2 receptors. Additional interactions were noted at the following receptors or channels (compound,  $K_i$ ,  $\mu$ M): 5HT<sub>1D</sub> (27, 6.5; 29, 5.2; 35, 5.5); 5HT<sub>2A</sub> (27, 6.5; 31, 9.2; 35, 7); H<sub>1</sub>

(43, 2.1); D<sub>4</sub> (29, 3.6); D<sub>5</sub> (25, 5.1);  $\alpha$ 2B (28, 1.7; 31, 1.2; 35, 3.6);  $\alpha$ 2C (27, 2.5; 29, 2.1);  $\beta$ 3 (25, 4.7; 29, 1.5; 33, 2.1); DOR (24, 3.9); KOR (24, 0.11), MOR (24, 3.5; 27, 5.7; 32, 4.9); TSPO (19, 2.1); DAT (**25**, 3.9; **26**, 7.9). Compounds **9**, **10** and **48** had no significant off-target interactions at 10  $\mu$ M (>50% inhibition of radioligand bound). The physicochemical parameters were calculated for compounds **11**, **15**, **36**, **43**, **45**, **48** and **51** using the StarDrop software. None of the compounds are predicted to cross the BBB, but **15** and **36** are in the predicted human intestinal absorption (HIA) category. Compound **43** had a LogS at pH 7.4 of 1.144 (predicted aqueous solubility of 14  $\mu$ g/mL), a LogD of 1.254 and TPSA of 116 Å<sup>2</sup>. The calculated ligand efficiency (LE) of **43** was 0.375.

**[0156]** The foregoing shows that 2-iodo modification modestly reduced 5-HT<sub>2c</sub>R affinity, and at the 5-HT<sub>2b</sub>R affinity was either the same or slightly increased. In the present set of compounds, a 2-iodo substitution moderately reduced A<sub>3</sub>AR affinity, but tended to preserve or slightly increase A<sub>1</sub>AR affinity. The N<sup>6</sup> group had a major effect on 5-HT<sub>2b</sub>/CR affinity, with branched substituents at the C $\alpha$  position favoring affinity: dicyclopropyl, dicyclobutyl, (R)-cyclobutyl-cyclopropyl, (R)-cyclopropyl-prop-2-yl. The highest 5-HT<sub>2b</sub>R affinities were K<sub>i</sub> 10 – 30 nM (N<sup>6</sup>-dicyclopropyl-methyl-2-iodo **11**, 2-chloro-5'-deoxy-5'-methylthio **15** and N<sup>6</sup>-(R)-cyclobutyl-cyclopropyl-methyl-2-iodo **43**), followed by **44** and **45**.

**[0157]** The enhancement of AR affinity of adenosine derivatives upon introducing an (N)-methanocarba modification often follows the order A<sub>3</sub> > A<sub>1</sub> >> A<sub>2A</sub>. However, substantial A<sub>1</sub>AR selectivity compared to A<sub>3</sub>AR was still present in many of these compounds, suggestive of dual acting compounds: 5-HT<sub>2b</sub> antagonist and A<sub>1</sub>AR agonist. However, the 5-HT<sub>2b</sub>R-enhancing 2-iodo and 3-deaza substitutions also decreased A<sub>1</sub>AR affinity. Given its affinity (17 nM) and moderate 5-HT<sub>2b</sub>R selectivity (32-fold vs. 5-HT<sub>2c</sub>R, 4-fold vs. A<sub>1A</sub>R), 2-iodo derivative **43** could potentially be useful for therapy targeting fibrosis. Compound **11** was a balanced mixed 5-HT<sub>2b</sub>R antagonist (K<sub>i</sub> 11 nM) and A<sub>1</sub>AR agonist (K<sub>i</sub> 13 nM). Compound **54** is likely a mixed HT<sub>2b</sub>R/A<sub>3</sub>AR antagonist, considering that adenine derivatives lacking a ribose moiety generally bind to ARs as antagonists. Although the Gq-coupled A<sub>2A</sub>AR is an established anti-inflammatory receptor, the A<sub>1</sub> and A<sub>3</sub>ARs also have anti-inflammatory effects in animal models, thus supporting the possible use of compounds with mixed activities. Unexpectedly, 2-chloro-5'-deoxy-5'-chloro-N<sup>6</sup>-dicyclohexyl-methyl analogue **36** displayed higher affinity at the 5-HT<sub>2c</sub>R (K<sub>i</sub> 73 nM) than at the 5-HT<sub>2b</sub>R. Only **35** showed moderate 5-HT<sub>2A</sub>R affinity (3.6  $\mu$ M).

[0158] Among the three analogues characterized as 5-HT<sub>2B</sub>R antagonists in functional assays, the selectivity for that subtype varied in the order **43** (426-fold), **45** (>300-fold) > **48** (98.7-fold). The corresponding binding selectivity for the two CH<sub>2</sub>OH analogues with asymmetric N<sup>6</sup> groups of opposite chirality was less pronounced with 32-fold for **43** and 18-fold for **45**.

#### EXAMPLE 4

[0159] This example illustrates affinity of certain adenosine derivatives at 5-HT<sub>2</sub> serotonin and adenosine receptors in accordance with an aspect of the invention, as set forth in Table 3.

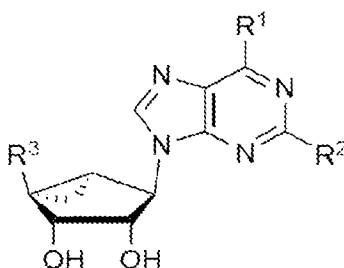
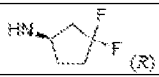
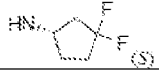
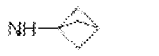
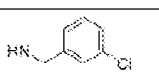
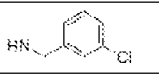
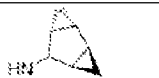
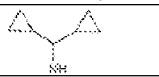
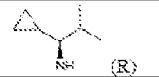
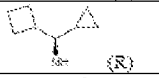
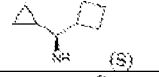
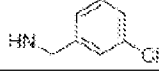
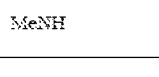
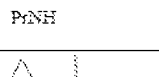
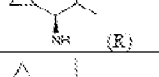
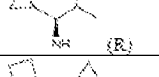
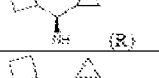
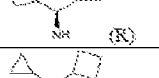
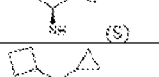
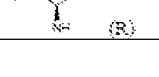
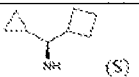
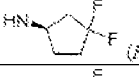
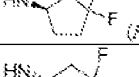
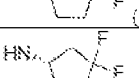
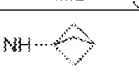
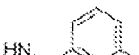
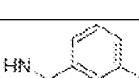
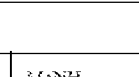
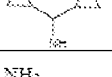
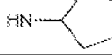
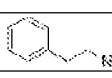
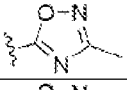
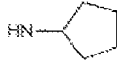
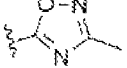
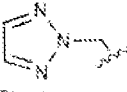


Table 3. Affinity of adenosine derivatives at 5-HT<sub>2</sub> serotonin and adenosine receptors

| Compound                                                                             | R <sup>1</sup> | R <sup>2</sup><br>(other<br>changes) | R <sup>3</sup>     | K <sub>i</sub> ,<br>5HT <sub>2A</sub><br>(nM or %<br>inhib.) <sup>c</sup> | K <sub>i</sub> , 5HT <sub>2B</sub><br>(nM or %<br>inhib.) <sup>c</sup> | K <sub>i</sub> , 5HT <sub>2C</sub><br>(nM or %<br>inhib.) <sup>c</sup> | K <sub>i</sub> , A <sub>1</sub> AR<br>(nM or %<br>inhib.) <sup>c</sup><br>(A <sub>2A</sub> AR) | K <sub>i</sub> , A <sub>2A</sub> AR<br>(nM or %<br>inhib.) <sup>c</sup> |
|--------------------------------------------------------------------------------------|----------------|--------------------------------------|--------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Various N <sup>6</sup> - and 2-substituted reference 4'-CH <sub>2</sub> OH compounds |                |                                      |                    |                                                                           |                                                                        |                                                                        |                                                                                                |                                                                         |
| 7,<br>MRS7134 <sup>a</sup><br>(14)34481                                              |                | Cl                                   | CH <sub>2</sub> OH | 0%                                                                        | 11.1±3.4                                                               | 83.5±24                                                                | 39±17<br>(2200 <sup>b</sup> )                                                                  | 1600±210                                                                |
| 10,<br>MRS7181<br>37702<br>(21 in 5HT)                                               |                | Cl                                   | CH <sub>2</sub> OH | 0%                                                                        | 77±3                                                                   | 208±68                                                                 | 144±32<br>(3940±320)                                                                           | 3470±490                                                                |
| 11,<br>MRS7925<br>58932                                                              |                | I                                    | CH <sub>2</sub> OH | 36%                                                                       | 17.4±3.7                                                               | 552±61                                                                 | 63.9±10.0<br>(K <sub>i</sub> /<br>62±12%)                                                      | 42±1%                                                                   |
| 13,<br>MRS7177 <sup>a</sup><br>37699<br>(18 in 5HT)                                  |                | Cl                                   | CH <sub>2</sub> OH | 1%                                                                        | 163±16                                                                 | 190±31                                                                 | 103±7<br>(2200±310)                                                                            | 1240±320                                                                |
| 14,<br>MRS7885<br>57357                                                              |                | I                                    | CH <sub>2</sub> OH | 7%                                                                        | 81.9±2.0                                                               | 904±131                                                                | 30.7±0.6<br>(60±9%)                                                                            | 11.700±300                                                              |
| 15,<br>MRS7186<br>37701<br>(20 in 5HT)                                               |                | Cl                                   | CH <sub>2</sub> OH | 1%                                                                        | 34±7                                                                   | 288±46                                                                 | 298±4<br>(2690±370)                                                                            | 3240±400                                                                |
| 16,<br>MRS8099<br>61857                                                              |                | I                                    | CH <sub>2</sub> OH | 29%                                                                       | 33.0±2.0                                                               | 607±337                                                                | (50±6%)                                                                                        | 34±6%                                                                   |
| 17a,<br>MRS8207<br>70063                                                             |                | I                                    | CH <sub>2</sub> OH | 10%                                                                       | 10.1±5.4                                                               | 2120±570                                                               | 101±12%<br>(35±19%)                                                                            |                                                                         |
| 17b,<br>MRS83xx<br>7xxx                                                              |                | I (3-Br)                             | CH <sub>2</sub> OH | x%                                                                        |                                                                        |                                                                        |                                                                                                |                                                                         |

|                                                                       |                                                                                     |                                                        |                     |              |                   |                  |                               |                   |
|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------|---------------------|--------------|-------------------|------------------|-------------------------------|-------------------|
| 18,<br>MRS8250<br>71586                                               |    | I                                                      | CH <sub>3</sub> OH  | -10%         | 42±8 <sup>d</sup> | 35% <sup>d</sup> | 152±64<br>(69±1%)             |                   |
| 19,<br>MRS8241<br>71355                                               |    | I                                                      | CH <sub>3</sub> OH  | 5%           | 155±23            | 16%              | 100±0%<br>(36.200)            |                   |
| 20,<br>MRS8198<br>62685                                               |    | I                                                      | CH <sub>3</sub> OH  | 9%           | 81.1±15.4         | 480±250          | 51% <sup>d</sup><br>(48±22%)  |                   |
| 21,<br>MRS1760 <sup>a</sup><br>Not sent                               |    | Cl                                                     | CH <sub>3</sub> OH  |              |                   |                  | 65±17<br>(1600±400)           | 1.9±0.7           |
| 22,<br>MRS8231<br>70233                                               |    | I                                                      | CH <sub>3</sub> OH  | 26%          | 153±71            | 1660±650         | (50±1%)                       |                   |
| New modifications of N <sup>6</sup> - and 4' positions and nucleobase |                                                                                     |                                                        |                     |              |                   |                  |                               |                   |
| 23,<br>MRS7978<br>59237                                               |    | Cl                                                     | CH <sub>3</sub> OH  | 8%           | 176±31            | 2510±1180        | 103±1%<br>(1880)              |                   |
| 24,<br>MRS8080<br>60476                                               |    | H (1 <i>H</i> -<br>pyrazolo[3,4- <i>b</i> ]pyrimidine) | CH <sub>3</sub> OH  | 12%          | 21%               | 1200±690         | 31±1%<br>(20±26%)             |                   |
| 25,<br>MRS7945<br>58533                                               |    | Cl                                                     | CHF <sub>3</sub>    | 0%           | 102±2             | 3500±770         | 26.0±2.8<br>(33±3%)           | 58±2%             |
| 26,<br>MRS8141<br>62209                                               |   | Cl                                                     | CHF <sub>3</sub>    | 15%          | 310±190           | 3600±130         | 230±51<br>(56±13%)            |                   |
| 27,<br>MRS8142<br>62210                                               |  | I                                                      | CHF <sub>3</sub>    | 31%          | 34.5±3.6          | 2570±150         | 1460±400<br>(58±20%)          |                   |
| 28,<br>MRS8140<br>62208                                               |  | I                                                      | CHF <sub>3</sub>    | 17%          | 97.5±21.5         | 2550±140         | (42±16%)                      | 54%               |
| 29,<br>MRS8235<br>71273                                               |  | I                                                      | CHF <sub>3</sub>    | 14%          | 139±11            | 1180±10          | (29±4%)                       | (SHT1E<br>2480)   |
| 30,<br>MRS7980<br>59238                                               |  | Cl                                                     | CN                  | 20%          | 33%               | 24%              | 54% <sup>d</sup><br>(-11±38%) | 6690±1830         |
| 31,<br>MRS8077<br>60473                                               |  | I                                                      | CN                  | 16%          | 421±31            | 213±53           | 17±6%<br>(20±25%)             | 1185 <sup>d</sup> |
| 32,<br>MRS8073<br>60396                                               |  | I                                                      | CN                  | 9%           | 30.9±4.4          | 151±67           | 39±2%<br>(29±5%)              | 2098 <sup>d</sup> |
| 33,<br>MRS8027<br>59381                                               |  | Cl                                                     | CN                  | 0%           | 21.3±3.9          | 158±9            | 97±4%<br>(27±5%)              | 43% <sup>d</sup>  |
| 34,<br>MRS8026<br>59380                                               |  | I                                                      | CN                  | 6%           | 15.4±4.6          | 130±10           | 43%<br>(10±5%)                | 56±2%             |
| 35,<br>MRS8072<br>60395                                               |  | I                                                      | CN                  | 29%          | 6.06±0.44         | 68.5±24.6        | 30±10%<br>(34±5%)             | 1886 <sup>d</sup> |
| 36,<br>MRS8226<br>70206                                               |  | I                                                      | CH <sub>3</sub> SCN | 1710±<br>840 | 26.2±10.8         | 48%              | (4±3%)                        |                   |
| 37,<br>MRS8100<br>61858                                               |  | I                                                      | CN                  | 37%          | 8.71±1.08         | 84.5±36.6        | (7±14%)                       |                   |
| 38,<br>MRS8154<br>62349                                               |  | I                                                      | CH <sub>3</sub> CN  | 28%          | 12.3±1.4          | 330±120          | (9±50%)                       |                   |

|                                                        |                                                                                     |                            |                                    |              |            |           |                                              |                        |
|--------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------|------------------------------------|--------------|------------|-----------|----------------------------------------------|------------------------|
| 39,<br>MRS8165<br>62358                                |    | I                          | CH <sub>3</sub> CN                 | 28%          | 34.1±7.9   | 415±153   | 80%<br>(45±13%)                              |                        |
| 40,<br>MRS8209<br>70084                                |    | I                          | CN                                 | 36%          | 3.45±1.05  | 202±33    | 59±2%<br>(41±23%)                            |                        |
| 41,<br>MRS8210<br>70085                                |    | I                          | CH <sub>3</sub> CN                 | 9%           | 3.34, 13.3 | 879±71    | 1520±650<br>(60±30%)                         |                        |
| 42,<br>MRS8251<br>71587                                |    | I                          | CN                                 | -12%         | 10.7±4.0   | 507±149   | 45±6%<br>(31±2%)                             |                        |
| 43,<br>MRS8252<br>71588                                |    | I                          | CH <sub>3</sub> CN                 | -8%          | 53.2±2.6   | 2290±714  | 92±5%<br>(54±13%)                            |                        |
| 44,<br>MRS8248<br>71584                                |    | I                          | CN                                 | 5%           | 39.9±3.1   | 969±241   | 59±5%<br>(42±7%)                             |                        |
| 45,<br>MRS8249<br>71585                                |    | I                          | CH <sub>3</sub> CN                 | -11%         | 155±4      | 39%       | (54±4%)                                      |                        |
| 46,<br>MRS8201<br>62687                                |    | I                          | CN                                 | 4%           | 10.2±0.1   | 28.3±1.8  | 37%<br>(45±13%)                              |                        |
| 47,<br>MRS8202<br>62688                                |  | I                          | CH <sub>3</sub> CN                 | 12%          | 98.3±12.8  | 464±1     | 76%<br>(50±8%)                               |                        |
| 48,<br>MRS8233<br>70235(DAT<br>enhancem.)              |  | I                          | CN                                 | 4920±<br>200 | 77.2±34.9  | 39.1±4.0  | 28±7%<br>(18±12%)                            |                        |
| 49,<br>MRS8232<br>70234                                |  | I                          | CH <sub>3</sub> CN                 | 19%          | 267±4      | 588±17    | 19±4%<br>(13±5%)                             |                        |
| New C2 position modifications                          |                                                                                     |                            |                                    |              |            |           |                                              |                        |
| 50, MRS8079<br>60475                                   | MeNH                                                                                | Cl-<br>thienyl             | CN                                 | 22%          | 2930±630   | 1240±730  | 45±11%<br>(53±14%)                           | 3875 <sup>a</sup>      |
| 51, MRS8076<br>60397                                   | PrNH                                                                                | Cl-<br>thienyl             | CN                                 | 4%           | 454±12     | 3390±1230 | 24±5%<br>(19.4±6.4%)                         | 4757 <sup>a</sup>      |
| 52, MRS8078<br>60474 (DAT<br>enhancem.)                | MeNH                                                                                | Cl-<br>thienyl-<br>ethynyl | CN                                 | 3%           | 5940±650   | 1970±830  | 9±0%<br>(25±21%)                             | <1000                  |
| 53, MRS7675<br>54375                                   | NH <sub>2</sub>                                                                     | S-<br>CH <sub>2</sub> Ph   | CH <sub>2</sub> OH                 | 56%          | 728±2      | 72.2±10.0 | 72±7%<br>(65±15%)                            | Published<br>49.8±5.5  |
| 54, MRS8176<br>62683                                   | MeNH                                                                                | S-<br>CH <sub>2</sub> Ph   | CH <sub>2</sub> OH                 | 46%          | 59.6±0.4   | 23.2±5.9  | (33±11%)                                     |                        |
| 55, MRS8197<br>62684                                   | MeNH                                                                                | S-<br>CH <sub>2</sub> Ph   | CH <sub>2</sub> CN                 | 29%          | 63.4±5.2   | 68.5±17.0 | 37±12%<br>(20±4%)                            |                        |
| 4'-CO ester and amide derivatives (including 7-deazas) |                                                                                     |                            |                                    |              |            |           |                                              |                        |
| 3, MRS7185 <sup>a</sup><br>38093<br>(23 amide)         |  | Cl                         | CONHCH <sub>3</sub>                | 9%           | 23±2       | 269±7     | 110±14<br>(4320±870)                         | 34±11                  |
| 9, MRS7221 <sup>a</sup><br>38093<br>(26 ester)         |  | Cl                         | COOCH <sub>2</sub> CH <sub>3</sub> | 19%          | 15±3       | 30±2      | 437±21<br>(1570±180)                         | 766±193                |
| 56, MRS7684<br>54183                                   | NH <sub>2</sub>                                                                     | I                          | CONHCH <sub>3</sub>                | -14%         | 2%         | -16%      | ND,<br>(5860±440) <sup>b</sup>               | 23.1±6.5 <sup>b</sup>  |
| 12, MRS8630<br>50820                                   |  | Cl                         | CONHCH <sub>3</sub>                | 0%           | 78.2±13.9  | 44%       | 18.3±6.3<br>(3250±300)                       | 3.7±0.9                |
| 57, MRS7142<br>62205                                   | MeNH                                                                                | I                          | CONHCH <sub>3</sub>                | 34%          | 860±140    | 29%       | 66±1<br>(32±8%)                              |                        |
| 58, MRS7632<br>53713                                   |  | I                          | CONHCH <sub>3</sub>                | -7%          | 116±16     | 1040±270  | 574±121 <sup>b</sup><br>(39±2%) <sup>b</sup> | 4.48±1.63 <sup>b</sup> |

|                         |                                                                                            |                            |                                                                                                  |          |           |           |                   |                  |
|-------------------------|--------------------------------------------------------------------------------------------|----------------------------|--------------------------------------------------------------------------------------------------|----------|-----------|-----------|-------------------|------------------|
| 59, MRS8040<br>59027    | MeNH                                                                                       | Cl-<br>thienyl             | CONHCH <sub>3</sub>                                                                              | 1%       | -14%      | 19%       | 66±5%<br>(40±5%)  | 17.2±4.9         |
| 60, MRS8049<br>60391    | PrNH                                                                                       | Cl-<br>thienyl             | CONHCH <sub>3</sub>                                                                              | -4%      | 1420±370  | 42%       | 84±1%<br>(35±10%) | 820±197          |
| 61, MRS5980<br>30519    | MeNH                                                                                       | Cl-<br>thienyl-<br>ethynyl | CONHCH <sub>3</sub>                                                                              | 19%      | 5%        | 29%       | 6±1%<br>(24±13%)  | 0.70±0.11        |
| 62, MRS8071<br>60394    | PrNH                                                                                       | P-<br>pyridyl              | CONHCH <sub>3</sub>                                                                              | 15%      | 252±5     | 1110±70   | 97±8%<br>(64±10%) | 173 <sup>d</sup> |
| 63, MRS7331<br>44229    | MeNH                                                                                       | I                          | COOCH <sub>2</sub> CH <sub>3</sub>                                                               | 16%      | 36%       | 41%       | (45±11%)          |                  |
| 64,<br>MRS7977<br>59176 | <br>(R)   | Cl-<br>thienyl-<br>ethynyl | CONHCH <sub>3</sub>                                                                              | 3390±150 | 2550±770  | 6620±2010 | (30±7%)           |                  |
| 65, MRS7625<br>53436    | MeNH                                                                                       | H (7-I)                    | COOCH <sub>2</sub> CH <sub>3</sub>                                                               | 15%      | 2280±70   | 19%       | (37±5%)           |                  |
| 4'-aryl derivatives     |                                                                                            |                            |                                                                                                  |          |           |           |                   |                  |
| 66, MRS8215<br>70086    | NH <sub>2</sub>                                                                            | I                          |                 | 12%      | 30.5±16.0 | 3590±620  | 72±6%<br>(51±2%)  |                  |
| 67, MRS8311<br>72194    |          | I                          |                | 7%       | 92%       |           | (21±16%)          |                  |
| 68,<br>MRS8225<br>70205 | <br>(R) | I                          | <br>Structure | 43%      | 425±145   | 3%        | (52±6%)           |                  |

n = 2-4, unless noted.

