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(54) Titre : COMPOSES ORGANIQUES
(54) Title: ORGANIC COMPOUNDS

(57) Abrégé/Abstract:
Optionally substituted 3-(thio, sulfinyl or sulfonyl)-7,8-dihydro-(1H or 2H)- imidazo[1,2-a]pyrazolo[4,3-e] pyrimidin-4(5H)-one or a substituted 3-(thio, sulfinyl or sulfonyl)-7,8,9- trihydro— (1H or 2H)-pyrimido[1,2-a]pyrazolo[4,3-e] pyrimidin-4(5H)- one compounds or Compounds of Formula (I), processes for their production, their use as pharmaceuticals and pharmaceutical compositions comprising them.

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(54) Title: ORGANIC COMPOUNDS

(57) Abstract: Optionally substituted 3-(thio, sulfinyl or sulfonyl)-7,8-dihydro-(1*H* or 2*H*)- imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(5*H*)-one or a substituted 3-(thio, sulfinyl or sulfonyl)-7,8,9-trihydro— (1*H* or 2*H*)-pyrimido[1,2-a]pyrazolo[4,3-e]pyrimidin-4(5H)- one compounds or Compounds of Formula (I), 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. 61/120,442, filed December 6, 2008, the contents of which are hereby incorporated by reference in their entirety.

TECHNICAL FIELD

[0001] The present invention relates to optionally substituted 3-(thio, sulfinyl or sulfonyl)-7,8-dihydro-(1*H* or 2*H*)-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(5*H*)-one or a substituted 3-(thio, sulfinyl or sulfonyl)-7,8,9-trihydro-(1*H* or 2*H*)-pyrimido[1,2-a]pyrazolo[4,3-e]pyrimidin-4(5H)-one compounds, e.g., compounds 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.

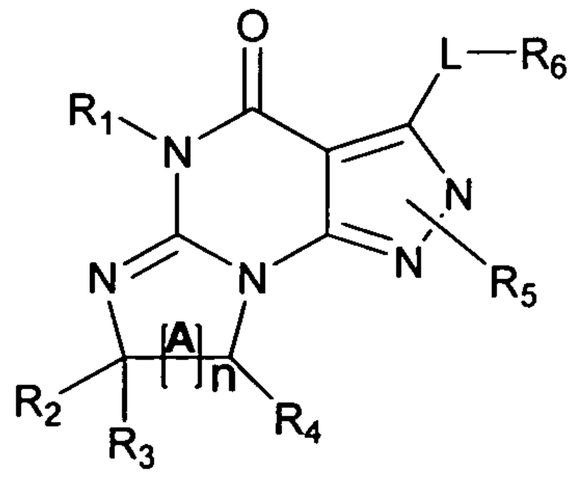
[0005] Phosphodiesterase (PDE) activity, in particular, phosphodiesterase 1 (PDE1) activity, functions in brain tissue as a regulator of locomotor activity and learning and memory. PDE1 is a therapeutic target for regulation of intracellular signaling pathways, preferably in the nervous system, including 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 or PDE1B activity.

SUMMARY OF THE INVENTION

[0007] The invention provides optionally substituted 3-(thio, sulfinyl or sulfonyl)-7,8-dihydro-(1H or 2H)-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(5H)-ones or a substituted 3-(thio, sulfinyl or sulfonyl)-7,8,9-trihydro-(1H or 2H)-pyrimido[1,2-a]pyrazolo[4,3-e]pyrimidin-4(5H)-one, e.g., (1 or 2 and/or 5)-substituted, e.g., a Compound of Formula II:



Formula II

wherein

(i) L is S, SO or SO_2;

(ii) R_1 is H or C_{1-4} alkyl (e.g., methyl or ethyl);

(iii) R_4 is H or C_{1-6} alkyl (e.g., methyl, isopropyl) and R_2 and R_3 are, independently, H or C_{1-6}alkyl (e.g., methyl or isopropyl) optionally substituted with halo or hydroxy (e.g., R_2 and R_3 are both methyl, or R_2 is H and R_3 is methyl, ethyl, isopropyl or hydroxyethyl), aryl, heteroaryl, (optionally hetero)arylalkoxy, (optionally hetero)arylC_{1-6}alkyl, or R_2 and R_3 together form a 3- to 6-membered ring;
or
R_2 is H and R_3 and R_4 together form a di-, tri- or tetramethylene bridge (pref. wherein the R_3 and R_4 together have the *cis* configuration, e.g., where the carbons carrying R_3 and R_4 have the R and S configurations, respectively);

(iv) R_5 is

a) –D-E-F, wherein:

D is C_{1-4}alkylene (e.g., methylene, ethylene or prop-2-yn-1-ylene);

E is a single bond, C_{2-4}alkynylene (e.g., –C≡C–), arylene (e.g., phenylene) or heteroarylene (e.g., pyridylene);

F is

H,

aryl (e.g., phenyl),

heteroaryl (e.g., pyridyl, diazolyl, triazolyl, for example, pyrid-2-yl, imidazol-1-yl, 1,2,4-triazol-1-yl),

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

haloC_{1-4}alkyl (e.g., trifluoromethyl),

-C(O)-R_{15},

-N(R_{16})(R_{17}),

-S(O)$_2R_{21}$ or

C_{3-7}cycloalkyl optionally containing at least one atom selected from a group consisting of N or O (e.g.,

cyclopentyl, cyclohexyl, pyrrolidinyl (e.g., pyrrolidin-3-yl), tetrahydro-*2H*-pyran-4-yl, or morpholinyl);

wherein D, E and F are independently and optionally substituted with one or more

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

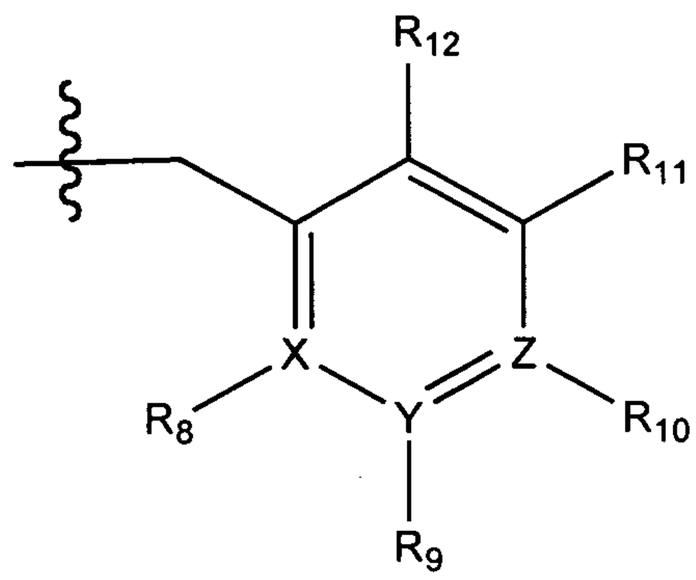
C_{1-4}alkyl (e.g., methyl),

haloC_{1-4}alkyl (e.g., trifluoromethyl),

for example, F is heteroaryl, e.g., pyridyl substituted with one or more halo (e.g., 6-fluoropyrid-2-yl, 5-fluoropyrid-2-yl, 6-fluoropyrid-2-yl, 3-fluoropyrid-2-yl, 4-fluoropyrid-2-yl, 4,6-dichloropyrid-2-yl), haloC_{1-4}alkyl (e.g., 5-trifluoromethylpyrid-2-yl) or C_{1-4}alkyl (e.g., 5-methylpyrid-2-yl), or F is aryl, e.g., phenyl, substituted with one or more halo (e.g., 4-fluorophenyl) or F is a C_{3-7}heterocycloalkyl (e.g., pyrrolidinyl) optionally substituted with a C_{1-6}alkyl (e.g., 1-methylpyrrolidin-3-yl); or

b) a substituted heteroarylalkyl, e.g., substituted with haloalkyl;

c) 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_{1-4}alkyl,

C_{3-7}cycloalkyl,

heteroC_{3-7}cycloalkyl (e.g. pyrrolidinyl or piperidinyl),

C_{1-4}haloalkyl (e.g., trifluoromethyl),
aryl (e.g., phenyl),
heteroaryl (e.g., pyridyl (for example pyrid-2-yl), or thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl)), diazolyl, triazolyl, tetrazolyl,
arylcarbonyl (e.g., benzoyl),
alkylsulfonyl (e.g., methylsulfonyl),
heteroarylcarbonyl, or
alkoxycarbonyl,

wherein said 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,

preferably R_{10} is phenyl, pyridyl, piperidinyl or pyrrolidinyl optionally substituted with the substituents previously defined, e.g. optionally substituted with halo or alkyl;

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

(v) R_6 is

H,
C_{1-4}alkyl (e.g., methyl),
C_{3-7}cycloalkyl (e.g., cyclopentyl),
aryl (e.g., phenyl),
heteroaryl (e.g., pyridyl, for example, pyrid-4-yl),
arylC_{1-4}alkyl (e.g., benzyl),
arylamino (e.g., phenylamino),
heterarylamino,
N,N-diC_{1-4}alkylamino,
N,N-diarylamino,
N-aryl-N-(arylC_{1-4}alkyl)amino (e.g., N-phenyl-N-(1,1'-biphen-4-ylmethyl)amino), or
$-N(R_{18})(R_{19})$;

wherein the aryl or heteroaryl is optionally substituted with one or more halo (e.g., F, Cl), hydroxy or C_{1-6}alkoxy (e.g., methoxy), for example, R_6 is 4-hydroxyphenyl or 4-fluorophenyl,

(vi) n = 0 or 1;

(vii) when n=1, **A** is -C($R_{13}R_{14}$)-, wherein R_{13} and R_{14}, are, independently, H or C_{1-4}alkyl, aryl, heteroaryl, (optionally hetero)arylC_{1-4}alkoxy or (optionally hetero)arylC_{1-4}alkyl or R_{13} or R_{14} can form a bridge with R_2 or R_4;

(viii) R_{15} is C_{1-4}alkyl, haloC_{1-4}alkyl, -OH or –OC_{1-4}alkyl (e.g., -OCH_3)

(ix) R_{16} and R_{17} are independently H or C_{1-4}alkyl;

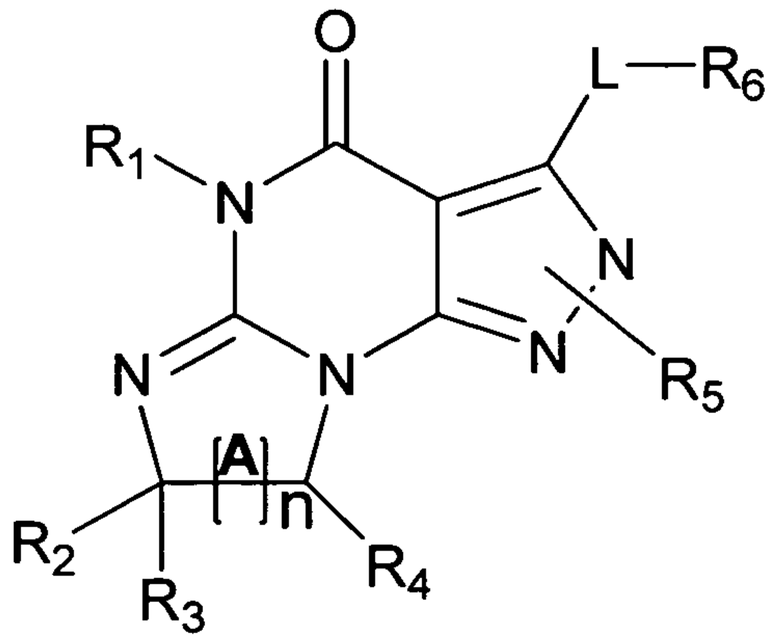
(x) R_{18} and R_{19} are independently H, C_{1-4}alky, C_{3-8}cycloalkyl, heteroC_{3-8}cycloalkyl, aryl (e.g., phenyl) or heteroaryl, wherein said aryl or heteroaryl is optionally substituted with one or more halo (e.g., fluorophenyl, e.g., 4-fluorophenyl), hydroxy (e.g., hydroxyphenyl, e.g., 4-hydroxyphenyl or 2-hydroxyphenyl), C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, aryl,heteroaryl, or C_{3-8}cycloalkyl,

(xi) R_{20} is H, C_{1-4}alkyl (e.g., methyl) or C_{3-7}cycloalkyl,

(xii) R_{21} is C_{1-6}alkyl;

in free or form.

[0008] In another embodiment, the invention provides a Compound of Formula I:



Formula I

wherein

(i) L is S, SO or SO_2;

(ii) R_1 is H or C_{1-4} alkyl (e.g., methyl or ethyl);

(iii) R_4 is H or C_{1-6} alkyl (e.g., methyl, isopropyl) and R_2 and R_3 are, independently, H or C_{1-6}alkyl (e.g., methyl or isopropyl) optionally substituted with halo or hydroxy (e.g., R_2 and R_3 are both methyl, or R_2 is H and R_3 is methyl, ethyl, isopropyl or hydroxyethyl), aryl, heteroaryl, (optionally hetero)arylalkoxy, or (optionally hetero)arylC_{1-6}alkyl;

or

R_2 is H and R_3 and R_4 together form a di-, tri- or tetramethylene bridge (pref. wherein the R_3 and R_4 together have the *cis* configuration, e.g., where the carbons carrying R_3 and R_4 have the R and S configurations, respectively);

(iv) R_5 is

a) –D-E-F, wherein:

D is C_{1-4}alkylene (e.g., methylene, ethylene or prop-2-yn-1-ylene);

E is a single bond, C_{2-4}alkynylene (e.g., –C≡C–), arylene (e.g., phenylene) or heteroarylene (e.g., pyridylene);

F is

H,

aryl (e.g., phenyl),

heteroaryl (e.g., pyridyl, diazolyl, triazolyl, for example, pyrid-2-yl, imidazol-1-yl, 1,2,4-triazol-1-yl),

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

haloC_{1-4}alkyl (e.g., trifluoromethyl),

$-C(O)-R_{15}$,

$-N(R_{16})(R_{17})$,

$-S(O)_2R_{21}$ or

C_{3-7}cycloalkyl optionally containing at least one atom selected from a group consisting of N or O (e.g., cyclopentyl, cyclohexyl, pyrrolidinyl (e.g., pyrrolidin-3-yl), tetrahydro-*2H*-pyran-4-yl, or morpholinyl);

wherein D, E and F are independently and optionally substituted with one or more

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

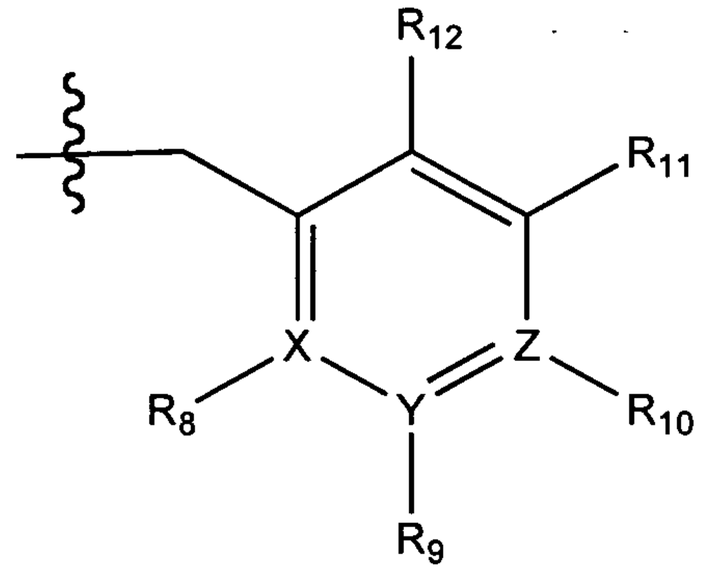
C_{1-4}alkyl (e.g., methyl),

haloC_{1-4}alkyl (e.g., trifluoromethyl),

for example, F is heteroaryl, e.g., pyridyl substituted with one or more halo (e.g., 6-fluoropyrid-2-yl, 5-fluoropyrid-2-yl, 6-fluoropyrid-2-yl, 3-fluoropyrid-2-yl, 4-fluoropyrid-2-yl, 4,6-dichloropyrid-2-yl), haloC_{1-4}alkyl (e.g., 5-trifluoromethylpyrid-2-yl) or C_{1-4}alkyl (e.g., 5-methylpyrid-2-yl), or F is aryl, e.g., phenyl, substituted with one or more halo (e.g., 4-fluorophenyl) or F is a C_{3-7}heterocycloalkyl (e.g., pyrrolidinyl) optionally substituted with a C_{1-6}alkyl (e.g., 1-methylpyrrolidin-3-yl); or

b) a substituted heteroarylalkyl, e.g., substituted with haloalkyl;

c) 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_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}haloalkyl (e.g., trifluoromethyl), aryl (e.g., phenyl), heteroaryl (e.g., pyridyl (for example pyrid-2-yl), or thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl)), diazolyl, triazolyl, tetrazolyl, arylcarbonyl (e.g., benzoyl), alkylsulfonyl (e.g., methylsulfonyl), heteroarylcarbonyl, or alkoxycarbonyl; provided that when X, Y, or Z is nitrogen, R_8, R_9, or R_{10}, respectively, is not present;

