(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 June 2010 (10.06.2010)

PCT

(10) International Publication Number
WO 2010/065152 A1

(51) **International Patent Classification**:
*A01N 43/90* (2006.01)

(21) **International Application Number**:
PCT/US2009/006443

(22) **International Filing Date**:
7 December 2009 (07.12.2009)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/120,444 6 December 2008 (06.12.2008) US

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published**:

— *with international search report (Art. 21(3))*

WO 2010/065152 A1

(54) **Title**: ORGANIC COMPOUNDS

(57) **Abstract**: Compounds of Formula (I) or (II), processes for their production, their use as pharmaceuticals and pharmaceutical compositions comprising them.

# ORGANIC COMPOUNDS

This application claims priority from U.S. Provisional Application No. 61/120,444, filed December 6, 2008, the contents of which are hereby incorporated by reference in their entirety.

## TECHNICAL FIELD

**[0001]** The present invention relates to a compound of Formula I as described below, processes for their production, their use as pharmaceuticals and pharmaceutical compositions comprising them. Of particular interest are novel compounds useful as inhibitors of phosphodiesterase 1 (PDE1), e.g., in the treatment of diseases involving disorders of the dopamine D1 receptor intracellular pathway, such as Parkinson's disease, depression, narcolepsy, damage to cognitive function, e.g., in schizophrenia, or disorders that may be ameliorated through enhanced progesterone-signaling pathway, e.g., female sexual dysfunction.

## BACKGROUND OF THE INVENTION

**[0002]** Eleven families of phosphodiesterases (PDEs) have been identified but only PDEs in Family I, the $Ca^{2+}$-calmodulin-dependent phosphodiesterases (CaM-PDEs), have been shown to mediate both the calcium and cyclic nucleotide (e.g. cAMP and cGMP) signaling pathways. The three known CaM-PDE genes, PDE1A, PDE1B, and PDE1C, are all expressed in central nervous system tissue. PDE1A is expressed throughout the brain with higher levels of expression in the CA1 to CA3 layers of the hippocampus and cerebellum and at a low level in the striatum. PDE1A is also expressed in the lung and heart. PDE1B is predominately expressed in the striatum, dentate gyrus, olfactory tract and cerebellum, and its expression correlates with brain regions having high levels of dopaminergic innervation. Although PDE1B is primarily expressed in the central nervous system, it may be detected in the heart. PDE1C is primarily expressed in olfactory epithelium, cerebellar granule cells, and striatum. PDE1C is also expressed in the heart and vascular smooth muscle.

**[0003]** Cyclic nucleotide phosphodiesterases decrease intracellular cAMP and cGMP signaling by hydrolyzing these cyclic nucleotides to their respective inactive 5'-monophosphates (5'AMP and 5'GMP). CaM-PDEs play a critical role in mediating signal transduction in brain cells, particularly within an area of the brain

known as the basal ganglia or striatum. For example, NMDA-type glutamate receptor activation and/or dopamine D2 receptor activation result in increased intracellular calcium concentrations, leading to activation of effectors such as calmodulin-dependent kinase II (CaMKII) and calcineurin and to activation of CaM-PDEs, resulting in reduced cAMP and cGMP. Dopamine D1 receptor activation, on the other hand, leads to activation of nucleotide cyclases, resulting in increased cAMP and cGMP. These cyclic nucleotides in turn activate protein kinase A (PKA; cAMP-dependent protein kinase) and/or protein kinase G (PKG; cGMP-dependent protein kinase) that phosphorylate downstream signal transduction pathway elements such as DARPP-32 (dopamine and cAMP-regulated phosphoprotein) and cAMP responsive element binding protein (CREB). Phosphorylated DARPP-32 in turn inhibits the activity of protein phosphates-1 (PP-1), thereby increasing the state of phosphorylation of substrate proteins such as progesterone receptor (PR), leading to induction of physiologic responses. Studies in rodents have suggested that inducing cAMP and cGMP synthesis through activation of dopamine D1 or progesterone receptor enhances progesterone signaling associated with various physiological responses, including the lordosis response associated with receptivity to mating in some rodents. See Mani, et al., Science (2000) 287: 1053, the contents of which are incorporated herein by reference.

**[0004]** CaM-PDEs can therefore affect dopamine-regulated and other intracellular signaling pathways in the basal ganglia (striatum), including but not limited to nitric oxide, noradrenergic, neurotensin, CCK, VIP, serotonin, glutamate (e.g., NMDA receptor, AMPA receptor), GABA, acetylcholine, adenosine (e.g., A2A receptor), cannabinoid receptor, natriuretic peptide (e.g., ANP, BNP, CNP), DARPP-32, and endorphin intracellular signaling pathways.

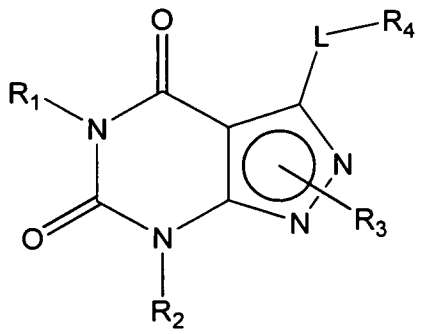
**[0005]** Phosphodiesterase (PDE) activity, in particular, phosphodiesterase 1 (PDE1) activity, functions in brain tissue as a regulator of locomotor activity and learning and memory. PDE1 is a therapeutic target for regulation of intracellular signaling pathways, preferably in the nervous system, including but not limited to a dopamine D1 receptor, dopamine D2 receptor, nitric oxide, noradrenergic, neurotensin, CCK, VIP, serotonin, glutamate (e.g., NMDA receptor, AMPA receptor), GABA, acetylcholine, adenosine (e.g., A2A receptor), cannabinoid receptor, natriuretic peptide (e.g., ANP, BNP, CNP) , endorphin intracellular

signaling pathway and progesterone signaling pathway. For example, inhibition of PDE1B should act to potentiate the effect of a dopamine D1 agonist by protecting cGMP and cAMP from degradation, and should similarly inhibit dopamine D2 receptor signaling pathways, by inhibiting PDE1 activity. Chronic elevation in intracellular calcium levels is linked to cell death in numerous disorders, particularly in neurodegerative diseases such as Alzheimer's, Parkinson's and Huntington's Diseases and in disorders of the circulatory system leading to stroke and myocardial infarction. PDE1 inhibitors are therefore potentially useful in diseases characterized by reduced dopamine D1 receptor signaling activity, such as Parkinson's disease, restless leg syndrome, depression, narcolepsy and cognitive impairment. PDE1 inhibitors are also useful in diseases that may be alleviated by the enhancement of progesterone-signaling such as female sexual dysfunction.

**[0006]** There is thus a need for compounds that selectively inhibit PDE1 activity, especially PDE1A and/or PDE1B activity.

## SUMMARY OF THE INVENTION

**[0007]** In the first embodiment, the invention provides a compound of Formula II




Formula II

wherein

(i) L is S, SO or $SO_2$;

(ii) $R_1$ is H or $C_{1-6}$alkyl (e.g., methyl or ethyl);

(iii) $R_2$ is

H,

$C_{1-6}$alkyl (e.g., isopropyl, isobutyl, neopentyl, 2-methylbutyl, 2,2-dimethylpropyl) wherein said alkyl group is optionally

substituted with halo (e.g., fluoro) or hydroxy (e.g., 1-hydroxypropan-2-yl, 3-hydroxy-2-methylpropyl),

$-C_{0-4}$alkyl-$C_{3-8}$cycloalkyl (e.g., cyclopentyl, cyclohexyl) optionally substituted with one or more amino (e.g., $-NH_2$), for example, 2-aminocyclopentyl or 2-aminocyclohexyl),wherein said cycloalkyl optionally contains one or more heteroatom selected from N and O and is optionally substituted with $C_{1-6}$alkyl (e.g., 1-methyl-pyrrolindin-2-yl, 1-methyl-pyrrolindin-3-yl, 1-methyl-pyrrolindin-2-yl-methyl or 1-methyl-pyrrolindin-3-yl-methyl),

$C_{3-8}$heterocycloalkyl (e.g., pyrrolidinyl, for example, pyrrolidin-3-yl) optionally substituted with $C_{1-6}$alkyl (e.g., methyl), for example, 1-methylpyrrolidin-3-yl,

$C_{3-8}$cycloalkyl-$C_{1-6}$alkyl (e.g.,cyclopropylmethyl),

halo$C_{1-6}$alkyl (e.g., trifluoromethyl, 2,2,2-trifluoroethyl),

$-N(R_{14})(R_{15})$-$C_{1-6}$alkyl (e.g., 2-(dimethylamino)ethyl,2-aminopropyl),

hydroxy$C_{1-6}$alkyl (e.g., (e.g., 3-hydroxy-2-methylpropyl, 1-hydroxyprop-2-yl),

aryl$C_{0-6}$alkyl (e.g., benzyl),

heteroaryl$C_{1-6}$alkyl (e.g., pyridinylmethyl),

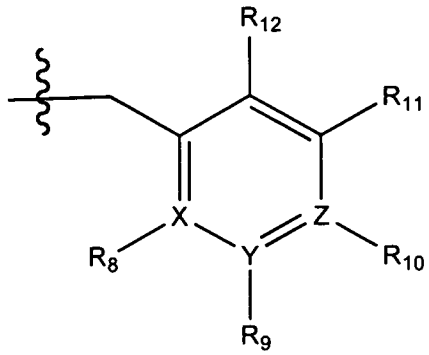
$C_{1-6}$alkoxyaryl$C_{1-6}$alkyl (e.g., 4-methoxybenzyl);

-G-J wherein:

G is a single bond or, alkylene (e.g., methylene);

J is cycloalkyl or heterocycloalkyl (e.g., oxetan-2-yl, pyrolyin-3-yl, pyrolyin-2-yl) optionally substituted with $C_{1-6}$alkyl (e.g., (1-methylpyrolidin-2-yl));

(iv) $R_3$ is attached to one of the nitrogens on the pyrazolo portion of Formula I and is a moiety of Formula A




Formula A

wherein X, Y and Z are, independently, N or C, and $R_8$, $R_9$, $R_{11}$ and $R_{12}$ are independently H or halogen (e.g., Cl or F); and $R_{10}$ is

halogen,

$C_{1-6}$alkyl,

$C_{3-8}$cycloalkyl,

hetero$C_{3-8}$cycloalkyl (e.g., pyrrolidinyl or piperidinyl)

halo$C_{1-6}$alkyl (e.g., trifluoromethyl),

aryl (e.g., phenyl),

heteroaryl (e.g., pyridyl, (for example, pyrid-2-yl) or e.g., thiadiazolyl (for example, 1,2,3-thiadiazol-4-yl), diazolyl, triazolyl (e.g., 1,2,4-triazol-1-yl), tetrazolyl (e.g., tetrazol-5-yl), alkoxadiazolyl (e.g., 5-methyl-1,2,4-oxadiazol), pyrazolyl (e.g., pyrazol-1-yl),

alkyl sulfonyl (e.g., methyl sulfonyl),

arylcarbonyl (e.g., benzoyl), or

heteroarylcarbonyl,

alkoxycarbonyl, (e.g., methoxycarbonyl),

aminocarbonyl;

preferably phenyl, pyridyl, e.g., 2-pyridyl, piperidinyl, or pyrrolidinyl;

wherein the aryl, heteroaryl cycloalkyl or heterocycloalkyl is optionally substituted with one or more halo (e.g., F or Cl), $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$haloalkyl (e.g., trifluoromethyl), and/or –SH,

provided that when X, Y or X is nitrogen, $R_8$, $R_9$ or $R_{10}$, respectively, is not present;

(v) $R_4$ is

H,

$C_{1-6}$alkyl (e.g., methyl, isopropyl),

$C_{3-8}$cycloalkyl (e.g., cyclopentyl),

$C_{3-8}$heterocycloalkyl (e.g., pyrrolidin-3-yl),

aryl (e.g., phenyl) or heteroaryl (e.g., pyrid-4-yl, pyrid-2-yl or pyrazol-3-yl) wherein said aryl or heteroaryl is optionally substituted with halo (e.g., 4-fluorophenyl), hydroxy (e.g., 4-hydroxyphenyl), $C_{1-6}$alkyl, $C_{1-6}$alkoxy or another aryl group (e.g., biphenyl-4-ylmethyl);

(vi) $R_{14}$ and $R_{15}$ are independently H or $C_{1-6}$alkyl,

in free or salt form.

**[0008]** In still another embodiment, the invention provides a Compound of Formula II as described above, wherein

$R_4$ is:

$C_{1-6}$alkyl (e.g., methyl, isopropyl),

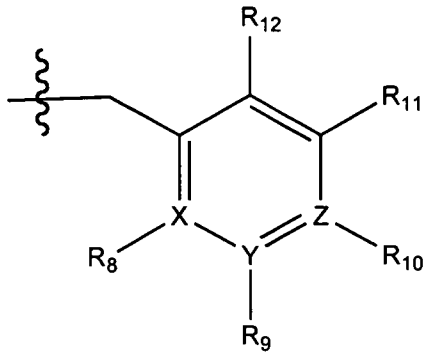
$C_{3-8}$cycloalkyl (e.g., cyclopentyl),

$C_{3-8}$heterocycloalkyl (e.g., pyrrolidin-3-yl),

aryl (e.g., phenyl) or heteroaryl (e.g., pyrid-4-yl, pyrid-2-yl or pyrazol-3-yl) wherein said aryl or heteroaryl is optionally substituted with halo (e.g., 4-fluorophenyl), hydroxy (e.g., 4-hydroxyphenyl), $C_{1-6}$alkyl, $C_{1-6}$alkoxy or another aryl group (e.g., biphenyl-4-ylmethyl);

and

$R_3$ is attached to one of the nitrogens on the pyrazolo portion of Formula I and is a moiety of Formula A




Formula A

wherein X, Y and Z are, independently, N or C, and $R_8$, $R_9$, $R_{11}$ and $R_{12}$ are independently H or halogen (e.g., Cl or F); and $R_{10}$ is

$C_{3-8}$cycloalkyl

hetero$C_{3-8}$cycloalkyl (e.g., pyrrolidinyl or piperidinyl)

aryl (e.g., phenyl), or

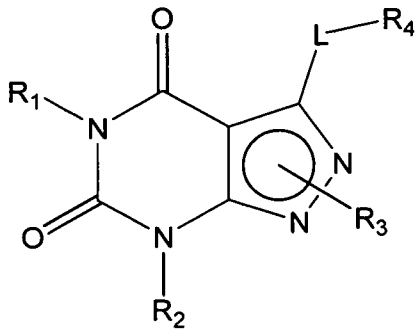
heteroaryl (e.g., pyridyl, (for example, pyrid-2-yl) or e.g., thiadiazolyl (for example, 1,2,3-thiadiazol-4-yl), diazolyl, triazolyl (e.g., 1,2,4-triazol-1-yl), tetrazolyl (e.g., tetrazol-5-yl), alkoxadiazolyl (e.g., 5-methyl-1,2,4-oxadiazol), pyrazolyl (e.g., pyrazol-1-yl),

wherein the aryl or heteroaryl is optionally substituted with one or more halo (e.g., F or Cl), $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$haloalkyl (e.g., trifluoromethyl), and/or –SH,

provided that when X, Y or X is nitrogen, $R_8$, $R_9$ or $R_{10}$, respectively, is not present;

in free or salt form.

**[0009]** The invention also provides a compound of formula I



Formula I

wherein

(i) L is S, SO or $SO_2$;

(ii) $R_1$ is H or $C_{1-6}$alkyl (e.g., methyl or ethyl);

(iii) $R_2$ is

H,

$C_{1-6}$alkyl (e.g., isopropyl, isobutyl, neopentyl, 2-methylbutyl, 2,2-dimethylpropyl) wherein said alkyl group is optionally substituted with halo (e.g., fluoro) or hydroxy (e.g., 1-hydroxypropan-2-yl, 3-hydroxy-2-methylpropyl),

–$C_{0-4}$alkyl-$C_{3-8}$cycloalkyl (e.g., cyclopentyl, cyclohexyl) optionally substituted with one or more amino (e.g., -$NH_2$), for example, 2-aminocyclopentyl or 2-aminocyclohexyl),wherein said cycloalkyl optionally contains one or more heteroatom selected from N and O and is optionally substituted with $C_{1-6}$alkyl (e.g., 1-methyl-pyrrolindin-2-yl, 1-methyl-pyrrolindin-3-yl, 1-methyl-pyrrolindin-2-yl-methyl or 1-methyl-pyrrolindin-3-yl-methyl),

$C_{3-8}$heterocycloalkyl (e.g., pyrrolidinyl, for example, pyrrolidin-3-yl) optionally substituted with $C_{1-6}$alkyl (e.g., methyl), for example, 1-methylpyrrolidin-3-yl,

$C_{3-8}$cycloalkyl-$C_{1-6}$alkyl (e.g.,cyclopropylmethyl),

halo$C_{1-6}$alkyl (e.g., trifluoromethyl, 2,2,2-trifluoroethyl),

-N($R_{14}$)($R_{15}$)-$C_{1-6}$alkyl (e.g., 2-(dimethylamino)ethyl,2-aminopropyl),

hydroxy$C_{1-6}$alkyl (e.g., (e.g., 3-hydroxy-2-methylpropyl, 1-hydroxyprop-2-yl),

aryl$C_{0-6}$alkyl (e.g., benzyl),

heteroaryl$C_{1-6}$alkyl (e.g., pyridinylmethyl),

$C_{1-6}$alkoxyaryl$C_{1-6}$alkyl (e.g., 4-methoxybenzyl);

-G-J wherein:

G is a single bond or, alkylene (e.g., methylene);

J is cycloalkyl or heterocycloalkyl (e.g., oxetan-2-yl, pyrolyin-3-yl, pyrolyin-2-yl) optionally substituted with $C_{1-6}$alkyl (e.g., (1-methylpyrolidin-2-yl));

(iv) $R_3$ is

1) –D-E-F wherein:

D is a single bond, $C_{1-6}$alkylene (e.g., methylene), or arylalkylene (e.g., pbenzylene or $–CH_2C_6H_4–$);

E is

a single bond,

$C_{1-4}$alkylene (e.g., methylene, ethynylene, prop-2-yn-1-ylene),

-$C_{0-4}$alkylarylene (e.g., phenylene or $–C_6H_4–$, -benzylene- or $–CH_2C_6H_4$-), wherein the arylene group is optionally substituted with halo (e.g., Cl or F),

heteroarylene (e.g., pyridinylene or pyrimidinylene),

amino$C_{1-6}$alkylene (e.g., $–CH_2N(H)–$),

amino (e.g., –N(H)–);

$C_{3-8}$cycloalkylene optionally containing one or more heteroatom selected from N or O (e.g., piperidinylene),