<sup>a</sup>Data from Tosh et al., 2016 and Tchilibon et al., 2005. <sup>b</sup>Data from Tosh et al., 2023.

<sup>c</sup>Radioligands (parental cells) used are: 5-HT<sub>2A</sub>, [<sup>3</sup>H]ketanserin (HEKT); 5-HT<sub>2B</sub>, [<sup>3</sup>H]LSD (stable HEK); 5-HT<sub>2C</sub>, [<sup>3</sup>H]mesulergine (Flp-IN HEK); A<sub>1</sub>, [<sup>3</sup>H]R-PIA (HEK); A<sub>2A</sub>, [<sup>3</sup>H]CGS21680 (HEK); A<sub>3</sub>, [<sup>125</sup>I]I-AB-MECA (HEK), according to published procedures. Data from D. K. Tosh et al. (2021), D. K. Tosh et al. (2019), and J. Besnard et al. (2012). When a percent is given, it refers to inhibition at 10 μM (or 1 μM, as noted).

<sup>d</sup>n = 1.

**[0160]** This example illustrates radioligand binding assays at h5-HT<sub>2B</sub>R using [<sup>3</sup>H]LSD, **68**. See Fig. 11. Curves for four compounds (A, **18**; B, **29**; C, **32** and D, **27**) are shown (mean, n = 3), compared to reference antagonist 3,5-dihydro-5-methyl-N-3-pyridinylbenzo[1,2-b:4,5-b']dipyrrole-1(2H)-carboxamide hydrochloride (SB206553).<sup>66</sup> Error bars represent SEM.

#### EXAMPLE 5

**[0161]** This example sets forth in Table 4 the results of functional assays at 5-HT<sub>2</sub> receptors of compounds in accordance with an aspect of the invention.

**[0162]** Table 4. Results of functional assays at 5-HT<sub>2</sub> receptors of compounds of the invention.

| Compound                                  | 5-HT <sub>2B</sub>           |                       |                   |      | 5-HT <sub>2C</sub>           |                       |                   |      | 2B/2C selectivity | 5-HT <sub>2A</sub>    |                   |      |
|-------------------------------------------|------------------------------|-----------------------|-------------------|------|------------------------------|-----------------------|-------------------|------|-------------------|-----------------------|-------------------|------|
|                                           | K <sub>i</sub> (binding, nM) | K <sub>B</sub> , nM   | pK <sub>B</sub>   | SEM  | K <sub>i</sub> (binding, nM) | K <sub>B</sub> , nM   | pK <sub>B</sub>   | SEM  |                   | K <sub>B</sub> , nM   | pK <sub>B</sub>   | SEM  |
| Clozapine                                 | NA                           | 16.9                  | 8.07              | 0.57 | NA                           | 16.2                  | 7.79              | 0.02 | 1.9               | 3.4                   | 8.47              | 0.05 |
| <b>27</b> ,<br>MRS8142                    | 34.2                         | 3.3                   | 8.54              | 0.15 | 2750                         | 3277                  | 5.68              | 0.30 | <b>724</b>        | > 10,000              | <5.00             | N/A  |
| <b>35</b> ,<br>MRS8072                    | 6.05                         | 1.3                   | 9.03              | 0.24 | 68.0                         | 3.4                   | 8.47              | 0.02 | <b>3.6</b>        | > 10,000              | <5.00             | N/A  |
| <b>37</b> ,<br>MRS8100                    | 8.75                         | 1.9                   | 8.86              | 0.24 | 85.0                         | 5.8                   | 8.25              | 0.08 | <b>4.1</b>        | > 10,000              | <5.00             | N/A  |
|                                           |                              | EC <sub>50</sub> , nM | pEC <sub>50</sub> | SEM  |                              | EC <sub>50</sub> , nM | pEC <sub>50</sub> | SEM  |                   | EC <sub>50</sub> , nM | pEC <sub>50</sub> | SEM  |
| 5-HT EC <sub>50</sub> , pEC <sub>50</sub> | NA                           | 0.70                  | 9.31              | 0.25 | NA                           | 0.51                  | 9.49              | 0.28 | NA                | 0.24                  | 9.68              | 0.19 |

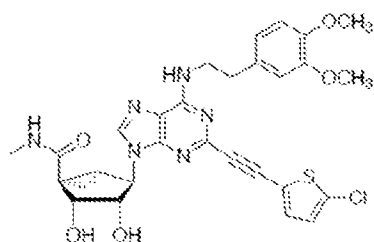
#### EXAMPLE 6

**[0163]** The ADMET properties of compound **35** were studied in vitro and in vivo (Tables 5 and 6). Comparable data for a known A<sub>3</sub>AR-selective (N)-methanocarba nucleoside (reference compound **21**) from Tosh et al. 2020 is presented. The oral bioavailability of **35** in the rat was 7.18%F (1.0 mg/kg) and 13.1%F (3.0 mg/kg and 10 mg/kg). Its in vivo half-life was 2.2 h at 1.0 mg/kg, 4.3 h at 3.0 mg/kg, and 1.75 h at 10 mg/kg. It was highly stable in the plasma of three species and simulated gastric and intestinal fluids, indicating that the N<sup>6</sup>-(cyclobutyl-cyclopropyl)-methyl group is not unstable in acid medium, as is the N<sup>6</sup>-(di-cyclopropyl)-methyl group (Tosh et al. 2016). *In vitro*, the inhibition of five human CYP enzymes by **35** was IC<sub>50</sub> >20 μM, except for CYP2C9 with an IC<sub>50</sub> of 8.64 μM. The lack of hERG inhibition and the microsomal stability are much more favorable than that of the reference compound. The CACO2 cell permeability was moderate with a low efflux ratio. The StarDrop software was used to predict properties of potent antagonists **27**, **35**, **37**, **40**, **66** and **67** (Table 5). All of the compounds were predicted to be peripherally selective, with BBB permeability (log([brain]:[blood])) of -0.73 to -1.14. The cLogD ranged from hydrophilic derivatives values 0.611 (**66**) and 0.829 (**40**) to more moderately hydrophobic, 2.03 (**27**). The predicted aqueous solubility at pH 7.4 ranged from 7.7 (**27**) to 243 (**66**) μg/mL.

**[0164]** Table 5. In vitro and in vivo ADMET data in male Wistar rats for representative 5-HT<sub>2B</sub>AR antagonist **21** (Reference Compound) in comparison to a dopamine-containing A<sub>3</sub>AR agonist **35**.

| Test                                                                                         | Reference compound                                       | 35                                                    |
|----------------------------------------------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------|
| Simulated intestinal fluid<br>(% remaining at 120 min)                                       | 100                                                      | 97.8                                                  |
| Simulated gastric fluid<br>(% remaining at 120 min)                                          | 100                                                      | 100                                                   |
| hCYP1A2 (IC <sub>50</sub> , μM)                                                              | 0.43                                                     | 46.5                                                  |
| hCYP2C9 (IC <sub>50</sub> , μM)                                                              | >30                                                      | 8.64                                                  |
| hCYP2C19 (IC <sub>50</sub> , μM)                                                             | 15.1                                                     | 22.5                                                  |
| hCYP2D6 (IC <sub>50</sub> , μM)                                                              | 17.7                                                     | 24.2                                                  |
| hCYP3A4 (IC <sub>50</sub> , μM)                                                              | 0.78                                                     | 35.6                                                  |
| Plasma stability (3 species) <sup>d</sup><br>(% remaining at 120 min)                        | 100 (h); 100 (r); 100 (m)                                | 93.3 (h); 100 (r); 94.4 (m)                           |
| Plasma protein binding (3<br>species) <sup>d</sup> , % bound                                 | 98.22 (h); 98.50 (r); 98.63<br>(m)                       | 98.62 (h); 98.37 (r); 99.42<br>(m)                    |
| CACO2 permeability<br>(P <sub>app</sub> , A to B (10 <sup>-6</sup> cm/sec); efflux<br>ratio) | 0.44; 46.6                                               | 5.97; 2.76<br>(moderate)                              |
| Microsomal stability<br>(units as indicated)                                                 | 6.72 (m), 11.5 (r), 2.00 (h)<br>[t <sub>1/2</sub> , min] | 72.6 (m), 72.9 (r), 68.1 (h)<br>[% remaining, 60 min] |
| HepG2 toxicity, IC <sub>50</sub> (μM)                                                        | 36.9                                                     | 17.2                                                  |
| hERG, IC <sub>50</sub> (μM or %)                                                             | 3.65 μM                                                  | 16% inhib. at 30 μM                                   |
| Aqueous solubility <sup>c</sup><br>(pH 7.4, μg/mL)                                           | 3.84±0.52                                                | 50.0±3.7                                              |

The structure of compound **21** is:



Mean ± SD, pION method.

Species tested for plasma stability were human, rat and mouse; species as indicated for microsomal stability.

## EXAMPLE 7

[0165] This example sets forth the results of in vivo pharmacokinetic parameters of a compound in accordance with an aspect of the invention.

[0166] Table 6. In vivo PK parameters of compound 35

| Dose<br>(mg/kg<br>, p.o.) | C <sub>max</sub><br>(ng/mL) | T <sub>max</sub><br>(h) | AUC <sub>0-<sup>∞</sup></sub><br>(h*ng/mL) | AUC <sub>0-<sup>∞</sup></sub><br>(h*ng/mL) | T <sub>1/2</sub><br>(h) | MRT <sub>las</sub><br>(h) | Vd<br>(mL/kg) | Kel<br>(1/h) | F<br>(%) | Cl<br>(mL/h/kg) |
|---------------------------|-----------------------------|-------------------------|--------------------------------------------|--------------------------------------------|-------------------------|---------------------------|---------------|--------------|----------|-----------------|
| 0.5                       | 176                         | 0.083                   | 129                                        | 133                                        | 1.00                    | 0.744                     | 5410          | 0.691        | 100      | 3740            |
| 1.0                       | 6.73                        | 1                       | 15.9                                       | 19.2                                       | 2.20                    | 1.590                     | 165,000       | 0.315        | 7.18     | 52,000          |
| 3.0                       | 23.5                        | 2                       | 66.4                                       | 105                                        | 4.30                    | 1.745                     | 177,000       | 0.161        | 13.1     | 28,500          |
| 10.0                      | 95.6                        | 2                       | 343                                        | 349                                        | 1.75                    | 2.330                     | 72200         | 0.397        | 13.1     | 28,600          |

## EXAMPLE 8

[0167] This example sets forth some of the calculated properties of compounds in accordance with an aspect of the invention.

Table 7. Calculated properties of compounds.

| Compound                                    | 27     | 35    | 37    | 40     | 66     | 67    |
|---------------------------------------------|--------|-------|-------|--------|--------|-------|
| K <sub>i</sub> at 5-HT <sub>2B</sub> R (nM) | 34.5   | 6.05  | 8.71  | 2.45   | 30.5   | TBD   |
| logS                                        | 0.6894 | 1.334 | 1.334 | 1.882  | 2.029  | 1.471 |
| logS @ pH7.4                                | 0.8845 | 1.04  | 1.04  | 1.191  | 2.387  | 2.157 |
| logD                                        | 2.032  | 1.687 | 1.687 | 0.8288 | 0.6106 | 1.279 |
| 2C9 pK <sub>i</sub>                         | 4.999  | 4.948 | 4.948 | 4.694  | 5.363  | 4.822 |
| hERG pIC <sub>50</sub>                      | 6.346  | 6.085 | 6.085 | 5.782  | 4.871  | 5.798 |

|                             |           |           |           |           |         |           |
|-----------------------------|-----------|-----------|-----------|-----------|---------|-----------|
| BBB<br>log([brain]:[blood]) | -0.7314   | -1.125    | -1.125    | -1.142    | -0.8523 | -0.8559   |
| BBB category                | -         | -         | -         | -         | -       | -         |
| HIA category                | +         | -         | -         | -         | -       | -         |
| P-gp category               | yes       | yes       | yes       | no        | yes     | yes       |
| 2D6 affinity category       | very high | very high | very high | very high | low     | very high |
| PPB90 category              | high      | high      | high      | low       | low     | low       |
| logP                        | 3.829     | 2.967     | 2.967     | 2.314     | 1.257   | 2.529     |
| MW                          | 531.3     | 506.3     | 506.3     | 466.3     | 455.2   | 523.3     |
| HBD                         | 3         | 3         | 3         | 3         | 3       | 3         |
| HBA                         | 7         | 8         | 8         | 8         | 10      | 10        |
| TPSA                        | 96.09     | 119.9     | 119.9     | 119.9     | 149     | 135       |
| Flexibility                 | 0.1714    | 0.1765    | 0.1765    | 0.1333    | 0.0689  | 0.1143    |
| Rotatable Bonds             | 6         | 6         | 6         | 4         | 2       | 4         |

**[0168]** The stability of the 4'-cyano nucleosides is enabled by the lack of a 4'-oxygen present in native ribosides, and no similar analogues have been reported among ribose derivatives. The nitrile group is present in dozens of approved pharmaceuticals. It has been shown here that a nitrile group at the 4'-position of (N)-methanocarba nucleosides substantially enhances 5-HT<sub>2B</sub>R affinity and selectivity. It modestly reduces AR affinity. The pharmacokinetic profile of **35** indicates that it is moderately stable in tissues.

#### EXAMPLE 9

**[0169]** This examples illustrates off-target activity of compounds in accordance with an aspect of the invention. The off-target activity was determined according to the published procedures: <https://pdsp.unc.edu/pdspweb/content/UNC-CH%20Protocol%20Book.pdf>. The results obtained are set forth in Table 8. Unless noted in the text, no significant interactions (<50% inhibition at 10  $\mu$ M) for any of the nucleosides were found at the following sites

(human unless noted): 5HT<sub>1A</sub>, 5HT<sub>1B</sub>, 5HT<sub>1D</sub>, 5HT<sub>1E</sub>, 5HT<sub>2A</sub>, 5HT<sub>2B</sub>, 5HT<sub>2C</sub>, 5HT<sub>3</sub>, 5HT<sub>5A</sub>, 5HT<sub>6</sub>, 5HT<sub>7</sub>,  $\alpha_{1A}$ ,  $\alpha_{1B}$ ,  $\alpha_{1D}$ ,  $\alpha_{2A}$ ,  $\alpha_{2B}$ ,  $\alpha_{2C}$ ,  $\beta_1$ ,  $\beta_2$ ,  $\beta_3$ , BZP rat brain site, D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, D<sub>5</sub>, GABA<sub>A</sub>, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, M<sub>1</sub>, M<sub>2</sub>, M<sub>5</sub>,  $\delta$ -opioid receptor (DOR),  $\kappa$ -opioid receptor (KOR),  $\mu$ -opioid receptor (MOR),  $\sigma_1$ ,  $\sigma_2$ , DAT, NET, SERT. K<sub>i</sub> values in  $\mu$ M, or % inhibition at 10  $\mu$ M, are given.

Table 8. Off-target activity of the compounds in accordance with an aspect of the invention.

Compound numbers and receptor interactions (other than 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub>, K<sub>i</sub>,  $\mu$ M) are as follows:

**9a**, none  
**9b**, none  
**10a**, none  
**10b**, none  
**11**,  $\sigma_1$  8.2,  $\sigma_2$  5.5  
**12**,  $\sigma_1$  7.5,  $\sigma_2$  4.8  
**13**,  $\sigma_2$ ,  $\alpha_{2B}$   
**14**, none  
**15**,  $\sigma_1$  6.2,  $\sigma_2$  3.4,  $\beta_1$  6.2  
**16**,  $\sigma_1$  0.95,  $\sigma_2$  1.2  
**17**, none  
**18**, none  
**19**,  $\sigma_2$  2.0, TSPO 2.1  
**20**,  $\beta_3$  1.7  
**21**, none  
**22**, none  
**23**,  $\sigma_1$  5.0,  $\sigma_2$  2.1  
**24**,  $\sigma_1$  4.0,  $\sigma_2$  2.3, DOR 3.9, KOR 0.11, MOR 3.5  
**25**,  $\sigma_1$  3.1,  $\sigma_2$  2.5, D<sub>5</sub> 5.1, DAT 2.8,  $\beta_3$  4.7  
**26**,  $\sigma_1$  1.9,  $\sigma_2$  1.2, DAT 7.9  
**27**,  $\sigma_1$  2.0,  $\sigma_2$  0.79, MOR 5.7, 5HT<sub>2A</sub> 6.5,  $\alpha_{2C}$  2.5  
**28**,  $\sigma_1$  1.8,  $\sigma_2$  1.5,  $\alpha_{2B}$  1.7  
**29**,  $\sigma_1$  1.8,  $\sigma_2$  1.0,  $\alpha_{2C}$  2.1,  $\beta_3$  1.5, D<sub>4</sub> 3.6, 5HT<sub>1D</sub> 5.2  
**30**,  $\sigma_2$  0.64  
**31**,  $\sigma_1$  0.47,  $\sigma_2$  0.7, 5HT<sub>2A</sub> 9.2,  $\alpha_{2B}$  1.2, D<sub>5</sub> 1.1  
**32**,  $\sigma_1$  0.58,  $\sigma_2$  1.4, MOR 4.9  
**33**,  $\beta_3$  2.1  
**34**,  $\sigma_2$  1.0  
**35**,  $\alpha_{2B}$  4.6, 5HT<sub>1D</sub> 5.5, 5HT<sub>2A</sub> 7,  $\sigma_1$  1.8,  $\sigma_2$  0.76  
**36**,  $\sigma_2$  0.30  
**37**, none  
**38**,  $\sigma_2$  3.2  
**39**, none

40,  $\alpha_{2B}$  8.9  
41, none  
42, none  
43,  $\sigma_2$  4.9,  $H_1$  2.1  
44, none  
45, TSPO 3.9  
46, none  
47,  $\sigma_1$  6.1,  $\sigma_2$  3.4,  $\alpha_{2A}$  3.2,  $\alpha_{2B}$  2.3,  $D_3$  5.2,  $\beta_3$  3.5  
48, TSPO 2.3,  $\sigma_2$  2.1,  $\alpha_{2B}$  1.4  
49, none  
50,  $\sigma_2$  4.7, KOR 4.4  
51, TSPO 7.6,  $5HT_{5A}$  1.4,  $D_2$  1.5,  $D_3$  0.70,  $D_4$  1.2,  $\beta_3$  4.6  
52, TSPO 1.9  
53, none  
54, TSPO 7.7,  $\sigma_2$  1.5  
55, none.

## EXAMPLE 10

[0170] This examples illustrates an advantageous property of a compound of formula (I) in accordance with an aspect of the invention.

[0171] The 4'-cyano derivative MRS8209 (compound 40) was tested in a mouse model of hypothermia, which is a known activity of AR agonists. The mice had implanted sensors to monitor changes in core body temperature and locomotor activity. Agonists of any of the four AR subtypes were previously found to reduce core body temperature and locomotor activity upon i.p. administration in the mouse. However, MRS8209, advantageously, failed to reduce core body temperature or locomotor activity at doses of 1 and 3 mg/kg, i.p.; see, Figure 10A and 10B, respectively. This indicates that the compound has no detectable in vivo AR agonist activity, which justifies use of this nucleoside analogue as a selective 5-HT<sub>2B</sub> antagonist in vivo.

## EXAMPLE 11

[0172] This examples illustrates advantageous properties of compound 34 as set forth in Table 9. The predicted aqueous solubility at pH 7.4 ranged from 7.7 for compound 27) to 243 for compound 34  $\mu\text{g/mL}$ .

Table 9. Calculated properties of selected molecules, using the StarDrop (v. 7.3.2) software.

| Compound                                    | 34        |
|---------------------------------------------|-----------|
| K <sub>i</sub> at 5-HT <sub>2B</sub> R (nM) | 43        |
| logS                                        | 1.471     |
| logS @ pH7.4                                | 2.157     |
| logD                                        | 1.279     |
| 2C9 pK <sub>i</sub>                         | 4.822     |
| hERG pIC <sub>50</sub>                      | 5.798     |
| BBB                                         | -         |
| log([brain]:[blood])                        | 0.8559    |
| BBB category                                | -         |
| HIA category                                | -         |
| P-gp category                               | yes       |
| 2D6 affinity category                       | very high |
| PPB90 category                              | low       |
| logP                                        | 2.529     |
| MW                                          | 523.3     |
| HBD                                         | 3         |
| HBA                                         | 10        |
| TPSA                                        | 135       |
| Flexibility                                 | 0.1143    |
| Rotatable Bonds                             | 4         |

## EXAMPLE 11

[0173] This example provides characterization data of additional compounds in accordance with aspects of the invention:

[0174] **(1R,2R,3S,4R,5S)-4-(6-(cyclobutylamino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxy bicyclo[3.1.0]hexane-1-carbonitrile**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.00 (s, 1H), 5.12 (d, *J* = 6.4 Hz, 1H), 4.79 (s, 1H), 4.69 (br s, 1H), 4.07 (d, *J* = 6.4 Hz, 1H), 2.46-2.41 (m, 2H), 2.39-2.35 (m, 1H), 2.13-2.07 (m, 2H), 1.94 (t, *J* = 4.8 Hz, 1H), 1.85-1.81 (m, 2H), 1.48-1.44 (m, 1H). HRMS calculated for C<sub>16</sub>H<sub>18</sub>N<sub>6</sub>O<sub>2</sub>I (M + H)<sup>+</sup>: 453.0536; found 453.0543.

[0175] **(1R,2R,3S,4R,5S)-4-(6-(cyclohexylamino)-2-iodo-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo [3.1.0]hexane-2,3-diol**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.38 (s, 1H), 4.81 (s, 1H), 4.77 (d, *J* = 6.4 Hz, 1H), 4.28 (d, *J* = 7.6 Hz, 1H), 4.10 (br s, 1H), 3.86 (d, *J* = 6.8 Hz, 1H), 3.37 (d, *J* = 7.6 Hz, 1H), 2.04-2.03 (m, 2H), 1.84-1.81 (m, 2H), 1.71-1.68 (m, 1H), 1.61-1.58 (m, 1H), 1.54 (t, *J* = 4.8 Hz, 1H), 1.50-1.47 (m, 1H), 1.44-1.23 (m, 4H), 0.78-0.74 (m, 1H). HRMS calculated for C<sub>18</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub>I (M + H)<sup>+</sup>: 486.1002; found 486.0998.