(v) R_6 is

H,

C_{1-4}alkyl (e.g., methyl),
C_{3-7}cycloalkyl (e.g., cyclopentyl),
aryl (e.g., phenyl),
heteroaryl (e.g., pyridyl, for example, pyrid-4-yl),
arylC_{1-4}alkyl (e.g., benzyl),
arylamino (e.g., phenylamino),
heterarylamino,
N,N-diC_{1-4}alkylamino,
N,N-diarylamino,
N-aryl-N-(arylC_{1-4}alkyl)amino (e.g., N-phenyl-N-(1,1'-biphen-4-ylmethyl)amino), or
$-N(R_{18})(R_{19})$;
wherein the aryl or heteroaryl is optionally substituted with one or more halo (e.g., F, Cl), hydroxy or C_{1-6}alkoxy (e.g., methoxy), for example, R_6 is 4-hydroxyphenyl or 4-fluorophenyl,

(vi) n = 0 or 1;

(vii) when n=1, **A** is $-C(R_{13}R_{14})-$, wherein R_{13} and R_{14}, are, independently, H or C_{1-4}alkyl, aryl, heteroaryl, (optionally hetero)arylC_{1-4}alkoxy or (optionally hetero)arylC_{1-4}alkyl;

(viii) R_{15} is C_{1-4}alkyl, haloC_{1-4}alkyl, -OH or $-OC_{1-4}$alkyl (e.g., $-OCH_3$)

(ix) R_{16} and R_{17} are independently H or C_{1-4}alkyl;

(x) R_{18} and R_{19} are independently H, C_{1-4}alky or aryl (e.g., phenyl) wherein said aryl is optionally substituted with one or more halo (e.g., fluorophenyl, e.g., 4-fluorophenyl) or hydroxy (e.g., hydroxyphenyl, e.g., 4-hydroxyphenyl or 2-hydroxyphenyl)

(xi) R_{20} is H, C_{1-4}alkyl (e.g., methyl) or C_{3-7}cycloalkyl,

(xii) R_{21} is C_{1-6}alkyl;

in free or salt form.

[0009] The invention further provides compounds of Formula I as follows:

1.1 Formula I, wherein L is a S, SO or SO_2;

1.2 Formula I or 1.1, wherein L is a S;

1.3 Formula I or 1.1, wherein L is -SO-;

1.4 Formula I or 1.1, wherein L is $-SO_2-$;

1.5 Formula I, or any of 1.1-1.4, wherein R_1 is H or C_{1-4} alkyl (e.g., methyl);

1.6 Formula 1.5, wherein R_1 is H;

1.7 Formula 1.5, wherein R_1 is C_{1-4} alkyl (e.g., methyl or ethyl);

1.8 Formula I, or any of 1.1-1.7, wherein R_4 is H or C_{1-6} alkyl (e.g., methyl, isopropyl) and R_2 and R_3 are, independently, H or C_{1-6}alkyl (e.g., methyl or isopropyl) optionally substituted with halo or hydroxy (e.g., R_2 and R_3 are both methyl, or R_2 is H and R_3 is methyl, ethyl, isopropyl or hydroxyethyl), aryl, heteroaryl, (optionally hetero)arylalkoxy, or (optionally hetero)arylC_{1-6}alkyl;

1.9 Formula 1.8, wherein R_2 or R_3 is H or C_{1-6}alkyl (e.g., methyl or isopropyl);

1.10 Formula 1.8, wherein R_2 or R_3 is H;

1.11 Formula 1.8, wherein R_2 or R_3 is C_{1-6}alkyl (e.g., methyl or isopropyl);

1.12 Formula 1.8, wherein R_2 or R_3 is methyl;

1.13 Formula 1.8, wherein R_2 or R_3 is isopropyl;

1.14 Formula I, or any of 1.1-1.7, wherein R_2 is H and R_3 and R_4 together form a di-, tri- or tetramethylene bridge (pref. wherein the R_3 and R_4 together have the *cis* configuration, e.g., where the carbons carrying R_3 and R_4 have the R and S configurations, respectively);

1.15 Formula I or any of 1.1-1.14, wherein R_5 is –D-E-F;

1.16 Formula 1.15, wherein D is C_{1-4}alkylene (e.g., methylene, ethylene or prop-2-yn-1-ylene);

1.17 Formula 1.16, wherein D is methylene;

1.18 Any of formulae 1.15-1.17, wherein E is a single bond, C_{2-4}alkynylene (e.g., –C≡C–), arylene (e.g., phenylene) or heteroarylene (e.g., pyridylene);

1.19 Any of formulae 1.15-1.17, wherein E is arylene (e.g., phenylene);

1.20 Any of formulae 1.15-1.17, wherein E is phenylene;

1.21 Any of formulae 1.15-1.17, wherein E is heteroarylene (e.g., pyridylene);

1.22 Any of formulae 1.15-1.17, wherein E is phenylene wherein F is para-substituted;

1.23 Any of formulae 1.15-1.17, wherein E is heteroarylene (e.g., pyridylene);

1.24 Any of formulae 1.15-1.17, wherein E is a single bond;

1.25 Any of formulae 1.15-1.24, wherein F is H, aryl (e.g., phenyl), heteroaryl (e.g., pyridyl, diazolyl, triazolyl, for example, pyrid-2-yl, imidazol-1-yl, 1,2,4-triazol-1-yl), halo (e.g., F, Br, Cl), haloC_{1-4}alkyl (e.g., trifluoromethyl), -C(O)-R_{15}, -N(R_{16})(R_{17}), -S(O)$_2R_{21}$ or C_{3-7}cycloalkyl optionally containing at least one atom selected from a group consisting of N or O (e.g., cyclopentyl, cyclohexyl, pyrrolidinyl (e.g., pyrrolidin-3-yl), tetrahydro-*2H*-pyran-4-yl, or morpholinyl);

1.26 Formula 1.25, wherein F is haloC_{1-4}alkyl (e.g., trifluoromethyl);

1.27 Formula 1.25, wherein F is trifluoromethyl;

1.28 Formula 1.25, wherein F is halo (e.g., F, Br, Cl);

1.29 Formula 1.25, wherein F is Cl;

1.30 Formula 1.25, wherein F is heteroaryl (e.g., pyridyl, e.g., pyrid-2-yl);

1.31 Formula 1.25, wherein F is pyridyl;

1.32 Formula 1.25, wherein F is pyrid-2-yl;

1.33 Formula 1.25, wherein F is C_{3-7}cycloalkyl optionally containing at least one atom selected from a group consisting of N or O (e.g., cyclopentyl, cyclohexyl, pyrrolidinyl (e.g., pyrrolidin-3-yl), tetrahydro-*2H*-pyran-4-yl, morpholinyl);

1.34 Formula 1.25, wherein F is cyclohexyl;

1.35 Formula 1.25, wherein F is pyrrolidinyl (e.g., pyrrolidin-3-yl);

1.36 Formula 1.25, wherein F is cyclopentyl;

1.37 Formula 1.25, wherein F is tetrahydro-*2H*-pyran-4-yl;

1.38 Formula 1.25, wherein F is aryl (e.g., phenyl);

1.39 Formula 1.25, wherein F is phenyl;

1.40 Formula 1.25, wherein F is 4-chlorophenyl;

1.41 Formula 1.25, wherein F is -S(O)$_2R_{21}$ wherein R_{21} is C_{1-6}alkyl (e.g., methyl);

1.42 Formula 1.25, wherein F is -C(O)-R_{15} and R_{15} is C_{1-4}alky (e.g., methyl), haloC_{1-4}alkyl (e.g., trifluoromethyl), -OH or –OC_{1-4}alkyl (e.g., -OCH_3);

1.43 Any of formulae 1.15-1.42, wherein D, E and F are independently and optionally substituted with one or more halo (e.g., F, Cl or Br), C_{1-4}alkyl (e.g., methyl), haloC_{1-4}alkyl (e.g., trifluoromethyl), for example, F is heteroaryl, e.g., pyridyl substituted with one or more halo (e.g., 6-fluoropyrid-2-yl, 5-fluoropyrid-2-yl, 6-fluoropyrid-2-yl, 3-fluoropyrid-2-yl, 4-fluoropyrid-2-yl, 4,6-dichloropyrid-2-yl), haloC_{1-4}alkyl (e.g., 5-trifluoromethylpyrid-2-yl) or C_{1-4}alkyl (e.g., 5-methylpyrid-2-yl), or F is aryl, e.g., phenyl, substituted with one or more halo (e.g., 4-fluorophenyl), or F is a or F is a C_{3-7}heterocycloalkyl (e.g., pyrrolidinyl) optionally substituted with a C_{1-6}alkyl (e.g., 1-methylpyrrolidin-3-yl);

1.44 Formula 1.43, wherein F is substituted with one or more halo (e.g., F, Cl or Br), $_{C1-4}$alkyl (e.g., methyl), halo$_{C1-4}$alkyl (e.g., trifluoromethyl);

1.45 Formula 1.43, wherein F is 6-fluoropyrid-2-yl;

1.46 Formula 1.43, wherein F is 3-fluoropyrid-2-yl;

1.47 Formula 1.43, wherein F is 4-fluoropyrid-2-yl;

1.48 Formula 1.43, wherein F is 5-fluoropyrid-2-yl;

1.49 Formula 1.43, wherein F is heteroaryl, e.g., pyridyl, optionally substituted with one or more haloC_{1-4}alkyl (e.g., 5-trifluoromethylpyrid-2-yl;

1.50 Formula 1.43, wherein F is 5-trifluoromethylpyrid-2-yl;

1.51 Formula 1.43, wherein F is heteroaryl, e.g., pyridyl, optionally substituted with one or more C_{1-4}alkyl (e.g., 5-methylpyrid-2-yl);

1.52 Formula 1.43, wherein F is 5-methylpyrid-2-yl;

1.53 Formula 1.25, wherein F is -C(O)-R_{15} and R_{15} is methyl;

1.54 Formula 1.25, wherein F is -C(O)-R_{15} and R_{15} is trifluoromethyl;

1.55 Formula 1.25, wherein F is -C(O)-R_{15} and R_{15} is –OH;

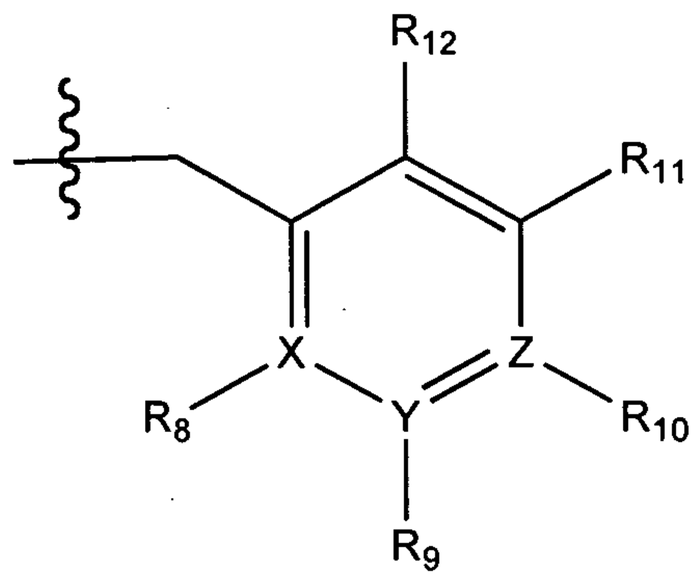
1.56 Formula 1.25, wherein F is -C(O)-R_{15} and R_{15} is –OC_{1-4}alkyl (e.g., -OCH_3);

1.57 Formula 1.25, wherein F is -C(O)-R_{15} and R_{15} is –OCH_3;

1.58 Formula 1.25, wherein F is -N(R_{16})(R_{17});

1.59 Formula I or any of 1.1-1.14, wherein R_5 is a substituted heteroarylalkyl, e.g., substituted with haloalkyl;

1.60 Formula I or any of 1.1-1.14, wherein R_5 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_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}haloalkyl (e.g., trifluoromethyl), aryl (e.g., phenyl), heteroaryl (e.g., pyridyl (for example pyrid-2-yl), or thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl)), diazolyl, triazolyl, tetrazolyl, arylcarbonyl (e.g., benzoyl), alkylsulfonyl (e.g., methylsulfonyl), heteroarylcarbonyl, or alkoxycarbonyl; provided that when X, Y, or Z is nitrogen, R_8, R_9, or R_{10}, respectively, is not present

1.61 Formula 1.60, wherein R_5 is a substituted heteroarylmethyl, e.g., para-substituted with haloalkyl;

1.62 Formula 1.60, wherein R_5 is a moiety of Formula A wherein R_8, R_9, R_{11}, and R_{12} are H and R_{10} is phenyl;

1.63 Formula 1.60, wherein R_5 is a moiety of Formula A wherein R_8, R_9, R_{11}, and R_{12} are H and R_{10} is pyridyl or thiadiazolyl;

1.64 Formula 1.60, wherein R_5 is a moiety of Formula A wherein R_8, R_9, R_{11}, and R_{12} are, independently, H or halogen, and R_{10} is haloalkyl;

1.65 Formula 1.60, wherein R_5 is a moiety of Formula A wherein R_8, R_9, R_{11}, and R_{12} are, independently, H, and R_{10} is alkyl sulfonyl;

1.66 Formula I or any of 1.1-1.65, wherein R_6 is H, C_{1-4}alkyl (e.g., methyl), C_{3-7}cycloalkyl (e.g., cyclopentyl), aryl, heteroaryl, arylC_{1-4}alkyl (e.g.,

benzyl), arylamino (e.g., phenylamino), heterarylamino, N,N-diC_{1-4}alkylamino, N,N-diarylamino, N-aryl-N-(arylC_{1-4}alkyl)amino (e.g., N-phenyl-N-(1,1'-biphen-4-ylmethyl)amino), or -N(R_{18})(R_{19}), wherein the aryl or heteroaryl is optionally substituted with one or more halo (e.g., F, Cl), hydroxy or C_{1-6}alkoxy (e.g., methoxy);

1.67 Formula 1.66, wherein R_6 is H;

1.68 Formula 1.66, wherein R_6 is C_{1-4}alkyl (e.g., methyl);

1.69 Formula 1.66, wherein R_6 is C_{3-7}cycloalkyl (e.g., cyclopentyl);

1.70 Formula 1.66, wherein R_6 is aryl (e.g., phenyl) optionally substituted with one or more halo (e.g., F, Cl), hydroxy or C_{1-6}alkoxy (e.g., methoxy);