F is

H,

halo (e.g., F, Br, Cl),

$C_{1-6}$alkyl (e.g., isopropyl or isobutyl),

halo$C_{1-6}$alkyl (e.g., trifluoromethyl),

aryl (e.g., phenyl),

$C_{3-8}$cycloalkyl optionally containing at least one atom selected from a group consisting of N or O (e.g., cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl, tetrahydro-*2H*-pyran-4-yl, or morpholinyl), and optionally substituted with $C_{1-6}$alkyl (e.g., methyl or isopropyl), for example, 1-methylpyrrolidin-2-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, piperidin-2-yl, 1-methylpiperidin-2-yl, 1-ethylpiperidin-2-yl,

heteroaryl optionally substituted with $C_{1-6}$alkyl, (e.g., pyridyl, (for example, pyrid-2-yl), pyrimidinyl (for example, pyrimidin-2-yl, pyrimidin-4-yl), thiadiazolyl (for example, 1,2,3-thiadiazol-4-yl), oxazolyl (e.g., oxazol-2-yl), diazolyl (e.g., pyrazolyl (for example, pyrazol-1-yl) or imidazolyl (for example, imidazol-1-yl, 4-methylimidazolyl, 1-methylimidazol-2-yl,), triazolyl (e.g., 1,2,4-triazol-1-yl), tetrazolyl (e.g., tetrazol-5-yl), alkoxadiazolyl (e.g., 5-methyl-1,2,4-oxadiazol), wherein said heteroaryl is optionally substituted with halo (e.g., fluoro) or halo$C_{1-6}$alkyl;

amino (e.g., $-NH_2$),

$C_{1-6}$alkoxy,

–O-halo$C_{1-6}$alkyl (e.g., $-O-CF_3$),

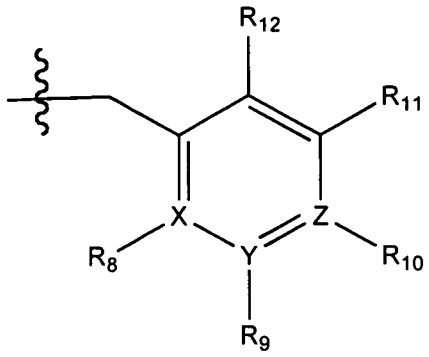
$C_{1-6}$alkylsulfonyl (for example, methylsulfonyl or $-S(O)_2CH_3$),

$-C(O)-R_{13}$,

$-N(R_{14})(R_{15})$; or

2) a substituted heteroarylaklyl, e.g., substituted with haloalkyl; or

3) attached to one of the nitrogens on the pyrazolo portion of Formula I and is a moiety of Formula A




Formula A

wherein X, Y and Z are, independently, N or C, and $R_8$, $R_9$, $R_{11}$ and $R_{12}$ are independently H or halogen (e.g., Cl or F); and $R_{10}$ is halogen, alkyl, cycloalkyl, haloalkyl (e.g., trifluoromethyl), aryl (e.g., phenyl), heteroaryl (e.g., pyridyl, (for example, pyrid-2-yl) or e.g., thiadiazolyl (for example, 1,2,3-thiadiazol-4-yl), diazolyl, triazolyl (e.g., 1,2,4-triazol-1-yl), tetrazolyl (e.g., tetrazol-5-yl), alkoxadiazolyl (e.g., 5-methyl-1,2,4-oxadiazol), pyrazolyl (e.g., pyrazol-1-yl), alkyl sulfonyl (e.g., methyl sulfonyl), arylcarbonyl (e.g., benzoyl), or heteroarylcarbonyl, alkoxycarbonyl, (e.g., methoxycarbonyl), aminocarbonyl; preferably phenyl or pyridyl, e.g., 2-pyridyl; provided that when X, Y or X is nitrogen, $R_8$, $R_9$ or $R_{10}$, respectively, is not present;

(v) $R_4$ is selected from:

H,

$C_{1-6}$alkyl (e.g., methyl, isopropyl),

$C_{3-8}$cycloalkyl (e.g., cyclopentyl),

$C_{3-8}$heterocycloalkyl (e.g., pyrrolidin-3-yl),

aryl (e.g., phenyl) or heteroaryl (e.g., pyrid-4-yl, pyrid-2-yl or pyrazol-3-yl) wherein said aryl or heteroaryl is optionally substituted with halo (e.g., 4-fluorophenyl), hydroxy (e.g., 4-hydroxyphenyl), $C_{1-6}$alkyl, $C_{1-6}$alkoxy or another aryl group (e.g., biphenyl-4-ylmethyl);

(vi) $R_{13}$ is $-N(R_{14})(R_{15})$, $C_{1-6}$alkyl (e.g., methyl), $-OC_{1-6}$alkyl (e.g., $-OCH_3$), halo$C_{1-6}$alkyl (trifluoromethyl), aryl (e.g., phenyl), or heteroaryl; and

(vii) $R_{14}$ and $R_{15}$ are independently H or $C_{1-6}$alkyl,

in free or salt form.

**[00010]** The invention further provides compounds of Formula I as follows:

1.1 Formula I, wherein $R_3$ is –D-E-F;

1.2 Formula 1.1, D is a single bond, $C_{1-6}$alkylene (e.g., methylene), or arylalkylene (e.g., benzylene or $–CH_2C_6H_4–$);

1.3 Formula 1.1, wherein D is a single bond;

1.4 Formula 1.1, wherein D is $C_{1-6}$alkylene (e.g., methylene);

1.5 Formula 1.1, wherein D is methylene;

1.6 Formula 1.1, wherein D is arylalkylene (e.g., benzylene or $–CH_2C_6H_4–$);

1.7 Formula 1.1, wherein D is benzylene or $–CH_2C_6H_4–$;

1.8 Any of formulae 1.1-1.7, wherein E is a single bond, $C_{2-4}$alkylene (e.g., methylene, ethynylene, prop-2-yn-1-ylene), -$C_{0-4}$alkylarylene (e.g., phenylene or $–C_6H_4–$, -benzylene- or $–CH_2C_6H_4$-), wherein the arylene group is optionally substituted with halo (e.g., Cl or F),heteroarylene (e.g., pyridinylene or pyrimidinylene),amino$C_{1-6}$alkylene (e.g., $–CH_2N(H)–$), amino (e.g., $–N(H)–$);$C_{3-8}$cycloalkylene optionally containing one or more heteroatom selected from N or O (e.g., piperidinylene);

1.9 Any of formulae 1.1-1.7, wherein E is a single bond;

1.10 Any of formulae 1.1-1.7, wherein E is $C_{2-4}$alkylene (e.g., methylene, ethynylene, prop-2-yn-1-ylene);

1.11 Any of formulae 1.1-1.7, wherein E is methylene;

1.12 Any of formulae 1.1-1.7, wherein E is ethynylene;

1.13 Any of formulae 1.1-1.7, wherein E is prop-2-yn-1-ylene;

1.14 Any of formulae 1.1-1.7, wherein E is -$C_{0-4}$alkylarylene (e.g., phenylene or $–C_6H_4–$, -benzylene- or $–CH_2C_6H_4$-), wherein the arylene group is optionally substituted with halo (e.g., Cl or F);

1.15 Any of formulae 1.1-1.7, wherein E is phenylene or $–C_6H_4–$;

1.16 Any of formulae 1.1-1.7, wherein E is heteroarylene (e.g., pyridinylene or pyrimidinylene);

1.17 Any of formulae 1.1-1.7, wherein E is pyridinylene;

1.18 Any of formulae 1.1-1.7, wherein E is pyrimidinylene;

1.19 Any of formulae 1.1-1.7, wherein E is amino$C_{1-6}$alkylene (e.g., –$CH_2N(H)$–);

1.20 Any of formulae 1.1-1.7, wherein E is amino (e.g., –N(H)–);

1.21 Any of formulae 1.1-1.7, wherein E is $C_{3-8}$cycloalkylene optionally containing one or more heteroatom selected from N or O (e.g., piperidinylene);

1.22 Any of formulae 1.1-1.21, wherein F is H, halo (e.g., F, Br, Cl), $C_{1-6}$alkyl (e.g., isopropyl or isobutyl), halo$C_{1-6}$alkyl (e.g., trifluoromethyl), aryl (e.g., phenyl), $C_{3-8}$cycloalkyl optionally containing at least one atom selected from a group consisting of N or O (e.g., cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl, tetrahydro-*2H*-pyran-4-yl, or morpholinyl), and optionally substituted with $C_{1-6}$alkyl (e.g., methyl or isopropyl), for example, 1-methylpyrrolidin-2-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, piperidin-2-yl, 1-methylpiperidin-2-yl, 1-ethylpiperidin-2-yl; heteroaryl optionally substituted with $C_{1-6}$alkyl (e.g., pyridyl, (for example, pyrid-2-yl), pyrimidinyl (for example, pyrimidin-2-yl, pyrimidin-4-yl), thiadiazolyl (for example, 1,2,3-thiadiazol-4-yl), oxazolyl (e.g., oxazol-2-yl), diazolyl (e.g., pyrazolyl (for example, pyrazol-1-yl) or imidazolyl (for example, imidazol-1-yl, 4-methylimidazolyl, 1-methylimidazol-2-yl,), triazolyl (e.g., 1,2,4-triazol-1-yl), tetrazolyl (e.g., tetrazol-5-yl), alkoxadiazolyl (e.g., 5-methyl-1,2,4-oxadiazol), pyrazolyl (e.g., pyrazol-1-yl), amino (e.g., -$NH_2$), $C_{1-6}$alkoxy, –O-halo$C_{1-6}$alkyl (e.g., –O-$CF_3$), $C_{1-6}$alkylsulfonyl (for example, methylsulfonyl or –$S(O)_2CH_3$), C(O)-$R_{13}$ or -$N(R_{14})(R_{15})$;

1.23 Any of formulae 1.1-1.22, wherein F is H;

1.24 Any of formulae 1.1-1.22, wherein F is halo (e.g., F, Br, Cl);

1.25 Any of formulae 1.1-1.22, wherein F is fluoro;

1.26 Any of formulae 1.1-1.22, wherein F is $C_{1-6}$alkyl (e.g., isopropyl or isobutyl);

1.27 Any of formulae 1.1-1.22, wherein F is isopropyl;

1.28 Any of formulae 1.1-1.22, wherein F is isobutyl;

1.29 Any of formulae 1.1-1.22, wherein F is halo$C_{1-6}$alkyl (e.g., trifluoromethyl);

1.30 Any of formulae 1.1-1.22, wherein F is trifluoromethyl;

1.31 Any of formulae 1.1-1.22, wherein F is aryl (e.g., phenyl);

1.32 Any of formulae 1.1-1.22, wherein F is phenyl;

1.33 Any of formulae 1.1-1.22, wherein F is $C_{3-8}$cycloalkyl optionally containing at least one atom selected from a group consisting of N or O (e.g., cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl tetrahydro-*2H*-pyran-4-yl, morpholinyl); and optionally substituted with $C_{1-6}$alkyl (e.g., methyl or isopropyl), for example, 1-methylpyrrolidin-2-yl, ), for example, 1-methylpyrrolidin-2-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, piperidin-2-yl, 1-methylpiperidin-2-yl, 1-ethylpiperidin-2-yl;

1.34 Any of formulae 1.1-1.22, wherein F is cyclopentyl or cyclohexyl;

1.35 Any of formulae 1.1-1.22, wherein F is 1-methylpyrrolidin-2-yl;

1.36 Any of formulae 1.1-1.22, wherein F is heteroaryl optionally substituted with $C_{1-6}$alkyl (e.g., pyridyl, (for example, pyrid-2-yl), pyrimidinyl (for example, pyrimidin-2-yl, pyrimidin-4-yl), thiadiazolyl (for example, 1,2,3-thiadiazol-4-yl), oxazolyl (e.g., oxazol-2-yl), diazolyl (e.g., pyrazolyl (for example, pyrazol-1-yl) or imidazolyl (for example, imidazol-1-yl, 4-methylimidazolyl, 1-methylimidazol-2-yl,), triazolyl (e.g., 1,2,4-triazol-1-yl), tetrazolyl (e.g., tetrazol-5-yl), alkoxadiazolyl (e.g., 5-methyl-1,2,4-oxadiazol), pyrazolyl (e.g., pyrazol-1-yl), wherein said heteroaryl is optionally substituted with halo (e.g., fluoro) or halo$C_{1-6}$alkyl;

1.37 Any of formulae 1.1-1.22, wherein F is pyrid-2-yl optionally substituted with halo (e.g., fluoro);

1.38 Any of formulae 1.1-1.22, wherein F is 6-fluoro-pyrid-2-yl;

1.39 Any of formulae 1.1-1.22, wherein F is pyrimidinyl (for example, pyrimidin-2-yl, pyrimidin-4-yl);

1.40 Any of formulae 1.1-1.22, wherein F is oxazolyl (e.g., oxazol-2-yl),

1.41 Any of formulae 1.1-1.22, wherein F is triazolyl (e.g., 1,2,4-triazol-1-yl);

1.42 Any of formulae 1.1-1.22, wherein F is diazolyl (e.g., pyrazolyl (for example, pyrazol-1-yl) or imidazolyl (for example, imidazol-1-yl, 4-methylimidazolyl, 1-methylimidazol-2-yl,);

1.43 Any of formulae 1.1-1.22, wherein F is C-$_{1-6}$alkyl-oxadiazolyl (e.g., 5-methyl-1,2,4-oxadiazolyl);

1.44 Any of formulae 1.1-1.22, wherein F is amino (e.g., -$NH_2$);

1.45 Any of formulae 1.1-1.22, wherein F is $C_{1-6}$alkoxy;

1.46 Any of formulae 1.1-1.22, wherein F is –O-halo$C_{1-6}$alkyl (e.g., –O-$CF_3$);

1.47 Any of formulae **Error! Reference source not found.**-1.22, wherein F is -C(O)-$R_{13}$;

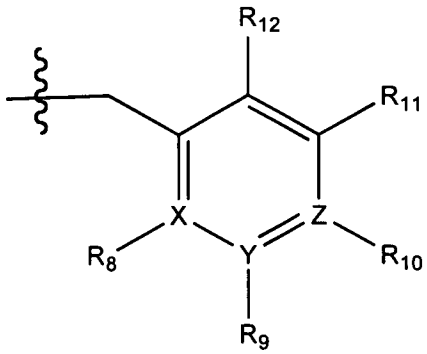
1.48 Any of formulae **Error! Reference source not found.**-1.22, wherein F is -N($R_{14}$)($R_{15}$);

1.49 Any of formulae **Error! Reference source not found.**-1.22, wherein F is $C_{1-6}$alkylsulfonyl;

1.50 Any of formulae **Error! Reference source not found.**-1.22, wherein F is methylsulfonyl or –$S(O)_2CH_3$;

1.51 Formula I or any of **Error! Reference source not found.**-1.21, wherein $R_3$ is a substituted heteroarylaklyl, e.g., substituted with haloalkyl;

1.52 Formula I or any of **Error! Reference source not found.**-1.21, wherein $R_3$ is attached to one of the nitrogens on the pyrazolo portion of Formula I and is a moiety of Formula A




Formula A

wherein X, Y and Z are, independently, N or C, and $R_8$, $R_9$, $R_{11}$ and $R_{12}$ are independently H or halogen (e.g., Cl or F); and $R_{10}$ is halogen, alkyl, cycloalkyl, haloalkyl (e.g., trifluoromethyl), aryl (e.g., phenyl), heteroaryl (e.g., pyridyl, (for example, pyrid-2-yl) or e.g., thiadiazolyl (for example, 1,2,3-thiadiazol-4-yl), diazolyl, triazolyl (e.g., 1,2,4-triazol-1-yl), tetrazolyl (e.g., tetrazol-5-yl), alkoxadiazolyl (e.g., 5-methyl-1,2,4-oxadiazol), pyrazolyl (e.g., pyrazol-1-yl), alkyl sulfonyl (e.g., methyl sulfonyl), arylcarbonyl (e.g., benzoyl), or heteroarylcarbonyl, alkoxycarbonyl, (e.g., methoxycarbonyl), aminocarbonyl; preferably phenyl or pyridyl, e.g., 2-pyridyl; provided that when X, Y or X is nitrogen, $R_8$, $R_9$ or $R_{10}$, respectively, is not present;

1.53 Formula 1.52, wherein $R_3$ is a moiety of Formula A, $R_8$, $R_9$, $R_{11}$ and $R_{12}$ are each H and $R_{10}$ is phenyl;

1.54 Formula 1.52, wherein $R_3$ is a moiety of Formula A, $R_8$, $R_9$, $R_{11}$ and $R_{12}$ are each H and $R_{10}$ is pyridyl or thiadizolyl;

1.55 Formula 1.52, wherein $R_3$ is a moiety of Formula A, $R_8$, $R_9$, $R_{11}$ and $R_{12}$ are each H and $R_{10}$ is pyrid-2-yl optionally substituted with halo (e.g., fluoro);

1.56 Formula 1.52, wherein $R_3$ is a moiety of Formula A and X, Y and Z are all C;

1.57 Formula 1.52, wherein $R_{10}$ is pyrimidinyl;

1.58 Formula 1.52, wherein $R_{10}$ is 5- fluoropyrmidinyl;

1.59 Formula 1.52, wherein $R_{10}$ is pyrazol-1-yl;

1.60 Formula 1.52, wherein $R_{10}$ is 1,2,4-triazol-l-yl;

1.61 Formula 1.52, wherein $R_{10}$ is aminocarbonyl;

1.62 Formula 1.52, wherein $R_{10}$ is methylsulfonyl;

1.63 Formula 1.52, wherein $R_{10}$ is 5-methyl-1,2,4- oxadiazol-3-yl;

1.64 Formula 1.52, wherein $R_{10}$ is 5-fluoropyrimidin-2-yl;

1.65 Formula 1.52, wherein $R_{10}$ is trifluoromethyl;

1.66 Formula 1.52, wherein $R_3$ is a moiety of Formula A, X and Z are C, and Y is N;

1.67 Formula I or any of **Error! Reference source not found.**-1.66, wherein $R_2$ is H; $C_{1-6}$alkyl (e.g., isopropyl, isobutyl, neopentyl, 2-methylbutyl, 2,2-dimethylpropyl) wherein said alkyl group is optionally substituted with halo (e.g., fluoro) or hydroxy (e.g., 1-hydroxypropan-2-yl, 3-hydroxy-2-methylpropyl); –$C_{0-4}$alkyl-$C_{3-8}$cycloalkyl (e.g., cyclopentyl, cyclohexyl) optionally substituted with one or more amino (e.g., -$NH_2$), for example, 2-aminocyclopentyl or 2-aminocyclohexyl),wherein said cycloalkyl optionally contains one or more heteroatom selected from N and O and is optionally substituted with $C_{1-6}$alkyl (e.g., 1-methyl-pyrrolindin-2-yl, 1-methyl-pyrrolindin-3-yl, 1-methyl-pyrrolindin-2-yl-methyl or 1-methyl-pyrrolindin-3-yl-methyl); $C_{3-8}$heterocycloalkyl (e.g., pyrrolidinyl, for example, pyrrolidin-3-yl) optionally substituted with $C_{1-6}$alkyl (e.g., methyl), for example, 1-methylpyrrolidin-3-yl; $C_{3-8}$cycloalkyl-$C_{1-6}$alkyl (e.g.,cyclopropylmethyl); halo$C_{1-6}$alkyl (e.g., trifluoromethyl, 2,2,2-trifluoroethyl); -N($R_{14}$)($R_{15}$)-$C_{1-6}$alkyl (e.g., 2-(dimethylamino)ethyl,2-aminopropyl); hydroxy$C_{1-6}$alkyl (e.g., (e.g., 3-hydroxy-2-methylpropyl, 1-hydroxyprop-2-yl); aryl$C_{0-6}$alkyl (e.g., benzyl); heteroaryl$C_{1-6}$alkyl (e.g., pyridinylmethyl); $C_{1-6}$alkoxyaryl$C_{1-6}$alkyl (e.g., 4-methoxybenzyl); -G-J wherein: G is a single bond or, alkylene (e.g., methylene) and J is cycloalkyl or heterocycloalkyl (e.g., oxetan-2-yl, pyrolyin-3-yl, pyrolyin-2-yl) optionally substituted with $C_{1-6}$alkyl (e.g., (1-methylpyrolidin-2-yl));