[0176] **(1R,2R,3S,4R,5S)-4-(6-(cyclohexylamino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo [3.1.0]hexane-1-carbonitrile**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.08 (s, 1H), 5.13 (d, *J* = 6.4 Hz, 1H), 4.81 (s, 1H), 4.13-4.07 (m, 2H), 2.39-2.36 (m, 1H), 2.05-2.02 (m, 2H), 1.94 (t, *J* = 5.2 Hz, 1H), 1.84-1.80 (m, 2H), 1.71-1.67 (m, 1H), 1.49-1.42 (m, 3H), 1.39-1.23 (m, 3H). HRMS calculated for C<sub>18</sub>H<sub>22</sub>N<sub>6</sub>O<sub>2</sub>I (M + H)<sup>+</sup>: 481.0849; found 481.0844.

[0177] **(1R,2R,3S,4R,5S)-4-(6-((2-cyclopropylethyl)amino)-2-iodo-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.38 (s, 1H), 4.81 (s, 1H), 4.78 (d, *J* = 6.4 Hz, 1H), 4.28 (d, *J* = 11.6 Hz, 1H), 3.87 (d, *J* = 6.8 Hz, 1H), 3.63 (br s, 2H), 3.37 (d, *J* = 11.6 Hz, 1H), 1.61-1.53 (m, 4H), 0.83-0.75 (m, 2H), 0.50-0.46 (m, 2H), 0.13-0.12 (m, 2H). HRMS calculated for C<sub>17</sub>H<sub>23</sub>N<sub>5</sub>O<sub>3</sub>I (M + H)<sup>+</sup>: 472.0846; found 472.0840.

[0178] **Ethyl (1S,2R,3S,4R,5S)-4-(6-((2-cyclopropylethyl)amino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carboxylate (14a)**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.01 (s, 1H), 5.24 (d, *J* = 6.4 Hz, 1H), 4.78 (s, 1H), 4.29-4.24 (m, 2H), 4.13 (d, *J* = 6.4 Hz, 1H), 3.63 (br s, 2H), 2.18-2.15 (m, 1H), 1.84 (d, *J* = 5.2 Hz,

1H), 1.63-1.54 (m, 3H), 1.33 (t,  $J = 7.2$  Hz, 3H), 0.86-0.75 (m, 1H), 0.50-0.45 (m, 2H), 0.14-0.10 (m, 2H). HRMS calculated for  $C_{19}H_{25}N_5O_4I$  (M + H)<sup>+</sup>: 514.0951; found 514.0945.

**[0179] (1S,2R,3S,4R,5S)-4-(6-((2-cyclopropylethyl)amino)-2-iodo-9H-purin-9-yl)-1-(mercaptomethyl)bicyclo[3.1.0]hexane-2,3-diol**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.28 (s, 1H), 4.80 (d,  $J = 6.8$  Hz, 1H), 4.71 (s, 1H), 4.05 (d,  $J = 6.8$  Hz, 1H), 3.66 (br s, 2H), 3.23 (d,  $J = 14.0$  Hz, 1H), 2.73 (d,  $J = 14.0$  Hz, 1H), 1.64-1.53 (m, 3H), 0.93-0.87 (m, 2H), 0.83-0.77 (m, 1H), 0.49-0.47 (m, 2H), 0.13-0.12 (m, 2H). HRMS calculated for  $C_{17}H_{23}N_5O_2IS$  (M + H)<sup>+</sup>: 488.0617; found 488.0610.

**[0180] (1R,2R,3S,4R,5S)-1-(hydroxymethyl)-4-(2-iodo-6-(phenylamino)-9H-purin-9-yl)bicyclo[3.1.0]hexane-2,3-diol**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.52 (s, 1H), 7.82 (d,  $J = 8.0$  Hz, 2H), 7.38 (t,  $J = 7.6$  Hz, 2H), 7.12 (t,  $J = 7.6$  Hz, 1H), 4.92 (s, 1H), 4.80 (d,  $J = 5.6$  Hz, 1H), 4.30 (d,  $J = 11.6$  Hz, 1H), 3.92 (d,  $J = 6.4$  Hz, 1H), 3.40 (d,  $J = 11.6$  Hz, 1H), 1.65 (m, 1H), 1.56 (d,  $J = 4.8$  Hz, 1H), 0.80-0.77 (m, 1H). HRMS calculated for  $C_{18}H_{19}N_5O_3I$  (M + H)<sup>+</sup>: 480.0533; found 480.0533.

**[0181] (1R,2R,3S,4R,5S)-2,3-dihydroxy-4-(2-iodo-6-(phenylamino)-9H-purin-9-yl)bicyclo[3.1.0]hexane-1-carbonitrile**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.11 (s, 1H), 7.83 (d,  $J = 8.0$  Hz, 2H), 7.38 (t,  $J = 7.6$  Hz, 2H), 7.12 (t,  $J = 7.2$  Hz, 1H), 5.17 (d,  $J = 6.8$  Hz, 1H), 4.85 (s, 1H), 4.12 (d,  $J = 6.8$  Hz, 1H), 2.42-2.39 (m, 1H), 1.97 (t,  $J = 5.2$  Hz, 1H), 1.50-1.46 (m, 1H). HRMS calculated for  $C_{18}H_{16}N_6O_2I$  (M + H)<sup>+</sup>: 475.0379; found 475.0376.

**[0182] 2-((1S,2R,3S,4R,5S)-2,3-dihydroxy-4-(2-iodo-6-(phenylamino)-9H-purin-9-yl)bicyclo[3.1.0]hexan-1-yl)acetonitrile**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.11 (s, 1H), 7.81 (d,  $J = 8.0$  Hz, 2H), 7.38 (t,  $J = 7.6$  Hz, 2H), 7.12 (t,  $J = 7.2$  Hz, 1H), 4.83 (s, 1H), 4.77 (d,  $J = 6.8$  Hz, 1H), 3.99 (d,  $J = 6.4$  Hz, 1H), 3.20-3.07 (m, 2H), 1.72-1.69 (m, 1H), 1.58 (t,  $J = 5.2$  Hz, 1H), 0.94-0.90 (m, 1H). HRMS calculated for  $C_{19}H_{18}N_6O_2I$  (M + H)<sup>+</sup>: 489.0536; found 489.0540.

**[0183] Ethyl (1S,2R,3S,4R,5S)-2,3-dihydroxy-4-(2-iodo-6-(phenylamino)-9H-purin-9-yl)bicyclo [3.1.0]hexane-1-carboxylate**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  8.04 (s, 1H), 7.80 (d,  $J = 8.0$  Hz, 2H), 7.37 (t,  $J = 7.6$  Hz, 2H), 7.11 (t,  $J = 7.2$  Hz, 1H), 5.27 (d,  $J = 6.8$  Hz, 1H), 4.81 (s, 1H), 4.31-4.26 (m, 2H), 4.16 (d,  $J = 6.8$  Hz, 1H), 2.21-2.17 (m, 1H), 1.86 (t,  $J = 5.2$  Hz, 1H), 1.64-1.60 (m, 1H), 1.34 (t,  $J = 7.2$  Hz, 3H). HRMS calculated for  $C_{20}H_{21}N_5O_4I$  (M + H)<sup>+</sup>: 522.0638; found 522.0646.

**[0184] (1S,2R,3S,4R,5S)-4-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(phenylamino)-9H-purin-9-yl)-2,3-dihydroxy-N-methylbicyclo[3.1.0]hexane-1-carboxamide**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.23 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 4.0 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 5.08 (d, *J* = 5.6 Hz, 1H), 4.92 (s, 1H), 4.06 (d, *J* = 6.4 Hz, 1H), 2.87 (s, 3H), 2.15-2.12 (m, 1H), 1.89 (t, *J* = 4.8 Hz, 1H), 1.43-1.39 (m, 1H). HRMS calculated for C<sub>25</sub>H<sub>22</sub>N<sub>6</sub>O<sub>3</sub>SCl (M + H)<sup>+</sup>: 521.1163; found 521.1154.

**[0185] (1R,2R,3S,4R,5S)-4-(6-((3-fluorophenyl)amino)-2-iodo-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.52 (s, 1H), 7.87-7.83 (m, 1H), 7.48-7.46 (m, 1H), 7.38-7.32 (m, 1H), 6.85-6.80 (m, 1H), 4.88 (s, 1H), 4.79 (d, *J* = 6.8 Hz, 1H), 4.29 (d, *J* = 11.6 Hz, 1H), 3.92 (d, *J* = 6.8 Hz, 1H), 3.40 (d, *J* = 11.6 Hz, 1H), 1.64-1.62 (m, 1H), 1.56 (t, *J* = 4.8 Hz, 1H), 0.80-0.76 (m, 1H). HRMS calculated for C<sub>18</sub>H<sub>18</sub>N<sub>5</sub>O<sub>3</sub>FI (M + H)<sup>+</sup>: 498.0438; found 498.0443.

**[0186] (1R,2R,3S,4R,5S)-4-(6-((3-fluorophenyl)amino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carbonitrile**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 10.43 (s, 1H), 8.32 (s, 1H), 7.90-7.86 (m, 1H), 7.71-7.68 (m, 1H), 7.41-7.35 (m, 1H), 6.92-6.87 (m, 1H), 5.61 (d, *J* = 5.2 Hz, 1H), 5.40 (d, *J* = 8.4 Hz, 1H), 5.00 (t, *J* = 7.2 Hz, 1H), 4.76 (s, 1H), 4.04-4.01 (m, 1H), 2.44-2.41 (m, 1H), 1.76 (t, *J* = 5.2 Hz, 1H), 1.43-1.40 (m, 1H). HRMS calculated for C<sub>18</sub>H<sub>15</sub>N<sub>6</sub>O<sub>2</sub>FI (M + H)<sup>+</sup>: 493.0285; found 493.0292.

**[0187] (1R,2R,3S,4R,5S)-4-(6-((3,5-difluorophenyl)amino)-2-iodo-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.55 (s, 1H), 7.55-7.49 (m, 2H), 6.67-6.61 (m, 1H), 4.89 (s, 1H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.30 (d, *J* = 11.6 Hz, 1H), 3.93 (d, *J* = 6.4 Hz, 1H), 3.40 (d, *J* = 11.6 Hz, 1H), 1.65-1.62 (m, 1H), 1.56 (t, *J* = 5.2 Hz, 1H), 0.81-0.77 (m, 1H). HRMS calculated for C<sub>18</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>FI (M + H)<sup>+</sup>: 516.0344; found 516.0339.

**[0188] (1R,2R,3S,4R,5S)-4-(6-((3,5-difluorophenyl)amino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carbonitrile**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 10.62 (s, 1H), 8.36 (s, 1H), 7.75-7.72 (m, 2H), 6.94-6.88 (m, 1H), 5.61 (d, *J* = 4.8 Hz, 1H), 5.40 (d, *J* = 8.0 Hz, 1H), 5.00 (t, *J* = 6.8 Hz, 1H), 4.77 (s, 1H), 4.03 (t, *J* = 5.2 Hz, 1H), 2.45-2.41 (m, 1H), 1.76 (t, *J* = 5.2 Hz, 1H), 1.44-1.41 (m, 1H). HRMS calculated for C<sub>18</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>FI (M + H)<sup>+</sup>: 511.0191; found 511.0195.

**[0189] (1R,2R,3S,4R,5S)-4-(6-((3,4-dichlorophenyl)amino)-2-iodo-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.53 (s, 1H), 8.19 (d, *J* = 2.4 Hz, 1H), 7.69-7.66 (m, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 4.88 (s, 1H), 4.81 (d, *J* = 5.6 Hz, 1H), 4.29 (d, *J* = 11.6 Hz, 1H), 3.93 (d, *J* = 6.8 Hz, 1H), 3.40 (d, *J* = 11.6 Hz, 1H), 1.53-1.62 (m, 1H), 1.56 (t, *J* = 4.8 Hz, 1H), 0.80-0.77 (m, 1H). HRMS calculated for C<sub>18</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>Cl<sub>2</sub>I (M + H)<sup>+</sup>: 547.9753; found 547.9747.

**[0190] Ethyl (1S,2R,3S,4R,5S)-4-(6-((3-chlorobenzyl)amino)-2-iodo-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carboxylate**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 8.73 (s, 1H), 8.02 (s, 1H), 7.41 (s, 1H), 7.35-7.29 (m, 3H), 5.33 (s, 1H), 4.99 (d, *J* = 5.6 Hz, 1H), 4.88 (s, 1H), 4.59-4.58 (br s, 3H), 4.16-4.11 (m, 2H), 4.11 (br s, 1H), 2.04-2.00 (m, 1H), 1.66 (t, *J* = 5.2 Hz, 1H), 1.46-1.43 (m, 1H), 1.19 (t, *J* = 7.2 Hz, 3H). HRMS calculated for C<sub>21</sub>H<sub>22</sub>N<sub>5</sub>O<sub>4</sub>ClI (M + H)<sup>+</sup>: 570.0405; found 570.0407.

**[0191] 2-((1S,2R,3S,4R,5S)-4-(6-((3-chlorobenzyl)amino)-2-((5-chlorothiophen-2-yl)ethynyl)-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hexan-1-yl)acetonitrile**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.21 (s, 1H), 7.42 (s, 1H) (d, *J* = 2.4 Hz, 1H), 7.33-7.22 (m, 4H), 7.00 (d, *J* = 4.0 Hz, 1H), 4.81 (s, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 3.96 (d, *J* = 6.4 Hz, 1H), 3.17 (d, *J* = 8.8 Hz, 1H), 2.98 (d, *J* = 8.8 Hz, 1H), 1.78-1.75 (m, 1H), 1.64 (t, *J* = 5.2 Hz, 1H), 0.90-0.87 (m, 1H). HRMS calculated for C<sub>26</sub>H<sub>21</sub>N<sub>6</sub>O<sub>2</sub>Cl<sub>2</sub>S (M + H)<sup>+</sup>: 551.0824; found 551.0818.

**[0192] (1R,2R,3S,4R,5S)-4-(6-((1H-pyrrol-1-yl)amino)-2-iodo-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.47 (s, 1H), 6.78-6.77 (m, 2H), 6.16-6.14 (m, 2H), 4.87 (s, 1H), 4.78 (d, *J* = 6.4 Hz, 1H), 4.28 (d, *J* = 11.6 Hz, 1H), 3.88 (d, *J* = 6.8 Hz, 1H), 3.38 (d, *J* = 11.6 Hz, 1H), 1.62-1.59 (m, 1H), 1.55 (d, *J* = 4.8 Hz, 1H), 0.79-0.75 (m, 1H). HRMS calculated for C<sub>16</sub>H<sub>18</sub>N<sub>6</sub>O<sub>3</sub>I (M + H)<sup>+</sup>: 469.0485; found 469.0485.

**[0193] (1R,2R,3S,4R,5S)-1-(hydroxymethyl)-4-(2-(pyrrolidin-1-yl)-6-(pyrrolidin-1-ylamino)-9H-purin-9-yl)bicyclo[3.1.0]hexane-2,3-diol**

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.14 (s, 1H), 4.82-4.80 (m, 2H), 4.23 (d, *J* = 11.6 Hz, 1H), 3.92 (d, *J* = 6.8 Hz, 1H), 3.65-3.61 (m, 4H), 3.35 (d, *J* = 11.6 Hz, 1H), 3.05 (br s, 4H), 2.00-1.98 (m, 4H), 1.97-1.93 (m, 4H), 1.57-1.54 (m, 1H), 1.49 (t, *J* = 4.8 Hz, 1H), 0.75-0.72 (m, 1H). HRMS calculated for C<sub>20</sub>H<sub>30</sub>N<sub>7</sub>O<sub>3</sub> (M + H)<sup>+</sup>: 416.2410; found 416.2408.

**[0194] 4-(cyclopentylamino)-7-((1S,2R,3S,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)bicyclo[3.1.0] hexan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile**  
<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.37 (s, 1H), 8.30 (s, 1H), 5.06 (s, 1H), 4.73 (d, *J* = 6.4 Hz, 1H), 4.58-4.52 (m, 1H), 4.31 (d, *J* = 11.6 Hz, 1H), 3.79 (d, *J* = 6.4 Hz, 1H), 3.28 (d, *J* = 11.6 Hz, 1H), 2.19-2.12 (m, 2H), 1.85-1.79 (m, 2H), 1.78-1.69 (m, 2H), 1.66-1.60 (m, 2H), 1.57-1.54 (m, 2H), 0.77-0.72 (m, 1H). HRMS calculated for C<sub>19</sub>H<sub>24</sub>N<sub>5</sub>O<sub>3</sub> (M + H)<sup>+</sup>: 370.1879; found 370.1877.

**[0195] 7-((1S,2R,3S,4R,5R)-5-cyano-3,4-dihydroxybicyclo[3.1.0]hexan-2-yl)-4-(cyclopentylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile**  
<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.32 (s, 1H), 7.94 (s, 1H), 4.99-4.96 (m, 2H), 4.58-4.52 (m, 1H), 4.06 (d, *J* = 6.8 Hz, 1H), 2.39-2.36 (m, 1H), 2.19-2.12 (m, 2H), 1.98 (t, *J* = 5.2 Hz, 1H), 1.85-1.81 (m, 2H), 1.79-1.70 (m, 2H), 1.66-1.59 (m, 2H), 1.50-1.46 (m, 1H). HRMS calculated for C<sub>19</sub>H<sub>21</sub>N<sub>6</sub>O<sub>2</sub> (M + H)<sup>+</sup>: 365.1726; found 365.1724.

**[0196] (1S,2R,3S,4R,5S)-4-(6-amino-2-iodo-9H-purin-9-yl)-1-(3-methyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane-2,3-diol**  
<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.99 (s, 1H), 5.42 (d, *J* = 6.4 Hz, 1H), 4.91 (s, 1H), 4.14 (d, *J* = 6.8 Hz, 1H), 2.41-2.38 (m, 4H), 2.16 (t, *J* = 5.2 Hz, 1H), 1.73-1.69 (m, 1H). HRMS calculated for C<sub>14</sub>H<sub>15</sub>N<sub>7</sub>O<sub>3</sub>I (M + H)<sup>+</sup>: 456.0281; found 456.0284.

**[0197] (1S,2R,3S,4R,5S)-4-(6-(cyclopentylamino)-2-iodo-9H-purin-9-yl)-1-(3-methyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane-2,3-diol**  
<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.92 (s, 1H), 5.41 (d, *J* = 6.8 Hz, 1H), 4.89 (s, 1H), 4.47 (br s, 1H), 4.12 (d, *J* = 7.2 Hz, 1H), 2.38 (s, 3H), 2.16 (t, *J* = 5.2 Hz, 1H), 2.10-2.04 (m, 2H), 1.82-1.70 (m, 2H), 1.69-1.66 (m, 3H), 1.62-1.56 (m, 2H), 1.27-1.23 (m, 1H). HRMS calculated for C<sub>19</sub>H<sub>23</sub>N<sub>7</sub>O<sub>3</sub>I (M + H)<sup>+</sup>: 524.0907; found 524.0902.

**[0198] (1R,2R,3S,4R,5S)-1-((2H-1,2,3-triazol-2-yl)methyl)-4-(6-(((R)-cyclobutyl(cyclopropyl) methyl)amino)-2-iodo-9H-purin-9-yl)bicyclo[3.1.0]hexane-2,3-diol**  
<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.84 (s, 1H), 7.76 (s, 2H), 5.13 (d, *J* = 14.4 Hz, 1H), 4.79 (s, 1H), 4.54-4.51 (m, 2H), 3.91 (d, *J* = 6.4 Hz, 1H), 3.78 (br s, 1H), 2.72-2.66 (m, 1H), 2.12-2.09 (m, 1H), 2.02-1.90 (m, 4H), 1.87-1.80 (m, 2H), 1.64 (d, *J* = 4.8 Hz, 1H), 0.95-0.87 (m, 2H), 0.58-0.53 (m, 1H), 0.40-0.37 (m, 3H). HRMS calculated for C<sub>22</sub>H<sub>28</sub>N<sub>8</sub>O<sub>2</sub>I (M + H)<sup>+</sup>: 563.1380; found 563.1376.

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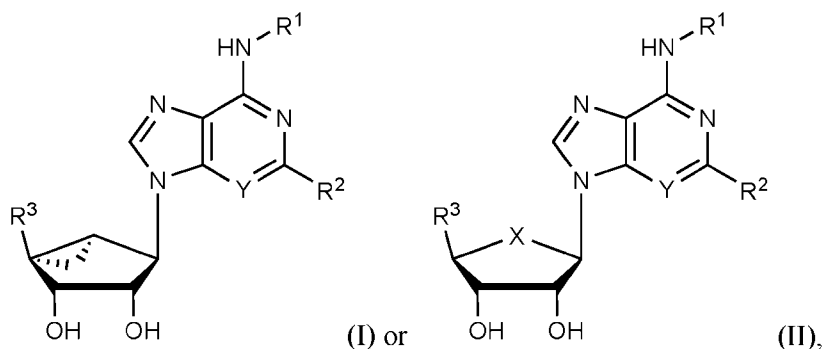
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- [0214] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0215] The use of the terms “a” and “an” and “the” and “at least one” and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term “at least one” followed by a list of one or more items (for example, “at least one of A and B”) is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to,”) unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0216] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

## CLAIMS:

1. A compound of formula (I) or formula (II), a salt thereof, or an optical isomer thereof,



wherein,

in the compound of formula (I),

$R^1$  is selected from the group consisting of aryl, arylalkyl, cycloalkyl, cycloalkyl alkyl, di-cycloalkylalkyl, di-bicycloalkyl, tricycloalkyl, alkyl, (cycloalkyl)(alkyl)alkylenyl, and H, wherein the aryl, alkyl, and cycloalkyl moieties can be optionally substituted with one or more of alkyl, halo, and cyano groups;

$R^2$  is selected from the group consisting of H, halo, alkylthio, arylalkylthio, heteroaryl, tetrahydropyrrolyl, cyano, and thienylalkynyl, wherein each of said moieties, other than H and halo, can be optionally substituted with one or more of alkyl, halo, and cyano groups; and

$R^3$  is selected from the group consisting of optionally substituted 5-membered aromatic heterocyclyl, 3-alkyl-1,2,4-oxadiazol-5-yl, triazolylalkyl, cyano, alkylaminocarbonyl, alkylaminothiocarbonyl, alkylloxycarbonyl, alkylloxythiocarbonyl, hydroxyalkyl, monohaloalkyl, dihaloalkyl, cyanoalkyl, and cyanothioalkyl; and

$Y = N$  or  $CH$ ; and

in the compound of formula (II),

$R^1$  is cycloalkyl or di-cycloalkylalkyl;

$R^2$  is halo;

X is NH, O, S, Se, or CH<sub>2</sub>, and

R<sup>3</sup> is COXR<sup>4</sup> or CSXR<sup>4</sup>, and R<sup>4</sup> is H, alkyl, or alkyloxy; and

Y = N or CH; and

wherein the optical isomer of compound or salt of formulas (I) and (II) can have *R* or *S* configuration at the –NH- moiety of –NH-R<sup>1</sup>;

with the provisos:

(i) in formula (II), when R<sup>3</sup> is CH<sub>2</sub>OH and R<sup>1</sup> is H, alkyl, di-cycloalkyl alkyl, or (cycloalkyl)(alkyl)alkylenyl, then R<sup>2</sup> is not chloro or H;

(ii) in formula (I), when R<sup>3</sup> is alkylaminocarbonyl and R<sup>1</sup> is di-cycloalkyl alkyl, or (chloro substituted aryl) alkyl, then R<sup>2</sup> is not chloro; and

(iii) in formula (I), when R<sup>3</sup> is alkylaminocarbonyl and R<sup>1</sup> is (chloro substituted aryl) alkyl, then R<sup>2</sup> is not (halo substituted thienyl)alkynyl.