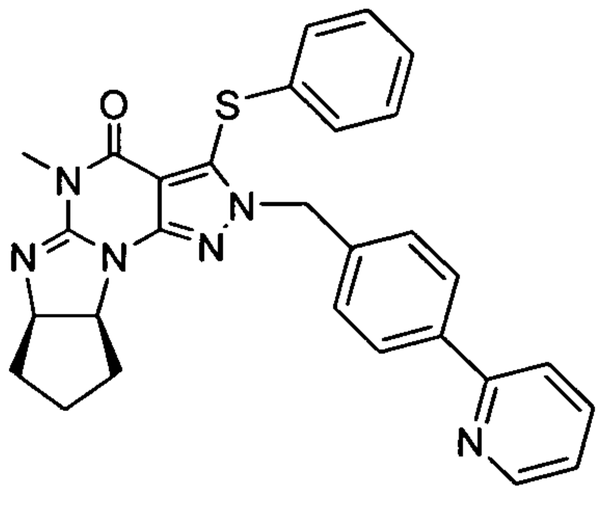
1.71 Formula 1.66, wherein R_6 is fluorophenyl (e.g., 4-fluorophenyl) or hydroxyphenyl (e.g., 4-hydroxyphenyl);

1.72 Formula I or any of 1.1-1.71, wherein n = 0;

1.73 Formula I or any of 1.1-1.71, wherein n = 1;

1.74 Formula 1.73, wherein n=1, **A** is -C($R_{13}R_{14}$)-, wherein R_{13} and R_{14}, are, independently, H or C_{1-4}alkyl, aryl, heteroaryl, (optionally hetero)arylC_{1-4}alkoxy or (optionally hetero)arylC_{1-4}alkyl;

1.75 any of the preceding formulae wherein the compound is selected from a group consisting of: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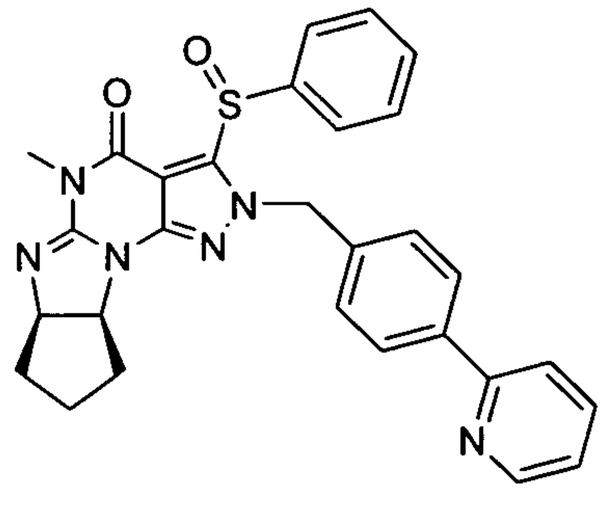
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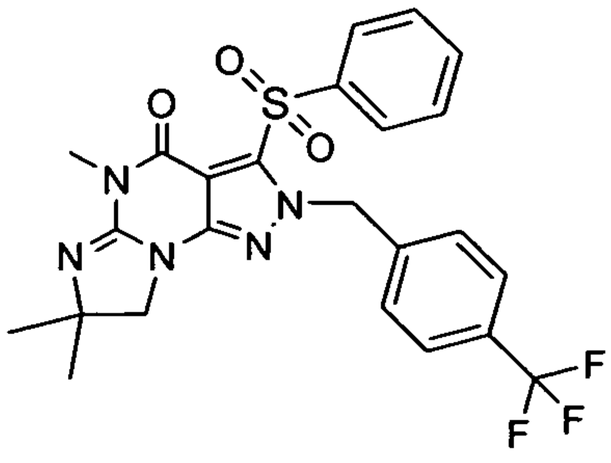
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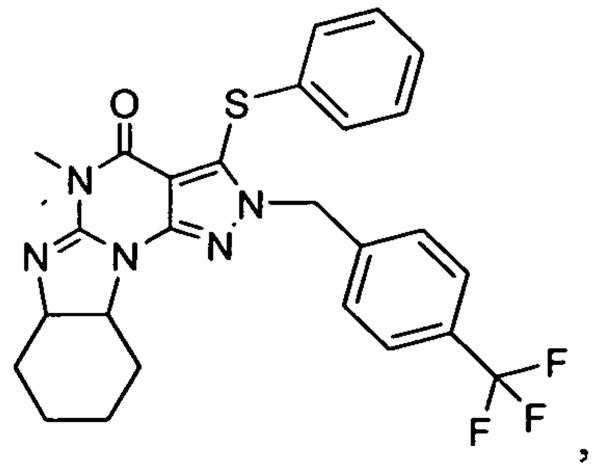
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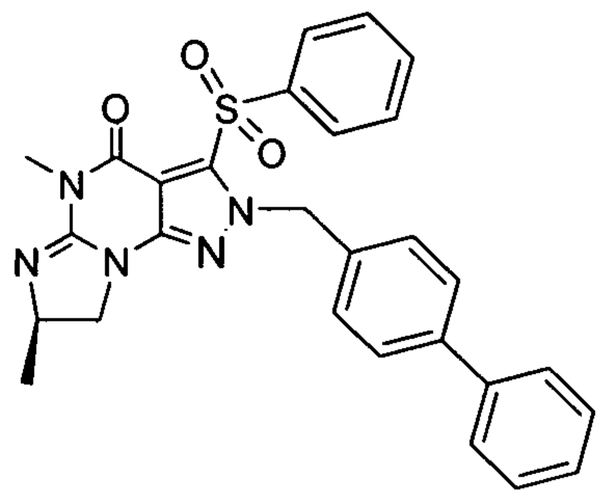
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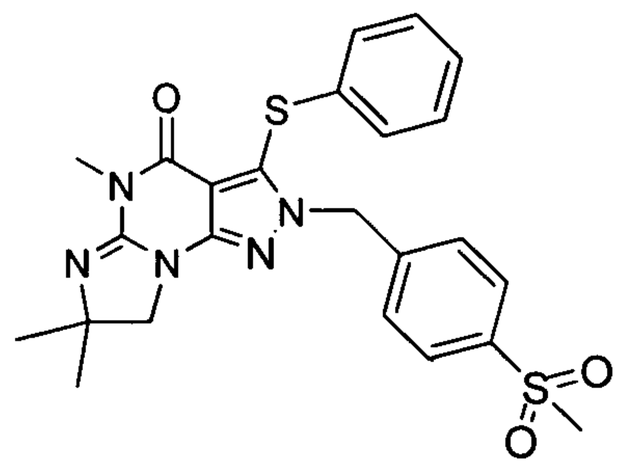
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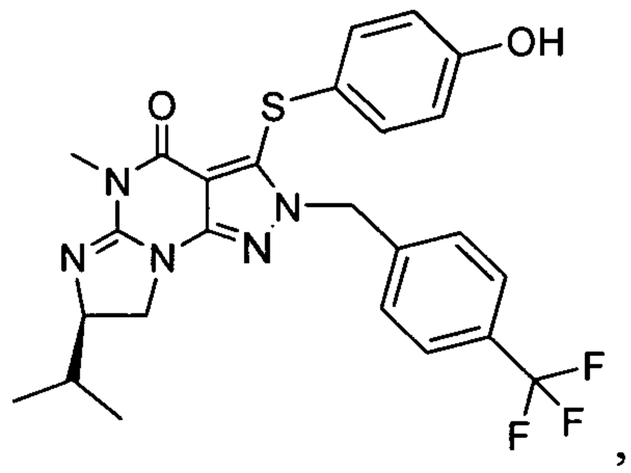
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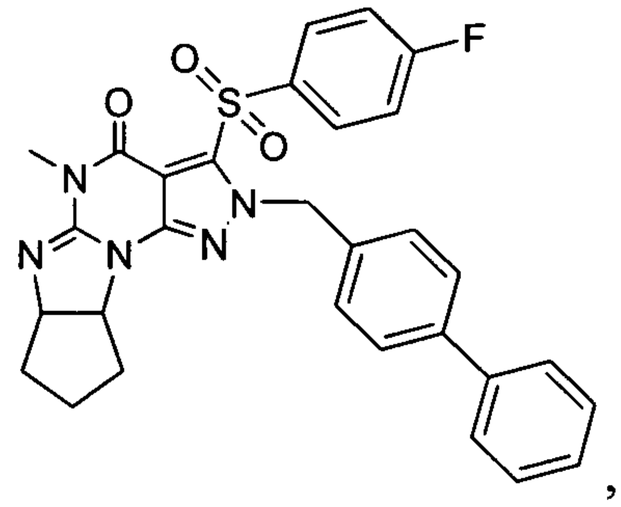
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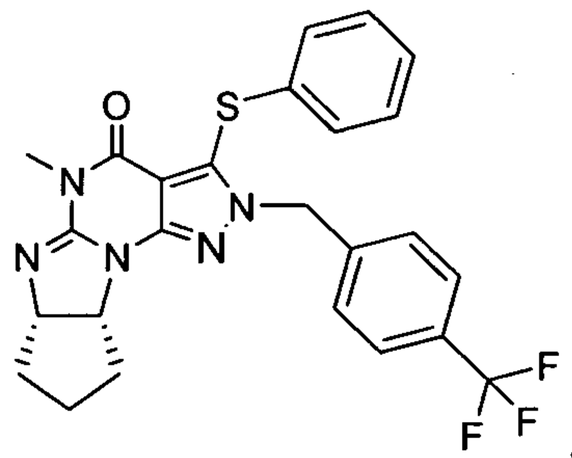
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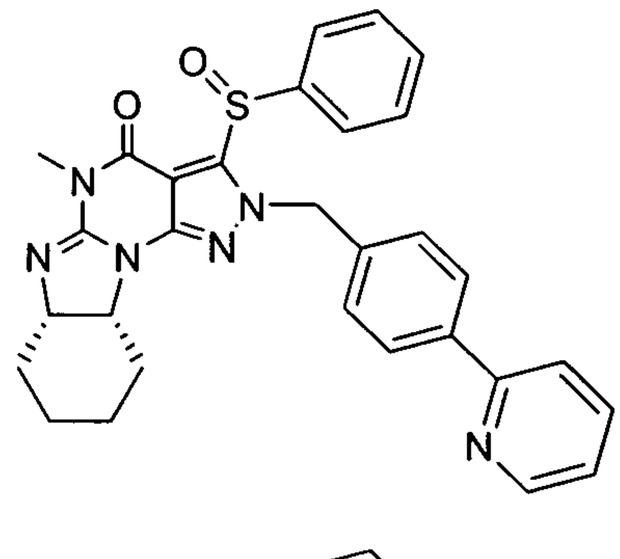
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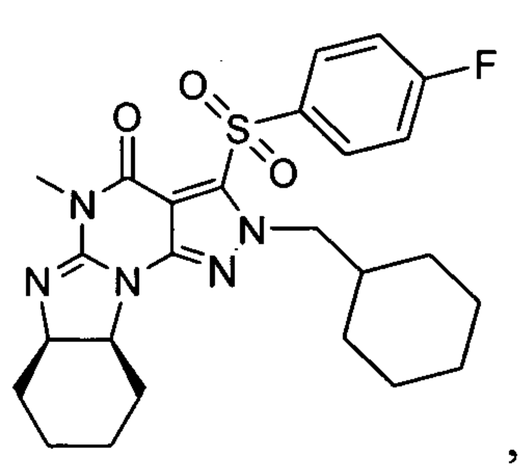
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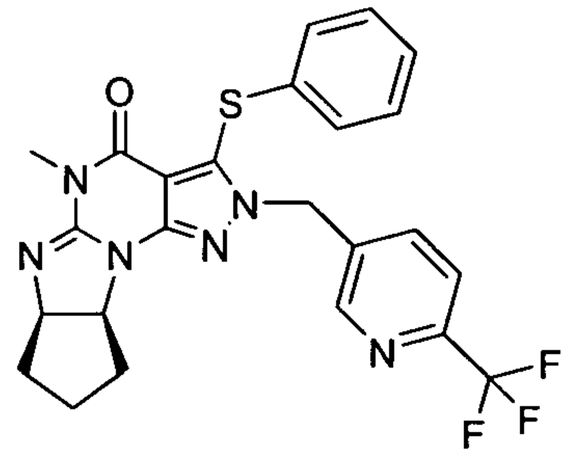
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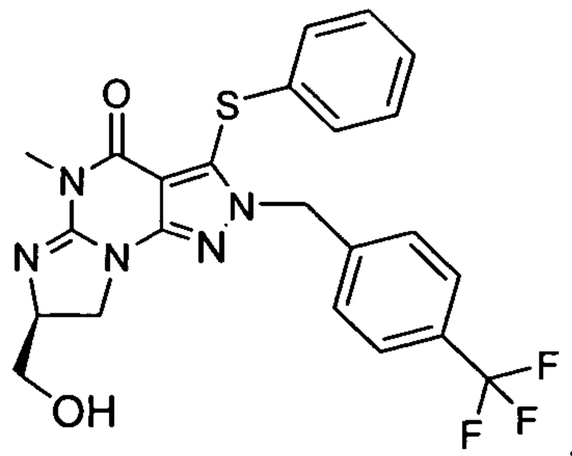
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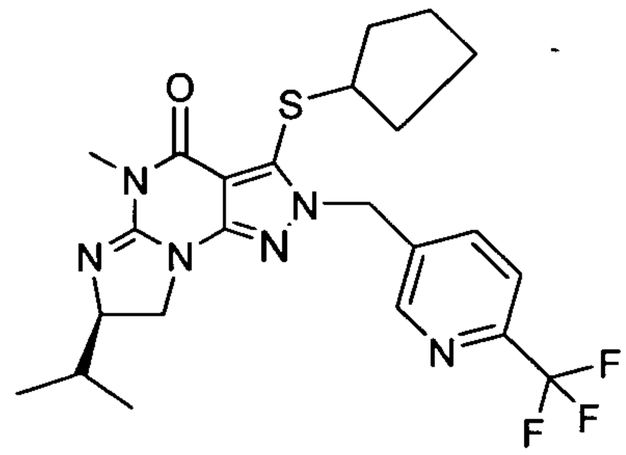
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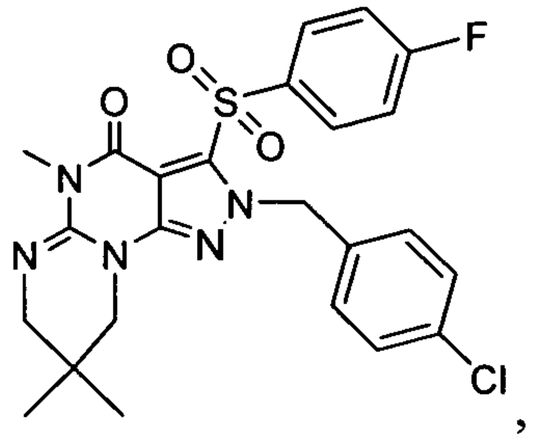
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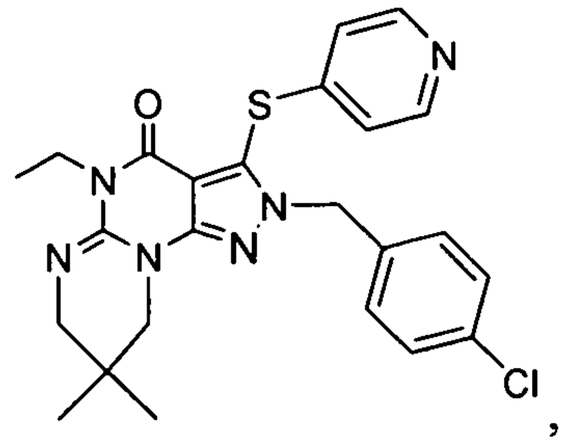
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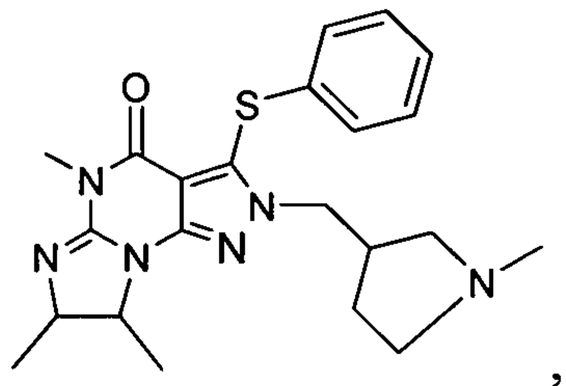
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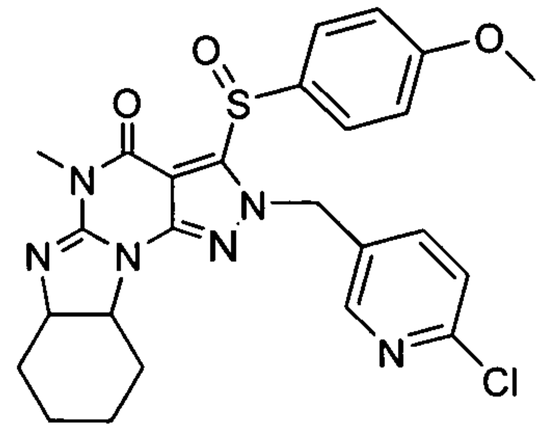
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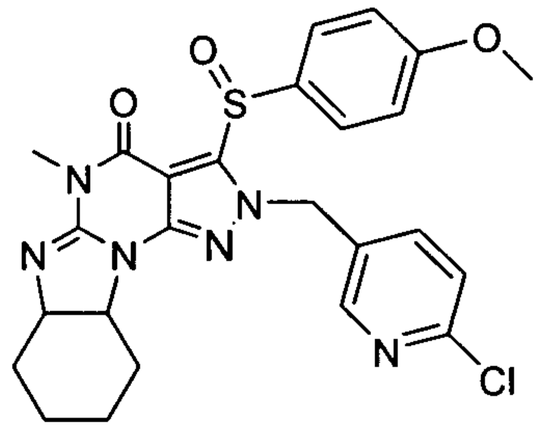
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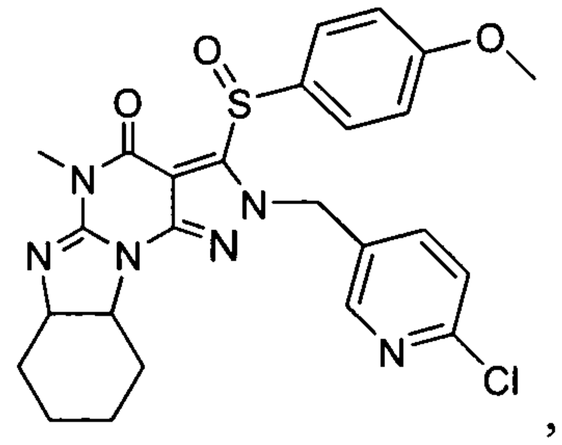
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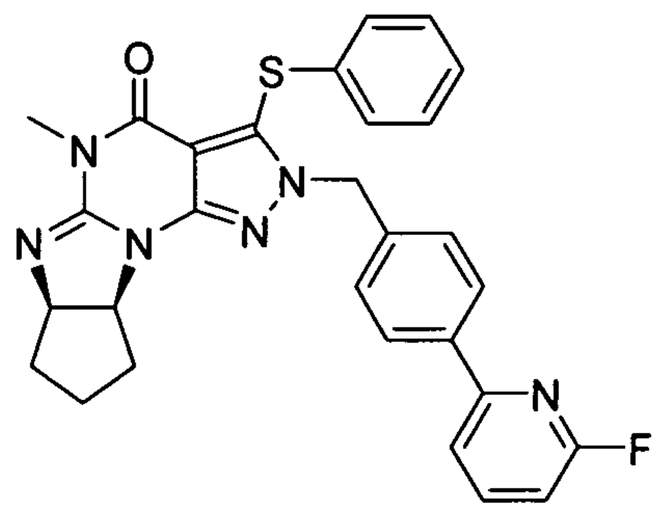
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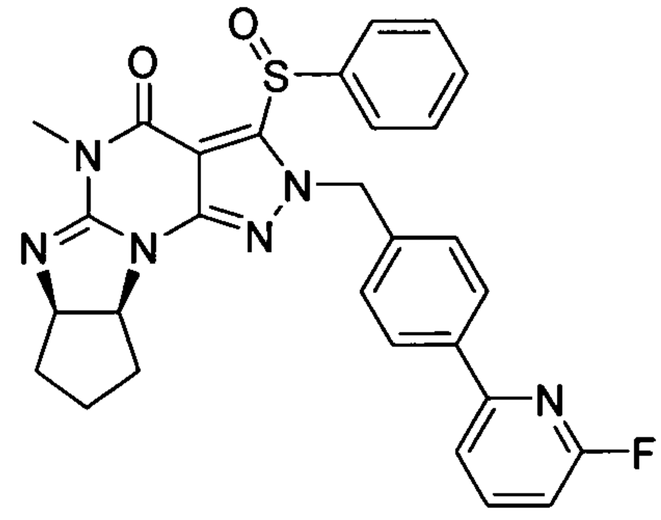
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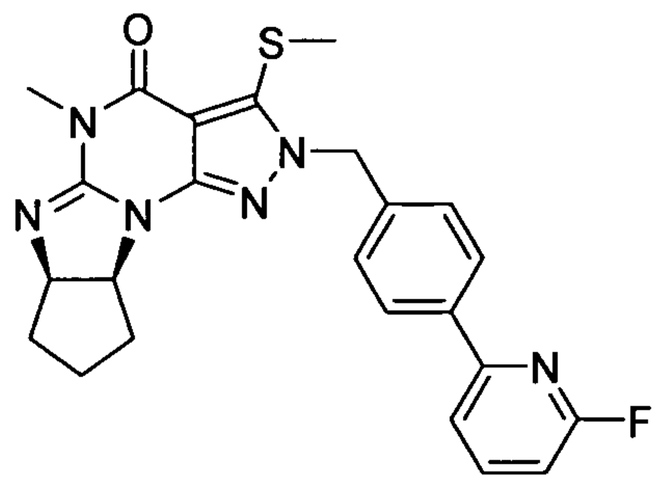
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1.76 any of the preceding formulae wherein the compounds inhibit phosphodiesterase-mediated (e.g., PDE1-mediated, especially PDE1B-mediated) hydrolysis of cGMP, e.g., with an IC_{50} of less than 1μM, preferably less than 500 nM, more preferably less than 50 nM in an