1.68 Formula 1.66, wherein $R_2$ is H;

1.69 Formula 1.66, wherein $R_2$ is $C_{1-6}$alkyl (e.g., isopropyl, isobutyl, neopentyl, 2-methylbutyl, 2,2-dimethylpropyl) wherein said alkyl group is optionally substituted with halo (e.g., trifluoroethyl) or hydroxy (e.g., 1-hydroxypropan-2-yl, 3-hydroxy-2-methylpropyl);

1.70 Formula 1.66, wherein $R_2$ is isobutyl;

1.71 Formula 1.66, wherein $R_2$ is 3-hydroxy-2-methylpropyl;

1.72 Formula 1.66, wherein $R_2$ is 1-hydroxypropan-2-yl;

1.73 Formula 1.66, wherein $R_2$ is $-C_{0-4}$alkyl-$C_{3-8}$cycloalkyl (e.g., cyclopentyl, cyclohexyl) optionally substituted with one or more amino (e.g., $-NH_2$), for example, 2-aminocyclopentyl or 2-aminocyclohexyl), wherein said cycloalkyl optionally contains one or more heteroatom selected from N and O and is optionally substituted with $C_{1-6}$alkyl (e.g., 1-methyl-pyrrolindin-2-yl, 1-methyl-pyrrolindin-3-yl, 1-methyl-pyrrolindin-2-yl-methyl or 1-methyl-pyrrolindin-3-yl-methyl);

1.74 Formula 1.66, wherein $R_2$ is 1-methyl-pyrrolindin-2-yl, 1-methyl-pyrrolindin-3-yl, 1-methyl-pyrrolindin-2-yl-methyl or 1-methyl-pyrrolindin-3-yl-methyl;

1.75 Formula 1.66, wherein $R_2$ is $C_{3-8}$heterocycloalkyl (e.g., pyrrolidinyl, for example, pyrrolidin-3-yl) optionally substituted with $C_{1-6}$alkyl (e.g., methyl), for example, 1-methylpyrrolidin-3-yl;

1.76 Formula 1.66, wherein $R_2$ is 1-methylpyrrolidin-3-yl;

1.77 Formula 1.66, wherein $R_2$ is $C_{3-8}$cycloalkyl-$C_{1-6}$alkyl (e.g.,cyclopropylmethyl);

1.78 Formula 1.66, wherein $R_2$ is $-N(R_{14})(R_{15})$-$C_{1-6}$alkyl (e.g., 2-(dimethylamino)ethyl, 2-aminopropyl);

1.79 Formula 1.66, wherein $R_2$ is heteroaryl$C_{1-6}$alkyl (e.g., pyridinylmethyl),

1.80 Formula 1.66, wherein $R_2$ is $C_{1-6}$alkoxyaryl$C_{1-6}$alkyl (e.g., 4-methoxybenzyl;

1.81 Formula 1.66, wherein $R_2$ is aryl$C_{0-6}$alkyl (e.g., benzyl);

1.82 Formula 1.66, wherein $R_2$ is cyclopentyl or cyclohexyl;

1.83 Formula I or any of **Error! Reference source not found.**-1.66, wherein $R_2$ is -G-J; G is a single bond or, alkylene (e.g., methylene); and J is cycloalkyl or heterocycloalkyl (e.g., oxetan-2-yl, pyrolyin-3-yl, pyrolyin-2-yl) optionally substituted with $C_{1-6}$alkyl (e.g., (1-methylpyrolidin-2-yl));

1.84 Formula 1.83, wherein G is alkylene (e.g., methylene);

1.85 Formula 1.83, wherein G is methylene;

1.86 Formula 1.83, wherein J is cycloalkyl or heterocycloalkyl (e.g., oxetan-2-yl, pyrolyin-3-yl, pyrolyin-2-yl) optionally substituted with alkyl (e.g., 1-methylpyrolidin-2-yl);

1.87 Formula 1.83, wherein J is oxetan-2-yl, pyrolyin-3-yl, pyrolyin-2-yl;

1.88 Formula 1.83, wherein J is (1-methylpyrolidin-2-yl);

1.89 Any of the preceding formulae wherein $R_4$ is selected from H, $C_{1-6}$alkyl (e.g., methyl, isopropyl), $C_{3-8}$cycloalkyl (e.g., cyclopentyl), $C_{3-8}$heterocycloalkyl (e.g., pyrrolidin-3-yl), or aryl (e.g., phenyl) or heteroaryl (e.g., pyrid-4-yl, pyrid-2-yl or pyrazol-3-yl) wherein said aryl or heteroaryl is optionally substituted with halo (e.g., 4-fluorophenyl), hydroxy (e.g., 4-hydroxyphenyl), $C_{1-6}$alkoxy $C_{1-6}$alkyl, or $C_{1-6}$alkoxy or another aryl group (e.g., biphenyl-4-ylmethyl);

1.90 Formula 1.89, wherein either $R_4$ is H;

1.91 Formula 1.89, wherein either $R_4$ or $R_5$ is $C_{1-6}$alkyl (e.g., methyl, isopropyl);

1.92 Formula 1.89, wherein either $R_4$ is isopropyl;

1.93 Formula 1.89, wherein either $R_4$ or $R_5$ is $C_{3-8}$cycloalkyl (e.g., cyclopentyl);

1.94 Formula 1.89, wherein either $R_4$ or $R_5$ is $C_{3-8}$heterocycloalkyl (e.g., pyrrolidin-3-yl);

1.95 Formula 1.89, wherein either $R_4$ or $R_5$ is aryl (e.g., phenyl) optionally substituted with halo (e.g., 4-fluorophenyl), hydroxy (e.g., 4-hydroxyphenyl), $C_{1-6}$alkyl, $C_{1-6}$alkoxy or another aryl group (e.g., biphenyl-4-ylmethyl);

1.96 Formula 1.89, wherein either $R_4$ or $R_5$ is 4-hydroxyphenyl;

1.97 Formula 1.89, wherein either $R_4$ or $R_5$ is 4-fluorophenyl;

1.98 Formula 1.89, wherein either $R_4$ or $R_5$ is heteroaryl (e.g., pyrid-4-yl, pyrid-2-yl or pyrazol-3-yl) optionally substituted with halo (e.g., 4-fluorophenyl), hydroxy (e.g., 4-hydroxyphenyl), $C_{1-6}$alkyl, $C_{1-6}$alkoxy or another aryl group (e.g., biphenyl-4-ylmethyl);

1.99 Formula 1.89, wherein either $R_4$ or $R_5$ is phenyl;

1.100 Any of the foregoing formulae, wherein $R^{13}$ is $-N(R_{14})(R_{15})$, $C_{1-6}$alkyl (e.g., methyl), $-OC_{1-6}$alkyl (e.g., $-OCH_3$), halo$C_{1-6}$alkyl, aryl (for example phenyl), or heteroaryl;

1.101 Formula 1.100, wherein $R^{13}$ is $-N(R_{14})(R_{15})$;

1.102 Formula 1.100, wherein $R^{13}$ is $-NH_2$;

1.103 Formula 1.100, wherein $R^{13}$ is $C_{1-6}$alkyl (e.g., methyl);

1.104 Formula 1.100, wherein $R^{13}$ is $-OC_{1-6}$alkyl (e.g., $-OCH_3$),

1.105 Formula 1.100, wherein $R^{13}$ is $-OCH_3$;

1.106 Formula 1.100, wherein $R^{13}$ is halo$C_{1-6}$alkyl (e.g., trifluoromethyl);

1.107 Formula 1.100, wherein $R^{13}$ is trifluoromethyl;

1.108 Formula 1.100, wherein $R^{13}$ is aryl (e.g., phenyl);

1.109 Formula 1.100, wherein $R^{13}$ is heteroaryl (e.g., pyridiyl);

1.110 Any of the preceding formulae, wherein $R_{14}$ and $R_{15}$ are independently H or $C_{1-6}$alkyl (e.g., methyl);

1.111 Formula I or any of 1.1-1.110, wherein either $R_{14}$ or $R_{15}$ is independently H;

1.112 Formula I or any of 1.1-1.110, wherein either $R_{14}$ or $R_{15}$ is $C_{1-6}$alkyl (e.g., methyl);

1.113 Formula I or any of 1.1-1.110, wherein either $R_{14}$ or $R_{15}$ is methyl;

1.114 Formula I or any of 1.1-1.110, wherein $R_{14}$ and $R_{15}$ are methyl;

1.115 any of the preceding formulae wherein $R_3$ is selected from a group consisting of 4-(pyrimidin-2-yl)benzyl, 4-(1,2,4-triazol-1-yl)benzyl, 4-(1-methylpyrrolidin-2-yl)benzyl, 4-(1-methylpiperid-2-yl)benzyl, 4-(pyrid-2-yl)benzyl, 4-(pyrazol-1-yl)benzyl, 4-(pyrrolidin-3-yl)benzyl, (6-chloropyridin-3-yl)methyl, (6-fluoropyridin-3-yl)methyl, 4-(imidazol-1-yl)benzyl, 4-(pyrimidin-4-yl)benzyl), 4-(oxazol-2-yl)benzyl, 4-(dimethylamino)benzyl, 4-(methylsulfonyl)benzyl, 4-(pyrrolidin-3-yl)benzyl, (1-isopropylpyiperidin-4-yl)methyl, and $-CH_2-C_2H_4-C(O)-NH_2$;

1.116 formula 1.115 wherein $R_3$ is 4-(pyrimidin-2-yl)benzyl;

1.117 formula 1.115 wherein $R_3$ is 4-(1,2,4-triazol-1-yl)benzyl;

1.118 formula 1.115 wherein $R_3$ is 4-(1-methylpyrrolidin-2-yl)benzyl;

1.119 formula 1.115 wherein $R_3$ is 4-(1-methylpiperid-2-yl)benzyl;

1.120 formula 1.115 wherein $R_3$ is 4-(pyrid-2-yl)benzyl;

1.121 formula 1.115 wherein $R_3$ is 4-(pyrazol-1-yl)benzyl;

1.122 formula 1.115 wherein $R_3$ is 4-(pyrrolidin-3-yl)benzyl;

1.123 formula 1.115 wherein $R_3$ is (6-chloropyridin-3-yl)methyl or (6-fluoropyridin-3-yl)methyl;

1.124 formula 1.115 wherein $R_3$ is 4-(imidazol-1-yl)benzyl;

1.125 formula 1.115 wherein $R_3$ is 4-(pyrimidin-4-yl)benzyl);

1.126 formula 1.115 wherein $R_3$ is 4-(oxazol-2-yl)benzyl;

1.127 formula 1.115 wherein $R_3$ is 4-(dimethylamino)benzyl;

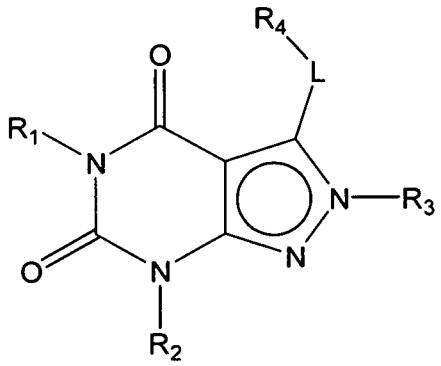
1.128 formula 1.115 wherein $R_3$ is 4-(methylsulfonyl)benzyl;

1.129 formula 1.115 wherein $R_3$ is 4-(pyrrolidin-3-yl)benzyl;

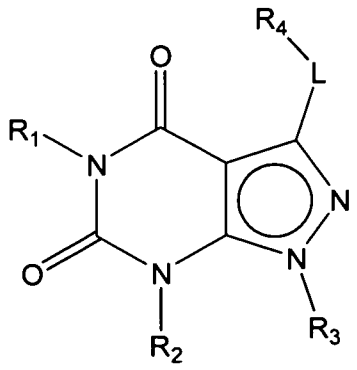
1.130 formula 1.115 wherein $R_3$ is (1-isopropylpyiperidin-4-yl)methyl;

1.131 formula 1.115 wherein $R_3$ is $-CH_2-C_2H_4-C(O)-NH_2$;

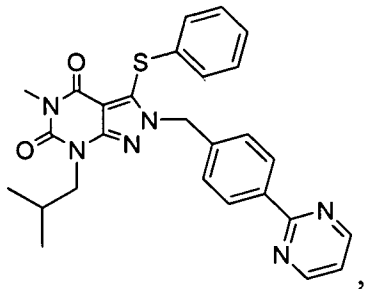
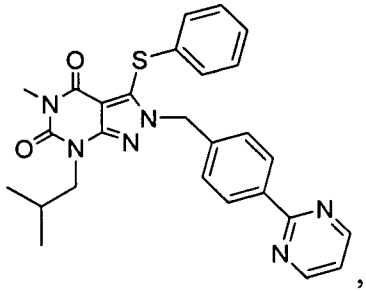
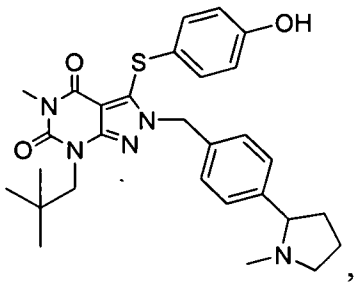
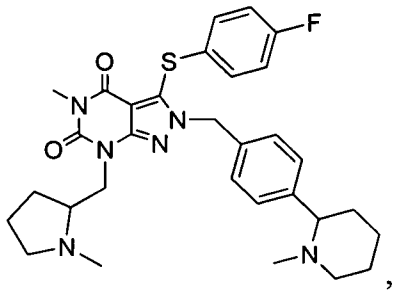
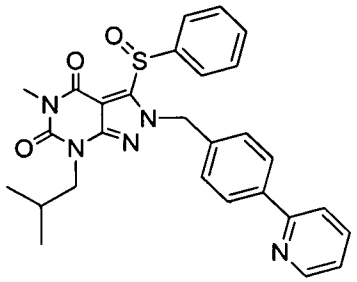
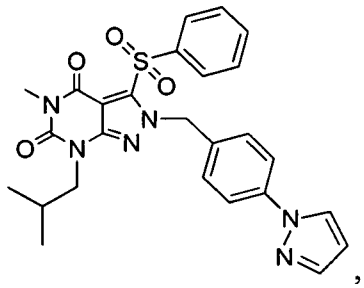
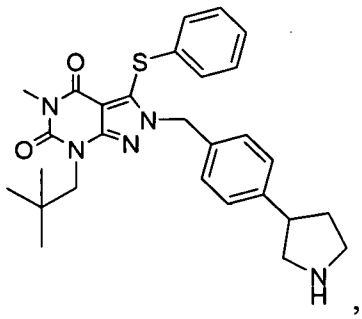
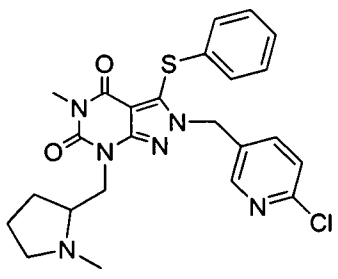
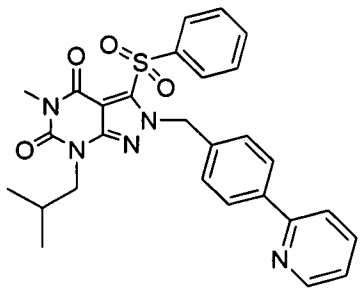
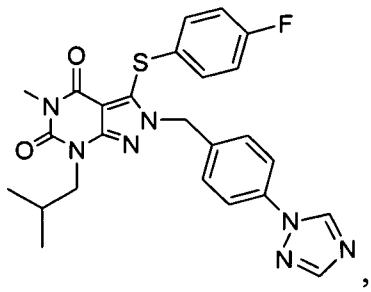
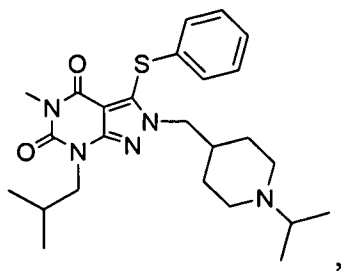
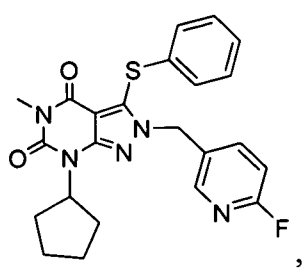
1.132 any of the preceding formulae wherein compound of formula I is

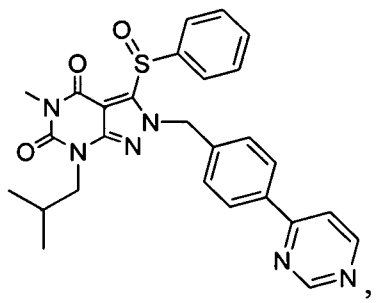



1.133 any of the preceding formulae wherein compound of formula I is




1.134 any of the preceding formulae wherein compound of formula I is selected from a group consisting of:

 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,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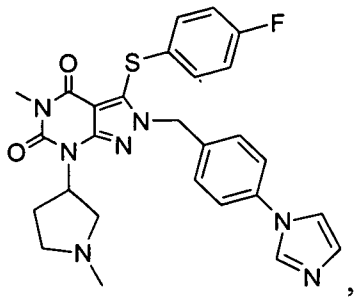
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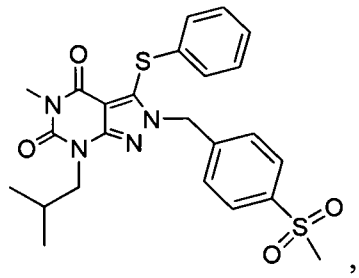
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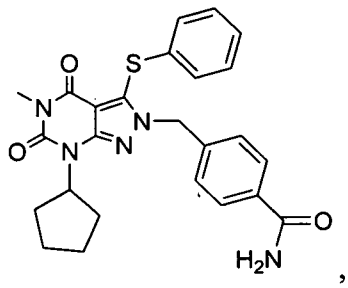
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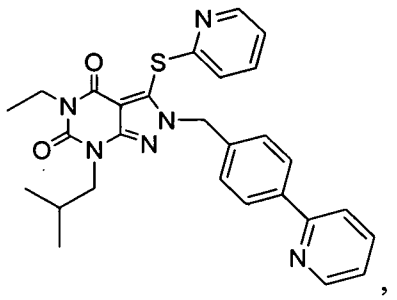
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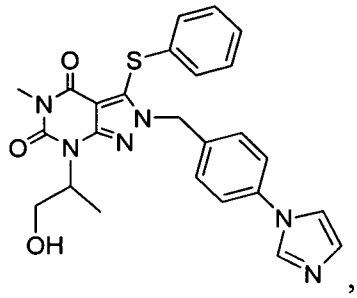
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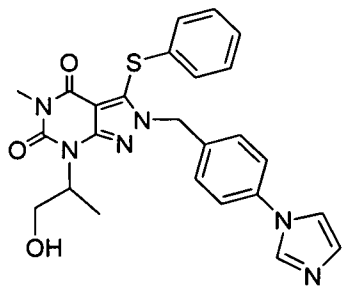
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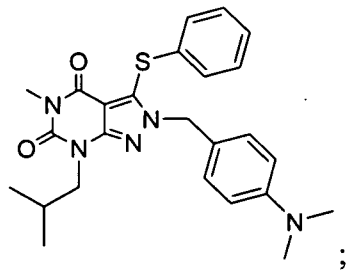

;

1.135 any of the preceding formulae wherein the compounds inhibit phosphodiesterase-mediated (e.g., PDE1-mediated, especially PDE1B-mediated) hydrolysis of cGMP, e.g., with an $IC_{50}$ of less than 10μM, preferably less than 1μM, preferably less than 500 nM, preferably less than 200 nM in an immobilized-metal affinity particle reagent PDE assay, for example, as described in Example 16,

in free or salt form.