2. The compound, salt, or optical isomer according to formula (I) of claim 1, wherein the aryl moiety of aryl and arylalkyl in R<sup>1</sup> is phenyl, biphenyl, naphthyl, anthracenyl, or pyrenyl.

3. The compound, salt, or optical isomer according to formula (I) of claim 1 or 2, wherein R<sup>1</sup> is phenyl optionally substituted with one or more of alkyl, halo, and cyano groups.

4. The compound, salt, or optical isomer according to formula (I) of any one of claims 1-3, wherein R<sup>3</sup> is an optionally substituted 5-membered aromatic heterocyclyl.

5. The compound, salt, or optical isomer according to formula (I) of claim 4, wherein R<sup>3</sup> is selected from the group consisting of thienyl, furyl, oxadiazolyl, diazolyl, thiazolyl, triazolyl, pyrazolyl, and pyrrolyl, each of which is optionally substituted with halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, or aryl C<sub>1</sub>-C<sub>6</sub> alkylthio.

6. The compound, salt, or optical isomer according to formula (I) of claim 5, wherein R<sup>3</sup> is 3-alkyl-1,2,4-oxadiazol-5-yl or triazolylalkyl.

7. The compound, salt, or optical isomer according to formula (I) of claim 1, wherein:

$R^1$  is selected from the group consisting of phenyl, phenylalkyl, halophenyl, dihalophenyl, halobenzyl,  $C_3$ - $C_8$  cycloalkyl, di- $C_3$ - $C_8$  cycloalkyl  $C_3$ - $C_8$  alkyl, and  $C_3$ - $C_8$  alkyl;

$R^2$  is selected from the group consisting of chloro, bromo, iodo,  $C_1$ - $C_8$  alkylthio, aryl  $C_1$ - $C_8$  alkylthio, heteroaryl, thienylalkynyl, pyrrolidinyl, and halothienylalkynyl; and

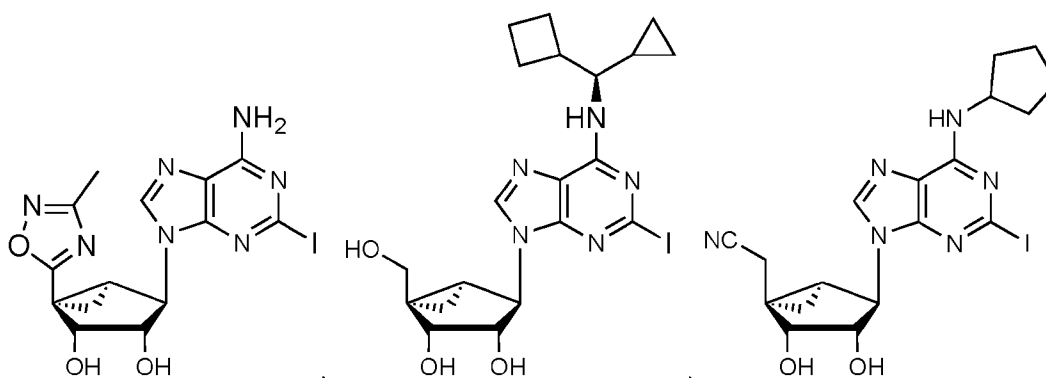
$R^3$  is selected from the group consisting of 3-methyl-1,2,4-oxadiazol-5-yl, cyano, hydroxy  $C_1$ - $C_8$  alkyl, cyano  $C_1$ - $C_8$  alkyl, and cyanothio  $C_1$ - $C_8$  alkyl.

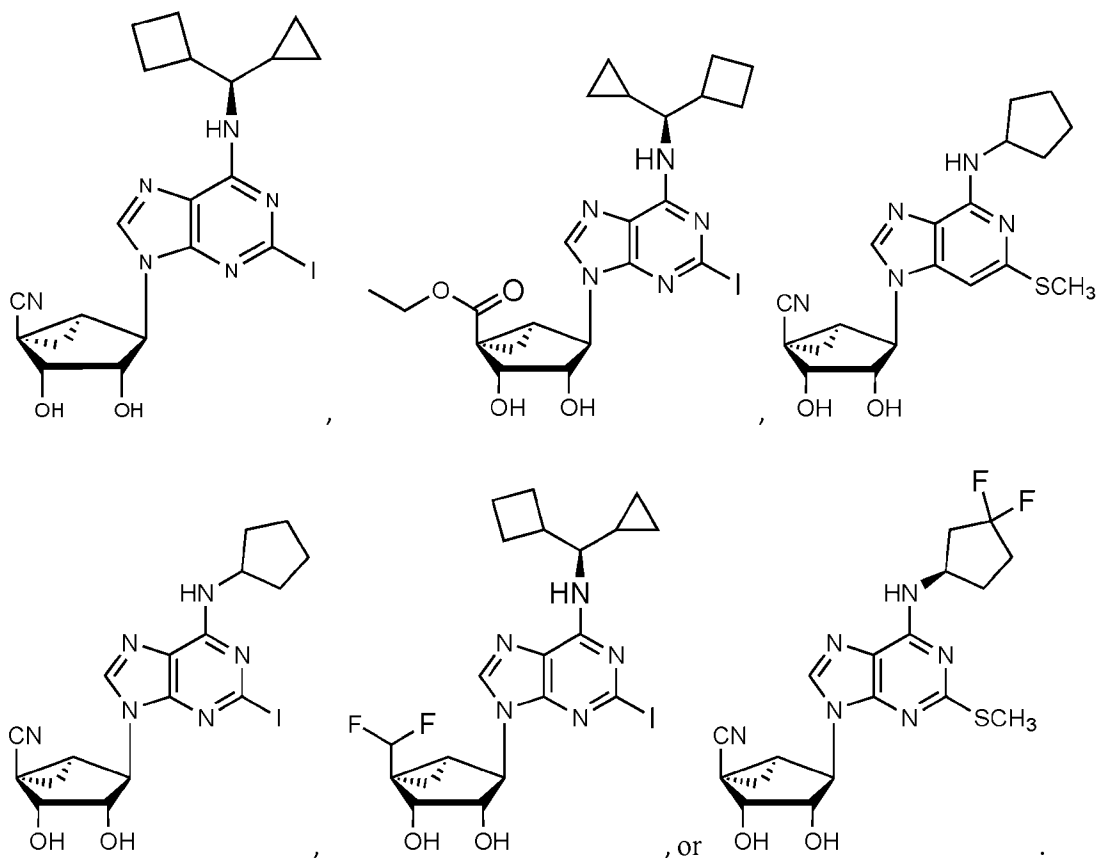
8. The compound, salt, or optical isomer according to formula (I) of any one of claims 1-7, wherein  $R^1$  is selected from the group consisting of di-cyclopropylmethyl, di-bicyclobutylmethyl, di-bicyclopentylmethyl, di-bicyclohexylmethyl, (isopropyl)(cyclopropyl)methyl, (cyclopropyl)(cyclobutyl)methyl, and dicyclopentylmethyl.

9. The compound, salt, or optical isomer according to formula (I) of any one of claims 1-8, wherein  $R^2$  is selected from the group consisting of methylthio, chloro, or iodo.

10. The compound, salt, or optical isomer according to formula (I) of any one of claims 1-9, wherein  $R^3$  is selected from the group consisting of 3-methyl-1,2,4-oxadiazol-5-yl, cyano, dihalomethyl, hydroxymethyl, cyanomethyl, methylaminocarbonyl, trizolylmethyl, and cyanothiomethyl.

11. The compound, salt, or optical isomer according to formula (I) of any one of claims 1-10, wherein the compound is:





12. The compound, salt, or optical isomer according to formula (I) of claim 1, wherein:

 R<sup>1</sup> is , R<sup>2</sup> is Cl, and R<sup>3</sup> is CH<sub>2</sub>OH;

 R<sup>1</sup> is , R<sup>2</sup> is H, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is di(cyclopropyl)methyl, R<sup>2</sup> is Cl, and R<sup>3</sup> is CHF<sub>2</sub>;

R<sup>1</sup> is isopropyl(cyclopropyl)methyl (*R*), R<sup>2</sup> is Cl, and R<sup>3</sup> is CHF<sub>2</sub>;

R<sup>1</sup> is (cyclopropyl)(cyclobutyl)methyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CHF<sub>2</sub>;

R<sup>1</sup> is (cyclopropyl)(cyclobutyl)methyl (*S*), R<sup>2</sup> is I, and R<sup>3</sup> is CHF<sub>2</sub>;

R<sup>1</sup> is *m*-chlorobenzyl, R<sup>2</sup> is I, and R<sup>3</sup> is CHF<sub>2</sub>;

R<sup>1</sup> is H, R<sup>2</sup> is Cl, and R<sup>3</sup> is CN;

R<sup>1</sup> is methyl, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is *n*-propyl, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is isopropyl(cyclopropyl)methyl (*R*), R<sup>2</sup> is Cl, and R<sup>3</sup> is CN;

R<sup>1</sup> is isopropyl(cyclopropyl)methyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (cyclobutyl)(cyclopropyl)methyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (cyclobutyl)(cyclopropyl)methyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>SCN;

R<sup>1</sup> is (cyclobutyl)(cyclopropyl)methyl (*S*), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (cyclobutyl)(cyclopropyl)methyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is (cyclopropyl)(cyclobutyl)methyl (*S*), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is cyclopentyl, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is cyclopentyl, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is 3-difluorocyclopentyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is 3-difluorocyclopentyl (*R*), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is 3-difluorocyclopentyl (*S*), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is 3-difluorocyclopentyl (*S*), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is bicyclo [1.1.2] butyl, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is bicyclo [1.1.2] butyl, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is *m*-chlorobenzyl, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is *m*-chlorobenzyl, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is Me, R<sup>2</sup> is 5-Cl-thien-2-yl, and R<sup>3</sup> is CN;

R<sup>1</sup> is *n*Pr, R<sup>2</sup> is 5-Cl-thien-2-yl, and R<sup>3</sup> is CN;

R<sup>1</sup> is Me, R<sup>2</sup> is 5-Cl-thien-2-yl-ethynyl, and R<sup>3</sup> is CN;

R<sup>1</sup> is H, R<sup>2</sup> is S-CH<sub>2</sub>Ph, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is Me, R<sup>2</sup> is S-CH<sub>2</sub>Ph, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is Me, R<sup>2</sup> is S-CH<sub>2</sub>Ph, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is (cyclopropyl)(cyclobutyl)methyl, R<sup>2</sup> is Cl, and R<sup>3</sup> is COOCH<sub>2</sub>CH<sub>3</sub>;

R<sup>1</sup> is H, R<sup>2</sup> is I, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is Me, R<sup>2</sup> is I, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is phenylethyl, R<sup>2</sup> is I, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is Me, R<sup>2</sup> is 5-Cl-thien-2-yl, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is nPr, R<sup>2</sup> is 5-Cl-thien-2-yl, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is Me, R<sup>2</sup> is 5-Cl-thien-2-yl-ethynyl, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is nPr, R<sup>2</sup> is 4-pyridyl, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is Me, R<sup>2</sup> is I, and R<sup>3</sup> is COOCH<sub>2</sub>CH<sub>3</sub>;

R<sup>1</sup> is (cyclopropyl)(isopropyl)methyl, R<sup>2</sup> is 5-Cl-thien-2-yl-ethynyl, and R<sup>3</sup> is CONHCH<sub>3</sub>; or

R<sup>1</sup> is Me, R<sup>2</sup> is H (Z=C-I), and R<sup>3</sup> is COOCH<sub>2</sub>CH<sub>3</sub>.

13. The compound, salt, or optical isomer according to formula (I) of claim 1, wherein:

R<sup>1</sup> is Me, R<sup>2</sup> is Cl-thienyl-ethynyl, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is c-Bu, R<sup>2</sup> is I; and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is c-Bu, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is c-Hex, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is c-Hex, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

13c': R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>Cl;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CO<sub>2</sub>Et;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>2</sub>cPr, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>SH;

R<sup>1</sup> is Ph, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is Ph, R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is Ph, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>CN;

R<sup>1</sup> is Ph, R<sup>2</sup> is I, and R<sup>3</sup> is CO<sub>2</sub>Et;

R<sup>1</sup> is Ph, R<sup>2</sup> is Cl-thienyl-ethynyl, and R<sup>3</sup> is CONHCH<sub>3</sub>;

R<sup>1</sup> is (cyclobutyl)(cyclopropyl)methyl, R<sup>2</sup> is Cl-thienyl-ethynyl, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is (CH<sub>2</sub>)<sub>5</sub>Ph, R<sup>2</sup> is Cl-thienyl-ethynyl, and R<sup>3</sup> is CO<sub>2</sub>Et;

R<sup>1</sup> is (3-F-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is (3-F-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (3,5-diCl-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

R<sup>1</sup> is (3,5-F-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is NH-(3,4-diCl-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

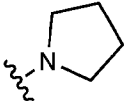
R<sup>1</sup> is (3,4-diCl-Ph), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (3-Cl-Bn), R<sup>2</sup> is I, and R<sup>3</sup> is CN;

R<sup>1</sup> is (3-Cl-Bn), R<sup>2</sup> is I, and R<sup>3</sup> is CO<sub>2</sub>Et;

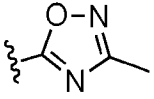
R<sup>1</sup> is (3-Cl-Bn), R<sup>2</sup> is Cl-thienyl-ethynyl, and R<sup>3</sup> is CH<sub>2</sub>CN;

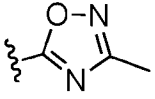
R<sup>1</sup> is pyrrolyl, R<sup>2</sup> is I, and R<sup>3</sup> is CH<sub>2</sub>OH;

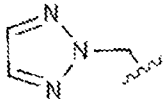
$R^1$  tetrahydropyrrolyl,  $R^2$  is , and  $R^3$  is  $\text{CH}_2\text{OH}$ ;

$R^1$  is tetrahydropyrrolyl,  $R^2$  is 2-H,  $Z=\text{C-CN}$ , and  $R^3$  is  $\text{CH}_2\text{OH}$ ;

$R^1$  is tetrahydropyrrolyl,  $R^2$  is 2-H,  $Z=\text{C-CN}$ , and  $R^3$  is  $\text{CN}$ ;

$R^1$  is H,  $R^2$  is I, and  $R^3$  is ;

$R^1$  is tetrahydropyrrolyl,  $R^2$  is I, and  $R^3$  is ; or

$R^1$  is (cyclopropyl)(cyclobutyl) (*R*),  $R^2$  is I, and  $R^3$  is .

14. The compound, salt, or isomer according to formula (II) of claim 1, wherein  $R^1$  is selected from the group consisting of cycloalkyl or di-cycloalkylalkyl;  $R^2$  is halo; and  $R^3$  is  $\text{CH}_2\text{OH}$  or  $\text{COOR}^4$ , wherein  $R^4$  is alkyl.

15. The compound, salt, or optical isomer of claim 14, wherein  $R^1$  is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl;  $R^2$  is chloro, iodo, or methylthio; and  $R^3$  is  $\text{COOR}^4$ , or  $\text{CONHR}^4$ , wherein  $R^4$  is  $\text{C}_1\text{-C}_3$  alkyl.

16. A pharmaceutical composition comprising a compound, salt, or optical isomer of any one of claims 1-15 and a pharmaceutically acceptable carrier.

17. A method of antagonizing a 5-HT<sub>2B</sub> serotonin receptor in an animal in need thereof comprising administering a compound, salt, or optical isomer of any one of claims 1-15 or a pharmaceutical composition of claim 16.

18. A method of treating fibrosis of the lung, skin, coronary and or liver fibrosis, pulmonary arterial hypertension, valvular heart disease, pain, or cancer in an animal in need thereof, comprising administering a compound, salt, or optical isomer of any one of claims 1-15 or a pharmaceutical composition of claim 16.

19. Use of a compound, salt, or optical isomer of any one of claims 1-15 or a pharmaceutical composition of claim 16 for antagonizing a 5-HT<sub>2B</sub> serotonin receptor in an animal in need thereof.

20. Use of a compound, salt, or optical isomer of any one of claims 1-15 or a pharmaceutical composition of claim 16 treating fibrosis of the lung, skin, coronary and or liver fibrosis, pulmonary arterial hypertension, valvular heart disease, pain, or cancer in an animal in need thereof.



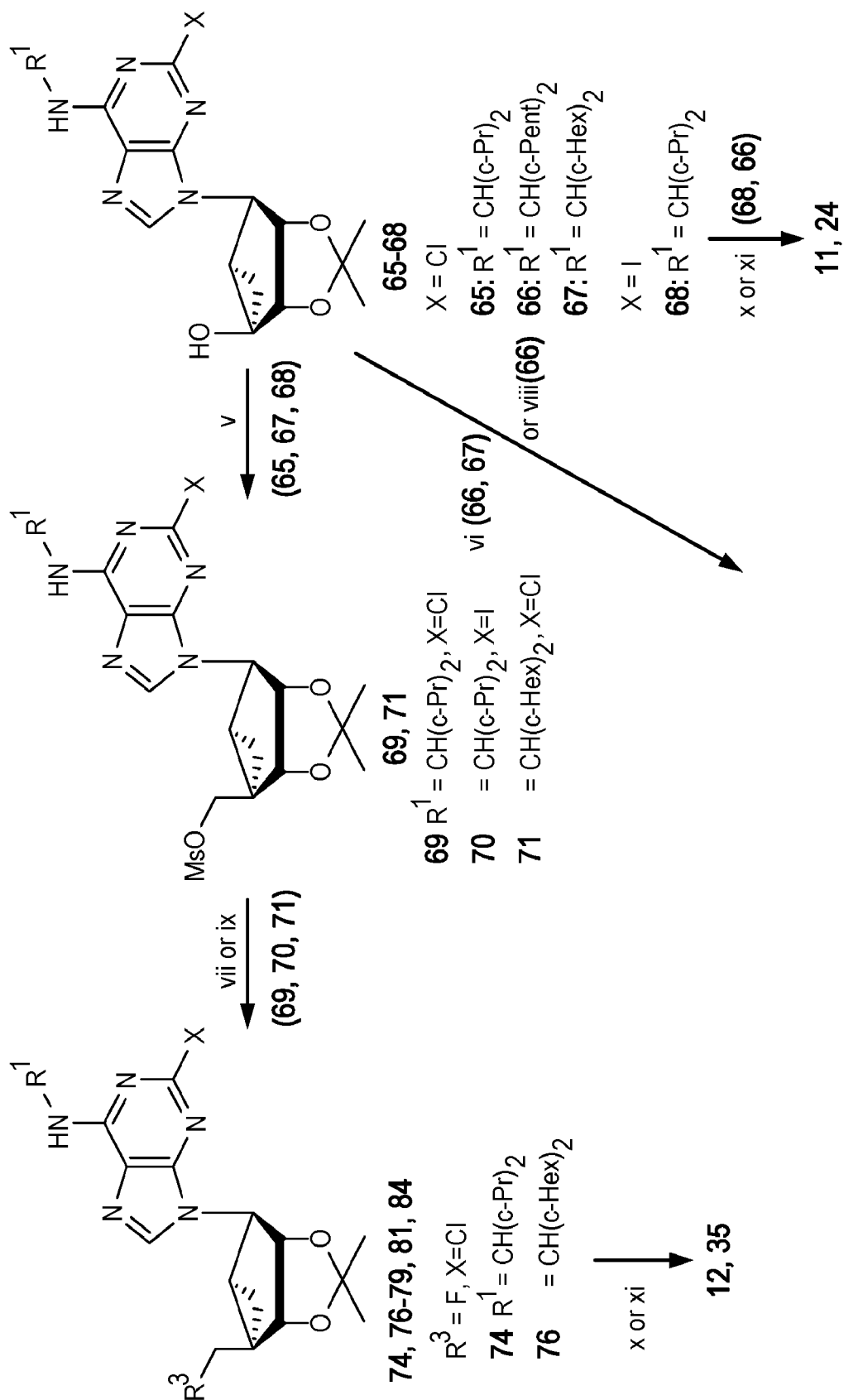
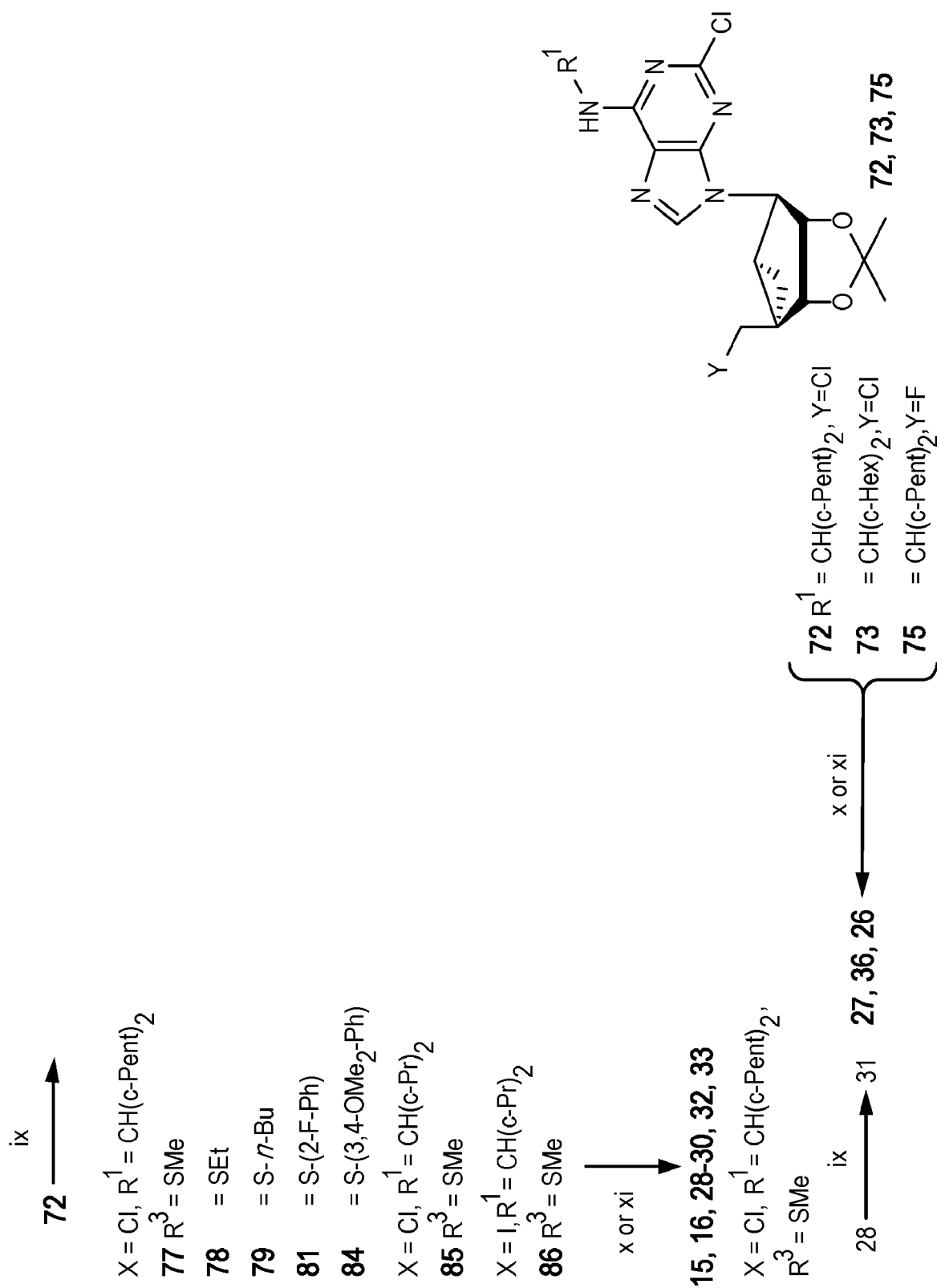