immobilized-metal affinity particle reagent PDE assay, for example, as described in Example 9,

in free or salt form.

[0010] In another embodiment, the invention provides a Compound of Formula I or II, wherein R_6 is:

H,

C_{1-4}alkyl (e.g., methyl),

C_{3-7}cycloalkyl (e.g., cyclopentyl),

aryl (e.g., phenyl),

heteroaryl (e.g., pyridyl, for example, pyrid-4-yl),

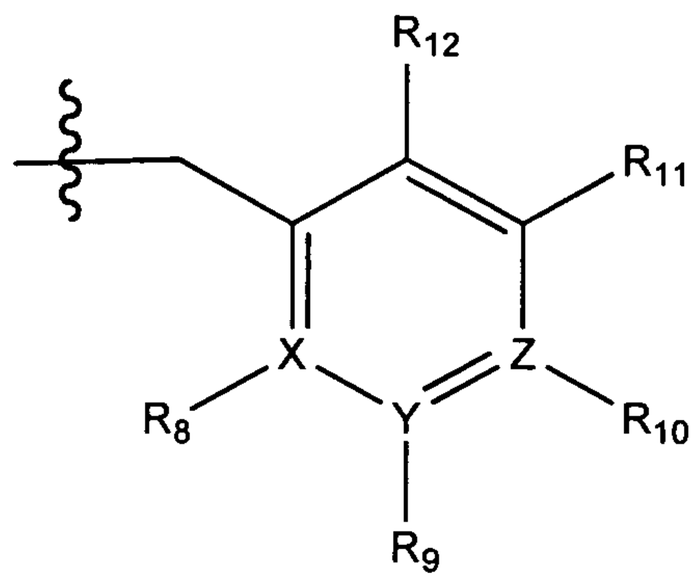
arylC_{1-4}alkyl (e.g., benzyl),

wherein the aryl or heteroaryl is optionally substituted with one or more halo (e.g., F, Cl), hydroxy or C_{1-6}alkoxy (e.g., methoxy), for example, R_6 is 4-hydroxyphenyl or 4-fluorophenyl,

and the remaining substituents are as previously defined in Formula I or II or any of 1.1-1.76, in free or salt form.

[0011] In another embodiment, the invention provides a Compound of Formula I or II, wherein

R_5 is attached to one of the nitrogens on the pyrazolo portion of Formula I or II 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_{1-4}alkyl,

C_{3-7}cycloalkyl,

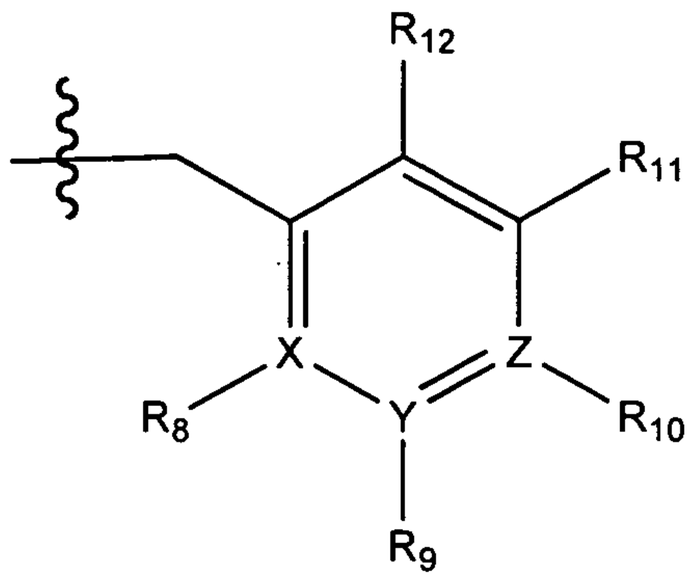
heterocycloalkyl (e.g., pyrrolidinyl or piperidinyl),
C_{1-4}haloalkyl (e.g., trifluoromethyl),
aryl (e.g., phenyl),
heteroaryl (e.g., pyridyl (for example pyrid-2-yl), or thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl)), diazolyl, triazolyl, tetrazolyl,
arylcarbonyl (e.g., benzoyl),
alkylsulfonyl (e.g., methylsulfonyl),
heteroarylcarbonyl, or
alkoxycarbonyl,
wherein said 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 Z is nitrogen, R_8, R_9, or R_{10}, respectively, is not present;

R_6 is:
H,
C_{1-4}alkyl (e.g., methyl),
C_{3-7}cycloalkyl (e.g., cyclopentyl),
aryl (e.g., phenyl),
heteroaryl (e.g., pyridyl, for example, pyrid-4-yl),
arylC_{1-4}alkyl (e.g., benzyl),
wherein the aryl or heteroaryl is optionally substituted with one or more halo (e.g., F, Cl), hydroxy or C_{1-6}alkoxy (e.g., methoxy), for example, R_6 is 4-hydroxyphenyl or 4-fluorophenyl,

and the remaining substituents are as previously defined in Formula I or II or any of 1.1-1.76, in free or salt form.

[0012] In still another embodiment, the invention provides a Compound of Formula I or II, wherein

R_5 is attached to one of the nitrogens on the pyrazolo portion of Formula I or II 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_{1-4}alkyl,

C_{3-7}cycloalkyl,

heterocycloalkyl (e.g., pyrrolidinyl or piperidinyl),

C_{1-4}haloalkyl (e.g., trifluoromethyl),

aryl (e.g., phenyl),

heteroaryl (e.g., pyridyl (for example pyrid-2-yl), or thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl)), diazolyl, triazolyl, tetrazolyl,

arylcarbonyl (e.g., benzoyl),

alkylsulfonyl (e.g., methylsulfonyl),

heteroarylcarbonyl, or

alkoxycarbonyl,

wherein said 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 Z is nitrogen, R_8, R_9, or R_{10}, respectively, is not present;

R_6 is:

H,

C_{1-4}alkyl (e.g., methyl),

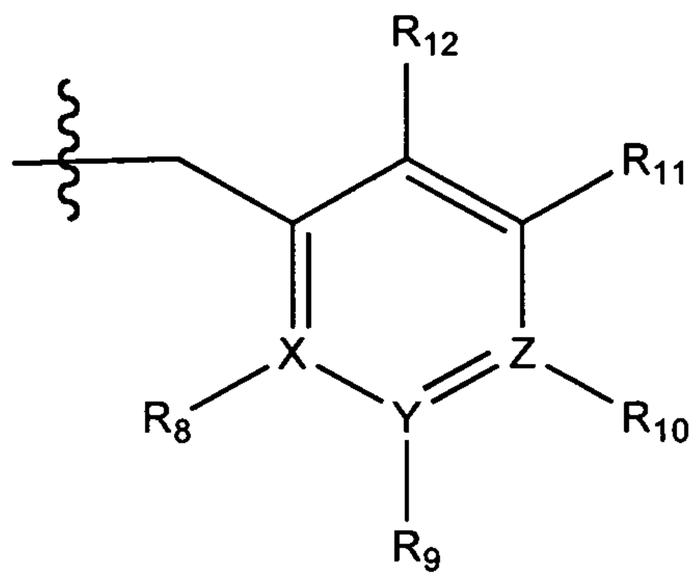
aryl (e.g., phenyl),

heteroaryl (e.g., pyridyl, for example, pyrid-4-yl),
wherein the aryl or heteroaryl is optionally substituted with one or more halo (e.g., F, Cl), hydroxy or C_{1-6}alkoxy (e.g., methoxy), for example, R_6 is 4-hydroxyphenyl or 4-fluorophenyl,

and the remaining substituents are as previously defined in Formula I or II or any of 1.1-1.76, in free or salt form.

[0013] In yet another embodiment, the invention provides a Compound of Formula I or II, wherein

R_5 is attached to one of the nitrogens on the pyrazolo portion of Formula I or II 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

heterocycloalkyl (e.g., pyrrolidinyl or piperidinyl),
aryl (e.g., phenyl),
heteroaryl (e.g., pyridyl (for example pyrid-2-yl), or thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl)), diazolyl, triazolyl, tetrazolyl,
wherein said aryl, heteroaryl 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 Z is nitrogen, R_8, R_9, or R_{10}, respectively, is not present;

R_6 is:

H,
C_{1-4}alkyl (e.g., methyl),

aryl (e.g., phenyl),

heteroaryl (e.g., pyridyl, for example, pyrid-4-yl),

wherein the aryl or heteroaryl is optionally substituted with one or more halo (e.g., F, Cl), hydroxy or C_{1-6}alkoxy (e.g., methoxy), for example, R_6 is 4-hydroxyphenyl or 4-fluorophenyl,

and the remaining substituents are as previously defined in Formula I or II or any of 1.1-1.76, in free or salt form.

[0014] 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 nine 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.

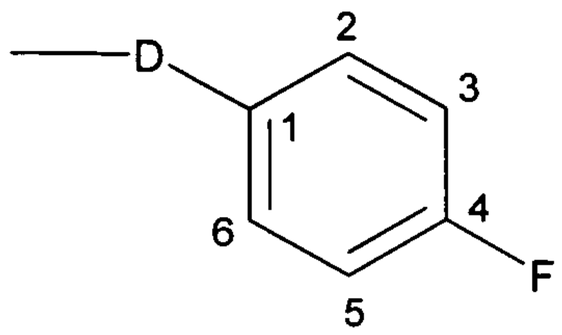
(c) "Heterocycloalkyl" is, unless otherwise indicated, saturated or unsaturated nonaromatic hydrocarbon moiety, preferably saturated, preferably comprising three to nine carbon atoms, at least some of which form a nonaromatic mono- or bicyclic, or bridged cyclic structure, wherein at least one carbon 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 $–CH_2–C_6H_4–$.