**[0010]** In a further embodiment, the Compound of the Invention is a Compound of Formula I, wherein $R_3$ is $C_{5-6}$heteroaryl$C_{1-6}$alkyl optionally substituted with halo, C1-6alkyl (e.g., (6-fluoropyrid-3-yl)methyl, (6-chloropyrid-3-yl)methyl).

**[0011]** In another embodiment, the Compound of the Invention is a Compound of Formula I, wherein $R_3$ is pyridyl$C_{1-6}$alkyl (e.g., pyridylmethyl) optionally substituted with halo, haloalkyl alkyl sulfonyl, -C(O)N($C_{0-6}$alkyl)($C_{0-6}$alkyl), heteroaryl (e.g., pyridyl, pyrimidinyl, oxazole, imidazole, triazolyl, pyrazolyl), amino, $C_{1-6}$alkylamino, and heterocycloalkyl (e.g., piperidinyl, pyrrolidinyl) which heterocycloalkyl, heteroaryl are further optionally substituted with $C_{1-6}$alkyl or halo.

**[0012]** In still another embodiment, the Compound of the Invention is a Compound of Formula I, wherein $R_3$ is benzyl substituted with aryl, heteroaryl (e.g., pyridyl, pyrimidinyl, oxazole, imidazole, triazolyl, pyrazolyl), $C_{3-7}$cycloalkyl, hetero$C_{3-7}$cycloalkyl (e.g., piperidinyl, pyrrolidinyl), alkyl sulfonyl, -C(O)N($C_{0-6}$alkyl)($C_{0-6}$alkyl), amino, $C_{1-6}$alkylamino, which aryl, heterocycloalkyl, heteroaryl are further optionally substituted with $C_{1-6}$alkyl or halo.

**[0013]** In a another embodiment, the Compound of the Invention is a Compound of Formula I wherein

(ii) $R_1$ is H or alkyl (e.g., methyl);

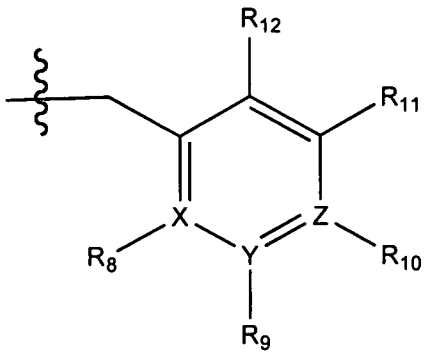
(iii) $R_2$ is H, alkyl (e.g., isobutyl, 2-methylbutyl, 2,2-dimethyl propyl), cycloalkyl (e.g., cyclopentyl, cyclohexyl), haloalkyl (e.g., trifluoromethyl, 2,2,2-trifluoroethyl), alkylaminoalkyl (e.g., 2-(dimethylamino)ethyl), hydroxyalkyl (e.g., 3-hydroxy-2-methyl propyl), arylalkyl (e.g., benzyl), heteroarylalkyl (e.g., pyridylmethyl), or alkoxyarylalkyl (e.g., 4-methoxybenzyl);

(iv) $R_3$ is a substituted heteroarylaklyl, e.g., substituted with haloalkyl

or

$R_3$ is attached to one of the nitrogens on the pyrazolo portion of Formula 1 and is

a moiety of Formula A




Formula A

wherein X, Y and Z are, independently, N or C, and $R_8$, $R_9$, $R_{11}$ and $R_{12}$ are independently H or halogen (e.g., Cl or F); and $R_{10}$ is halogen, alkyl, cycloalkyl, haloalkyl (e.g., trifluoromethyl), aryl (e.g., phenyl), heteroaryl (e.g., pyridyl, (for example, pyrid-2-yl) or e.g., thiadiazolyl (for example, 1,2,3-thiadiazol-4-yl), diazolyl, triazolyl (e.g., 1,2,4-triazol-1-yl), tetrazolyl (e.g., tetrazol-5-yl), alkoxadiazolyl (e.g., 5-methyl-1,2,4-oxadiazol), pyrazolyl (e.g., pyrazol-1-yl), alkyl sulfonyl (e.g., methyl sulfonyl), arylcarbonyl (e.g., benzoyl), or heteroarylcarbonyl, alkoxycarbonyl, (e.g., methoxycarbonyl), aminocarbonyl; preferably phenyl or pyridyl, e.g., 2-pyridyl; provided that when X, Y or X is nitrogen, $R_8$, $R_9$ or $R_{10}$, respectively, is not present;

(v) $R_4$ is aryl (e.g., phenyl) or heteroaryl;

(vi) $R_5$ is H, alkyl, cycloalkyl (e.g., cyclopentyl), heteroaryl, aryl, p-benzylaryl (e.g., biphenyl-4-ylmethyl);

(vii) $R_6$ is H, $C_{1\text{-}6}$alkyl (e.g., methyl) or $C_{3\text{-}8}$cycloalkyl;

(viii) $R_{13}$ is $-N(R_{14})(R_{15})$, $C_{1\text{-}6}$alkyl (e.g., methyl), $-OC_{1\text{-}6}$alkyl (e.g., $-OCH_3$), halo$C_{1\text{-}6}$alkyl (trifluoromethyl), aryl (e.g., phenyl), or heteroaryl; and

(vii) $R_{14}$ and $R_{15}$ are independently H or $C_{1\text{-}6}$alkyl,

in free or salt form (hereinafter, Compound of Formula I(i)).

**[0014]** In still another embodiment, the Compound of the Invention is a Compound of Formula I wherein

(i) $R_1$ is H or alkyl (e.g., methyl);

(ii) $R_2$ is H, alkyl (e.g., isopropyl, isobutyl, 2-methylbutyl, 2,2-dimethyl propyl), cycloalkyl (e.g., cyclopentyl, cyclohexyl), haloalkyl (e.g., trifluoromethyl, 2,2,2-trifluoroethyl), alkylaminoalkyl (e.g., 2-(dimethylamino)ethyl), hydroxyalkyl (e.g., 3-hydroxy-2-methyl propyl), arylalkyl (e.g., benzyl), heteroarylalkyl (e.g., pyridylmethyl), or alkoxyarylalkyl (e.g., 4-methoxybenzyl);

(iii) $R_3$ is D-E-F wherein

1. D is single bond, alkylene (e.g., methylene), or arylalkylene (e.g., benzylene or $-CH_2C_6H_4-$);
2. E is a alkylene (e.g., methylene, ethynylene, prop-2-yn-1-ylene), arylene (e.g., phenylene or $-C_6H_4-$), alkylarylene (e.g., -

benzylene- or $-CH_2C_6H_4-$), aminoalkylene (e.g., $-CH_2N(H)-$) or amino (e.g., –N(H)–); and

3. F is alkyl (e.g., isobutyl), aryl (e.g., phenyl), heteroaryl (e.g., pyrid-2-yl, 1,2,4-triazolyl), hetero$C_{3-8}$cycloalkyl (e.g., pyrolidin-1-yl), amino (e.g., $-NH_2$), $C_{1-6}$alkoxy, or –O-haloalkyl (e.g., $-O-CF_3$);

(iv) $R_4$ is aryl (e.g., phenyl), heteroaryl (e.g., pyrid-4-yl, pyrid-2-yl or pyrazol-3-yl) or heterocycloalkyl (e.g., pyrrolidin-3-yl); and

(v) $R_5$ is H, alkyl, cycloalkyl (e.g., cyclopentyl), heteroaryl, aryl, p-benzylaryl (e.g., biphenyl-4-ylmethyl);

(vi) $R_6$ is H, $C_{1-6}$alkyl (e.g., methyl) or $C_{3-8}$cycloalkyl;

(vii) $R_{13}$ is $-N(R_{14})(R_{15})$, $C_{1-6}$alkyl (e.g., methyl), $-OC_{1-6}$alkyl (e.g., $-OCH_3$), halo$C_{1-6}$alkyl (trifluoromethyl), aryl (e.g., phenyl), or heteroaryl; and

(viii) $R_{14}$ and $R_{15}$ are independently H or alkyl,

wherein "alk", "alkyl", "haloalkyl" or "alkoxy" refers to $C_{1-6}$ alkyl and "cycloalkyl" refers to $C_{3-8}$ cycloalkyl unless specifically specified;

in free or salt form (hereinafter, Compound of Formula I(ii)).

**[0015]** If not otherwise specified or clear from context, the following terms herein have the following meanings:

**(a)** "Alkyl" as used herein is a saturated or unsaturated hydrocarbon moiety, preferably saturated, preferably having one to six carbon atoms, which may be linear or branched, and may be optionally mono-, di- or tri- substituted, e.g., with halogen (e.g., chloro or fluoro), hydroxy, or carboxy.

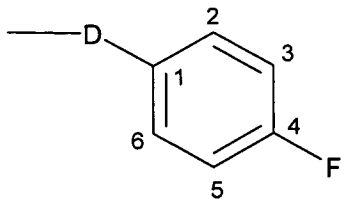
**(b)** "Cycloalkyl" as used herein is a saturated or unsaturated nonaromatic hydrocarbon moiety, preferably saturated, preferably comprising three to eight carbon atoms, at least some of which form a nonaromatic mono- or bicyclic, or bridged cyclic structure, and which may be optionally substituted, e.g., with halogen (e.g., chloro or fluoro), hydroxy, or carboxy. Wherein the cycloalkyl optionally contains one or more atoms selected from N and O and/or S, said cycloalkyl may also be a heterocycloalkyl.

**(c)** "Heterocycloalkyl" is, unless otherwise indicated, saturated or unsaturated nonaromatic hydrocarbon moiety, preferably saturated, preferably comprising three to nine carbon atoms, at least some of which form a nonaromatic mono- or bicyclic, or bridged cyclic structure, wherein at least one carbon atom is replaced with N, O or S, which heterocycloalkyl may be optionally substituted, e.g., with halogen (e.g., chloro or fluoro), hydroxy, or carboxy.

**(d)** "Aryl" as used herein is a mono or bicyclic aromatic hydrocarbon, preferably phenyl, optionally substituted, e.g., with alkyl (e.g., methyl), halogen (e.g., chloro or fluoro), haloalkyl (e.g., trifluoromethyl), hydroxy, carboxy, or an additional aryl or heteroaryl (e.g., biphenyl or pyridylphenyl).

**(e)** "Heteroaryl" as used herein is an aromatic moiety wherein one or more of the atoms making up the aromatic ring is sulfur or nitrogen rather than carbon, e.g., pyridyl or thiadiazolyl, which may be optionally substituted, e.g., with alkyl, halogen, haloalkyl, hydroxy or carboxy.

**(f)** Wherein E is phenylene, the numbering is as follows:




**(g)** It is intended that wherein the substituents end in "ene", for example, alkylene, phenylene or arylalkylene, said substitutents are intended to bridge or be connected to two other substituents. Therefore, methylene is intended to be $–CH_2–$ and phenylene intended to be $–C_6H_4–$ and arylalkylene is intended to be $–C_6H_4–CH_2–$ or $–CH_2–C_6H_4–$.

**[0016]** Compounds of the Invention may exist in free or salt form, e.g., as acid addition salts. In this specification unless otherwise indicated, language such as "Compounds of the Invention" is to be understood as embracing the compounds of Formula I, or any of 1.1-1.135, a Compound of Formula I(i) or I(ii), in any form, for example free or acid addition salt form, or where the compounds contain acidic substituents, in base addition salt form. The Compounds of the Invention are intended

for use as pharmaceuticals, therefore pharmaceutically acceptable salts are preferred. Salts which are unsuitable for pharmaceutical uses may be useful, for example, for the isolation or purification of free Compounds of the Invention or their pharmaceutically acceptable salts, are therefore also included.

**[0017]** Compounds of the Invention may in some cases also exist in prodrug form. A prodrug form is compound which converts in the body to a Compound of the Invention. For example, when the Compounds of the Invention contain hydroxy or carboxy substituents, these substituents may form physiologically hydrolysable and acceptable esters. As used herein, "physiologically hydrolysable and acceptable ester" means esters of Compounds of the Invention which are hydrolysable under physiological conditions to yield acids (in the case of Compounds of the Invention which have hydroxy substituents) or alcohols (in the case of Compounds of the Invention which have carboxy substituents) which are themselves physiologically tolerable at doses to be administered. Therefore, wherein the Compound of the Invention contains a hydroxy group, for example, Compound-OH, the acyl ester prodrug of such compound, i.e., Compound-O-C(O)-$C_{1-4}$alkyl, can hydrolyze in the body to form physiologically hydrolysable alcohol (Compound-OH) on the one hand and acid on the other (e.g., HOC(O)-$C_{1-4}$alkyl). Alternatively, wherein the Compound of the Invention contains a carboxylic acid, for example, Compound-C(O)OH, the acid ester prodrug of such compound, Compound-C(O)O-$C_{1-4}$alkyl can hydrolyze to form Compound-C(O)OH and HO-$C_{1-4}$alkyl. As will be appreciated, the term thus embraces conventional pharmaceutical prodrug forms.

**[0018]** The invention also provides methods of making the Compounds of the Invention and methods of using the Compounds of the Invention for treatment of diseases and disorders as set forth below (especially treatment of diseases characterized by reduced dopamine D1 receptor signaling activity, such as Parkinson's disease, Tourette's Syndrome, Autism, fragile X syndrome, ADHD, restless leg syndrome, depression, cognitive impairment of schizophrenia, narcolepsy and diseases that may be alleviated by the enhancement of progesterone-signaling such as female sexual dysfunction), or a disease or disorder such as psychosis or glaucoma). This list is not intended to be exhaustive and may include other diseases and disorders as set forth below.

**[0019]** In another embodiment, the invention further provides a pharmaceutical composition comprising a Compound of the Invention, e.g., a Compound of Formula I, or any of 1.1-1.135, or a Compound of Formula I(i) or I(ii), or any described in this specification, in free or pharmaceutically acceptable salt form, in admixture with a pharmaceutically acceptable carrier.

## DETAILED DESCRIPTION OF THE INVENTION

*Methods of Making Compounds of the Invention*

**[0020]** The Compounds of the Invention and their pharmaceutically acceptable salts may be made using the methods as described and exemplified herein and by methods similar thereto and by methods known in the chemical art. Such methods include, but not limited to, those described below. If not commercially available, starting materials for these processes may be made by procedures, which are selected from the chemical art using techniques which are similar or analogous to the synthesis of known compounds. In particular, the intermediates and starting materials for the Compounds of the Invention may be prepared by methods and processes as described in PCT/US2007/070551. All references cited herein are hereby incorporated by reference in their entirety.

**[0021]** The Compounds of the Invention include their enantiomers, diastereoisomers, tautomers and racemates, as well as their polymorphs, hydrates, solvates and complexes. Some individual compounds within the scope of this invention may contain double bonds. Representations of double bonds in this invention are meant to include both the E and the Z isomer of the double bond. In addition, some compounds within the scope of this invention may contain one or more asymmetric centers. This invention includes the use of any of the optically pure stereoisomers as well as any combination of stereoisomers.

**[0022]** It is also intended that the Compounds of the Invention encompass their stable and unstable isotopes. Stable isotopes are nonradioactive isotopes which contain one additional neutron compared to the abundant nuclides of the same species (i.e., element). It is expected that the activity of compounds comprising such isotopes would be retained, and such compound would also have utility for measuring pharmacokinetics of the non-isotopic analogs. For example, the hydrogen atom at a certain position on the Compounds of thé Invention may be replaced with deuterium

(a stable isotope which is non-raradioactive). Examples of known stable isotopes include, but not limited to, deuterium, $^{13}C$, $^{15}N$, $^{18}O$. Alternatively, unstable isotopes, which are radioactive isotopes which contain additional neutrons compared to the abundant nuclides of the same species (i.e., element), e.g., $^{123}I$, $^{131}I$, $^{125}I$, $^{11}C$, $^{18}F$, may replace the corresponding abundant species of I, C and F. Another example of useful isotope of the compound of the invention is the $^{11}C$ isotope. These radio isotopes are useful for radio-imaging and/or pharmacokinetic studies of the compounds of the invention.

**[0023]** Melting points are uncorrected and (dec) indicates decomposition. Temperature are given in degrees Celsius (°C); unless otherwise stated, operations are carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C. Chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) is carried out on silica gel plates. NMR data is in the delta values of major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard. Conventional abbreviations for signal shape are used. Coupling constants (J) are given in Hz. For mass spectra (MS), the lowest mass major ion is reported for molecules where isotope splitting results in multiple mass spectral peaks Solvent mixture compositions are given as volume percentages or volume ratios. In cases where the NMR spectra are complex, only diagnostic signals are reported.

**[0024]** Terms and abbreviations:

BuLi = n-butyllithium

Bu$^t$OH = *tert*-butyl alcohol,

CAN = ammonium cerium (IV) nitrate,

DIPEA = diisopropylethylamine,

DMF = N,N-dimethylforamide,

DMSO = dimethyl sulfoxide,

$Et_2O$ = diethyl ether,

EtOAc = ethyl acetate,

equiv. = equivalent(s),

h = hour(s),

HPLC =high performance liquid chromatography,

LDA = lithium diisopropylamide

MeOH = methanol,

NBS = N-bromosuccinimide

NCS = N-chlorosuccinimide

$NaHCO_3$ = sodium bicarbonate,

$NH_4OH$ = ammonium hydroxide,

$Pd_2(dba)_3$ = tris[dibenzylideneacetone]dipalladium(0)

PMB = p-methoxybenzyl,

$POCl_3$ = phosphorous oxychloride,

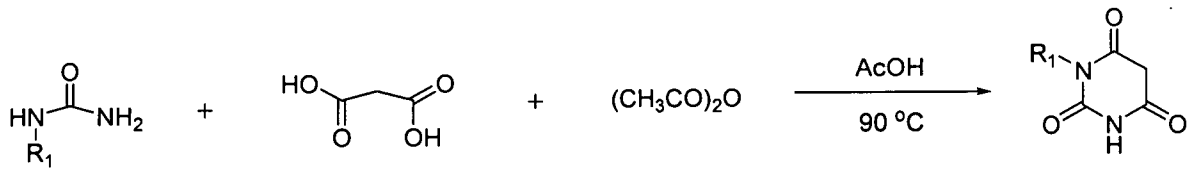
$SOCl_2$ = thionyl chloride,

TFA = trifluoroacetic acid,

THF = tetrahedrofuran.

**[0025]** The synthetic methods in this invention are illustrated below. The significances for the R groups are as set forth above for formula I unless otherwise indicated.