FIG. 1A Continued



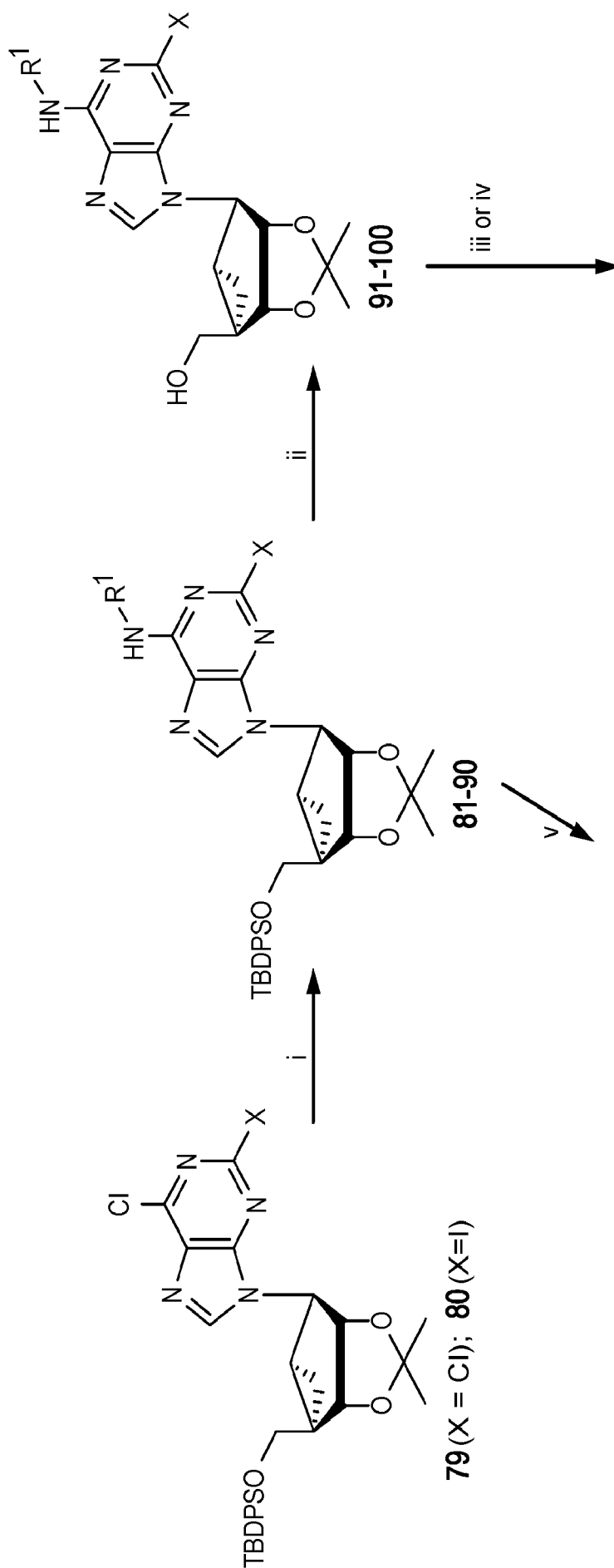
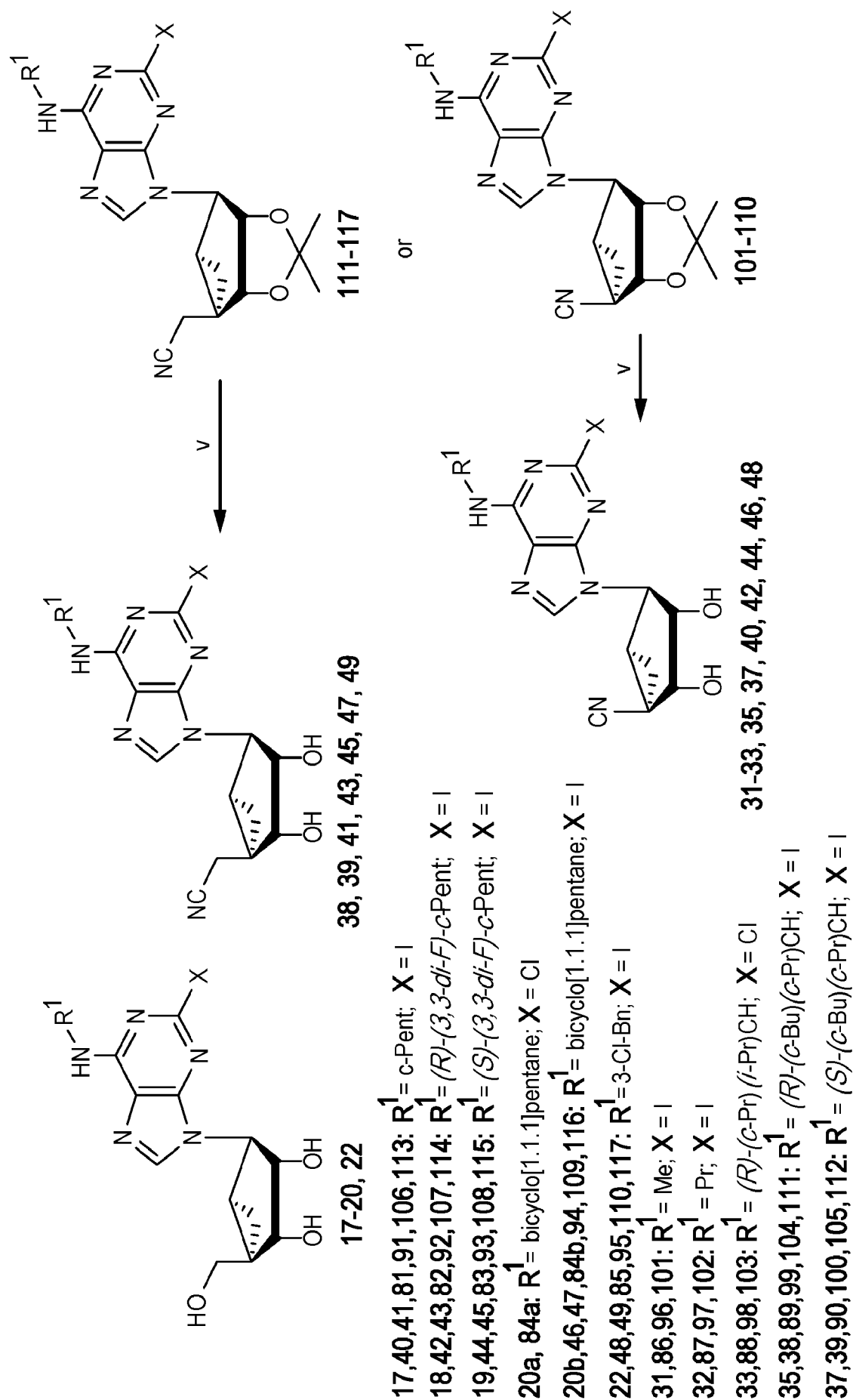