[0015] Compounds of the Invention, e.g., substituted 4,5,7,8-tetrahydro-(1H or 2H)-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine or a substituted 3-(thio, sulfinyl or sulfonyl)-7,8,9-trihydro-(1H or 2H)-pyrimido[1,2-a]pyrazolo[4,3-e]pyrimidin-4(5H)-one compounds, e.g., Compounds of Formula I, e.g., any of formulae 1.1-1.76, 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 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.

[0016] 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.

[0017] 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.

[0018] In another embodiment, the invention further provides a pharmaceutical composition comprising a Compound of the Invention, in free, pharmaceutically acceptable salt or prodrug form, in admixture with a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

Methods of Making Compounds of the Invention

[0019] 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. Various starting materials and/or Compounds of the Invention may be prepared using methods described in WO 2006/133261 and PCT/US2007/070551. All references cited herein are hereby incorporated by reference in their entirety.

[0020] The Compounds of the Invention include their enantiomers, diastereoisomers 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.

[0021] 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 the 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.

[0022] 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.

[0023] Terms and abbreviations:

BuLi = n-butyllithium

Bu^tOH = *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,

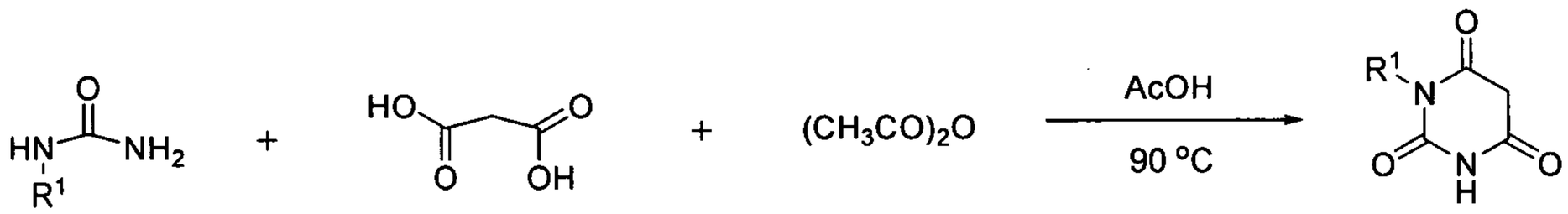
TFA = trifluoroacetic acid,

TFMSA = trifluoromethanesulfonic acid

THF = tetrahedrofuran.

[0024] The synthetic methods in this invention are illustrated below. The significances for the R groups are as set forth above for formula I or II unless otherwise indicated.

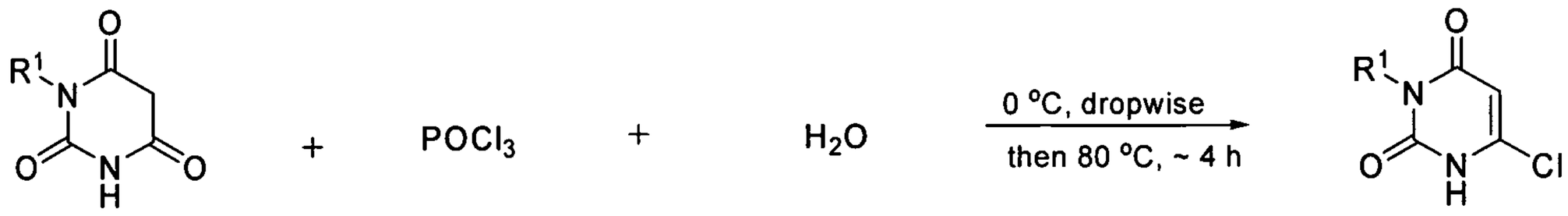
[0025] In an aspect of the invention, intermediate compounds of formula **IIb** can be synthesized by reacting a compound of formula **IIa** with a dicarboxylic acid, acetic anhydride and acetic acid mixing with heat for about 3 hours and then cooled:



(IIa) **(IIb)**

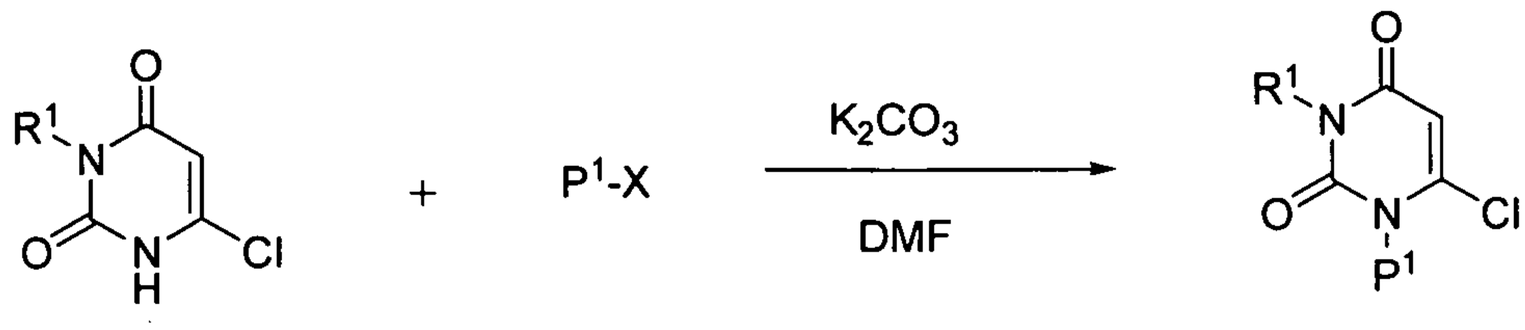
wherein R^1 is methyl.

[0026] 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)**

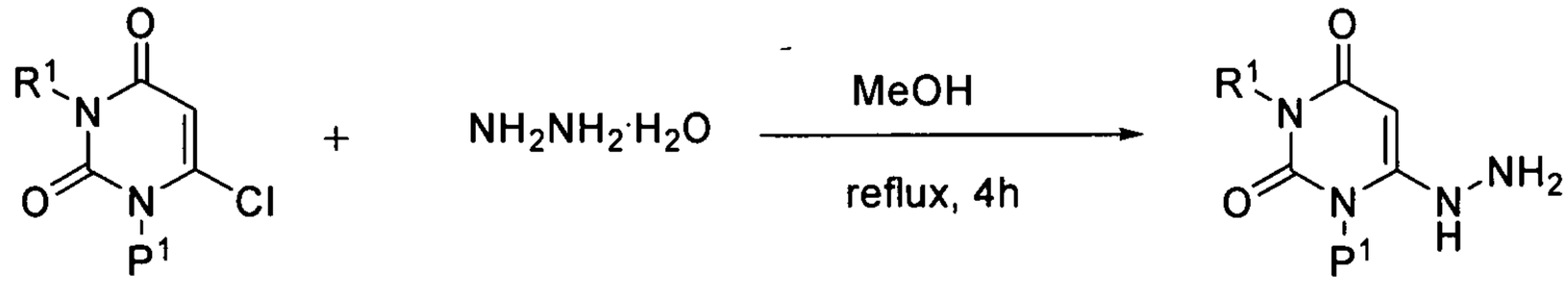
[0027] Intermediate **IId** may be formed by reacting a compound of **IIc** with for example a P^1-X in a solvent such as DMF and a base such as K_2CO_3 at room temperature or with heating:



(IIc) (IId)

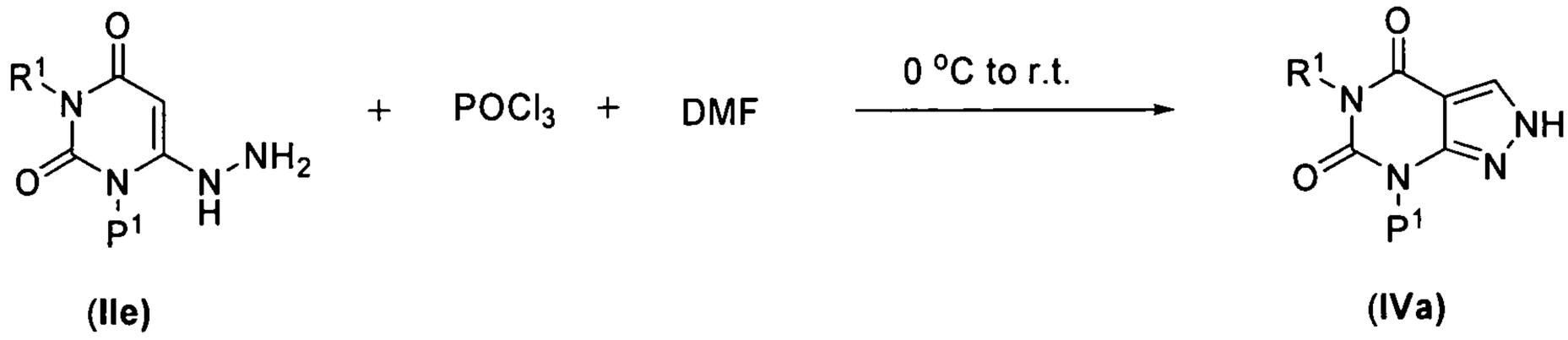
wherein P^1 is a protective group [e.g., *p*-methoxybenzyl group (PMB)]; X is a leaving group such as a halogen, mesylate, or tosylate.

[0028] 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)

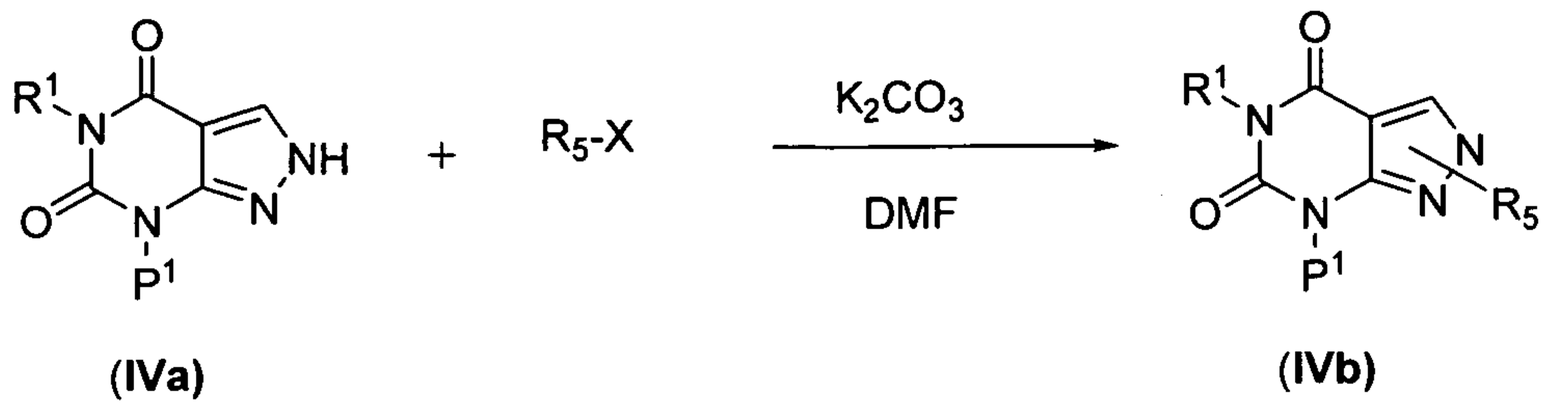
[0029] Intermediate **IVa** may be formed by for example reacting a compound of **IIe** with $POCl_3$ and DMF:



(IIe) (IVa)

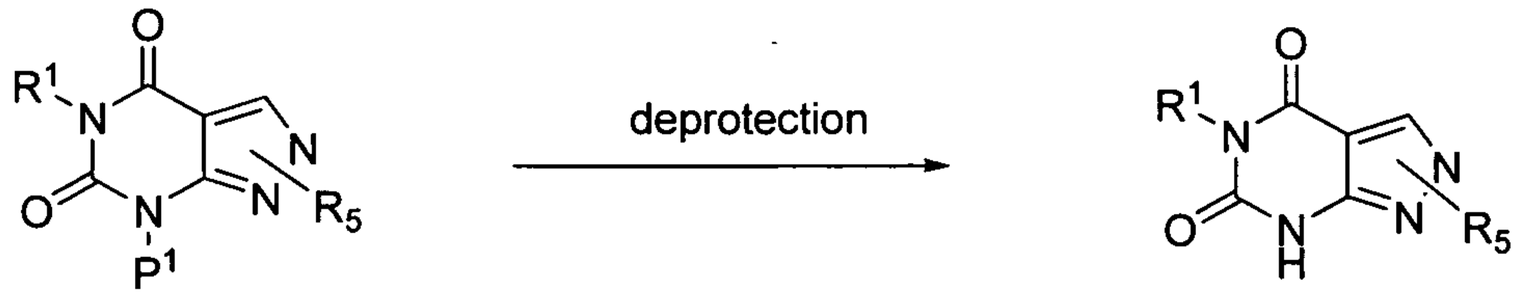
wherein R^1 is as defined previously in Formula I or II, e.g., such as a methyl group.

[0030] Intermediate **IVb** may be formed by reacting a compound of **IVa** with for example a R_5-X in a solvent such as DMF and a base such as K_2CO_3 at room temperature or with heating:



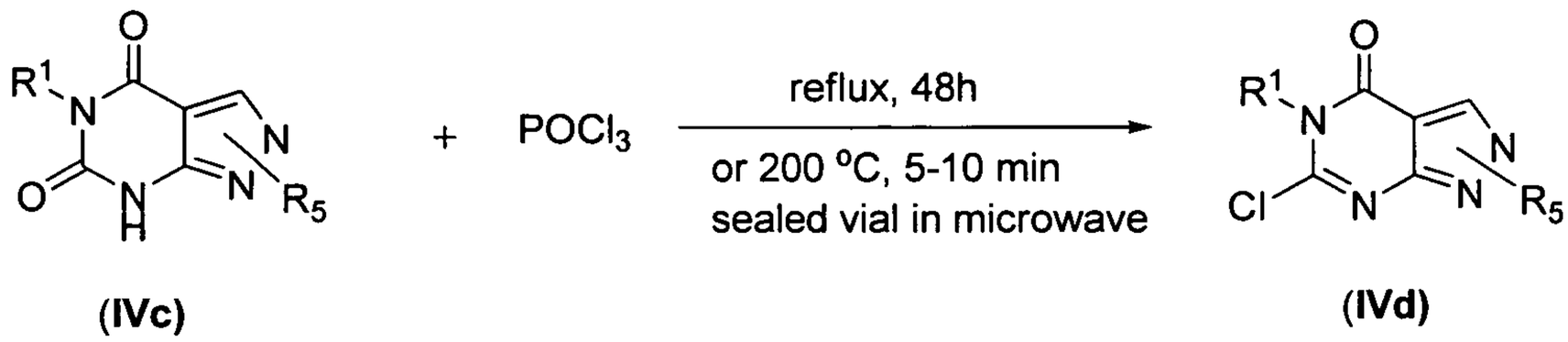
(IVa) (IVb)

[0031] Intermediate **IVc** may be synthesized from a compound of **IVb** by removing the protective group P^1 with an appropriate method. For example, if P^1 is a PMB group, then it can be removed with CAN or TFA/TFMSA at room temperature:



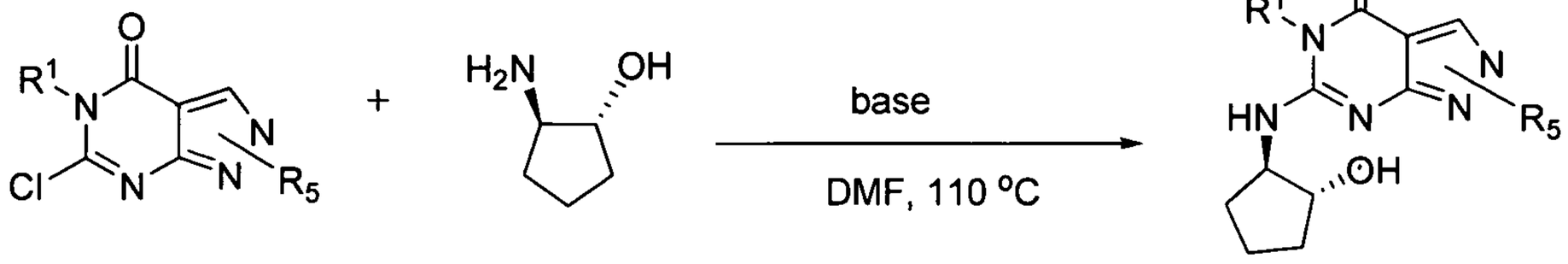
(IVb) (IVc)