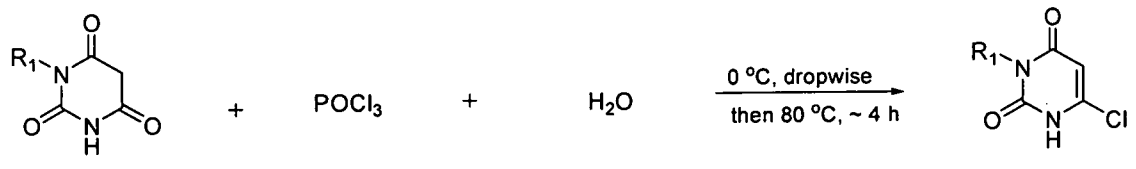
**[0026]** In an aspect of the invention, intermediate compounds of formula **IIb** can be synthesized by reacting a compound of formula **IIa** with a dicarboxylic acid, acetic anhydride and acetic acid mixing with heat for about 3 hours and then cooled:




**(IIa)** **(IIb)**

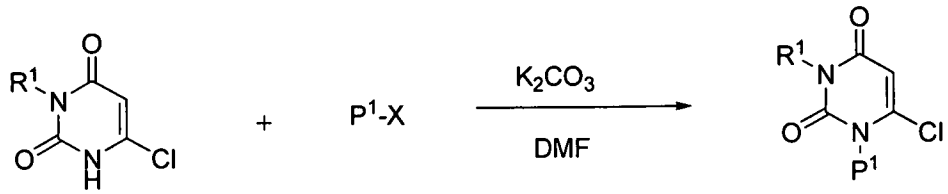
wherein $R_1$ is H or $C_{1-4}$alkyl [e.g., methyl].

**[0027]** Intermediate **IIc** can be prepared by for example reacting a compound of **IIb** with for example a chlorinating compound such as $POCl_3$, sometimes with small amounts of water and heated for about 4 hours and then cooled:




**(IIb)** **(IIc)**

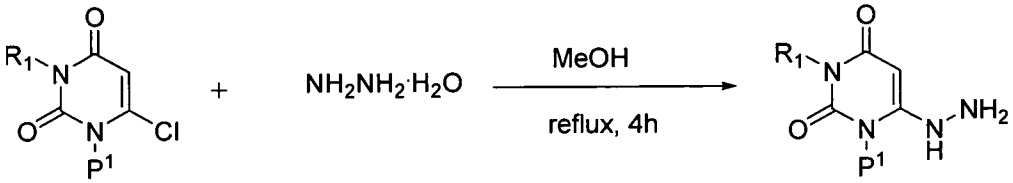
**[0028]** Intermediate **IId** may be formed by reacting a compound of **IIc** with for example a $P^1$-X in a solvent such as DMF and a base such as $K_2CO_3$ at room temperature or with heating:




**(IIc)** **(IId)**

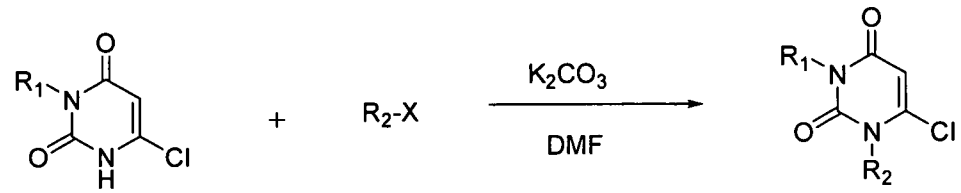
wherein $P^1$ is a protective group [e.g., *p*-methoxybenzyl group (PMB)]; X is a leaving group such as a halogen, mesylate, or tosylate.

**[0029]** Intermediate **IIe** may be prepared by reacting a compound of **IId** with hydrazine or hydrazine hydrate in a solvent such as methanol and refluxed for about 4 hours and then cooled:



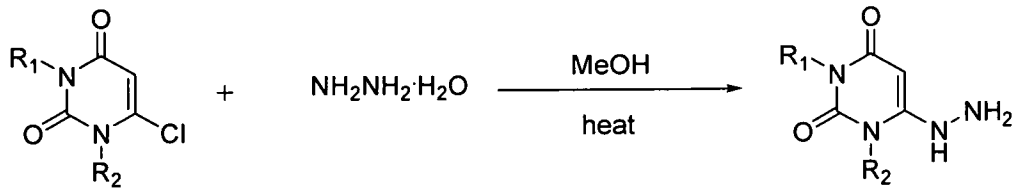

**(IId)** **(IIe)**

**[0030]** Alternatively, Intermediate **IIIa** may be formed by reacting a compound of **IIc** with for example a $R_2$-X wherein X is a leaving group such as a halogen, mesylate, or tosylate, in a solvent such as DMF and a base such as $K_2CO_3$ at room temperature or with heating:



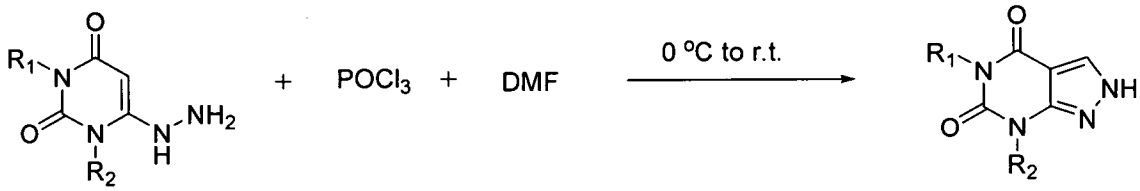

**(IIc)** **(IIIa)**

**[0031]** Intermediate **IIIb** may be prepared by reacting a compound of **IIIa** with hydrazine or hydrazine hydrate in a solvent such as methanol and heated for several hours and then cooled:



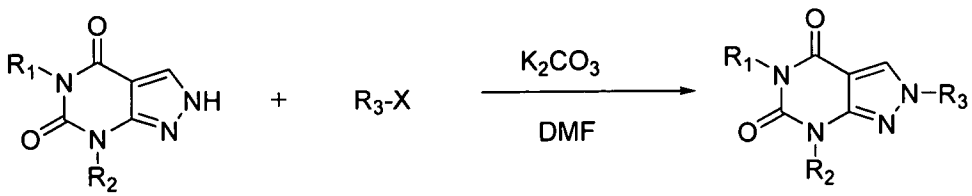

**(IIIa)** **(IIIb)**

**[0032]** Intermediate **IVa** may be formed by for example reacting a compound of **IIIb** with $POCl_3$ and DMF.



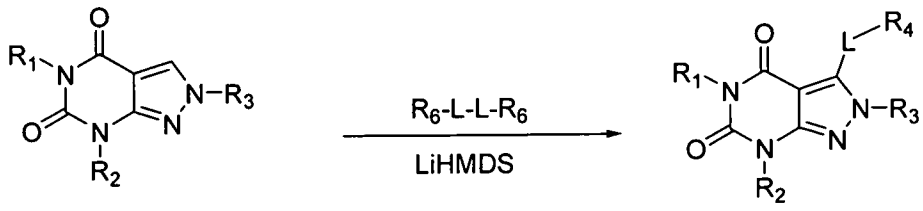

**(IIIb)** **(IVa)**

**[0033]** Intermediate **IVb** may be formed by reacting a compound of **IVa** with for example a $R_3$-X wherein X here is a leaving group, e.g., halogen, mesylate, or tosylate, in a solvent such as DMF and a base such as $K_2CO_3$ at room temperature or with heating.




**(IVa)** **(IVb)**

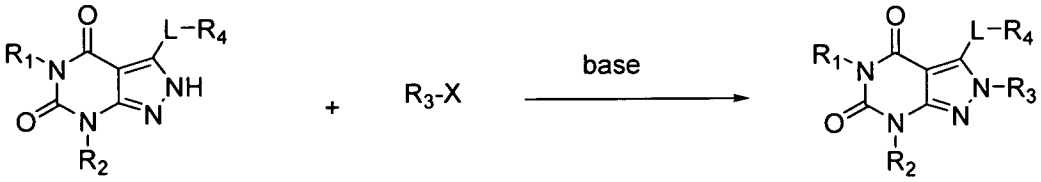
**[0034]** The thio Compounds of the Invention, e.g., Formula I wherein L is S or Compound **(I)-E** may be prepared by reacting a compound (**IVb**) with a disulfide $R_4$-L-L-$R_4$ or a thiol $R_4$-LH in the presence of a strong base, such as a lithium reagent (e.g. LiHMDS) in a solvent such as THF.




(IVb) (I)-E

**[0035]** The sulfinyl or sulfonyl derivative, e.g. Formula I wherein L is SO or $SO_2$, may be formed by reacting a 3-thio compounds **(I)-E** with an oxidizer such as a peroxide (e.g. oxone or hydrogen peroxide) at room temperature in a solvent such as acetonitrile and methanol.

**[0036]** Alternatively, a compound of Formula **(I)-E** can be prepared by reacting, for example, Compounds **1-A** with, for example, $R_3$-X, in a solvent such as DMF and a base such as $K_2CO_3$ at room temperature or with heating:




1-A (I)-E

wherein all the substituents are as defined previously; X is a leaving group such as a halogen, mesylate, or tosylate.

*Methods of using Compounds of the Invention*

**[0037]** The Compounds of the Invention are useful in the treatment of diseases characterized by disruption of or damage to cAMP and cGMP mediated pathways, e.g., as a result of increased expression of PDE1 or decreased expression of cAMP and cGMP due to inhibition or reduced levels of inducers of cyclic nucleotide synthesis, such as dopamine and nitric oxide (NO). By preventing the degradation of cAMP and cGMP by PDE1B, thereby increasing intracellular levels of cAMP and

cGMP, the Compounds of the Invention potentiate the activity of cyclic nucleotide synthesis inducers.

**[0038]** The invention provides methods of treatment of any one or more of the following conditions:

(i) Neurodegenerative diseases, including Parkinson's disease, restless leg, tremors, dyskinesias, Huntington's disease, Alzheimer's disease, and drug-induced movement disorders;

(ii) Mental disorders, including depression, attention deficit disorder, attention deficit hyperactivity disorder, bipolar illness, anxiety, sleep disorders, e.g., narcolepsy, cognitive impairment, dementia, Tourette's syndrome, autism, fragile X syndrome, psychostimulant withdrawal, and drug addiction;

(iii) Circulatory and cardiovascular disorders, including cerebrovascular disease, stroke, congestive heart disease, hypertension, pulmonary hypertension, and sexual dysfunction;

(iv) Respiratory and inflammatory disorders, including asthma, chronic obstructive pulmonary disease, and allergic rhinitis, as well as autoimmune and inflammatory diseases;

(v) Any disease or condition characterized by low levels of cAMP and/or cGMP (or inhibition of cAMP and/or cGMP signaling pathways) in cells expressing PDE1; and/or

(vi) Any disease or condition characterized by reduced dopamine D1 receptor signaling activity,

comprising administering an effective amount of a Compound of the Invention, e.g., a compound according to any of Formula I or 1.1-1.135, or a composition comprising a Compound of the Invention, e.g., a compound according to any of Formula I or 1.1-1.135, or any described in this specification, in free or pharmaceutically acceptable salt form, to a human or animal patient in need thereof. In another aspect, the invention provides a method of treatment of the conditions disclosed above comprising administering a therapeutically effective amount of a Compound of Formula II as hereinbefore described, in free or pharmaceutically acceptable salt form, to a human or animal patient in need thereof.

**[0039]** In an especially preferred embodiment, the invention provides methods of treatment or prophylaxis for narcolepsy. In this embodiment, PDE 1 Inhibitors may be used as a sole therapeutic agent, but may also be used in combination or for co-administration with other active agents. Thus, the invention further comprises a method of treating narcolepsy comprising administering simultaneously, sequentially, or contemporaneously administering therapeutically effective amounts of

(i) a PDE 1 Inhibitor of the Invention, e.g., a compound according to any of Formula I or any of 1.1-1.135, or I(i) or I(ii), or any described in this specification; and

(ii) a compound to promote wakefulness or regulate sleep, e.g., selected from (a) central nervous system stimulants-amphetamines and amphetamine like compounds, e.g., methylphenidate, dextroamphetamine, methamphetamine, and pemoline; (b) modafinil, (c) antidepressants, e.g., tricyclics (including imipramine, desipramine, clomipramine, and protriptyline) and selective serotonin reuptake inhibitors (including fluoxetine and sertraline); and/or (d) gamma hydroxybutyrate (GHB),

in free or pharmaceutically acceptable salt form, to a human or animal patient in need thereof. In another embodiment, the invention provides methods of treatment or prophylaxis for narcolepsy as herein before described, wherein the PDE1 inhibitor is in a form of a pharmaceutical composition. In still another embodiment, the methods of treatment or prophylaxis for narcolepsy as hereinbefore described, comprises administering a therapeutically effective amount of a Compound of Formula II as hereinbefore described, in free or pharmaceutically acceptable salt form, as a sole therapeutic agent or use in combination for co-administered with another active agent.

**[0040]** In another embodiment, the invention further provides methods of treatment or prophylaxis of a condition which may be alleviated by the enhancement of the progesterone signaling comprising administering an effective amount of a Compound of the Invention, e.g., a compound according to any of Formula 1.1-1.135 or Formula I, I(i) or I(ii), or any described in this specification, in free or

pharmaceutically acceptable salt form, to a human or animal patient in need thereof. The invention also provides methods of treatment as disclosed here, comprising administering a therapeutically effective amount of a Compound of Formula II, in free or pharmaceutically acceptable salt form. Disease or condition that may be ameliorated by enhancement of progesterone signaling include, but are not limited to, female sexual dysfunction, secondary amenorrhea (e.g., exercise amenorrhoea, anovulation, menopause, menopausal symptoms, hypothyroidism), pre-menstrual syndrome, premature labor, infertility, for example infertility due to repeated miscarriage, irregular menstrual cycles, abnormal uterine bleeding, osteoporosis, autoimmmune disease, multiple sclerosis, prostate enlargement, prostate cancer, and hypothyroidism. For example, by enhancing progesterone signaling, the PDE 1 inhibitors may be used to encourage egg implantation through effects on the lining of uterus, and to help maintain pregnancy in women who are prone to miscarriage due to immune response to pregnancy or low progesterone function. The novel PDE 1 inhibitors, e.g., as described herein, may also be useful to enhance the effectiveness of hormone replacement therapy, e.g., administered in combination with estrogen/estradiol/estriol and/or progesterone/progestins in postmenopausal women, and estrogen-induced endometrial hyperplasia and carcinoma. The methods of the invention are also useful for animal breeding, for example to induce sexual receptivity and/or estrus in a nonhuman female mammal to be bred.

**[0041]** In this embodiment, PDE 1 Inhibitors may be used in the foregoing methods of treatment or prophylaxis as a sole therapeutic agent, but may also be used in combination or for co-administration with other active agents, for example in conjunction with hormone replacement therapy. Thus, the invention further comprises a method of treating disorders that may be ameliorated by enhancement of progesterone signaling comprising administering simultaneously, sequentially, or contemporaneously administering therapeutically effective amounts of

(i) a PDE 1 Inhibitor, e.g., a compound according to any of Formula I, any of 1.1-1.135 or I(i) or I(ii), or any described in this specification and

(ii) a hormone, e.g., selected from estrogen and estrogen analogues (e.g., estradiol, estriol, estradiol esters) and progesterone and progesterone analogues (e.g., progestins)

in free or pharmaceutically acceptable salt form, to a human or animal patient in need thereof. In another embodiment, the invention provides the method described above wherein the PDE 1 inhibitor is a Compound of Formula II, in free or pharmaceutically acceptable salt form.

5

**[0042]** The invention also provides a method for enhancing or potentiating dopamine D1 intracellular signaling activity in a cell or tissue comprising contacting said cell or tissue with an amount of a Compound of the Invention sufficient to inhibit
10 PDE1B activity.

**[0043]** The invention also provides a method for enhancing or potentiating progesterone signaling activity in a cell or tissue comprising contacting said cell or tissue with an amount of a Compound of the Invention sufficient to inhibit PDE1B
15 activity.

**[0044]** The invention also provides a method for treating a PDE1-related, especially PDE1B-related disorder, a dopamine D1 receptor intracellular signaling pathway disorder, or disorders that may be alleviated by the enhancement of the progesterone signaling pathway in a patient in need thereof comprising administering
20 to the patient an effective amount of a Compound of the Invention that inhibits PDE1B, wherein PDE1B activity modulates phosphorylation of DARPP-32 and/or the GluR1 AMPA receptor.

**[0045]** In another aspect, the invention also provides a method for the treatment
25 for glaucoma or elevated intraocular pressure comprising topical administration of a therapeutically effective amount of a phospodiesterase type I (PDE1) Inhibitor of the Invention, in free or pharmaceutically acceptable salt form, in an opthalmically compatible carrier to the eye of a patient in need thereof. However, treatment may alternatively include a systemic therapy. Systemic therapy includes treatment that can
30 directly reach the bloodstream, or oral methods of administration, for example.

**[0046]** The invention further provides a pharmaceutical composition for topical ophthalmic use comprising a PDE1 inhibitor; for example an ophthalmic solution, suspension, cream or ointment comprising a PDE1 Inhibitor of the

Invention, in free or ophthamalogically acceptable salt form, in combination or association with an ophthamologically acceptable diluent or carrier.

**[0047]** Optionally, the PDE1 inhibitor may be administered sequentially or simultaneously with a second drug useful for treatment of glaucoma or elevated intraocular pressure. Where two active agents are administered, the therapeutically effective amount of each agent may be below the amount needed for activity as monotherapy. Accordingly, a subthreshold amount (i.e., an amount below the level necessary for efficacy as monotherapy) may be considered therapeutically effective and also may also be referred alternatively as an effective amount. Indeed, an advantage of administering different agents with different mechanisms of action and different side effect profiles may be to reduce the dosage and side effects of either or both agents, as well as to enhance or potentiate their activity as monotherapy.

**[0048]** The invention thus provides the method of treatment of a condition selected from glaucoma and elevated intraocular pressure comprising administering to a patient in need thereof an effective amount, e.g., a subthreshold amount, of an agent known to lower intraocular pressure concomitantly, simultaneously or sequentially with an effective amount, e.g., a subthreshold amount, of a PDE1 Inhibitor of the Invention, in free or pharmaceutically acceptable salt form, such that amount of the agent known to lower intraocular pressure and the amount of the PDE1 inhibitor in combination are effective to treat the condition.

**[0049]** In one embodiment, one or both of the agents are administered topically to the eye. Thus the invention provides a method of reducing the side effects of treatment of glaucoma or elevated intraocular pressure by administering a reduced dose of an agent known to lower intraocular pressure concomitantly, simultaneously or sequentially with an effective amount of a PDE1 inhibitor. However, methods other than topical administration, such as systemic therapeutic administration, may also be utilized.

**[0050]** The optional additional agent or agents for use in combination with a PDE1 inhibitor may, for example, be selected from the existing drugs comprise typically of instillation of a prostaglandin, pilocarpine, epinephrine, or topical beta-blocker treatment, e.g. with timolol, as well as systemically administered inhibitors of carbonic anhydrase, e.g. acetazolamide. Cholinesterase inhibitors such as

physostigmine and echothiopate may also be employed and have an effect similar to that of pilocarpine. Drugs currently used to treat glaucoma thus include, e.g.,

1. Prostaglandin analogs such as latanoprost (Xalatan), bimatoprost (Lumigan) and travoprost (Travatan), which increase uveoscleral outflow of aqueous humor. Bimatoprost also increases trabecular outflow.
2. Topical beta-adrenergic receptor antagonists such as timolol, levobunolol (Betagan), and betaxolol, which decrease aqueous humor production by the ciliary body.
3. Alpha$_2$-adrenergic agonists such as brimonidine (Alphagan), which work by a dual mechanism, decreasing aqueous production and increasing uveo-scleral outflow.
4. Less-selective sympathomimetics like epinephrine and dipivefrin (Propine) increase outflow of aqueous humor through trabecular meshwork and possibly through uveoscleral outflow pathway, probably by a beta$_2$-agonist action.
5. Miotic agents (parasympathomimetics) like pilocarpine work by contraction of the ciliary muscle, tightening the trabecular meshwork and allowing increased outflow of the aqueous humour.
6. Carbonic anhydrase inhibitors like dorzolamide (Trusopt), brinzolamide (Azopt), acetazolamide (Diamox) lower secretion of aqueous humor by inhibiting carbonic anhydrase in the ciliary body.
7. Physostigmine is also used to treat glaucoma and delayed gastric emptying.