FIG. 1B

FIG. 1B Continued



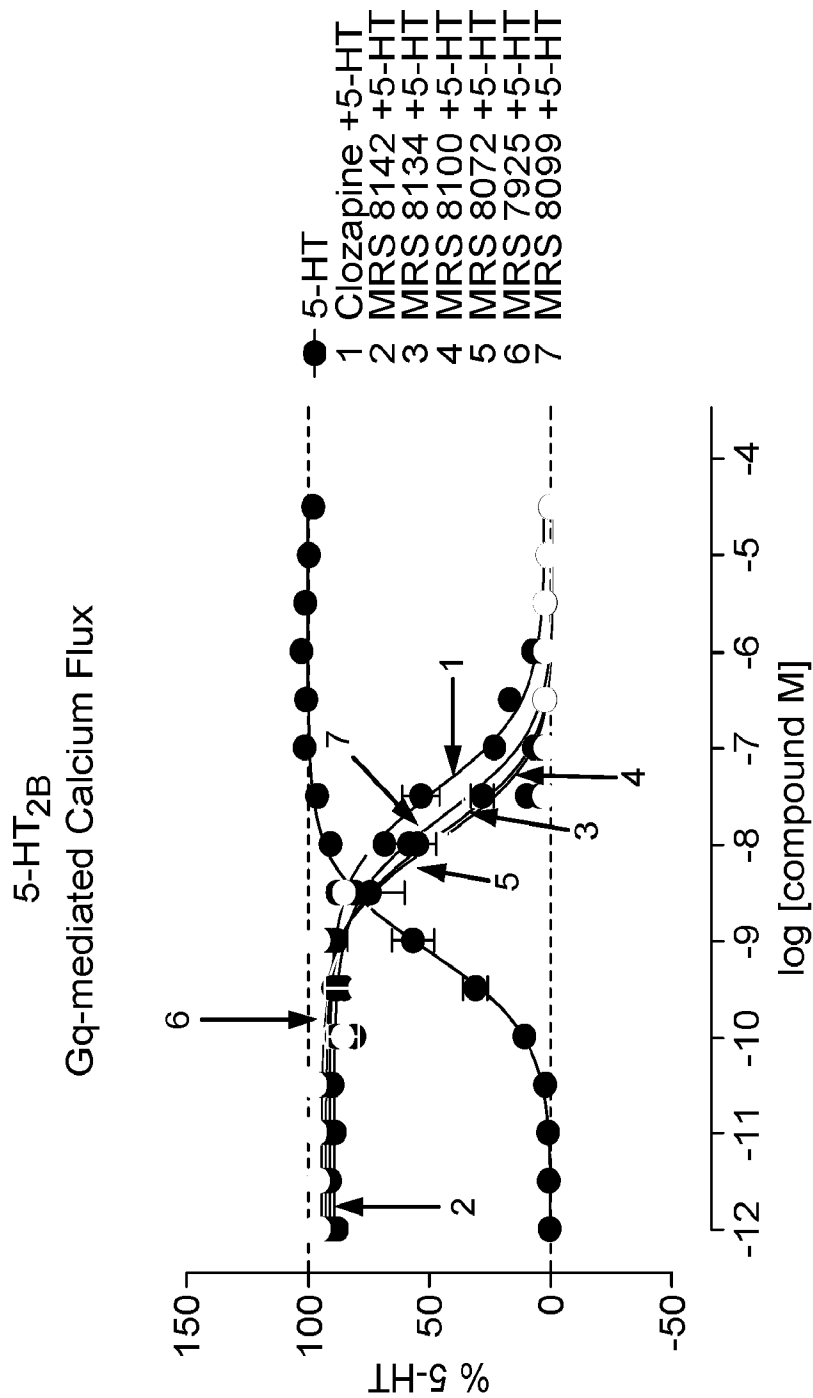


FIG. 2A

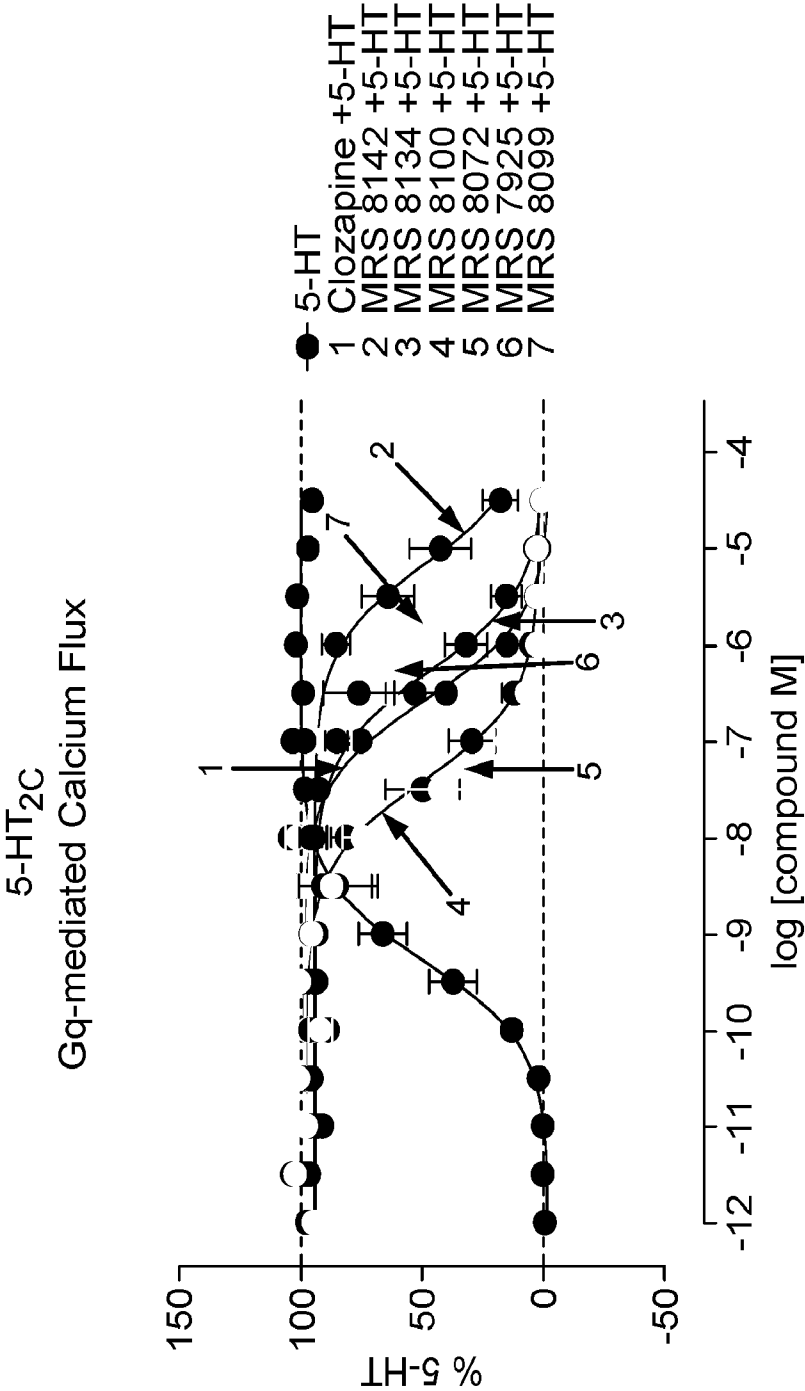


FIG. 2B

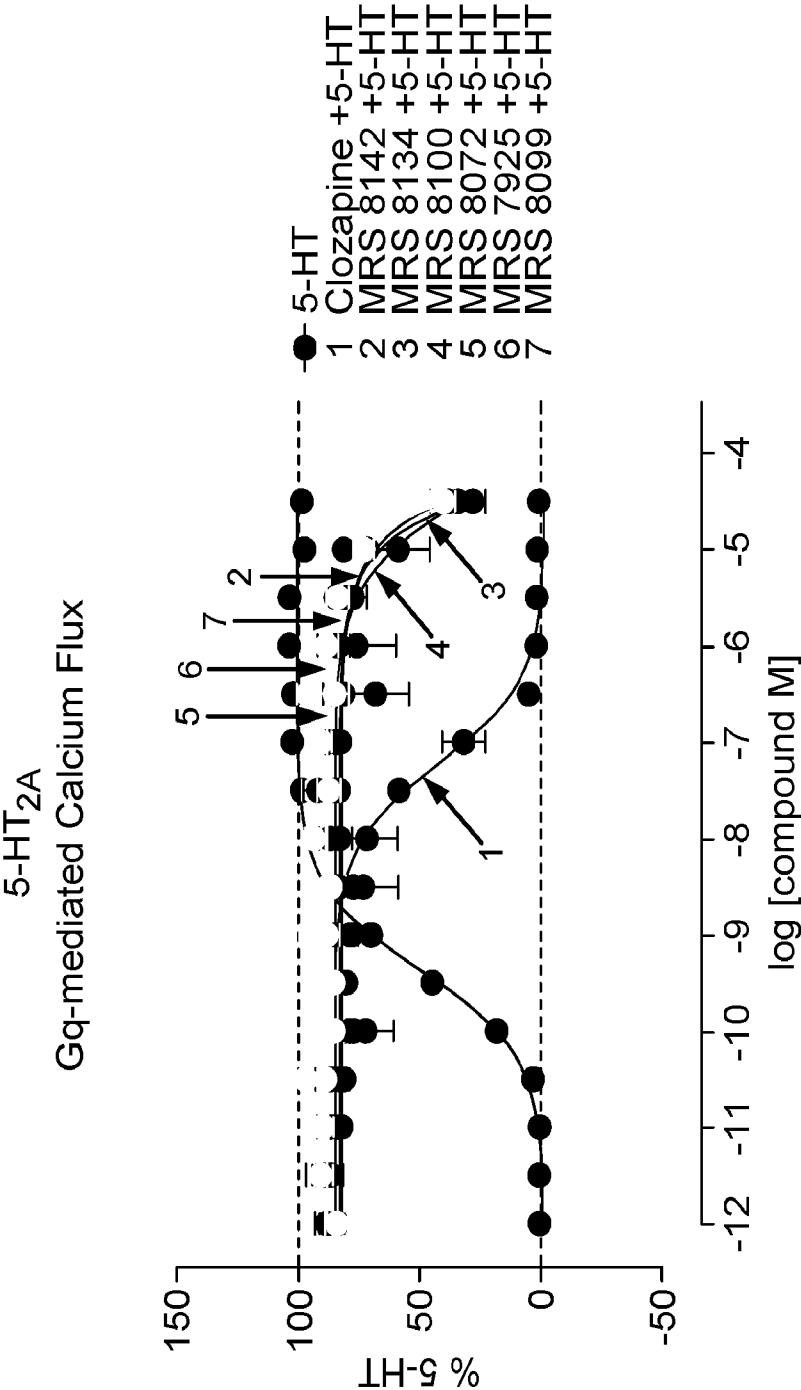


FIG. 2C

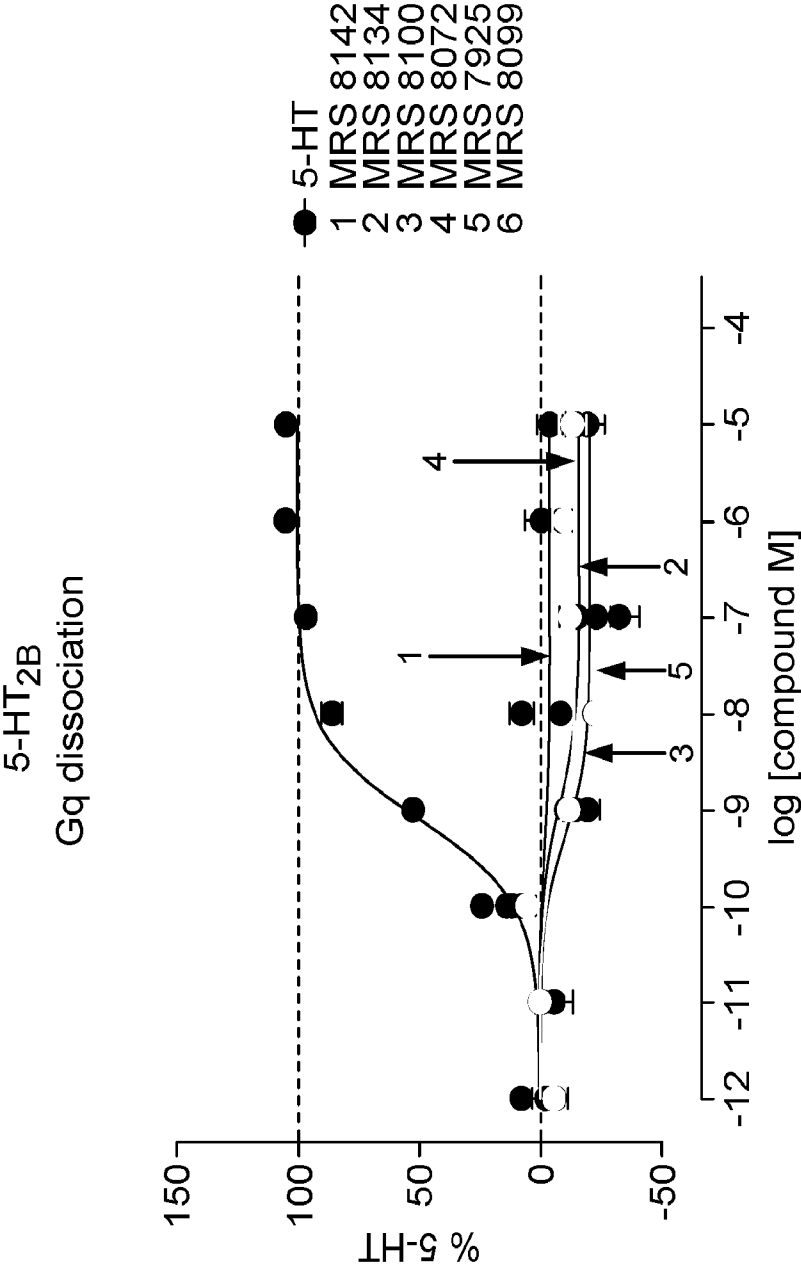


FIG. 2D

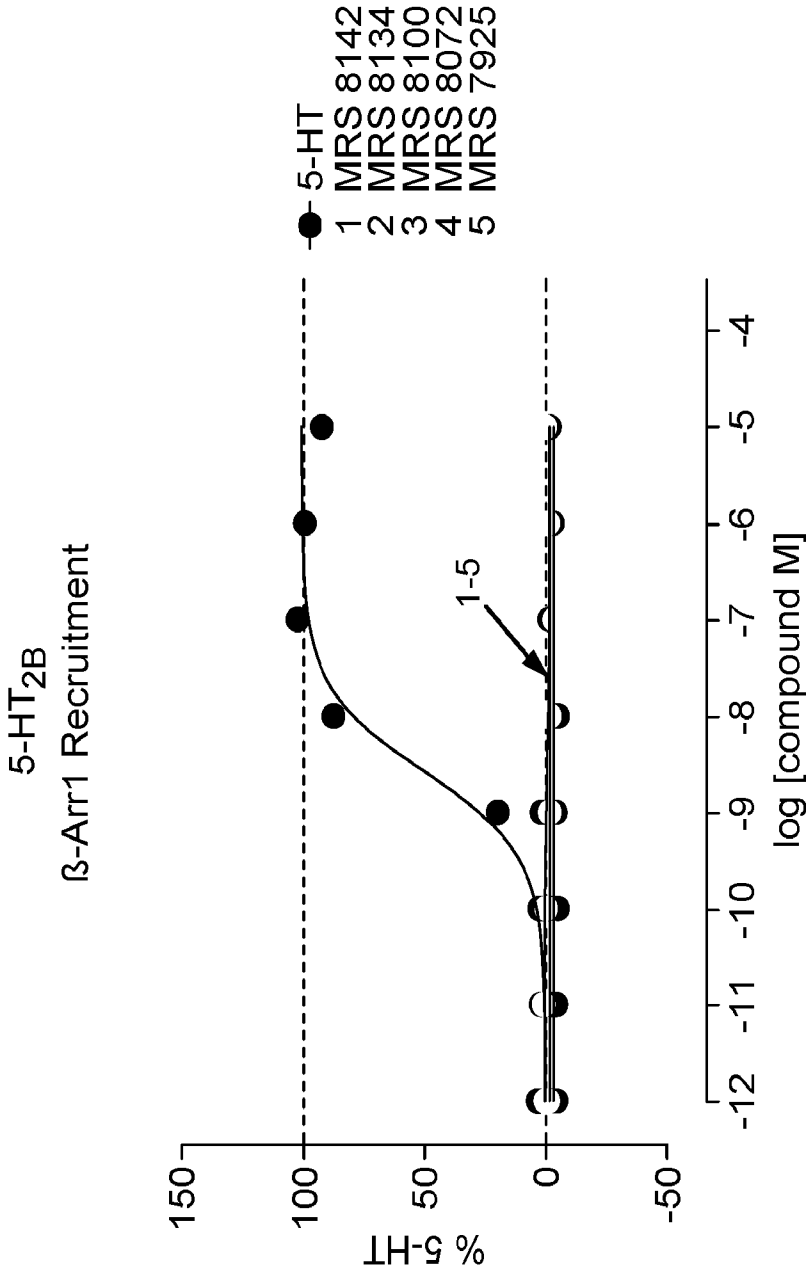


FIG. 2E

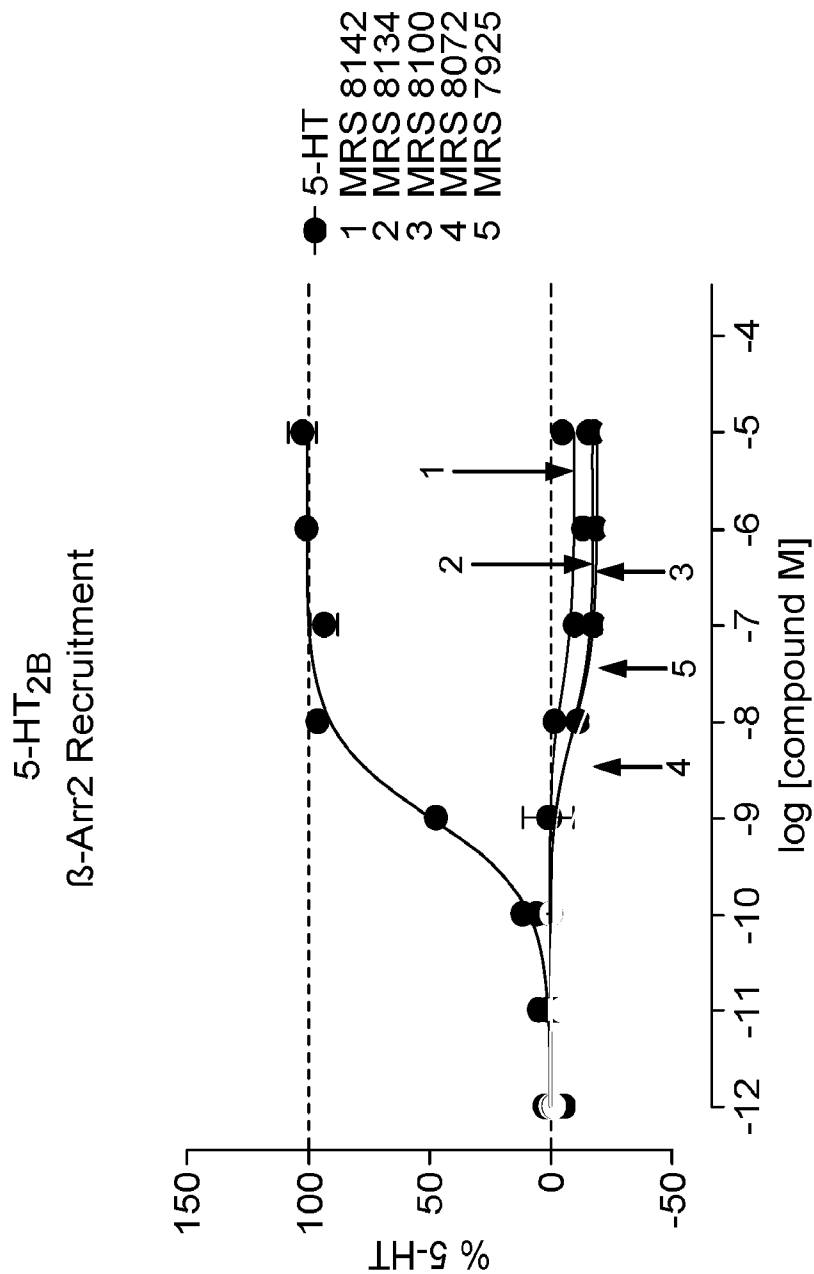


FIG. 2F

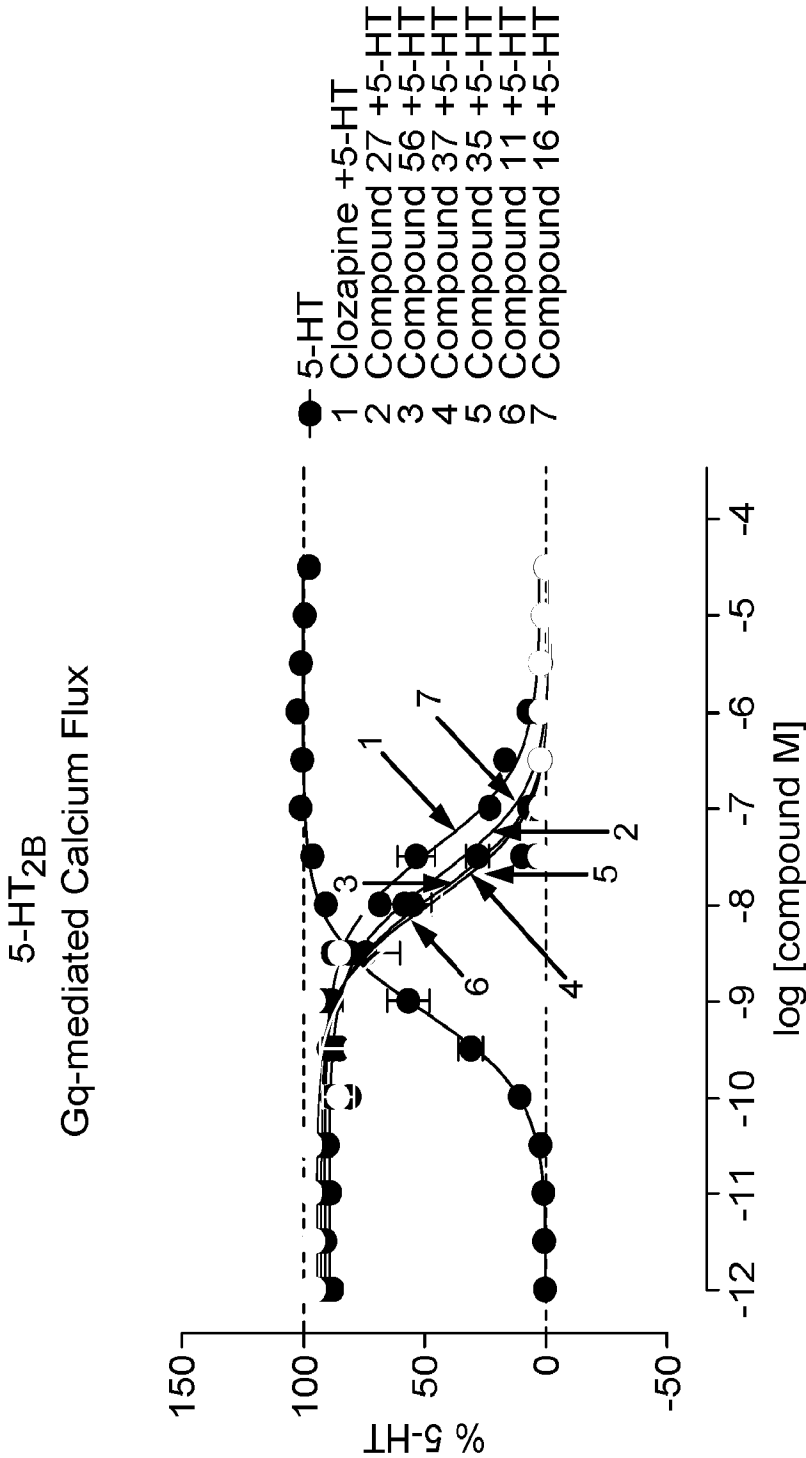


FIG. 2G

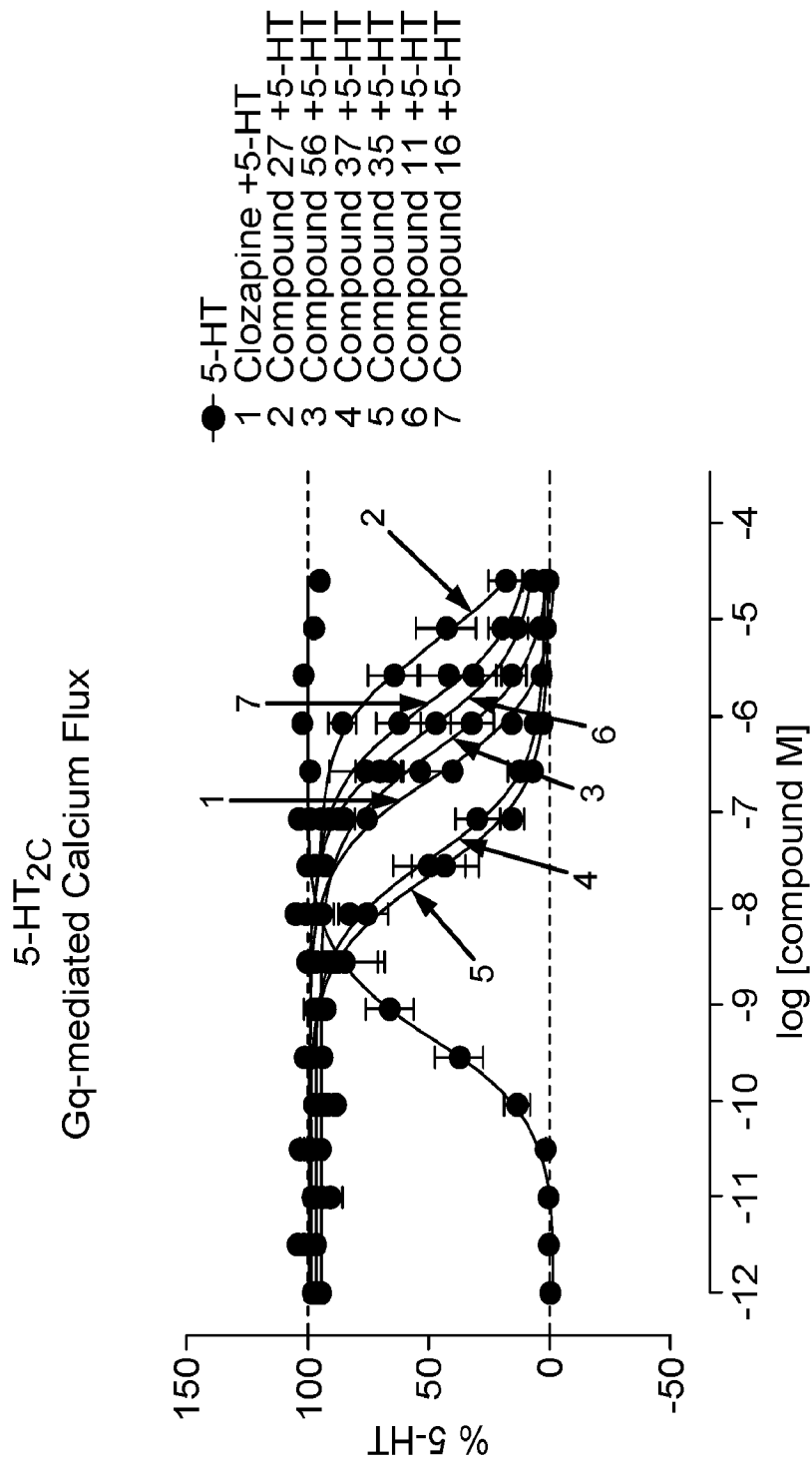


FIG. 2H

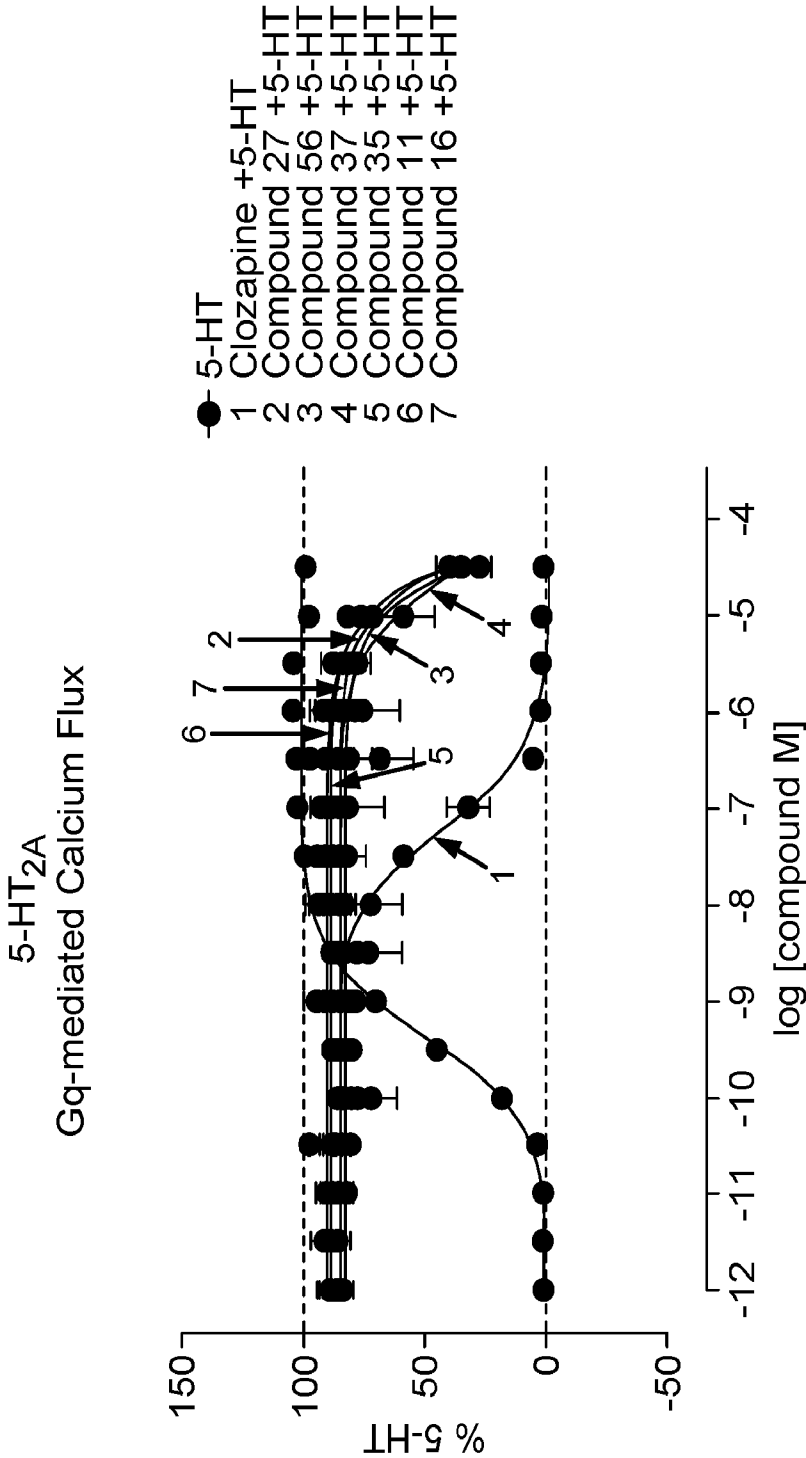


FIG. 2I