[0032] Intermediate **IVd** can be prepared by reacting a compound of **IVc** with for example a chlorinating compound such as $POCl_3$ and refluxed for about 2 days, or heated at 150~200 °C for about 10 min in a sealed vial with a microwave instrument and then cooled:



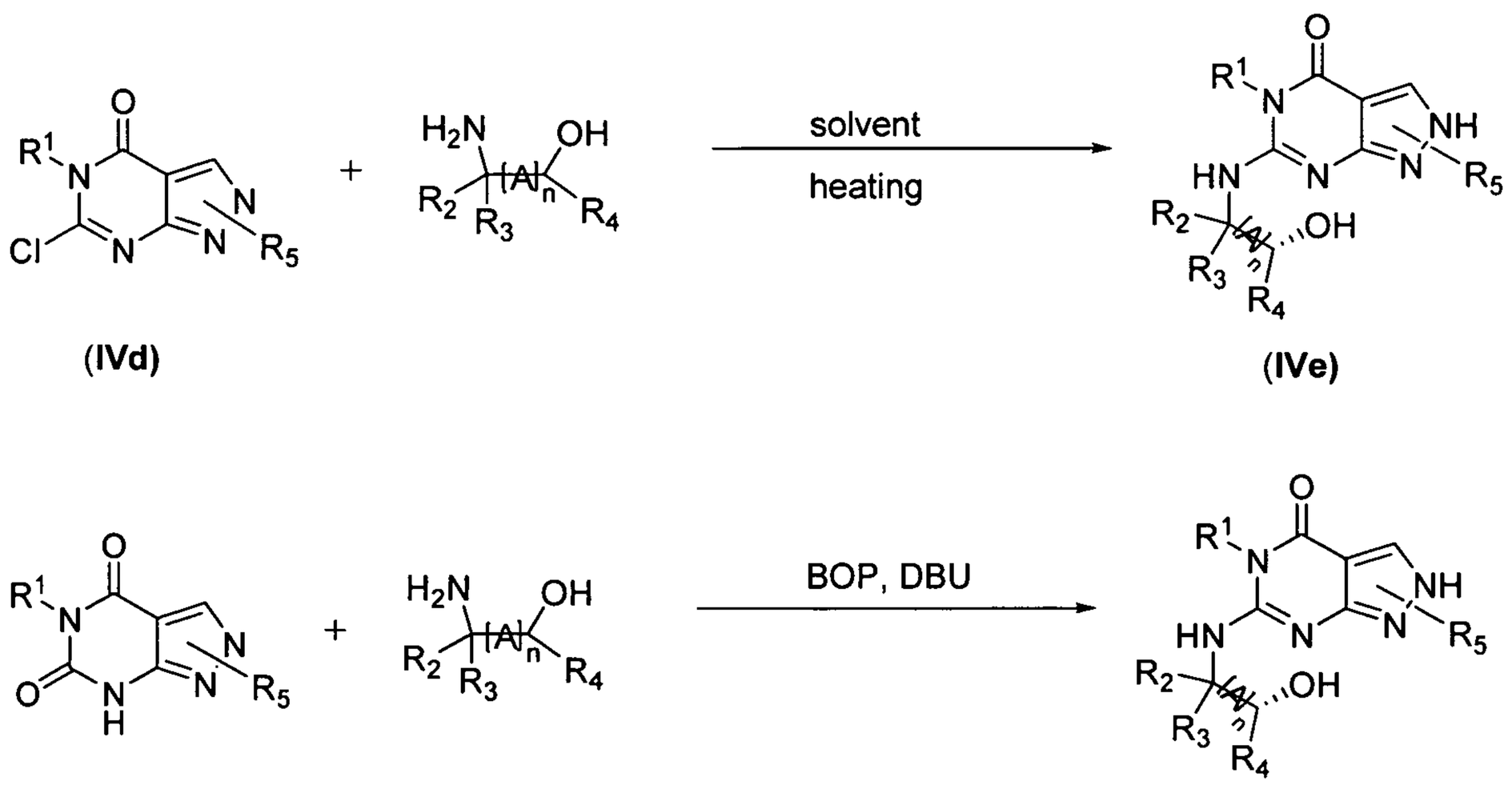
(IVc) (IVd)

[0033] Intermediate **IVe** can be formed by reacting a compound of **IVd** with an amino alcohol under basic condition in a solvent such as DMF and heated overnight then cooled:



(IVd) **(IVe)**

[0034] Alternatively, intermediate **IVe** can be synthesized directly from a compound of **IVc** by reacting with an amino alcohol and a coupling reagent such as BOP in the presence of a base such as DBU:

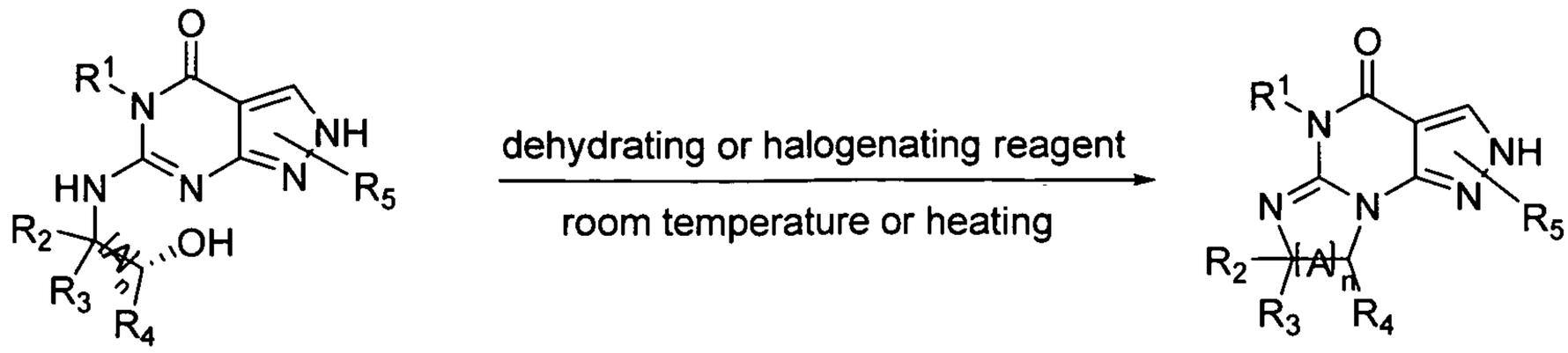


(IVd) **(IVe)**

(IVc) **(IVe)**

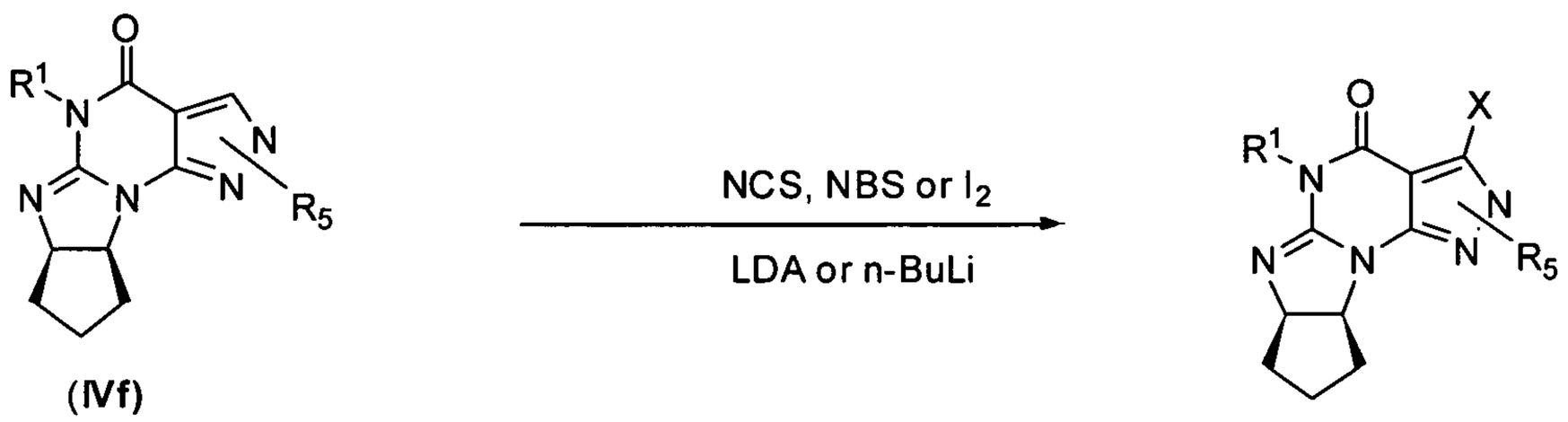
wherein all the substituents are as defined previously.

[0035] Compound **IVf** may be formed by reacting a compound of **IVe** with for example a dehydrating/halogenating agent such as $SOCl_2$ in a solvent such as CH_2Cl_2 at room temperature overnight or heated at 35 °C for several hours, and then cooled.



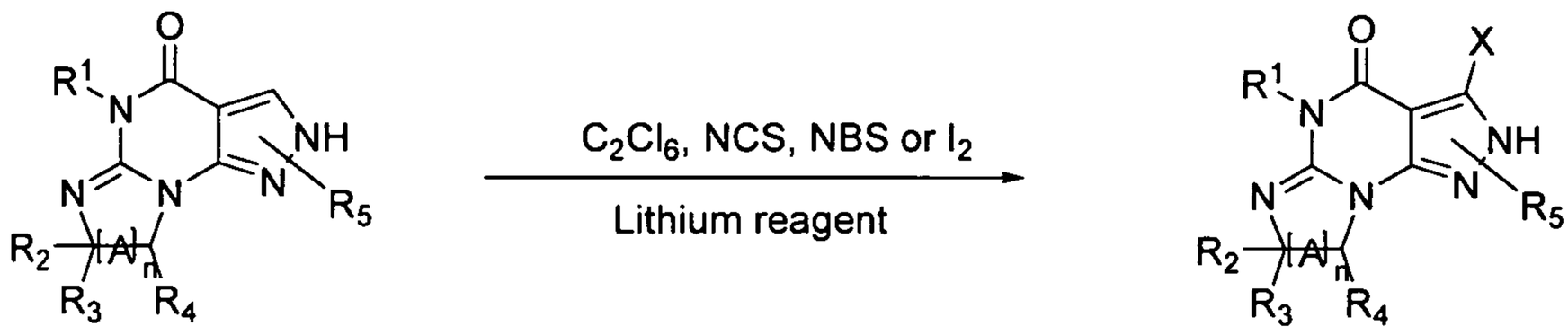
(IVe) (IVf)

[0036] Compound **IVg** may be formed by reacting a compound of **IVf** with for example a halogenating agent such as NCS and a base such as LDA in a solvent such as THF at low temperature for several hours.



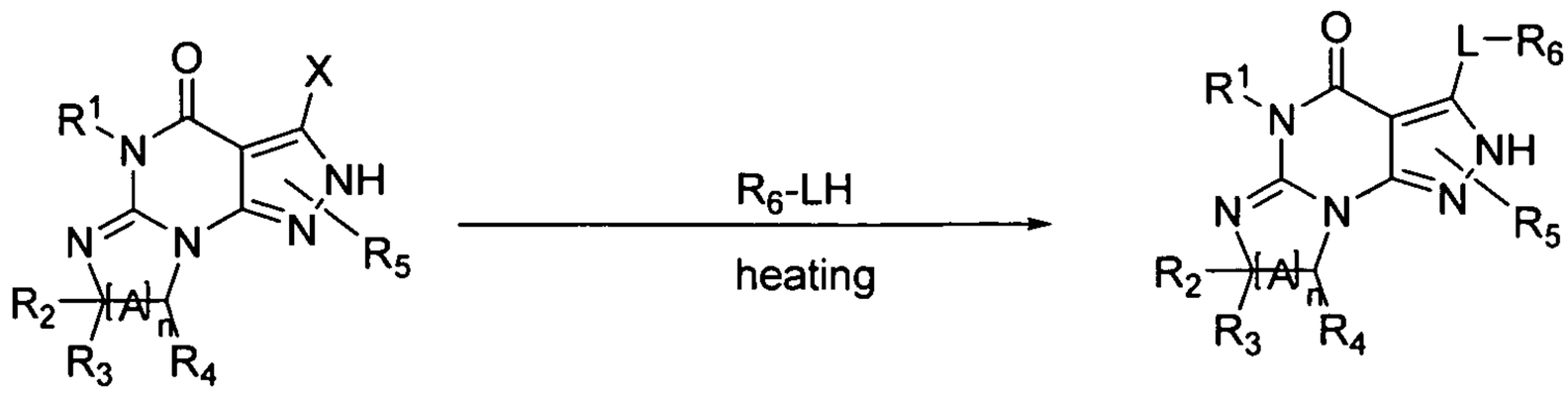
(IVf) (IVg)

[0037] Alternatively, Compound **IVg** may be formed by reacting a compound of **IVf** with for example a halogenating agent such as hexachloroethane and a base such as LiHMDS in a solvent such as THF at low temperature for several hours:



(IVf) (IVg)

[0038] Compound **I** may be formed by reacting a compound of **IVg** with R_6-LH for example a thiol upon heating.

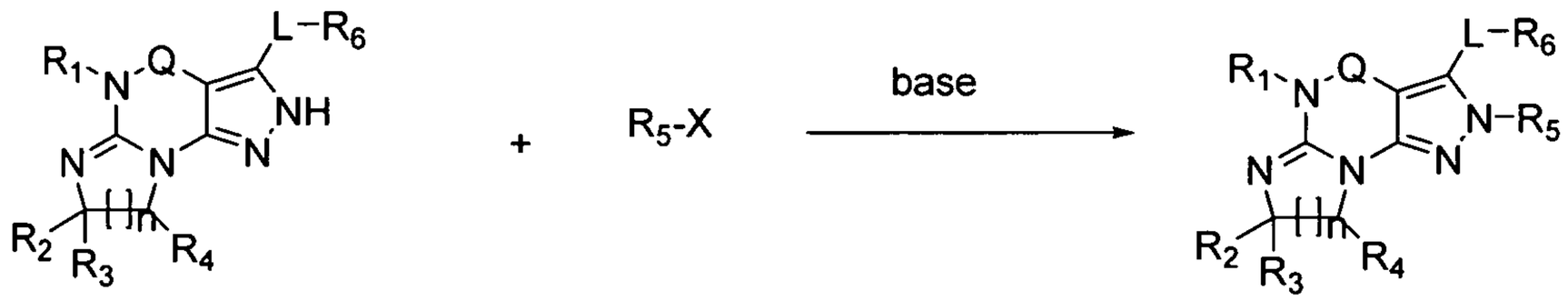


(IVg) (I)

[0039] Alternatively, compound **I** may be formed by reacting a compound of **IVf** with a thiol R_6-LH or a disulfide R_6-L-L-R_6 in the presence of a strong base, such as a lithium reagent (e.g. LiHMDS) in a solvent such as THF.

[0040] The corresponding sulfinyl or sulfonyl derivative may be formed by reacting the 3-thio compound (e.g., wherein L is –S-) with an oxidizer such as a peroxide (e.g. oxone or hydrogen peroxide) at room temperature in a solvent such as acetonitrile.