**[0051]** For example, the invention provides pharmaceutical compositions comprising a PDE1 Inhibitor of the Invention and an agent selected from (i) the prostanoids, unoprostone, latanoprost, travoprost, or bimatoprost; (ii) an alpha adrenergic agonist such as brimonidine, apraclonidine, or dipivefrin and (iii) a muscarinic agonist, such as pilocarpine. For example, the invention provides ophthalmic formulations comprising a PDE-1 Inhibitor of the Invention together with bimatoprost, abrimonidine, brimonidine, timolol, or combinations thereof, in free or ophthamalogically acceptable salt form, in combination or association with an ophthamologically acceptable diluent or carrier. In addition to selecting a combination, however, a person of ordinary skill in the art can select an appropriate selective receptor subtype agonist or antagonist. For example, for alpha adrenergic agonist, one can select an agonist selective for an alpha 1 adrenergic receptor, or an

agonist selective for an alpha$_2$ adrenergic receptor such as brimonidine, for example. For a beta-adrenergic receptor antagonist, one can select an antagonist selective for either $\beta_1$, or $\beta_2$, or $\beta_3$, depending on the appropriate therapeutic application. One can also select a muscarinic agonist selective for a particular receptor subtype such as $M_1$-$M_5$.

**[0052]** The PDE 1 inhibitor may be administered in the form of an ophthalmic composition, which includes an ophthalmic solution, cream or ointment. The ophthalmic composition may additionally include an intraocular-pressure lowering agent.

**[0053]** In yet another example, the PDE-1 Inhibitors disclosed may be combined with a subthreshold amount of an intraocular pressure-lowering agent which may be a bimatoprost ophthalmic solution, a brimonidine tartrate ophthalmic solution, or brimonidine tartrate/timolol maleate ophthalmic solution.

**[0054]** In addition to the above-mentioned methods, it has also been surprisingly discovered that PDE1 inhibitors are useful to treat psychosis, for example, any conditions characterized by psychotic symptoms such as hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, e.g., schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder, delusional disorder, and mania, such as in acute manic episodes and bipolar disorder. Without intending to be bound by any theory, it is believed that typical and atypical antipsychotic drugs such as clozapine primarily have their antagonistic activity at the dopamine D2 receptor. PDE1 inhibitors, however, primarily act to enhance signaling at the dopamine D1 receptor. By enhancing D1 receptor signaling, PDE1 inhibitors can increase NMDA receptor function in various brain regions, for example in nucleus accumbens neurons and in the prefrontal cortex. This enhancement of function may be seen for example in NMDA receptors containing the NR2B subunit, and may occur e.g., via activation of the Src and protein kinase A family of kinases.

**[0055]** Therefore, the invention provides a new method for the treatment of psychosis, e.g., schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder, delusional disorder, and mania, such as in acute manic episodes and bipolar disorder, comprising administering a therapeutically effective amount of a

phosphodiesterase-1 (PDE1) Inhibitor of the Invention, in free or pharmaceutically acceptable salt form, to a patient in need thereof.

**[0056]** PDE 1 Inhibitors may be used in the foregoing methods of treatment prophylaxis as a sole therapeutic agent, but may also be used in combination or for co-administration with other active agents. Thus, the invention further comprises a method of treating psychosis, e.g., schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder, delusional disorder, or mania, comprising administering simultaneously, sequentially, or contemporaneously administering therapeutically effective amounts of:

(i) a PDE 1 Inhibitor of the invention, in free or pharmaceutically acceptable salt form; and

(ii) an antipsychotic, e.g.,

Typical antipsychotics, e.g.,

Butyrophenones, e.g. Haloperidol (Haldol, Serenace), Droperidol (Droleptan);

Phenothiazines, e.g., Chlorpromazine (Thorazine, Largactil), Fluphenazine (Prolixin), Perphenazine (Trilafon), Prochlorperazine (Compazine), Thioridazine (Mellaril, Melleril), Trifluoperazine (Stelazine), Mesoridazine, Periciazine, Promazine, Triflupromazine (Vesprin), Levomepromazine (Nozinan), Promethazine (Phenergan), Pimozide (Orap);

Thioxanthenes, e.g., Chlorprothixene, Flupenthixol (Depixol, Fluanxol), Thiothixene (Navane), Zuclopenthixol (Clopixol, Acuphase);

Atypical antipsychotics, e.g.,

Clozapine (Clozaril), Olanzapine (Zyprexa), Risperidone (Risperdal), Quetiapine (Seroquel), Ziprasidone (Geodon), Amisulpride (Solian), Paliperidone (Invega), Aripiprazole (Abilify), Bifeprunox; norclozapine,

in free or pharmaceutically acceptable salt form, to a patient in need thereof.

**[0057]** In a particular embodiment, the Compounds of the Invention are particularly useful for the treatment or prophylaxis of schizophrenia.

**[0058]** Compounds of the Invention, in free or pharmaceutically acceptable salt form, are particularly useful for the treatment of Parkinson's disease, schizophrenia, narcolepsy, glaucoma and female sexual dysfunction.

**[0059]** In still another aspect, the invention provides a method of lengthening or enhancing growth of the eyelashes by administering an effective amount of a prostaglandin analogue, e.g., bimatoprost, concomitantly, simultaneously or sequentially with an effective amount of a PDE1 inhibitor of the Invention, in free or pharmaceutically acceptable salt form, to the eye of a patient in need thereof.

**[0060]** In yet another aspect, the invention provides a method for the treatment or prophylaxis of traumatic brain injury comprising administering a therapeutically effective amount of a PDE1 inhibitor of the invention, in free or pharmaceutically acceptable salt form, to a patient in need thereof. Traumatic brain injury (TBI) encompasses primary injury as well as secondary injury, including both focal and diffuse brain injuries. Secondary injuries are multiple, parallel, interacting and interdependent cascades of biological reactions arising from discrete subcellular processes (e.g., toxicity due to reactive oxygen species, overstimulation of glutamate receptors, excessive influx of calcium and inflammatory upregulation) which are caused or exacerbated by the inflammatory response and progress after the initial (primary) injury. Abnormal calcium homeostasis is believed to be a critical component of the progression of secondary injury in both grey and white matter. For a review of TBI, see Park et al., CMAJ (2008) 178(9):1163-1170, the contents of which are incorporated herein in their entirety. Studies have shown that the cAMP–PKA signaling cascade is downregulated after TBI and treatment of PDE IV inhibitors such as rolipram to raise or restore cAMP level improves histopathological outcome and decreases inflammation after TBI. As Compounds of the present invention is a PDE1 inhibitor, it is believed that these compounds are also useful for the treatment of TBI, e.g., by restoring cAMP level and/or calcium homeostasis after traumatic brain injury.

**[0061]** The present invention also provides

(i) a Compound of the Invention for use as a pharmaceutical, for example for use in any method or in the treatment of any disease or condition as hereinbefore set forth,

(ii) the use of a Compound of the Invention in the manufacture of a medicament for treating any disease or condition as hereinbefore set forth,

(iii) a pharmaceutical composition comprising a Compound of the Invention in combination or association with a pharmaceutically acceptable diluent or carrier, and

(iv) a pharmaceutical composition comprising a Compound of the Invention in combination or association with a pharmaceutically acceptable diluent or carrier for use in the treatment of any disease or condition as hereinbefore set forth.

**[0062]** Therefore, the invention provides use of a Compound of the Invention for the manufacture of a medicament for the treatment or prophylactic treatment of the following diseases: Parkinson's disease, restless leg, tremors, dyskinesias, Huntington's disease, Alzheimer's disease, and drug-induced movement disorders; depression, attention deficit disorder, attention deficit hyperactivity disorder, bipolar illness, anxiety, sleep disorder, narcolepsy, cognitive impairment, dementia, Tourette's syndrome, autism, fragile X syndrome, psychostimulant withdrawal, and/or drug addiction; cerebrovascular disease, stroke, congestive heart disease, hypertension, pulmonary hypertension, and/or sexual dysfunction; asthma, chronic obstructive pulmonary disease, and/or allergic rhinitis, as well as autoimmune and inflammatory diseases; and/or female sexual dysfunction, exercise amenorrhoea, anovulation, menopause, menopausal symptoms, hypothyroidism, pre-menstrual syndrome, premature labor, infertility, irregular menstrual cycles, abnormal uterine bleeding, osteoporosis, multiple sclerosis, prostate enlargement, prostate cancer, hypothyroidism, estrogen-induced endometrial hyperplasia or carcinoma; and/or any disease or condition characterized by low levels of cAMP and/or cGMP (or inhibition of cAMP and/or cGMP signaling pathways) in cells expressing PDE1, and/or by reduced dopamine D1 receptor signaling activity; and/or any disease or condition that may be ameliorated by the enhancement of progesterone signaling;.

**[0063]** The invention also provides use of a Compound of the Invention, in free or pharmaceutically acceptable salt form, for the manufacture of a medicament for the treatment or prophylactic treatment of:

a) glaucoma or elevated intraocular pressure,

b) psychosis, for example, any conditions characterized by psychotic symptoms such as hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, e.g., schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder, delusional disorder, and mania, such as in acute manic episodes and bipolar disorder,

c) traumatic brain injury.

**[0064]** The phrase "Compounds of the Invention" or "PDE 1 inhibitors of the Invention" encompasses any and all of the compounds disclosed within this specification.

**[0065]** The words "treatment" and "treating" are to be understood accordingly as embracing prophylaxis and treatment or amelioration of symptoms of disease as well as treatment of the cause of the disease

**[0066]** For methods of treatment, the word "effective amount" is intended to encompass a therapeutically effective amount to treat a specific disease or disorder.

**[0067]** The term "pulmonary hypertension" is intended to encompass pulmonary arterial hypertension.

**[0068]** The term "patient" include human or non-human (i.e., animal) patient. In particular embodiment, the invention encompasses both human and nonhuman. In another embodiment, the invention encompasses nonhuman. In other embodiment, the term encompasses human.

**[0069]** The term "comprising" as used in this disclosure is intended to be open-ended and does not exclude additional, unrecited elements or method steps.

**[0070]** Compounds of the Invention are in particular useful for the treatment of Parkinson's disease, narcolepsy and female sexual dysfunction.

**[0071]** Compounds of the Invention may be used as a sole therapeutic agent, but may also be used in combination or for co-administration with other active agents. For example, as Compounds of the Invention potentiate the activity of D1 agonists, such as dopamine, they may be simultaneously, sequentially, or contemporaneously administered with conventional dopaminergic medications, such as levodopa and

levodopa adjuncts (carbidopa, COMT inhibitors, MAO-B inhibitors), dopamine agonists, and anticholinergics, e.g., in the treatment of a patient having Parkinson's disease. In addition, the novel PDE 1 inhibitors of the Invention, e.g., the Compounds of the Invention as described herein, may also be administered in combination with estrogen/estradiol/estriol and/or progesterone/progestins to enhance the effectiveness of hormone replacement therapy or treatment of estrogen-induced endometrial hyperplasia or carcinoma.

**[0072]** Dosages employed in practicing the present invention will of course vary depending, e.g. on the particular disease or condition to be treated, the particular Compound of the Invention used, the mode of administration, and the therapy desired. Compounds of the Invention may be administered by any suitable route, including orally, parenterally, transdermally, or by inhalation, but are preferably administered orally. In general, satisfactory results, e.g. for the treatment of diseases as hereinbefore set forth are indicated to be obtained on oral administration at dosages of the order from about 0.01 to 2.0 mg/kg. In larger mammals, for example humans, an indicated daily dosage for oral administration will accordingly be in the range of from about 0.75 to 150 mg, conveniently administered once, or in divided doses 2 to 4 times, daily or in sustained release form. Unit dosage forms for oral administration thus for example may comprise from about 0.2 to 75 or 150 mg, e.g. from about 0.2 or 2.0 to 50, 75 or 100 mg of a Compound of the Invention, together with a pharmaceutically acceptable diluent or carrier therefor.

**[0073]** Pharmaceutical compositions comprising Compounds of the Invention may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets, capsules, solutions, suspensions and the like.

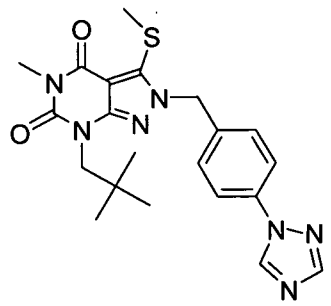
## EXAMPLES

**[0074]** The synthetic methods for various Compounds of the Present Invention are illustrated below. Other compounds of the Invention and their salts may be made using the methods as similarly described below and/or by methods similar to those

generally described in the detailed description and by methods known in the chemical art.

**Example 1:**

**2-(4-(1H-1,2,4-triazol-1-yl)benzyl)-5-methyl-3-(methylthio)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**1) 2-(4-(1H-1,2,4-triazol-1-yl)benzyl)-5-methyl-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**

**[0075]** 5-methyl-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (200 mg, 0.847 mmol), 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole (202 mg, 0.847 mmol) and $K_2CO_3$ (117 mg, 0.847 mmol) are suspended in 5 mL of anhydrous DMF. The reaction mixture is stirred at room temperature for 5 h, and then evaporated to dryness under reduced pressure. The residue is treated with water, and then extracted with dichloromethane three times. The combined organic phase is dried with anhydrous sodium sulfate, filtered, and then evaporated to dryness to give 337 mg of crude product, which is used in the next step without further purification. MS (ESI) m/z 394.2 $[M+H]^+$.

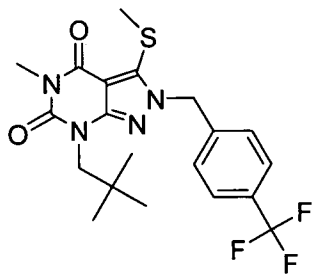
**2) 2-(4-(1H-1,2,4-triazol-1-yl)benzyl)-5-methyl-3-(methylthio)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**

**[0076]** 2-(4-(1H-1,2,4-triazol-1-yl)benzyl)-5-methyl-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (52 mg, 0.132 mmol) and methyl disulfide (12 μL, 0.13 mmol) are dissolved in 2 mL of anhydrous $CH_2Cl_2$, and then 1.0 M LiHMDS (190 μL, 0.19 mmol) in THF is added dropwise. The reaction mixture is stirred at room temperature for 30 min, and then quenched with saturated ammonium chloride aqueous solution. After routine workup, the obtained crude

product is purified by silica gel column chromatography to give pure product as off-white solids. MS (ESI) m/z 440.2 $[M+H]^+$.

**Example 2:**

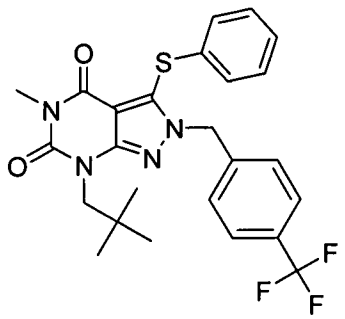
**5-methyl-3-(methylthio)-7-neopentyl-2-(4-(trifluoromethyl)benzyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0077]** The synthetic procedure of this compound is analogous to **EXAMPLE 1** wherein 1-(bromomethyl)-4-(trifluoromethyl)benzene is used in step 1 instead of 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole. MS (ESI) m/z 441.2 $[M+H]^+$.

**Example 3:**

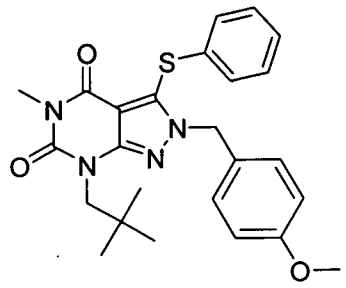
**5-methyl-7-neopentyl-3-(phenylthio)-2-(4-(trifluoromethyl)benzyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0078]** The synthetic procedure of this compound is analogous to **EXAMPLE 1** wherein 1-(bromomethyl)-4-(trifluoromethyl)benzene is used in step 1 instead of 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole, and phenyl disulfide is used in step 2 instead of methyl disulfide. MS (ESI) m/z 503.2 $[M+H]^+$.

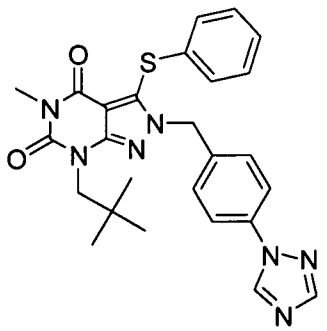
**Example 4:**

**2-(4-methoxybenzyl)-5-methyl-7-neopentyl-3-(phenylthio)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0079]** The synthetic procedure of this compound is analogous to **EXAMPLE 1** wherein 4-methoxybenzyl bromide is used in step 1 instead of 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole, and phenyl disulfide is used in step 2 instead of methyl disulfide. MS (ESI) m/z 465.2 $[M+H]^+$.

**Example 5:**
**2-(4-(1H-1,2,4-triazol-1-yl)benzyl)-5-methyl-7-neopentyl-3-(phenylthio)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**

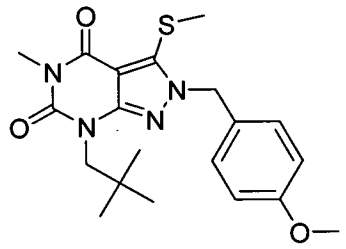


**[0080]** 2-(4-methoxybenzyl)-5-methyl-7-neopentyl-3-(phenylthio)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (2.7 g, 5.9 mmol) is dissolved in $CH_2Cl_2$ (20 mL) containing TFA (4.2 mL) and TFMSA (1.0 mL). The mixture is stirred at room temperature overnight. Solvents are removed, and the residue is dissolved in ethyl acetate (250 mL), followed by washing with saturate $NaHCO_3$ and water successively. After dried over anhydrous sodium sulfate, the organic phase is evaporated to dryness. The obtained crude product is used in the next step without further purification.

**[0081]** Crude 5-methyl-7-neopentyl-3-(phenylthio)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (40 mg, 0.12 mmol), 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole (28 mg, 0.12 mmol) and $K_2CO_3$ (16 mg, 0.12 mmol) are suspended in 5 mL of anhydrous DMF. The reaction mixture is stirred at room temperature overnight, and then evaporated to dryness under reduced pressure. The residue is purified by silica gel column chromatography to give pure product as white solids. MS (ESI) m/z 502.2 $[M+H]^+$.

**Example 6:**

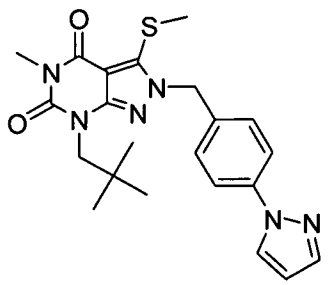
**2-(4-methoxybenzyl)-5-methyl-3-(methylthio)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0082]** The synthetic procedure of this compound is analogous to **EXAMPLE 1** wherein 4-methoxybenzyl bromide is used in step 1 instead of 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole. MS (ESI) m/z 403.2 $[M+H]^+$.