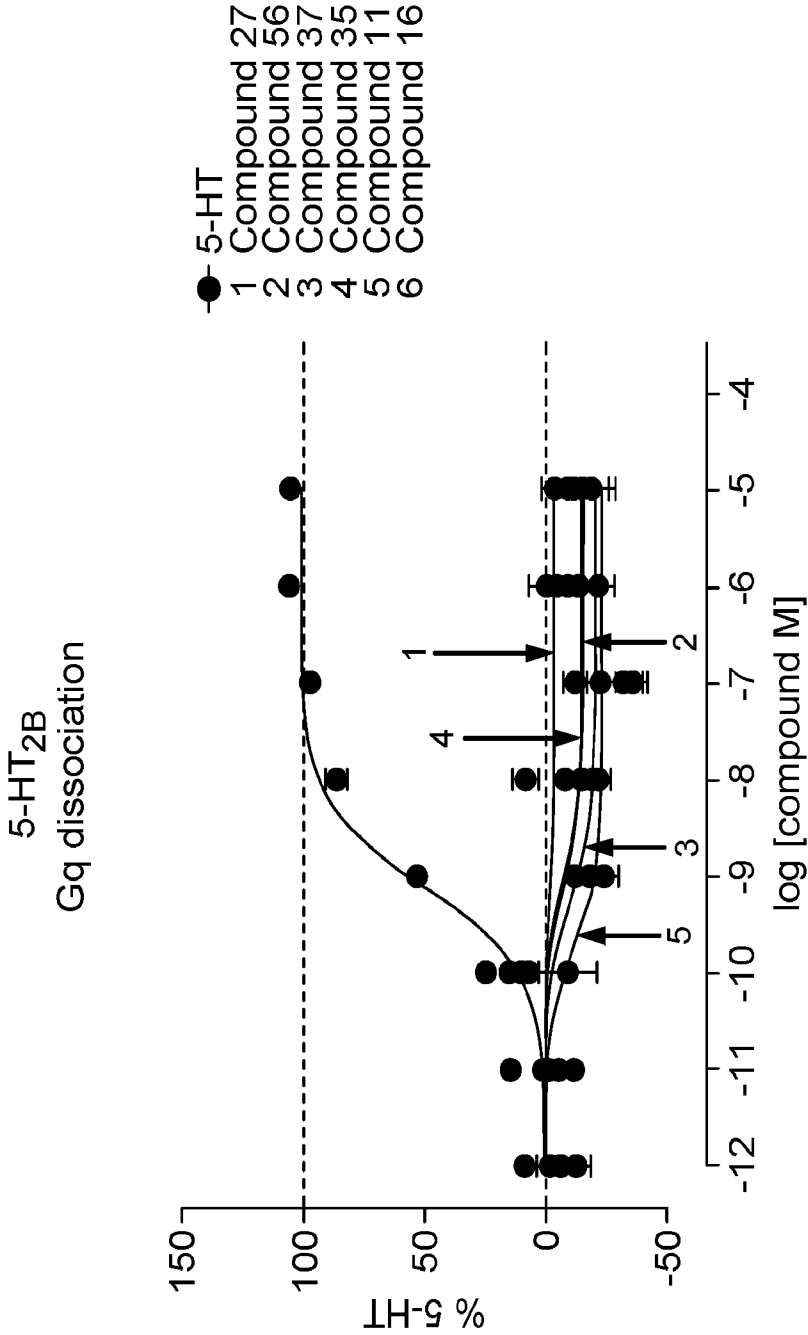


FIG. 2J

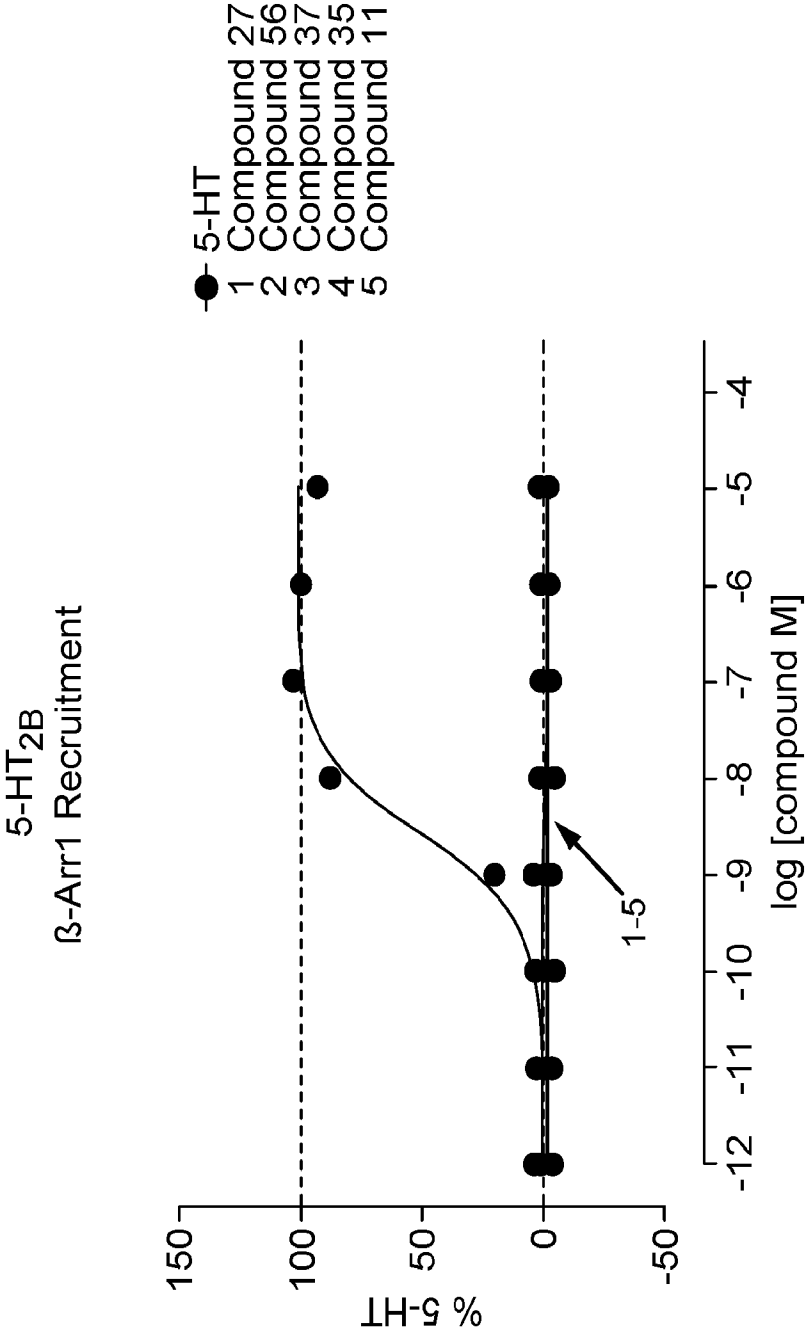


FIG. 2K

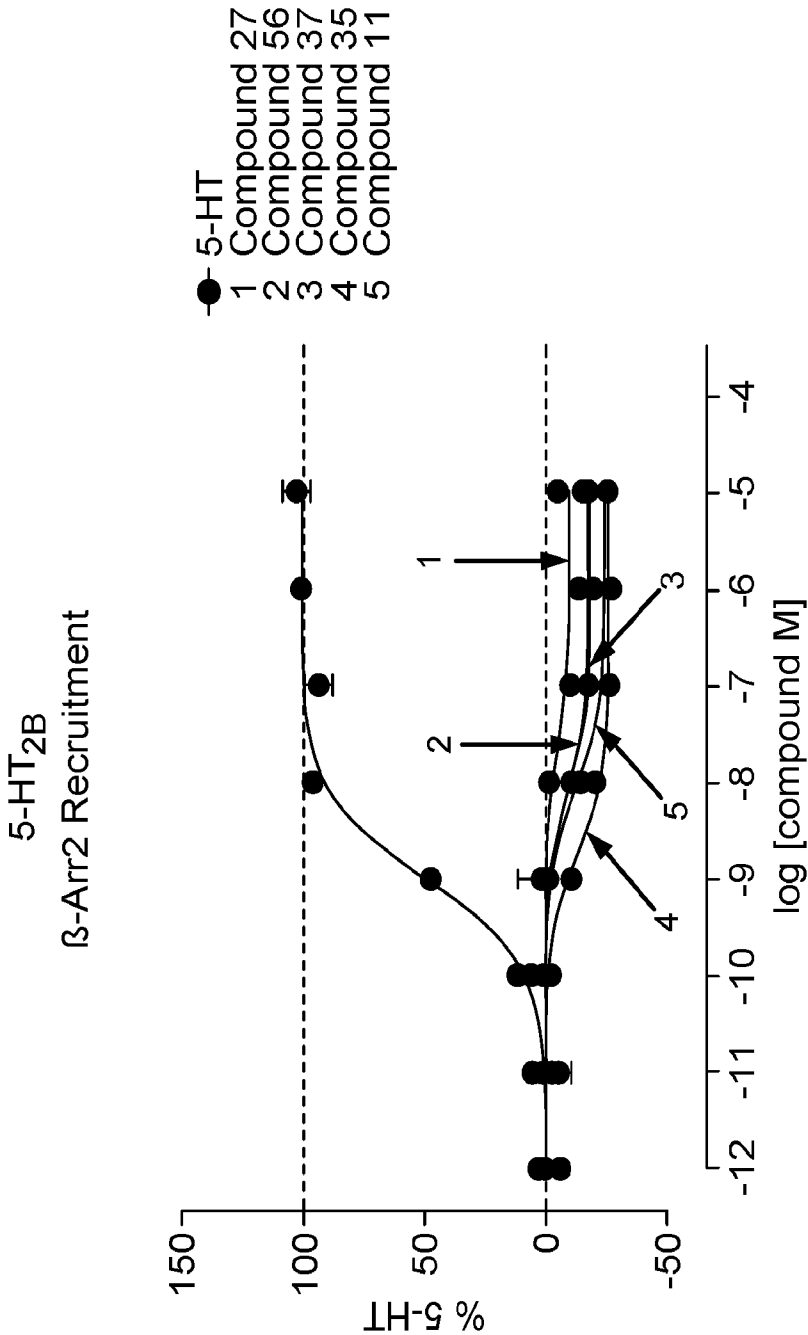


FIG. 2L

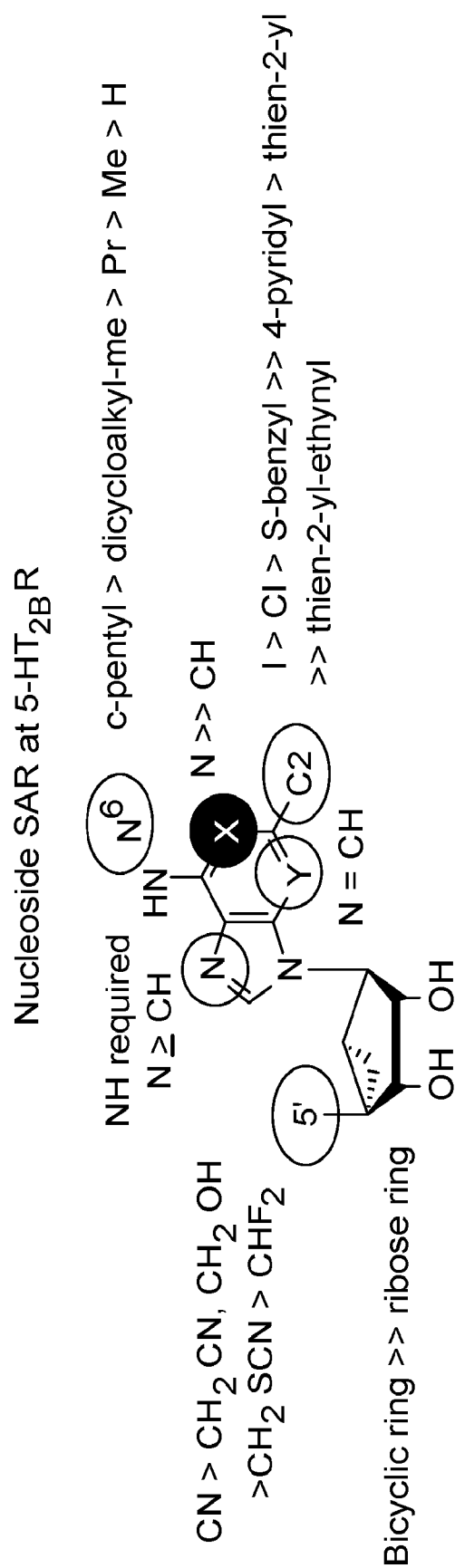
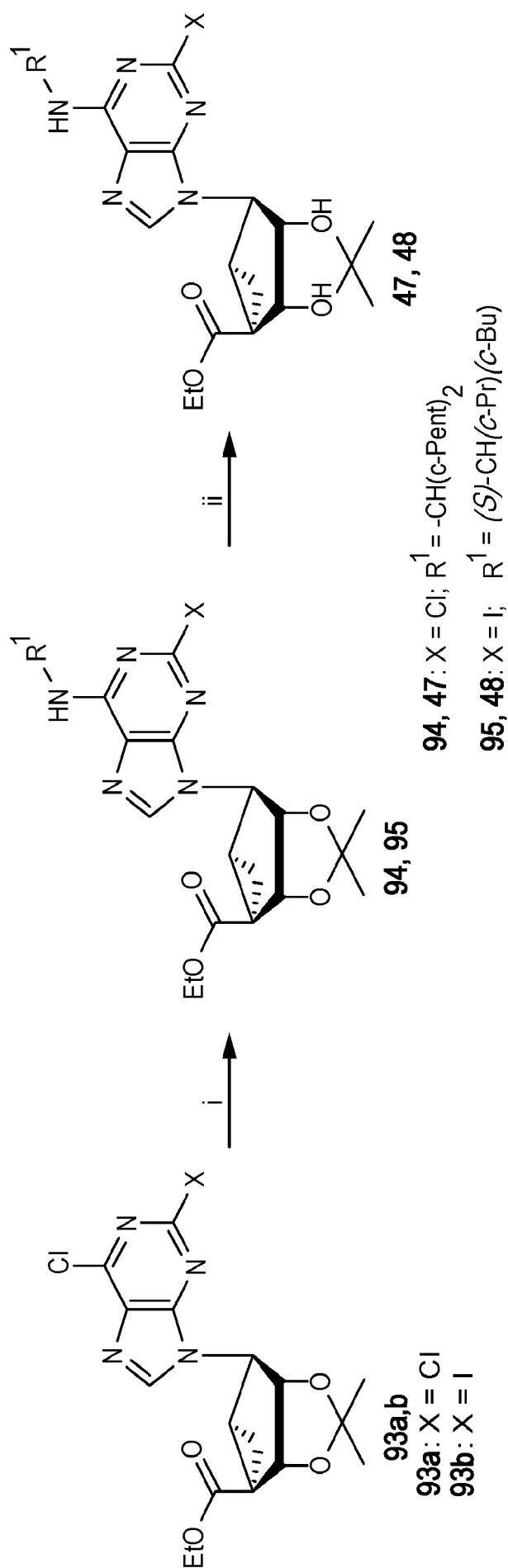


FIG. 3



<sup>a</sup> Reagents and Conditions: (i)  $R^1NH_2 \cdot HCl$ , DIPEA, 2-propanol, rt; (ii) 10% TFA, MeOH, 70 °C.

**FIG. 4**

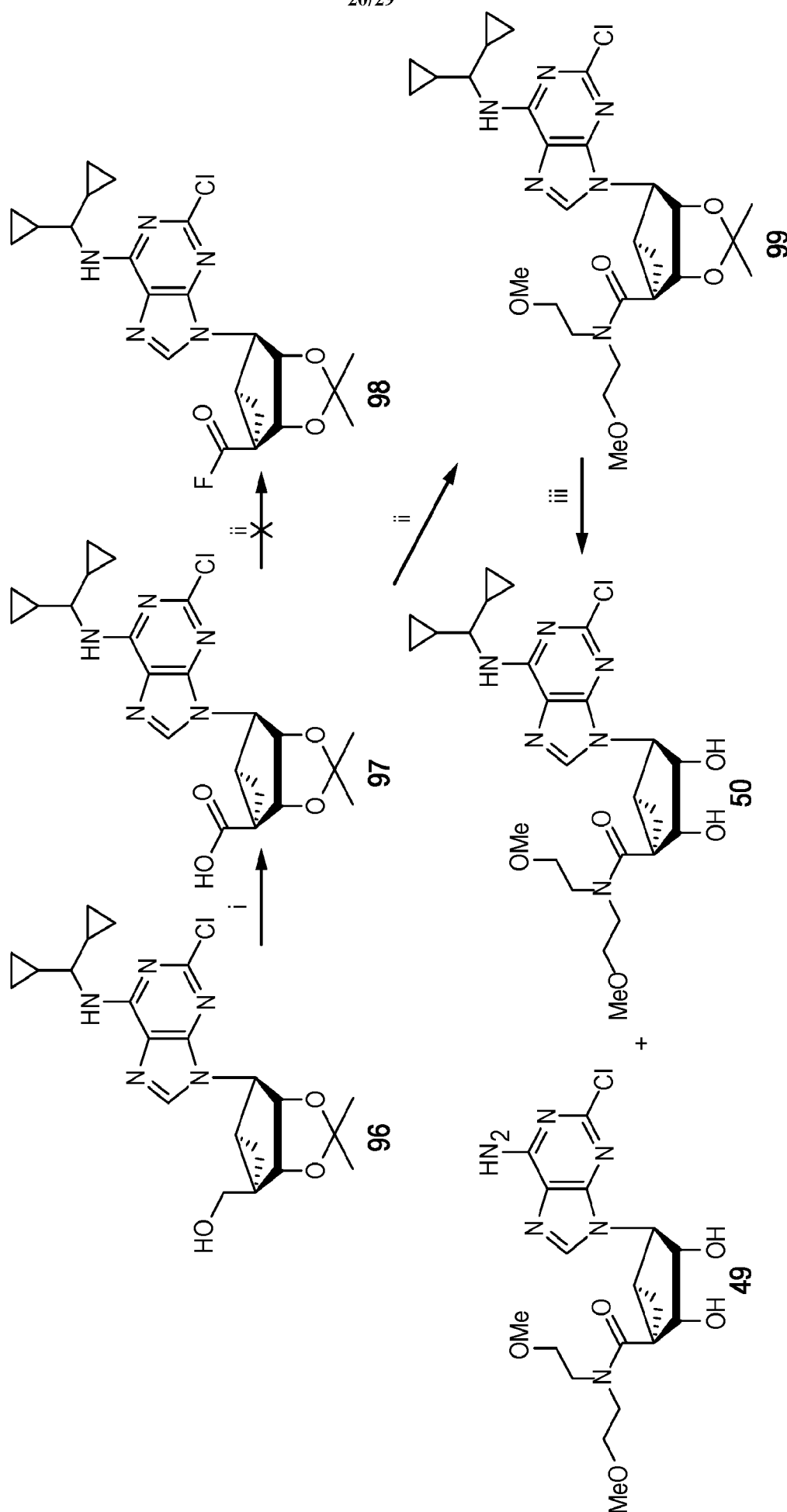
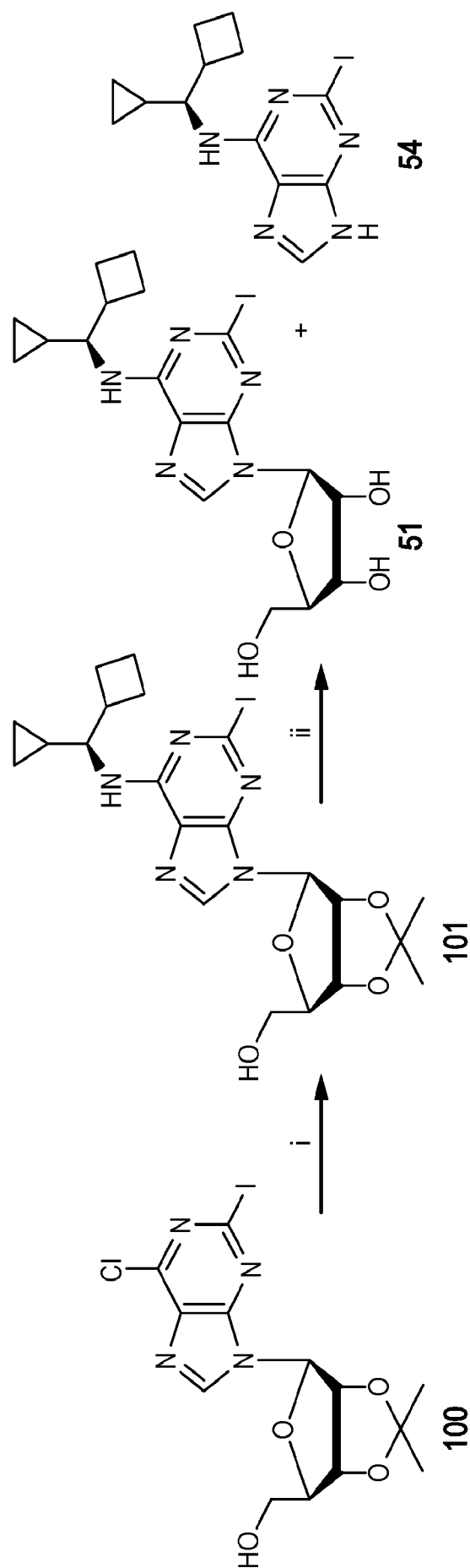
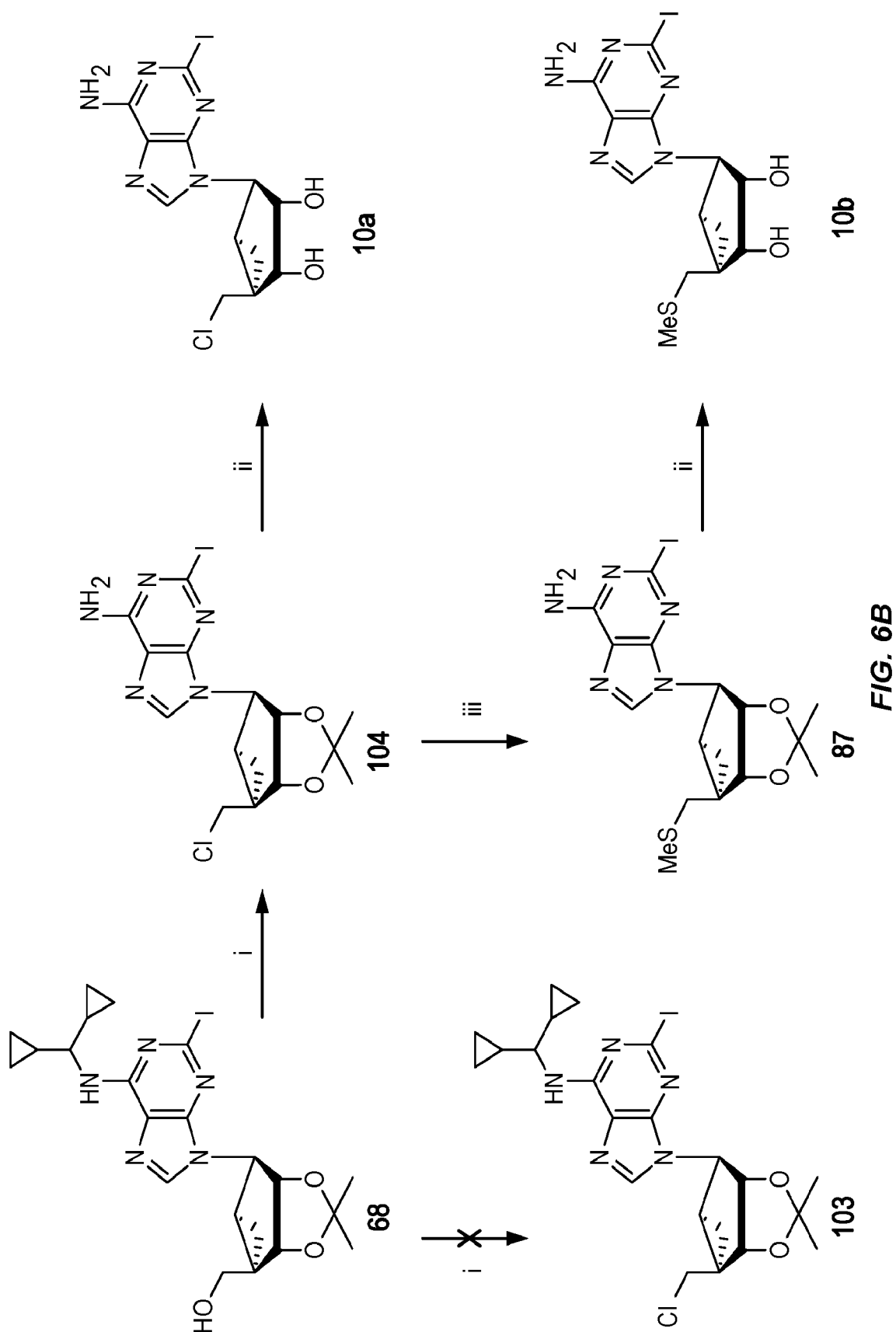