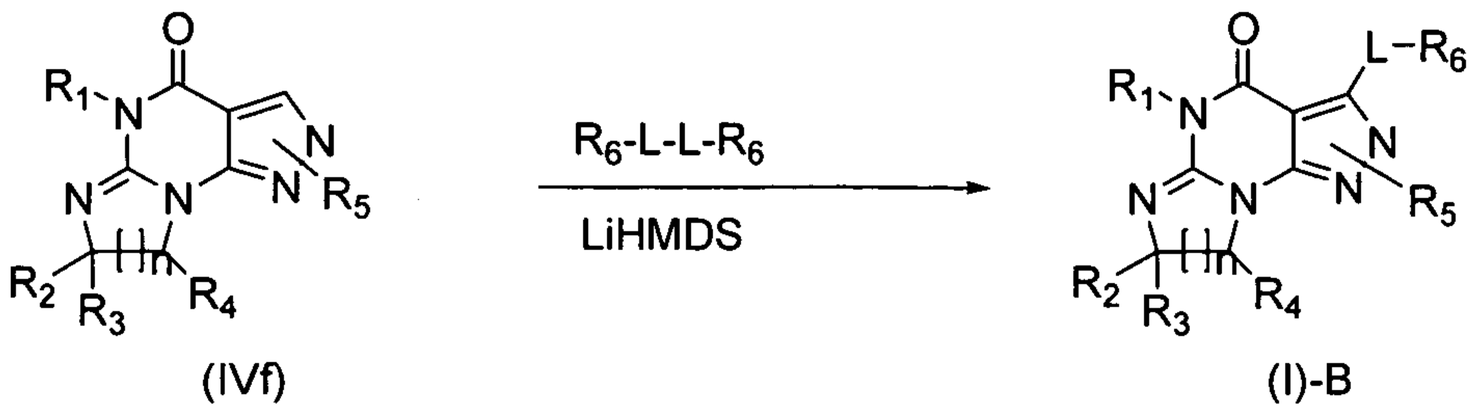
[0041] In another aspect of the invention, The invention thus provides methods of making Compounds of Formula I or II, for example, comprising reacting Compounds **1-A** with, for example, R_5-X, in a solvent such as DMF and a base such as K_2CO_3 at room temperature or with heating:



1-A (I)-A

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

[0042] The thio Compounds of the Invention, e.g., Formula I or II wherein L is S or Compound **(I)-B** may be prepared by reacting compound (**IVf**), e.g., with a disulfide and lithium bis(trimethylsilyl)azanide (LiHMDS).



(IVf) (I)-B

[0043] The sulfinyl or sulfonyl derivatives of the Invention, e.g., Formula I or II, wherein L is SO or SO_2 may be prepared by **(I)-B** oxidation using, e.g. oxone, in a solvent such as acetonitrile and methanol.

[0044] *Methods of using Compounds of the Invention*

[0045] 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.

[0046] 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 any of 1.1-1.76, in free, pharmaceutically acceptable salt or prodrug 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, in free or pharmaceutically acceptable salt form.

[0047] 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, e.g., a compound according to any of Formula I or any of 1.1-1.76, 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, pharmaceutically acceptable salt or prodrug form, to a human or animal patient in need thereof. 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.

[0048] 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 I or any of any of 1.1-1.76, in free, pharmaceutically acceptable salt or prodrug 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.

[0049] 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 or any of any of 1.1-1.76, 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, pharmaceutically acceptable salt or prodrug 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.

[0050] 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, e.g., Formula I or any of any of 1.1-1.76, sufficient to inhibit PDE1B activity. The invention further 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 Formula II, in free or salt form, sufficient to inhibit PDE1 activity, e.g., PDE1A or PDE1B activity.

[0051] 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 to the patient an effective amount of a Compound of the Invention, e.g., Formula I or any of any of 1.1-1.76, in that inhibits PDE1B, wherein PDE1B activity modulates phosphorylation of DARPP-32 and/or the GluR1 AMPA receptor. Similarly, the invention 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 to the patient an effective amount of a Compound of Formula II as hereinbefore described, in free or pharmaceutically acceptable salt form.

[0052] In another aspect, the invention also provides a method for the treatment 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 directly reach the bloodstream, or oral methods of administration, for example.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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 β_1, or β_2, or β_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.

[0059] 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.

[0060] 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] In a particular embodiment, the Compounds of the Invention are particularly useful for the treatment or prophylaxis of schizophrenia.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] The present invention also provides

(i) a Compound of the Invention, e.g., Formula I or any of any of 1.1-1.76, or Formula II as hereinbefore described in free, pharmaceutically acceptable salt or prodrug form 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, e.g., Formula I or any of 1.1-1.76, or Formula II as hereinbefore described, in free, pharmaceutically acceptable salt or prodrug form, 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, e.g., Formula I or any of 1.1-1.76, or Formula II as hereinbefore described, in free, pharmaceutically acceptable salt or prodrug form, in combination or association with a pharmaceutically acceptable diluent or carrier, and

(iv) a pharmaceutical composition comprising a Compound of the Invention, e.g., Formula I or any of 1.1-1.76, or Formula II as hereinbefore described, in free, pharmaceutically acceptable salt or prodrug form, 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.

[0069] Therefore, the invention provides use of a Compound of the Invention, e.g., Formula I or any of 1.1-1.76, or Formula II as hereinbefore described, in free, pharmaceutically acceptable salt or prodrug form, or a Compound of the Invention in a pharmaceutical composition form, 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.

[0070] 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.

[0071] The phrase "Compounds of the Invention" or "PDE 1 inhibitors of the Invention" encompasses any and all of the compounds disclosed herewith, e.g., a Compound of Formula I or any of 1.1-1.76, or Formula II as hereinbefore described, in free or salt form.

[0072] 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.

[0073] For methods of treatment, the word "effective amount" is intended to encompass a therapeutically effective amount to treat a specific disease or disorder.

[0074] The term "pulmonary hypertension" is intended to encompass pulmonary arterial hypertension.

[0075] 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.

[0076] The term "comprising" as used in this disclosure is intended to be open-ended and does not exclude additional, unrecited elements or method steps.

[0077] Compounds of the Invention are in particular useful for the treatment of Parkinson's disease, narcolepsy and female sexual dysfunction.

[0078] Compounds of the Invention, e.g., Formula I or any of 1.1-1.76, or Formula II as hereinbefore described, in free or pharmaceutically acceptable salt form 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, e.g., 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.

[0079] 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.

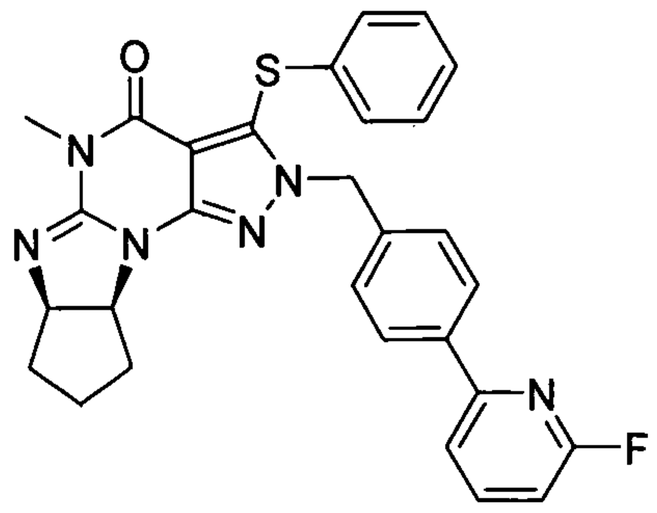
[0080] Pharmaceutical compositions comprising Compounds of the Invention may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets, capsules, solutions, suspensions and the like.

EXAMPLES

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:

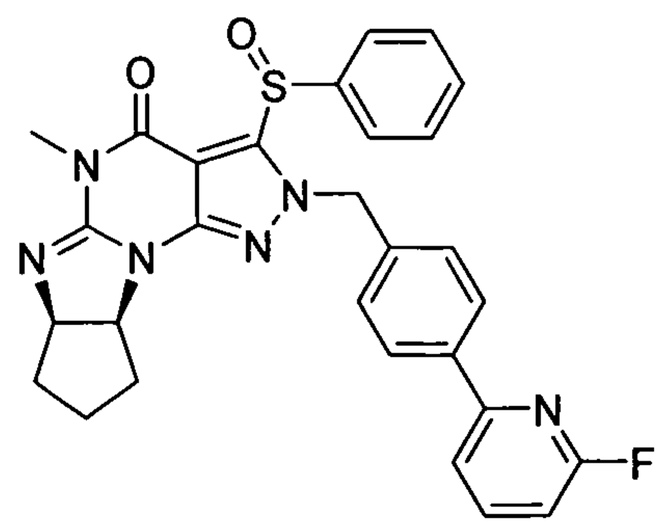
(6aR,9aS)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylthio)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(2H)-one



[0081] (6a*R*,9a*S*)-5,6a,7,8,9,9a-hexahydro-5-methyl-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-4(2*H*)-one (56.8 mg, 0.136 mmol) and phenyl disulfide (59.6 mg, 0.273 mmol) are dissolved in 1 mL of anhydrous THF, and then 273 uL of 1.0 M LiHMDS in THF is added dropwise. The reaction mixture is stirred at room temperature for an hour, and then quenched with saline. The mixture is separated with a semi-preparative HPLC to give 27 mg of pure product as yellow solids. MS (ESI) m/z 525.2 $[M+H]^+$.

Example 2:

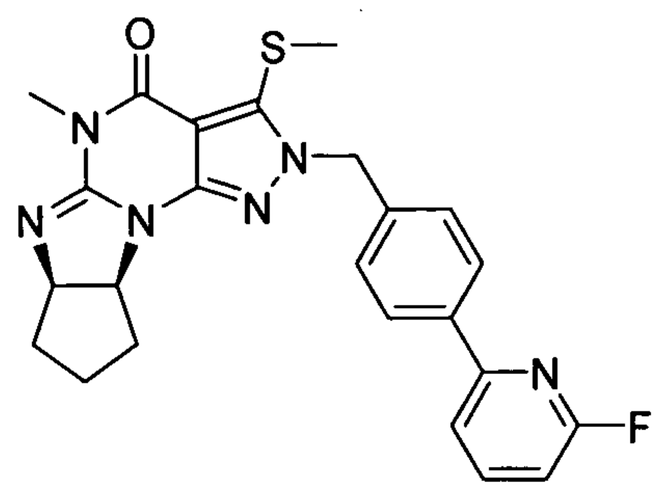
(6aR,9aS)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylsulfinyl)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(2H)-one



[0082] (6aR,9aS)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylthio)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(2H)-one (12 mg, 0.023 mmol) is dissolved in CH_3CN (2 mL) and CH_3OH (2 mL), and then an aqueous solution of oxone is added. The reaction mixture is stirred at room temperature for a week, and then purified by a semi-preparative HPLC to give pure product as white solids. MS (ESI) m/z 541.2 $[M+H]^+$.

Example 3:

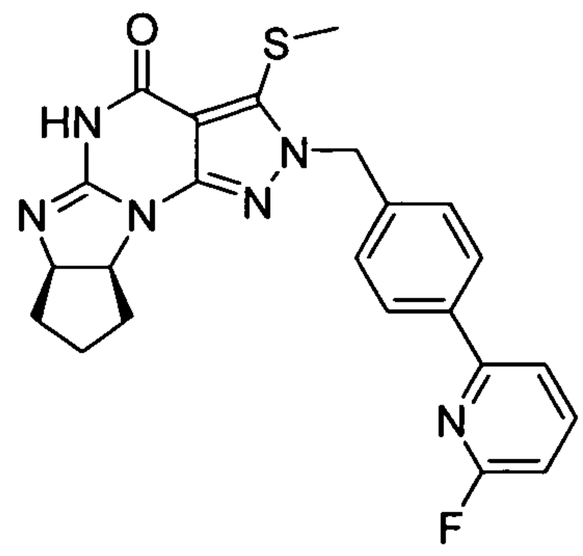
(6aR,9aS)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(methylthio)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(2H)-one



[0083] (6a*R*,9a*S*)-5,6a,7,8,9,9a-hexahydro-5-methyl-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-4(2*H*)-one (50 mg, 0.12 mmol) and methyl disulfide (21.3 μL, 0.24 mmol) are dissolved in 1 mL of anhydrous THF, and then 360 uL of 1.0 M LDA in THF is added dropwise. The reaction mixture is stirred at room temperature for an hour, and then quenched with saline. The mixture is separated with a semi-preparative HPLC to give 6.8 mg of pure product as pale yellow solids. MS (ESI) m/z 463.2 $[M+H]^+$.

Example 4:

(6aR,9aS)-5,6a,7,8,9,9a-hexahydro -3-(methylthio)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(2H)-one

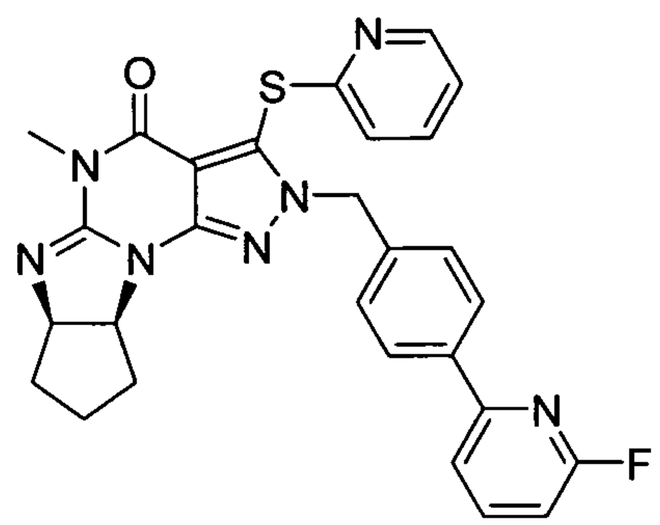


[0084] (6aR,9aS)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(methylthio)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(2H)-one (25 mg, 0.054 mmol) and P_4S_{10} (48.1 mg, 0.108 mmol) are placed in a

Biotage microwave vial, and then 1.0 mL of 7N ammonia in MeOH is added. The sealed vial is heated in a Biotage microwave at 150 °C for 6 h. After solvent is removed, the residue is suspended in DMF, and then filtered. The obtained filtrate is purified by a semi-preparative HPLC to give 10.6 mg of pure product as pale yellow solids (yield: 44%). MS (ESI) m/z 449.2 $[M+H]^+$.

Example 5:

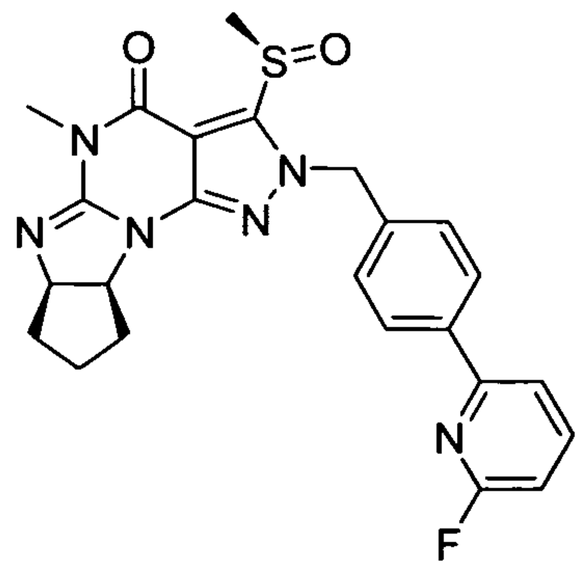
(6aR,9aS)-5,6a,7,8,9,9a-hexahydro -3-(pyridin-2-ylthio)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(2H)-one



[0085] The synthetic procedure of this compound is analogous to **EXAMPLE 1** wherein 2-pyridyl disulfide is used instead of phenyl disulfide. MS (ESI) m/z 526.2 $[M+H]^+$.