**Example 7:**

**2-(4-(1H-pyrazol-1-yl)benzyl)-5-methyl-3-(methylthio)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**

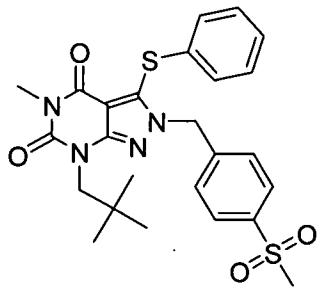


**[0083]** The synthetic procedure of this compound is analogous to **EXAMPLE 5** wherein 2-(4-methoxybenzyl)-5-methyl-3-(methylthio)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione is used instead of 2-(4-methoxybenzyl)-

5-methyl-7-neopentyl-3-(phenylthio)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, and 1-(4-(bromomethyl)phenyl)-1H-pyrazole is used instead of 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole. MS (ESI) m/z 439.2 $[M+H]^+$.

**Example 8:**

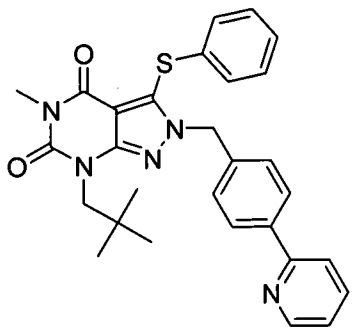
**5-methyl-2-(4-(methylsulfonyl)benzyl)-7-neopentyl-3-(phenylthio)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0084]** The synthetic procedure of this compound is analogous to **EXAMPLE 5** wherein 1-(bromomethyl)-4-(methylsulfonyl)benzene is used instead of 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole. MS (ESI) m/z 513.2 $[M+H]^+$.

**Example 9:**

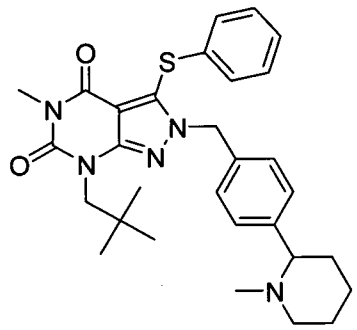
**5-methyl-7-neopentyl-3-(phenylthio)-2-(4-(pyridin-2-yl)benzyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0085]** The synthetic procedure of this compound is analogous to **EXAMPLE 1** wherein 2-(4-(bromomethyl)phenyl)pyridine is used in step 1 instead of 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole, and phenyl disulfide is used in step 2 instead of methyl disulfide. MS (ESI) m/z 512.3 $[M+H]^+$.

**Example 10:**

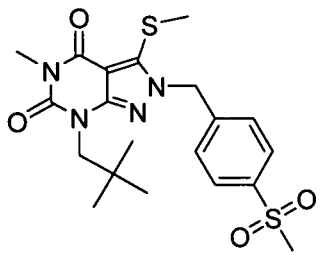
**5-methyl-2-(4-(1-methylpiperidin-2-yl)benzyl)-7-neopentyl-3-(phenylthio)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0086]** The synthetic procedure of this compound is analogous to **EXAMPLE 5** wherein 2-(4-(chloromethyl)phenyl)-1-methylpiperidine is used instead of 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole. MS (ESI) m/z 532.3 $[M+H]^+$.

**Example 11:**

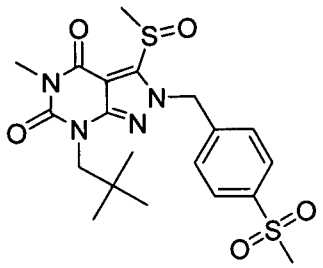
**5-methyl-2-(4-(methylsulfonyl)benzyl)-3-(methylthio)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0087]** The synthetic procedure of this compound is analogous to **EXAMPLE 5** wherein 2-(4-methoxybenzyl)-5-methyl-3-(methylthio)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione is used instead of 2-(4-methoxybenzyl)-5-methyl-7-neopentyl-3-(phenylthio)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, and 1-(bromomethyl)-4-(methylsulfonyl)benzene is used instead of 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole. MS (ESI) m/z 451.1 $[M+H]^+$.

**Example 12:**

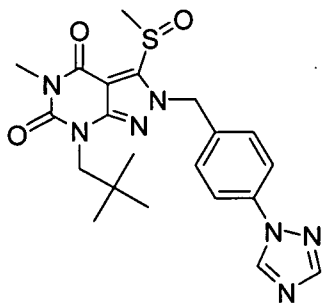
**5-methyl-3-(methylsulfinyl)-2-(4-(methylsulfonyl)benzyl)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0088]** 5-methyl-2-(4-(methylsulfonyl)benzyl)-3-(methylthio)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (11.4 mg, 0.022 mmol) is dissolved in $CH_2Cl_2$ (200 μL) and $CH_3CN$ (100 μL), and then 30% $H_2O_2$ aqueous solution (75 μL, 0.66 mmol) is added, followed by acetic acid (6.6 mg, 0.11 mmol). The reaction mixture is stirred at room temperature over a weekend, and then purified by a semi-preparative HPLC to give 6 mg of product as white solids. MS (ESI) m/z 467.1 $[M+H]^+$.

**Example 13:**

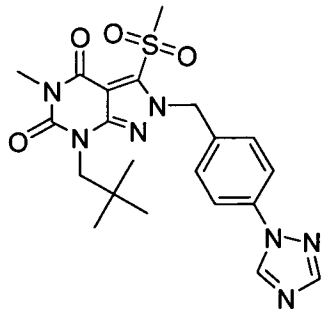
**2-(4-(1H-1,2,4-triazol-1-yl)benzyl)-5-methyl-3-(methylsulfinyl)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0089]** 2-(4-(1H-1,2,4-triazol-1-yl)benzyl)-5-methyl-3-(methylthio)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (16 mg, 0.036 mmol) is dissolved in $CH_2Cl_2$ (500 μL) and MeOH (500 μL), and then an aqueous solution of Oxone (22.4 mg, 0.036 mmol) is added. The reaction mixture is stirred at room temperature for 2 days, and then purified by a semi-preparative HPLC to give 8 mg of product as off-white solids. MS (ESI) m/z 456.2 $[M+H]^+$.

**Example 14:**

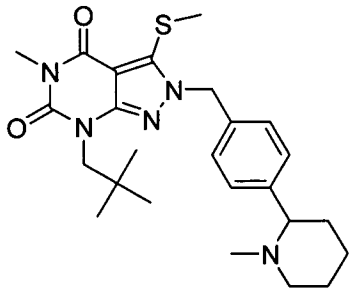
**2-(4-(1H-1,2,4-triazol-1-yl)benzyl)-5-methyl-3-(methylsulfonyl)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0090]** The synthetic procedure of this compound is the same as **EXAMPLE 13**. 2-(4-(1H-1,2,4-triazol-1-yl)benzyl)-5-methyl-3-(methylsulfonyl)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione is obtained as a minor product of the reaction. MS (ESI) m/z 472.2 $[M+H]^+$.

**Example 15:**

**5-methyl-2-(4-(1-methylpiperidin-2-yl)benzyl)-3-(methylthio)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**



**[0091]** The synthetic procedure of this compound is analogous to **EXAMPLE 5** wherein 2-(4-methoxybenzyl)-5-methyl-3-(methylthio)-7-neopentyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione is used instead of 2-(4-methoxybenzyl)-5-methyl-7-neopentyl-3-(phenylthio)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, and 2-(4-(chloromethyl)phenyl)-1-methylpiperidine is used instead of 1-(4-(bromomethyl)phenyl)-1H-1,2,4-triazole. MS (ESI) m/z 439.2 $[M+H]^+$.

**EXAMPLE 16**

**Measurement of PDE1B inhibition *in vitro* using IMAP Phosphodiesterase Assay Kit**

**[0092]** Phosphodiesterase 1B (PDE1B) is a calcium/calmodulin dependent phosphodiesterase enzyme that converts cyclic guanosine monophosphate (cGMP) to 5'-guanosine monophosphate (5'-GMP). PDE1B can also convert a modified cGMP substrate, such as the fluorescent molecule cGMP-fluorescein, to the corresponding GMP-fluorescein. The generation of GMP-fluorescein from cGMP-fluorescein can be quantitated, using, for example, the IMAP (Molecular Devices, Sunnyvale, CA) immobilized-metal affinity particle reagent.

**[0093]** Briefly, the IMAP reagent binds with high affinity to the free 5'-phosphate that is found in GMP-fluorescein and not in cGMP-fluorescein. The resulting GMP-fluorescein – IMAP complex is large relative to cGMP-fluorescein. Small fluorophores that are bound up in a large, slowly tumbling, complex can be distinguished from unbound fluorophores, because the photons emitted as they fluoresce retain the same polarity as the photons used to excite the fluorescence.

**[0094]** In the phosphodiesterase assay, cGMP-fluorescein, which cannot be bound to IMAP, and therefore retains little fluorescence polarization, is converted to GMP-fluorescein, which, when bound to IMAP, yields a large increase in fluorescence polarization (Δmp). Inhibition of phosphodiesterase, therefore, is detected as a decrease in Δmp.

**[0095]** Enzyme assay

Materials: All chemicals are available from Sigma-Aldrich (St. Louis, MO) except for IMAP reagents (reaction buffer, binding buffer, FL-GMP and IMAP beads), which are available from Molecular Devices (Sunnyvale, CA).

Assay: 3',5'-cyclic-nucleotide-specific bovine brain phosphodiesterase (Sigma, St. Louis, MO) is reconstituted with 50% glycerol to 2.5 U/ml. One unit of enzyme will hydrolyze 1.0 μmole of 3',5'-cAMP to 5'-AMP per min at pH 7.5 at 30°C. One part enzyme is added to 1999 parts reaction buffer (30 μM $CaCl_2$, 10 U/ml of calmodulin (Sigma P2277), 10mM Tris-HCl pH 7.2, 10mM $MgCl_2$, 0.1% BSA, 0.05% $NaN_3$) to yield a final concentration of 1.25mU/ml. 99 μl of diluted enzyme solution is added into each well in a flat bottom 96-well polystyrene plate to which 1 μl of test compound dissolved in 100% DMSO is added. Selected Compounds of the Invention are mixed and pre-incubated with the enzyme for 10 min at room temperature.

**[0096]** The FL-GMP conversion reaction is initiated by combining 4 parts enzyme and inhibitor mix with 1 part substrate solution (0.225 μM) in a 384-well

microtiter plate. The reaction is incubated in dark at room temperature for 15 min. The reaction is halted by addition of 60 µl of binding reagent (1:400 dilution of IMAP beads in binding buffer supplemented with 1:1800 dilution of antifoam) to each well of the 384-well plate. The plate is incubated at room temperature for 1 hour to allow IMAP binding to proceed to completion, and then placed in an Envision multimode microplate reader (PerkinElmer, Shelton, CT) to measure the fluorescence polarization (Δmp).

**[0097]** A decrease in GMP concentration, measured as decreased Δmp, is indicative of inhibition of PDE activity. $IC_{50}$ values are determined by measuring enzyme activity in the presence of 8 to 16 concentrations of compound ranging from 0.0037 nM to 80,000 nM and then plotting drug concentration versus ΔmP, which allows $IC_{50}$ values to be estimated using nonlinear regression software (XLFit; IDBS, Cambridge, MA).

**[0098]** The Compounds of the Invention may be selected and tested in an assay as described or similarly described herein for PDE1 inhibitory activity. The exemplified compounds of the invention generally have $IC_{50}$ values of less than 5µM, some less than 1µM, some less than 250nM, some with PDE1A activities.

**Example 17**

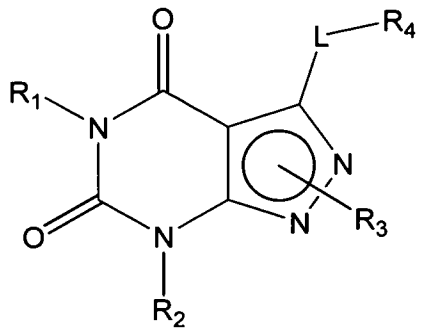
**PDE1 inhibitor effect on sexual response in female rats**

**[0099]** The effect of PDE1 inhibitors on Lordosis Response in female rats is measured as described in Mani, et al., Science (2000) 287: 1053. Ovariectomized and cannulated wild-type rats are primed with 2 µg estrogen followed 24 hours later by intracerebroventricular (icv) injection of progesterone (2 µg), PDE1 inhibitors of the present invention (0.1mg, 1.0mg or 2.5mg) or sesame oil vehicle (control). The rats are tested for lordosis response in the presence of male rats. Lordosis response is quantified by the lordosis quotient (LQ = number of lordosis/10 mounts x 100). The LQ for estrogen-primed female rats receiving Compounds of the Invention, at 0.1 mg, will likely be similar to estrogen-primed rats receiving progesterone and higher than for estrogen-primed rats receiving vehicle.

CLAIMS

What is claimed is:

1. A compound of Formula II:



Formula II

wherein

(i) L is S, SO or $SO_2$;

(ii) $R_1$ is H or $C_{1-6}$alkyl (e.g., methyl or ethyl);

(iii) $R_2$ is

H,

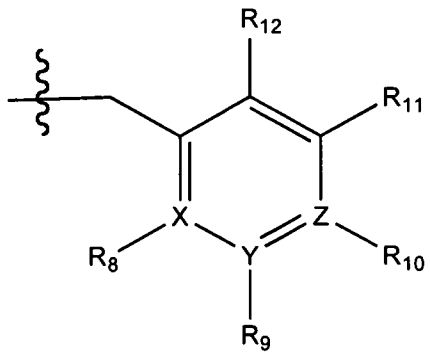
$C_{1-6}$alkyl (e.g., isopropyl, isobutyl, neopentyl, 2-methylbutyl, 2,2-dimethylpropyl) wherein said alkyl group is optionally substituted with halo (e.g., fluoro) or hydroxy (e.g., 1-hydroxypropan-2-yl, 3-hydroxy-2-methylpropyl),

–$C_{0-4}$alkyl-$C_{3-8}$cycloalkyl (e.g., cyclopentyl, cyclohexyl) optionally substituted with one or more amino (e.g., -$NH_2$), for example, 2-aminocyclopentyl or 2-aminocyclohexyl),wherein said cycloalkyl optionally contains one or more heteroatom selected from N and O and is optionally substituted with $C_{1-6}$alkyl (e.g., 1-methyl-pyrrolindin-2-yl, 1-methyl-pyrrolindin-3-yl, 1-methyl-pyrrolindin-2-yl-methyl or 1-methyl-pyrrolindin-3-yl-methyl),

$C_{3-8}$heterocycloalkyl (e.g., pyrrolidinyl, for example, pyrrolidin-3-yl) optionally substituted with $C_{1-6}$alkyl (e.g., methyl), for example, 1-methylpyrrolidin-3-yl,

$C_{3-8}$cycloalkyl-$C_{1-6}$alkyl (e.g.,cyclopropylmethyl),
halo$C_{1-6}$alkyl (e.g., trifluoromethyl, 2,2,2-trifluoroethyl),
-N($R_{14}$)($R_{15}$)-$C_{1-6}$alkyl (e.g., 2-(dimethylamino)ethyl,2-aminopropyl),
hydroxy$C_{1-6}$alkyl (e.g., (e.g., 3-hydroxy-2-methylpropyl, 1-hydroxyprop-2-yl),
aryl$C_{0-6}$alkyl (e.g., benzyl),
heteroaryl$C_{1-6}$alkyl (e.g., pyridinylmethyl),
$C_{1-6}$alkoxyaryl$C_{1-6}$alkyl (e.g., 4-methoxybenzyl);
-G-J wherein:
G is a single bond or, alkylene (e.g., methylene);
J is cycloalkyl or heterocycloalkyl (e.g., oxetan-2-yl, pyrolyin-3-yl, pyrolyin-2-yl) optionally substituted with $C_{1-6}$alkyl (e.g., (1-methylpyrolidin-2-yl));

(iv) $R_3$ is attached to one of the nitrogens on the pyrazolo portion of Formula I and is a moiety of Formula A




Formula A

wherein X, Y and Z are, independently, N or C, and $R_8$, $R_9$, $R_{11}$ and $R_{12}$ are independently H or halogen (e.g., Cl or F); and $R_{10}$ is
halogen,
$C_{1-6}$alkyl,
$C_{3-8}$cycloalkyl,
hetero$C_{3-8}$cycloalkyl (e.g., pyrrolidinyl or piperidinyl),
halo$C_{1-6}$alkyl (e.g., trifluoromethyl),
aryl (e.g., phenyl),

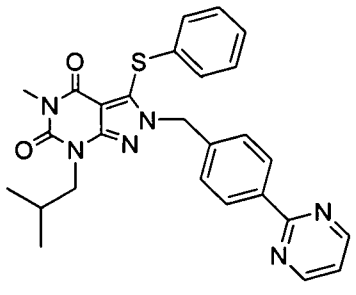
heteroaryl (e.g., pyridyl, (for example, pyrid-2-yl) or e.g., thiadiazolyl (for example, 1,2,3-thiadiazol-4-yl), diazolyl, triazolyl (e.g., 1,2,4-triazol-1-yl), tetrazolyl (e.g., tetrazol-5-yl), alkoxadiazolyl (e.g., 5-methyl-1,2,4-oxadiazol), pyrazolyl (e.g., pyrazol-1-yl),
alkyl sulfonyl (e.g., methyl sulfonyl),
arylcarbonyl (e.g., benzoyl), or
heteroarylcarbonyl,
alkoxycarbonyl, (e.g., methoxycarbonyl),
aminocarbonyl;
preferably $R_{10}$ is phenyl, pyridyl, e.g., 2-pyridyl, pyrrolidinyl or piperidinyl,
wherein the aryl, heteroaryl, cycloalkyl or heterocycloalkyl is optionally substituted with one or more halo (e.g., F or Cl), $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$haloalkyl (e.g., trifluoromethyl), and/or –SH,
provided that when X, Y or X is nitrogen, $R_8$, $R_9$ or $R_{10}$, respectively, is not present;

(v) $R_4$ is
H,
$C_{1-6}$alkyl (e.g., methyl, isopropyl),
$C_{3-8}$cycloalkyl (e.g., cyclopentyl),
$C_{3-8}$heterocycloalkyl (e.g., pyrrolidin-3-yl),
aryl (e.g., phenyl) or heteroaryl (e.g., pyrid-4-yl, pyrid-2-yl or pyrazol-3-yl) wherein said aryl or heteroaryl is optionally substituted with halo (e.g., 4-fluorophenyl), hydroxy (e.g., 4-hydroxyphenyl), $C_{1-6}$alkyl, $C_{1-6}$alkoxy or another aryl group (e.g., biphenyl-4-ylmethyl);

(vi) $R_{14}$ and $R_{15}$ are independently H or $C_{1-6}$alkyl,

in free or salt form.