FIG. 5





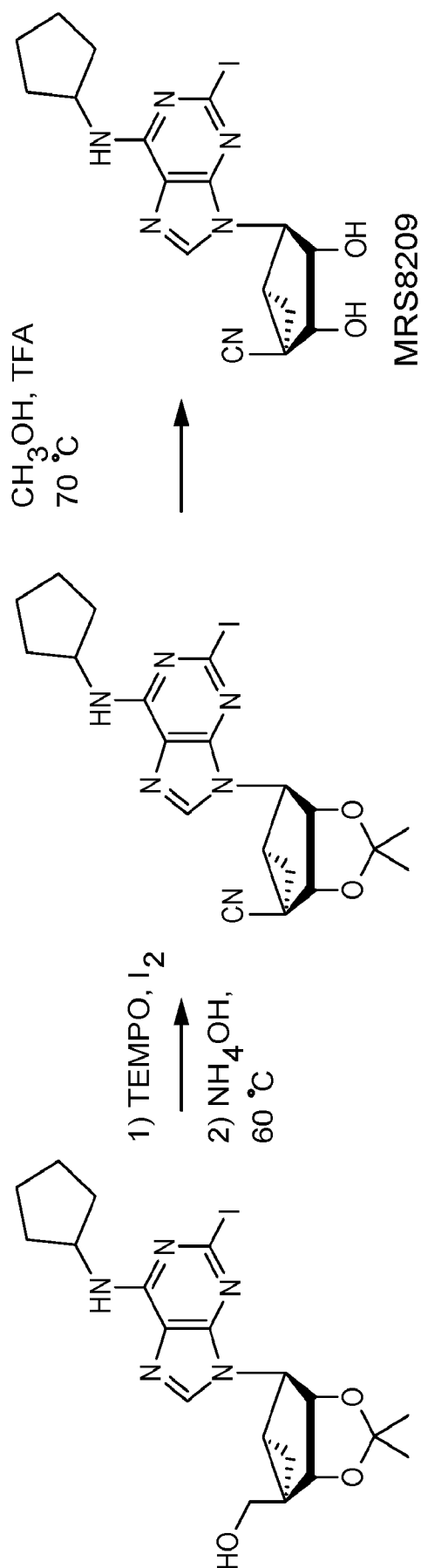


FIG. 7



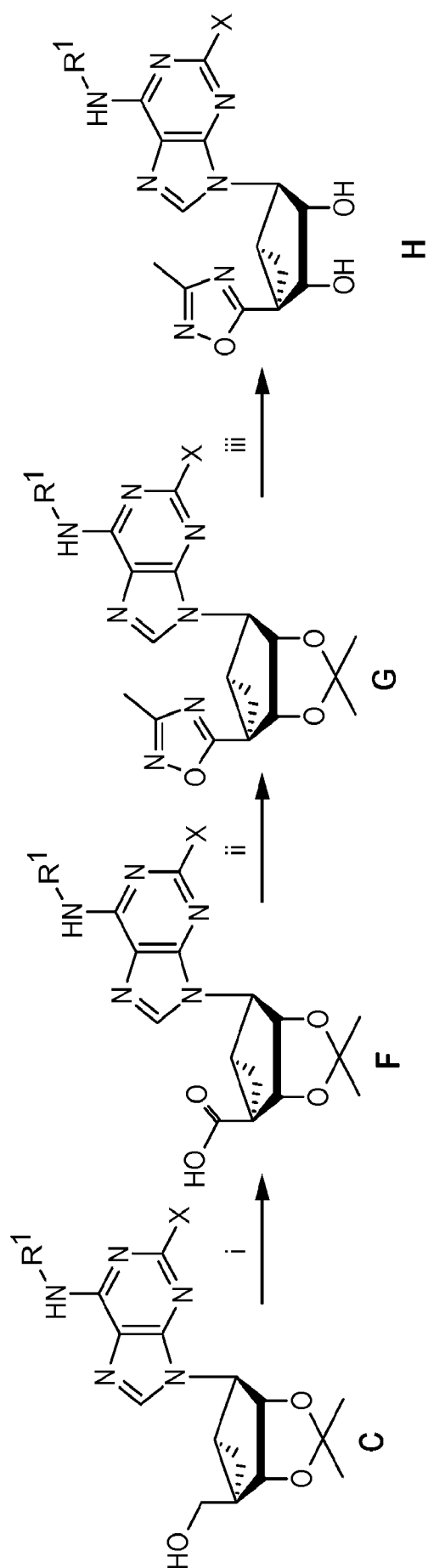


FIG. 9

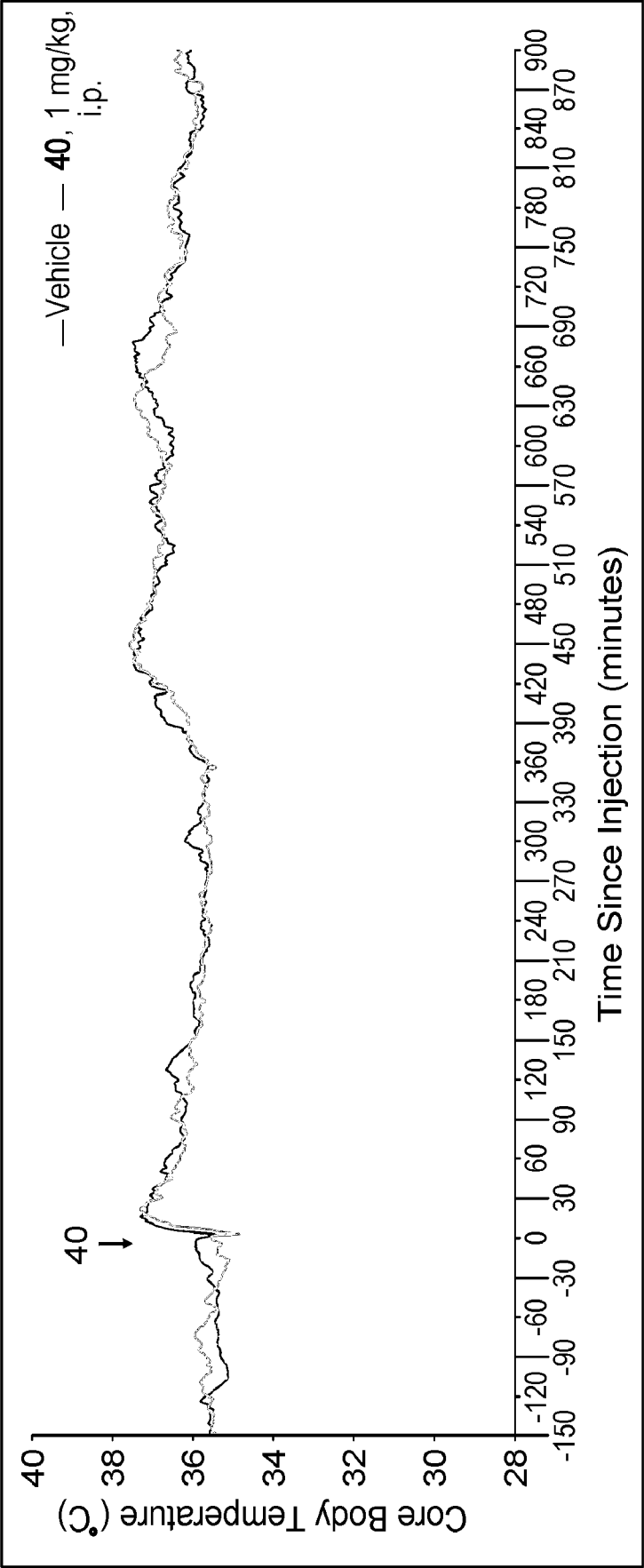


FIG. 10A

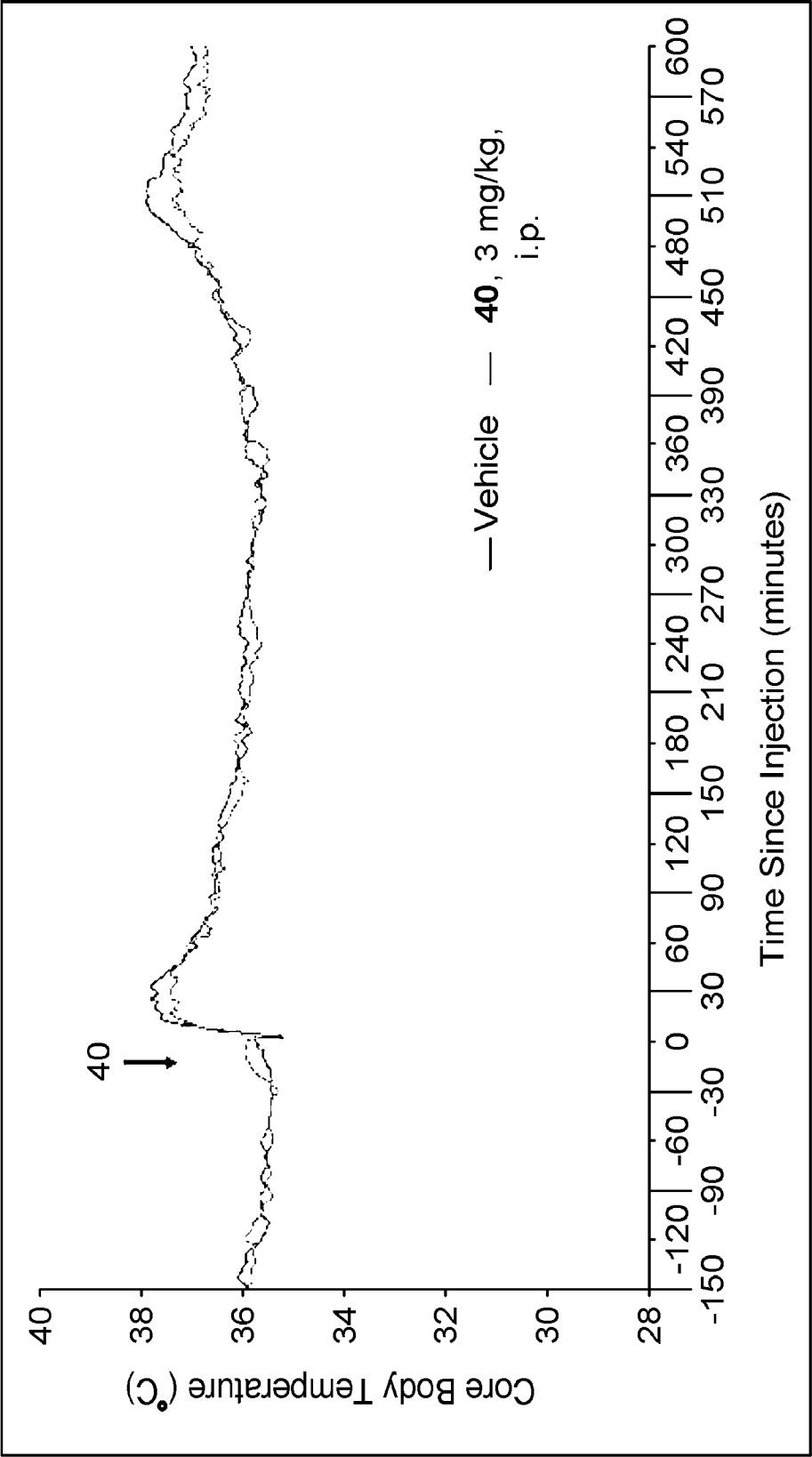


FIG. 10B

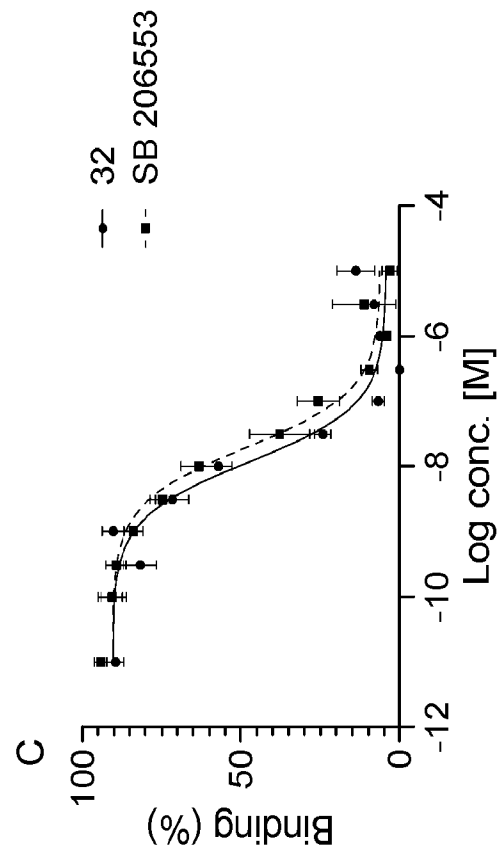
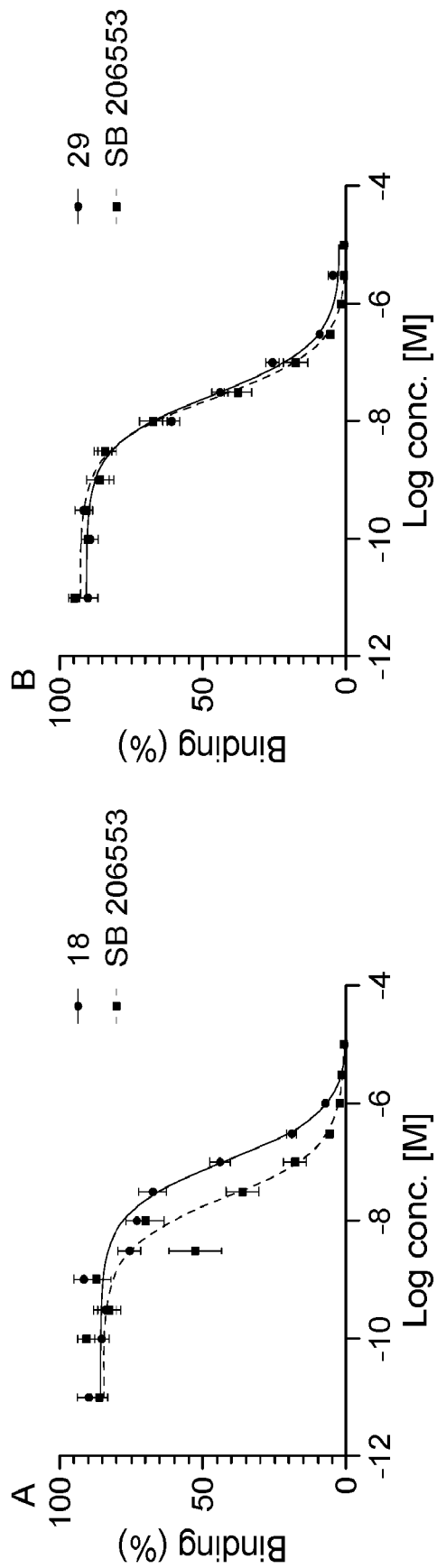


FIG. 11B

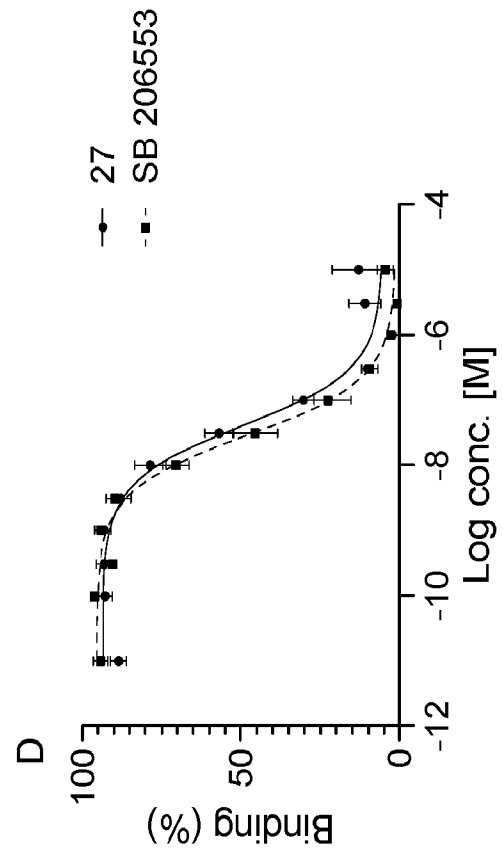
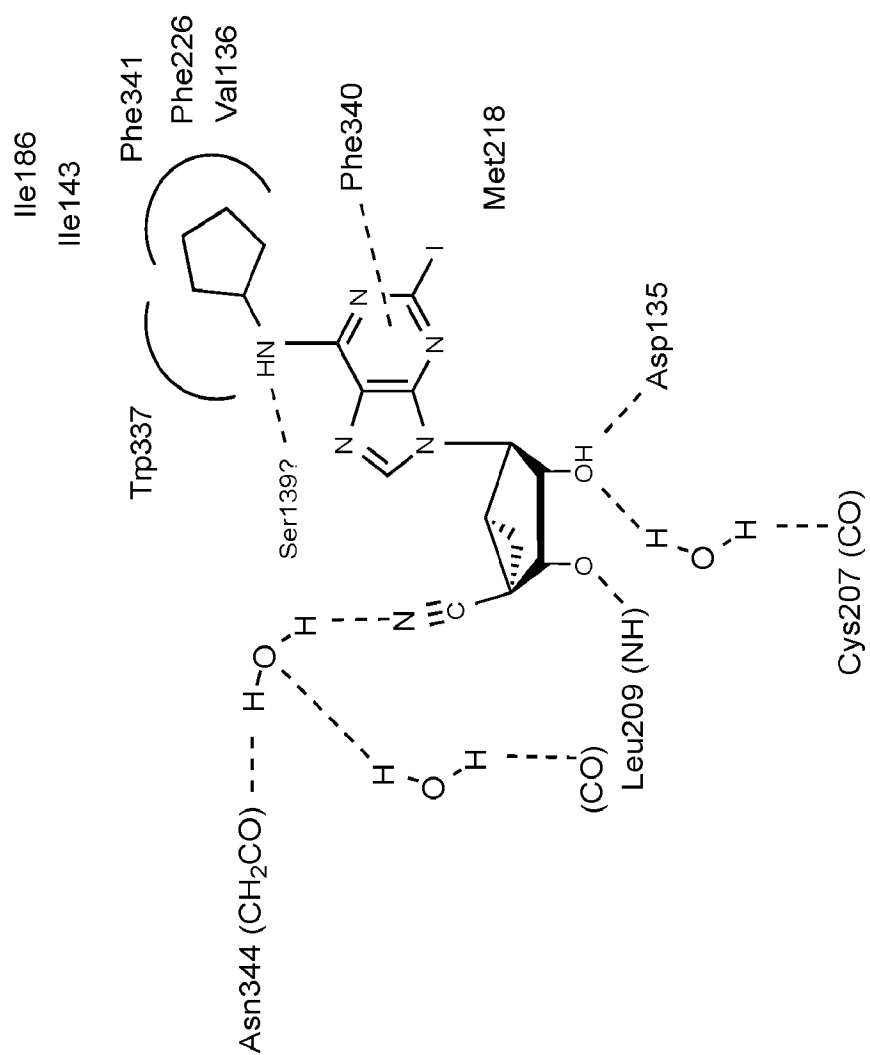


FIG. 11

**FIG. 12**

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/038286

**A. CLASSIFICATION OF SUBJECT MATTER**

**C07D 473/40**(2006.01)i; **C07D 471/04**(2006.01)i; **C07D 473/36**(2006.01)i; **A61K 31/52**(2006.01)i; **A61P 43/00**(2006.01)i; **A61P 9/00**(2006.01)i; **A61P 9/12**(2006.01)i; **A61P 11/00**(2006.01)i; **A61P 29/00**(2006.01)i; **A61P 35/00**(2006.01)i

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)

C07D 473/40(2006.01); A61K 31/52(2006.01); C07D 473/00(2006.01)

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), STN(Registry, CAplus) & Keywords: 5-HT 2B serotonin receptor, antagonist, purine, diol

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                    | Relevant to claim No. |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | WO 2006-031505 A1 (GOVERNMENT OF THE UNITED STATES OF AMERICA, REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES et al.) 23 March 2006 (2006-03-23)<br>claims 1, 60; figure 2                                                                     | 1-3,7,12,13           |
| A         |                                                                                                                                                                                                                                                                       | 14,15                 |
| X         | STORME, J. et al., "Probing structure-activity relationship in $\beta$ -arrestin2 recruitment of diversely substituted adenosine derivative", Biochemical pharmacology, 2018, Vol. 158, pp, 103-113<br>table 2                                                        | 1,14                  |
| X         | JEONG, L. S. et al., "Structure-activity relationships of 2-chloro-N6-substituted-4'-thioadenosine-5'-uro namides as highly potent and selective agonists at the human A3 adenosine receptor", Journal of medicinal chemistry, 2006, Vol. 49, pp. 273-281<br>scheme 3 | 1,15                  |

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

☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

**04 November 2024**

Date of mailing of the international search report

**04 November 2024**

Name and mailing address of the ISA/KR

**Korean Intellectual Property Office  
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35208, Republic of Korea**

Facsimile No. **+82-42-481-8578**

Authorized officer

**HEO, Joo Hyung**

Telephone No. **+82-42-481-5373**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                         | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | TOSH, D. K. et al., "Structure-based scaffold repurposing for G protein-coupled receptors: transformation of adenosine derivatives into 5HT2B/5HT2C serotonin receptor antagonists", Journal of medicinal chemistry, 2016, Vol. 59, No. 24, pp. 11006-11026<br>scheme 2 (compounds 25, 27) | 1                     |
| X         | TCHILIBON, S. et al., "(N)-Methanocarba 2,N6-disubstituted adenine nucleosides as highly potent and selective A3 adenosine receptor agonists", Journal of medicinal chemistry, 2005, Vol. 48, No. 6, pp. 1745-1758<br>chart 1 (compounds 4, 5)                                             | 1                     |

# INTERNATIONAL SEARCH REPORT

International application No.

**PCT/US2024/038286**

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

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

1. ☒ Claims Nos.: **17, 18**  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Claims 17 and 18 pertain to methods for treatment of the human body by surgery or therapy as well as diagnostic methods (PCT Article 17(2)(a)(i) and Rule 39.1(iv)).
2. ☒ Claims Nos.: **5, 6**  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
Claims 5 and 6 are regarded to be unclear because they refer to claims which do not comply with PCT Rule 6.4(a).
3. ☒ Claims Nos.: **4, 8-11, 16-20**  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**INTERNATIONAL SEARCH REPORT**  
**Information on patent family members**

International application No.  
**PCT/US2024/038286**

| Patent document<br>cited in search report |             |    | Publication date<br>(day/month/year) | Patent family member(s) |                 |    | Publication date<br>(day/month/year) |
|-------------------------------------------|-------------|----|--------------------------------------|-------------------------|-----------------|----|--------------------------------------|
| WO                                        | 2006-031505 | A1 | 23 March 2006                        | AU                      | 2005-285284     | A1 | 23 March 2006                        |
|                                           |             |    |                                      | AU                      | 2005-285284     | B2 | 02 June 2011                         |
|                                           |             |    |                                      | BR                      | PI0515030       | A  | 01 July 2008                         |
|                                           |             |    |                                      | CA                      | 2601996         | A1 | 23 March 2006                        |
|                                           |             |    |                                      | CN                      | 101056879       | A  | 17 October 2007                      |
|                                           |             |    |                                      | CN                      | 101056879       | B  | 05 October 2011                      |
|                                           |             |    |                                      | EP                      | 1794162         | A1 | 13 June 2007                         |
|                                           |             |    |                                      | IL                      | 181716          | A  | 04 July 2007                         |
|                                           |             |    |                                      | JP                      | 2008-512457     | A  | 24 April 2008                        |
|                                           |             |    |                                      | JP                      | 2012-229215     | A  | 22 November 2012                     |
|                                           |             |    |                                      | KR                      | 10-2007-0050484 | A  | 15 May 2007                          |
|                                           |             |    |                                      | US                      | 2007-0232626    | A1 | 04 October 2007                      |
|                                           |             |    |                                      | US                      | 7825126         | B2 | 02 November 2010                     |
|                                           |             |    |                                      |                         |                 |    |                                      |