2. The compound according to claim 1 selected from: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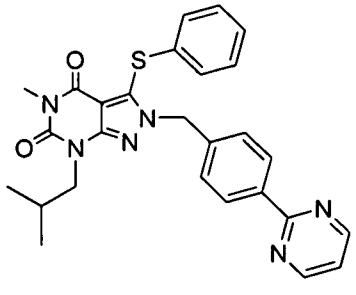
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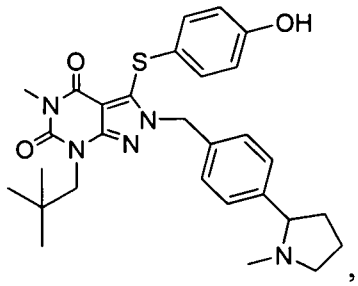
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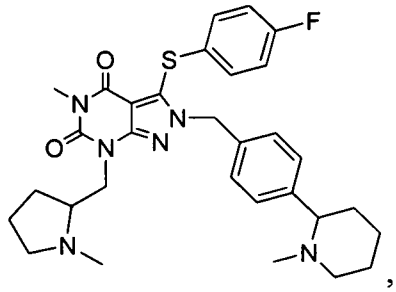
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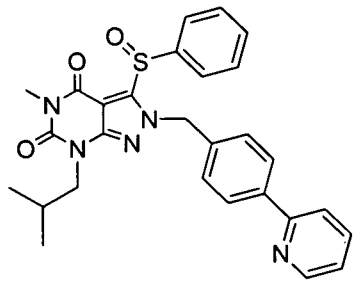
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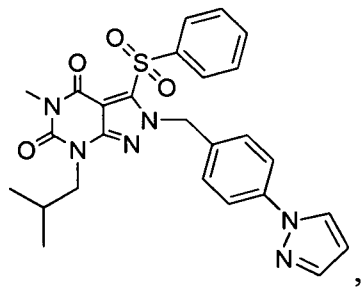
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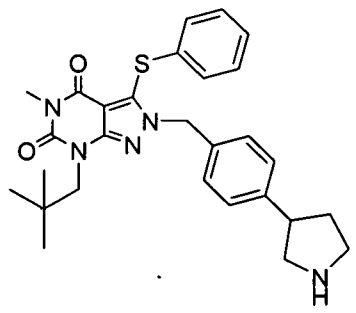
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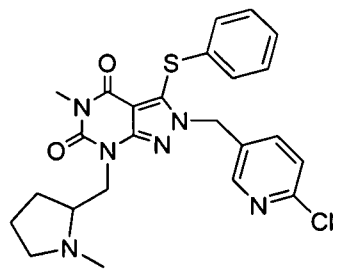
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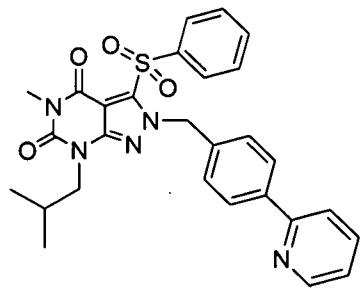
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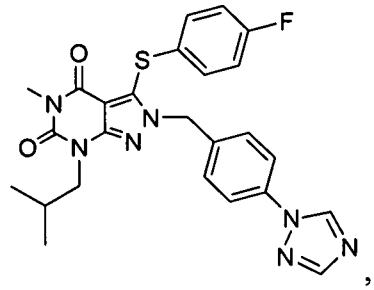
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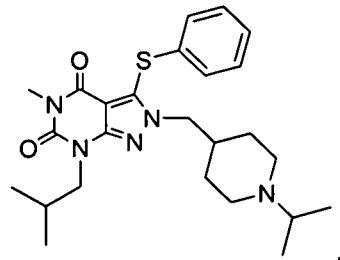
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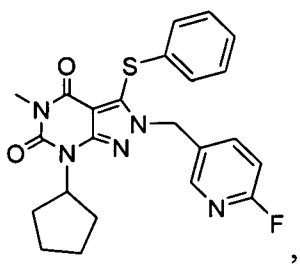
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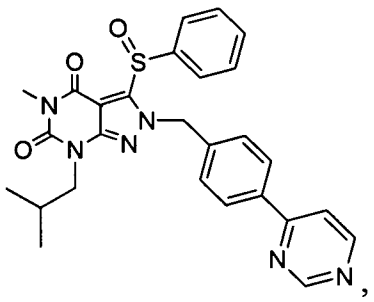
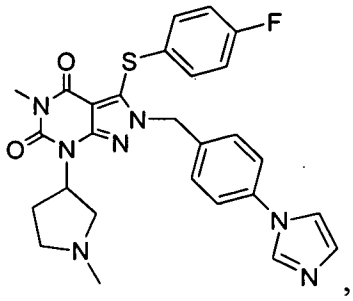
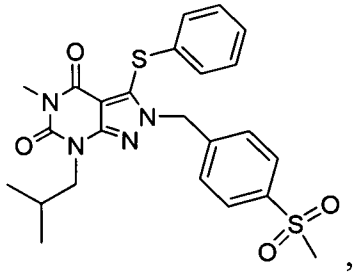
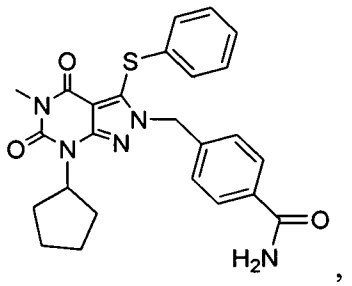
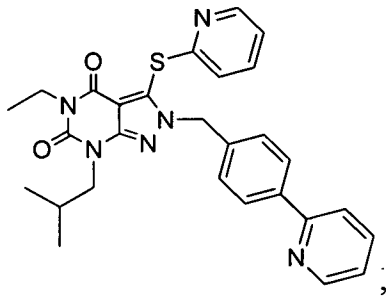
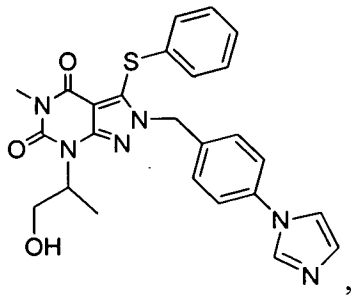
 ,

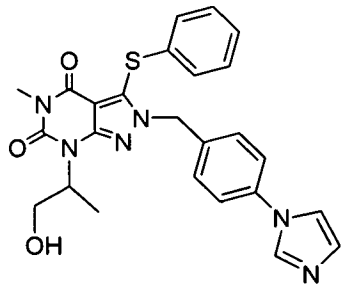
 ,

 ,

 ,

 ,

 ,



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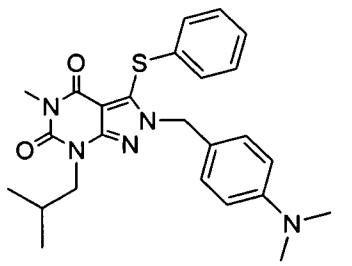
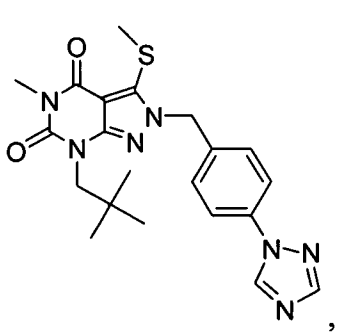


in free or salt form

3. The compound according to claim 1, selected from any of the following: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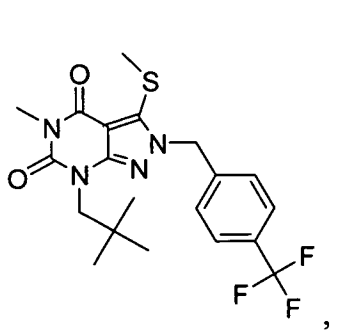
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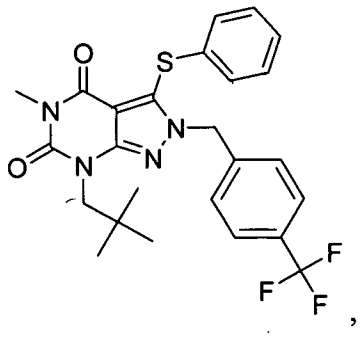
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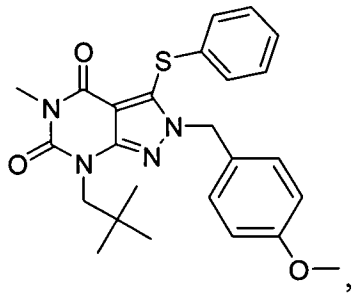
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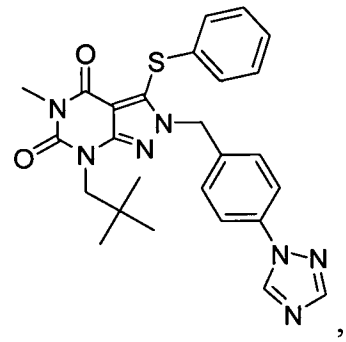
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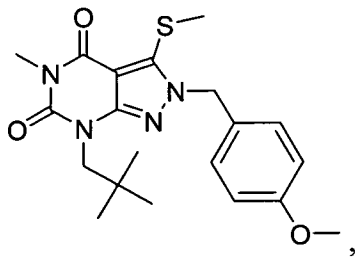
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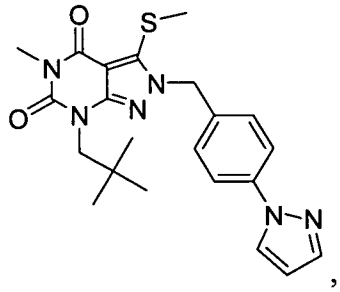
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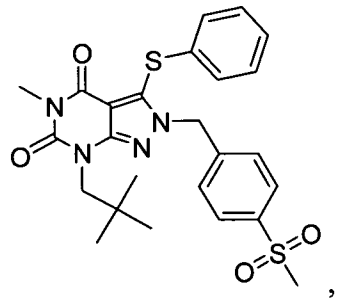
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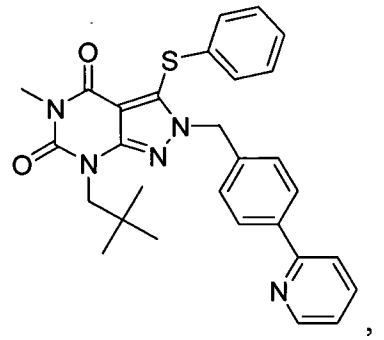
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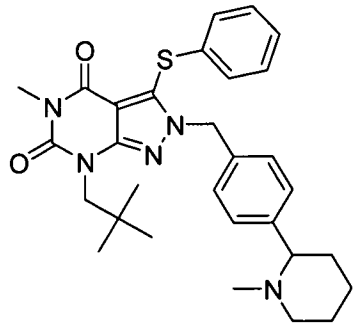
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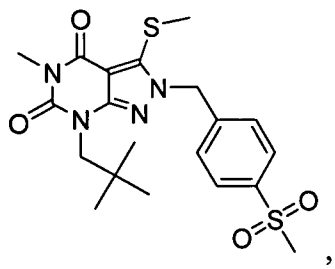
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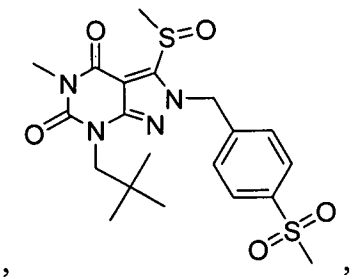
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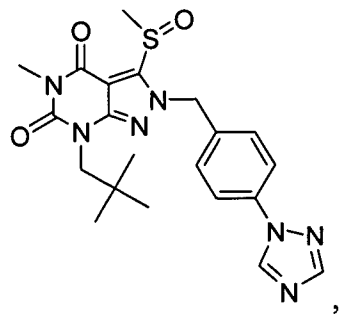
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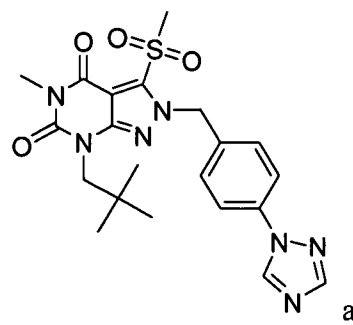
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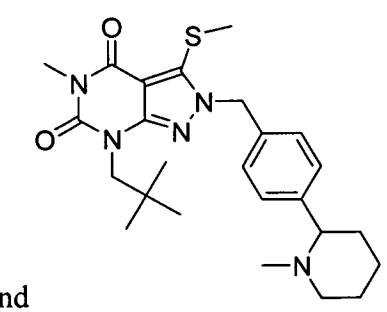
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in free or salt form.

4. A pharmaceutical composition comprising a compound according to any of claims 1-3 in admixture with a pharmaceutically acceptable diluent or carrier.

5. A method of treating any of the following conditions: Parkinson's disease, restless leg, tremors, dyskinesias, Huntington's disease, Alzheimer's disease, and drug-induced movement disorders; depression, attention deficit disorder, attention deficit hyperactivity disorder, bipolar illness, anxiety, sleep disorder, narcolepsy, cognitive impairment, dementia, Tourette's syndrome, autism, fragile X syndrome, psychostimulant withdrawal, and/or drug addiction; cerebrovascular disease, stroke, congestive heart disease, hypertension, pulmonary hypertension, and/or sexual dysfunction; asthma, chronic obstructive pulmonary disease, and/or allergic rhinitis, as well as autoimmune and inflammatory diseases; and/or female sexual dysfunction, exercise amenorrhoea, anovulation, menopause, menopausal symptoms, hypothyroidism, pre-menstrual syndrome, premature labor, infertility, irregular menstrual cycles, abnormal uterine bleeding, osteoporosis, multiple sclerosis, prostate enlargement, prostate cancer, hypothyroidism, estrogen-induced endometrial hyperplasia or carcinoma; and/or any disease or condition characterized by low levels of cAMP and/or cGMP (or inhibition of cAMP and/or cGMP signaling pathways) in cells expressing PDE1, and/or by reduced dopamine D1 receptor signaling activity; and/or any disease or condition that may be ameliorated by the enhancement of progesterone signaling; comprising administering an effective amount of a compound according to any of claims 1-3, or a pharmaceutical composition according to claim 4, to a patient in need of such treatment.

6. The method of claim 5, wherein the condition is Parkinson's disease.

7. The method of claim 5, wherein the condition is cognitive impairment.

8. The method of claim 5, wherein the condition is narcolepsy.

9. The method of claim 8 further comprising administering a compound or compounds selected from central nervous system stimulants, modafinil, antidepressants, and gamma hydroxybutyrate, to a patient in need thereof.

10. The method of claim 5, wherein said condition is female sexual dysfunction.

11. The method of claim 10, further comprising administering a compound or compounds selected from a group consisting of estradiol, estriol, estradiol esters, progesterone and progestins to a patient in need thereof.

12. A method for the treatment of treatment for glaucoma or elevated intraocular pressure comprising topical administration of a therapeutically effective amount of a compound according to any of claims 1-3, in free or pharmaceutically acceptable salt form, in an opthalmically compatible carrier to the eye of a patient in need thereof.

13. A method for the treatment of psychosis, schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder, delusional disorder, and mania, such as in acute manic episodes and bipolar disorder, comprising administering a therapeutically effective amount of a compound according to any of claims 1-3, in free or pharmaceutically acceptable salt form, to a patient in need thereof.

14. A method for the treatment of traumatic brain injury comprising admistering to a patient in need thereof, a compound according to any of claims 1-3, in free or pharmaceutically acceptable salt form.

15. A method for lengthening or enhancing growth of the eyelashes by administering an effective amount of a prostaglandin analogue, e.g., bimatoprost, concomitantly, simultaneously or sequentially with an effective amount of a compound according to any of claims 1-3, in free or salt form.

16. Use of a compound according to any of claims 1-3 for the manufacture of a medicament for the treatment or prophylactic treatment of the following diseases: Parkinson's disease, restless leg, tremors, dyskinesias, Huntington's disease,

Alzheimer's disease, and drug-induced movement disorders; depression, attention deficit disorder, attention deficit hyperactivity disorder, bipolar illness, anxiety, sleep disorder, narcolepsy, cognitive impairment, dementia, Tourette's syndrome, autism, fragile X syndrome, psychostimulant withdrawal, and/or drug addiction; cerebrovascular disease, stroke, congestive heart disease, hypertension, pulmonary hypertension, and/or sexual dysfunction; asthma, chronic obstructive pulmonary disease, and/or allergic rhinitis, as well as autoimmune and inflammatory diseases; and/or female sexual dysfunction, exercise amenorrhoea, anovulation, menopause, menopausal symptoms, hypothyroidism, pre-menstrual syndrome, premature labor, infertility, irregular menstrual cycles, abnormal uterine bleeding, osteoporosis, multiple sclerosis, prostate enlargement, prostate cancer, hypothyroidism, estrogen-induced endometrial hyperplasia or carcinoma; and/or any disease or condition characterized by low levels of cAMP and/or cGMP (or inhibition of cAMP and/or cGMP signaling pathways) in cells expressing PDE1, and/or by reduced dopamine D1 receptor signaling activity; and/or any disease or condition that may be ameliorated by the enhancement of progesterone signaling.

17. Use of the Compound according to any of claims 1-3, in free or pharmaceutically acceptable salt form, or a pharmaceutical composition according to claim 4, for the manufacture of a medicament for the treatment or prophylactic treatment of a disease or condition selected from:

glaucoma or elevated intraocular pressure;

psychosis, schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder, delusional disorder, and mania, such as in acute manic episodes and bipolar disorder;

traumatic brain injury.

18. A pharmaceutical comprising a Compound according to any of claims 1-3, in free or pharmaceutically acceptable salt form, in combination or association with a pharmaceutically acceptable diluent or carrier for use in the treatment of any disease or condition selected from:

Parkinson's disease, restless leg, tremors, dyskinesias, Huntington's disease, Alzheimer's disease, and drug-induced movement disorders; depression, attention deficit disorder, attention deficit hyperactivity disorder, bipolar

illness, anxiety, sleep disorder, narcolepsy, cognitive impairment, dementia, Tourette's syndrome, autism, fragile X syndrome, psychostimulant withdrawal, and/or drug addiction; cerebrovascular disease, stroke, congestive heart disease, hypertension, pulmonary hypertension, and/or sexual dysfunction; asthma, chronic obstructive pulmonary disease, and/or allergic rhinitis, as well as autoimmune and inflammatory diseases; and/or female sexual dysfunction, exercise amenorrhoea, anovulation, menopause, menopausal symptoms, hypothyroidism, pre-menstrual syndrome, premature labor, infertility, irregular menstrual cycles, abnormal uterine bleeding, osteoporosis, multiple sclerosis, prostate enlargement, prostate cancer, hypothyroidism, estrogen-induced endometrial hyperplasia or carcinoma; and/or any disease or condition characterized by low levels of cAMP and/or cGMP (or inhibition of cAMP and/or cGMP signaling pathways) in cells expressing PDE1, and/or by reduced dopamine D1 receptor signaling activity; and/or any disease or condition that may be ameliorated by the enhancement of progesterone signaling;

glaucoma or elevated intraocular pressure;

psychosis, schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder, delusional disorder, and mania, such as in acute manic episodes and bipolar disorder; and

traumatic brain injury.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/06443

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/90 (2010.01)
USPC - 514/262.1
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)
USPC: 514/262.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/262.1,249;544/256,330

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB); Google Scholar
Search terms: thioxo, imino, imidazo, pyrazolo, pyrimidin, ones, trihydro, pyrimido, Parkinson's, depression, narcolepsy, PDE1, PDE1A, PDEAB

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 2007/143705 A2 (WENNOGLE et al) 13 December 2007 (13.12.2007); entire document, especially para [0009] | 1-4, 12-16, 18 |
| Y | US 2003/0092908 A1 (PITTS et al) 15 May 2003 (15.05.2003); entire document, especially para [0012] | 1-4, 12-16, 18 |

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 January 2010 (20.01.2010) | 26 FEB 2010 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (July 2009)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/06443

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-11, 17
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.