Example 6:

(6a*R*,9a*S*)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-((*R*)-methylsulfinyl)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(2H)-one

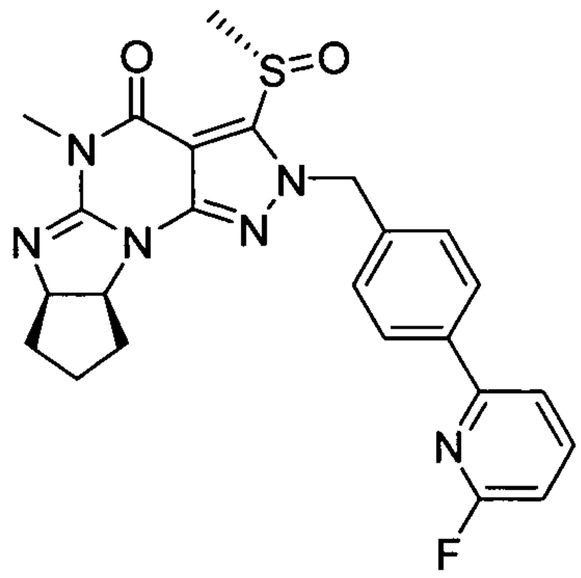


[0086] (6aR,9aS)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(methylthio)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-

4(2H)-one (35.2 mg, 0.076 mmol) is dissolved in CH_3CN (0.5 mL) and CH_3OH (2 mL), and then an aqueous solution of oxone (93.7 mg, 0.152 mmol) is added. The reaction mixture is stirred at room temperature for 20 h, and then purified by a semi-preparative HPLC to give pure product as white solids. MS (ESI) m/z 479.2 $[M+H]^+$.

Example 7:

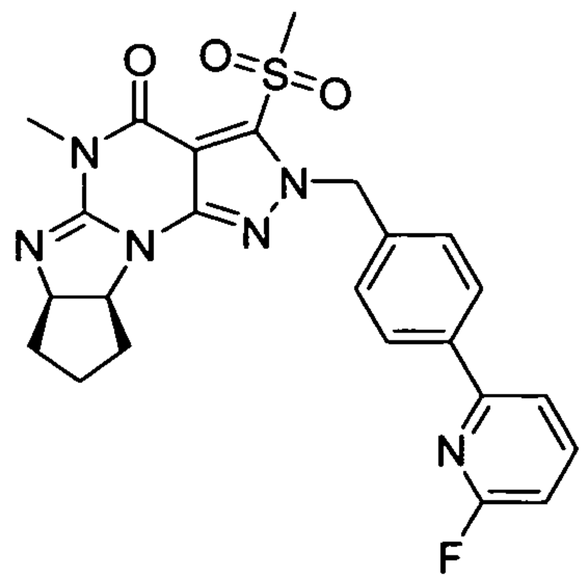
(6a*R*,9a*S*)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-((*S*)-methylsulfinyl)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(2H)-one



[0087] The synthetic procedure of this compound is the same as **EXAMPLE 6.** A pair of diastereoisomers is obtained during the synthesis. Both diastereoisomers can be separated using an achiral reversed-phase HPLC column. Product is obtained as white solids. MS (ESI) m/z 479.2 $[M+H]^+$.

Example 8:

(6a*R*,9a*S*)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(methylsulfonyl)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(2H)-one



[0088] (6aR,9aS)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(methylthio)-2-(4-(6-fluoropyridin-2-yl)benzyl)-cyclopent[4,5]imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-

4(2H)-one (35.2 mg, 0.076 mmol) is dissolved in CH_3CN (0.5 mL) and CH_3OH (2 mL), and then an aqueous solution of oxone (139 mg, 0.226 mmol) is added. The reaction mixture is stirred at room temperature for 2 days, and then purified by a semi-preparative HPLC to give pure product as white solids. MS (ESI) m/z 495.2 $[M+H]^+$.

EXAMPLE 9

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

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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. The compounds are mixed and pre-incubated with the enzyme for 10 min at room temperature.

[0093] 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).

[0094] 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).

[0095] 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 1μM, e.g., some less than 250nM, some less than 10nM, some less than 5nM, e.g., the Compounds of Examples 1, 2 and 3 generally have IC_{50} values of less than 250 nM.

Example 10

PDE1 inhibitor effect on sexual response in female rats

[0096] The effect of PDE1 inhibitors on Lordosis Response in female rats may be measured as described in Mani, et al., Science (2000) 287: 1053. Ovariectomized and cannulated wild-type rats are primed with 2 μg estrogen followed

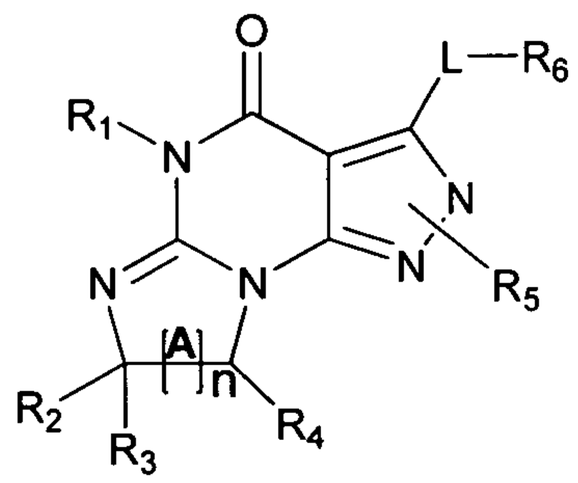
24 hours later by intracerebroventricular (icv) injection of progesterone (2 μg), PDE1 inhibitors of the present invention (0.1mg, 1.0mg or 2.5mg) or sesame oil vehicle (control). The rats are tested for lordosis response in the presence of male rats. Lordosis response is quantified by the lordosis quotient (LQ = number of lordosis/10 mounts x 100).

CLAIMS

What is claimed is:

1. An optionally substituted 3-(thio, sulfinyl or sulfonyl)-7,8-dihydro-(1H or 2H)-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidin-4(5H)-ones or or a substituted 3-(thio, sulfinyl or sulfonyl)-7,8,9-trihydro-(1H or 2H)-pyrimido[1,2-a]pyrazolo[4,3-e]pyrimidin-4(5H)-one, in free or salt form.

2. The compound according to claim 1, wherein said compound is a Compound of Formula II



Formula II

wherein

(i) L is S, SO or SO_2;

(ii) R_1 is H or C_{1-4} alkyl (e.g., methyl or ethyl);

(iii) R_4 is H or C_{1-6} alkyl (e.g., methyl, isopropyl) and R_2 and R_3 are, independently, H or C_{1-6}alkyl (e.g., methyl or isopropyl) optionally substituted with halo or hydroxy (e.g., R_2 and R_3 are both methyl, or R_2 is H and R_3 is methyl, ethyl, isopropyl or hydroxyethyl), aryl, heteroaryl, (optionally hetero)arylalkoxy, (optionally hetero)arylC_{1-6}alkyl or R_2 and R_3 together form a 3- to 6-membered ring;

or

R_2 is H and R_3 and R_4 together form a di-, tri- or tetramethylene bridge (pref. wherein the R_3 and R_4 together have the *cis* configuration, e.g., where the carbons carrying R_3 and R_4 have the R and S configurations, respectively);

(iv) R_5 is

d) –D-E-F, wherein:

D is C_{1-4}alkylene (e.g., methylene, ethylene or prop-2-yn-1-ylene);

E is a single bond, C_{2-4}alkynylene (e.g., –C≡C–), arylene (e.g., phenylene) or heteroarylene (e.g., pyridylene);

F is

H,

aryl (e.g., phenyl),

heteroaryl (e.g., pyridyl, diazolyl, triazolyl, for example, pyrid-2-yl, imidazol-1-yl, 1,2,4-triazol-1-yl),

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

haloC_{1-4}alkyl (e.g., trifluoromethyl),

-C(O)-R_{15},

-N(R_{16})(R_{17}),

-S(O)$_2R_{21}$ or

C_{3-7}cycloalkyl optionally containing at least one atom selected from a group consisting of N or O (e.g., cyclopentyl, cyclohexyl, pyrrolidinyl (e.g., pyrrolidin-3-yl), tetrahydro-*2H*-pyran-4-yl, or morpholinyl);

wherein D, E and F are independently and optionally substituted with one or more

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

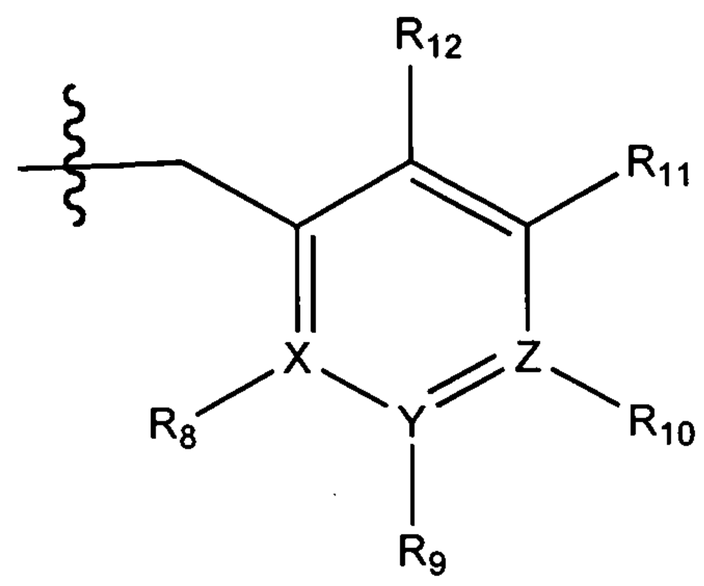
C_{1-4}alkyl (e.g., methyl),

haloC_{1-4}alkyl (e.g., trifluoromethyl),

for example, F is heteroaryl, e.g., pyridyl substituted with one or more halo (e.g., 6-fluoropyrid-2-yl, 5-fluoropyrid-2-yl, 6-fluoropyrid-2-yl, 3-fluoropyrid-2-yl, 4-fluoropyrid-2-yl, 4,6-dichloropyrid-2-yl), haloC_{1-4}alkyl (e.g., 5-trifluoromethylpyrid-2-yl) or C_{1-4}alkyl (e.g., 5-methylpyrid-2-yl), or F is aryl, e.g., phenyl, substituted with one or more halo (e.g., 4-fluorophenyl) or F is a C_{3-7}heterocycloalkyl (e.g., pyrrolidinyl) optionally substituted with a C_{1-6}alkyl (e.g., 1-methylpyrrolidin-3-yl); or

e) a substituted heteroarylalkyl, e.g., substituted with haloalkyl;

f) 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_{1-4}alkyl,

C_{3-7}cycloalkyl,

heteroC_{3-7}cycloalkyl (e.g., pyrrolidinyl or piperidinyl),

C_{1-4}haloalkyl (e.g., trifluoromethyl),

aryl (e.g., phenyl),

heteroaryl (e.g., pyridyl (for example pyrid-2-yl), or thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl)), diazolyl, triazolyl, tetrazolyl,

arylcarbonyl (e.g., benzoyl),

alkylsulfonyl (e.g., methylsulfonyl),

heteroarylcarbonyl, or

alkoxycarbonyl,

wherein said 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 Z is nitrogen, R_8, R_9, or R_{10}, respectively, is not present;

(v) R_6 is

H,

C_{1-4}alkyl (e.g., methyl),

C_{3-7}cycloalkyl (e.g., cyclopentyl),

aryl (e.g., phenyl),

heteroaryl (e.g., pyridyl, for example, pyrid-4-yl),

arylC_{1-4}alkyl (e.g., benzyl),

arylamino (e.g., phenylamino),

heterarylamino,

N,N-diC_{1-4}alkylamino,

N,N-diarylamino,

N-aryl-N-(arylC_{1-4}alkyl)amino (e.g., N-phenyl-N-(1,1'-biphen-4-ylmethyl)amino), or

$-N(R_{18})(R_{19})$;

wherein the aryl or heteroaryl is optionally substituted with one or more halo (e.g., F, Cl), hydroxy or C_{1-6}alkoxy (e.g., methoxy), for example, R_6 is 4-hydroxyphenyl or 4-fluorophenyl,

(vi) n = 0 or 1;

(vii) when n=1, **A** is $-C(R_{13}R_{14})-$, wherein R_{13} and R_{14}, are, independently, H or C_{1-4}alkyl, aryl, heteroaryl, (optionally hetero)arylC_{1-4}alkoxy or (optionally hetero)arylC_{1-4}alkyl or R_{13} or R_{14} can form a bridge with R_2 or R_4;

(viii) R_{15} is C_{1-4}alkyl, haloC_{1-4}alkyl, -OH or $-OC_{1-4}$alkyl (e.g., $-OCH_3$)

(ix) R_{16} and R_{17} are independently H or C_{1-4}alkyl;

(x) R_{18} and R_{19} are independently H, C_{1-4}alky, C_{3-8}cycloalkyl, heteroC_{3-8}cycloalkyl, aryl (e.g., phenyl) or heteroaryl, wherein said aryl or heteroaryl is optionally substituted with one or more halo (e.g., fluorophenyl, e.g., 4-fluorophenyl), hydroxy (e.g., hydroxyphenyl, e.g., 4-hydroxyphenyl or 2-hydroxyphenyl), C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, aryl,heteroaryl, or C_{3-8}cycloalkyl,

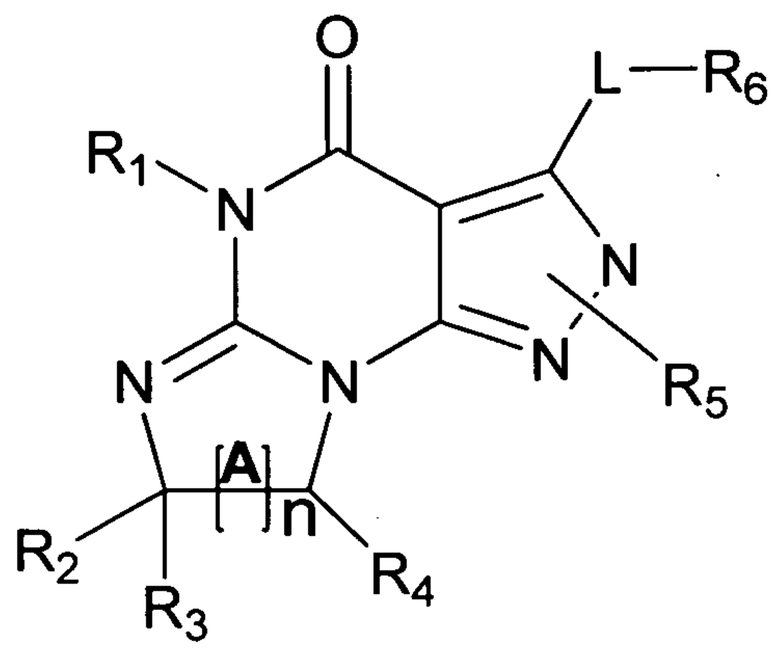
(xi) R_{20} is H, C_{1-4}alkyl (e.g., methyl) or C_{3-7}cycloalkyl,

(xii) R_{21} is C_{1-6}alkyl;

in free, salt or prodrug form.

3. The compound according to claim 1, wherein said compound is a Compound of

Formula I



Formula I

wherein

(i) L is a single bond, S, SO or SO_2;

(ii) R_1 is H or C_{1-4} alkyl (e.g., methyl or ethyl);

(iii) R_4 is H or C_{1-6} alkyl (e.g., methyl, isopropyl) and R_2 and R_3 are, independently, H or C_{1-6}alkyl (e.g., methyl or isopropyl) optionally substituted with halo or hydroxy (e.g., R_2 and R_3 are both methyl, or R_2 is H and R_3 is methyl, ethyl, isopropyl or hydroxyethyl), aryl, heteroaryl, (optionally hetero)arylalkoxy, or (optionally hetero)arylC_{1-6}alkyl;

or

R_2 is H and R_3 and R_4 together form a di-, tri- or tetramethylene bridge (pref. wherein the R_3 and R_4 together have the *cis* configuration, e.g., where the carbons carrying R_3 and R_4 have the R and S configurations, respectively);

(iv) R_5 is

a) –D-E-F, wherein:

D is C_{1-4}alkylene (e.g., methylene, ethylene or prop-2-yn-1-ylene);

E is a single bond, C_{2-4}alkynylene (e.g., –C≡C–), arylene (e.g., phenylene) or heteroarylene (e.g., pyridylene);

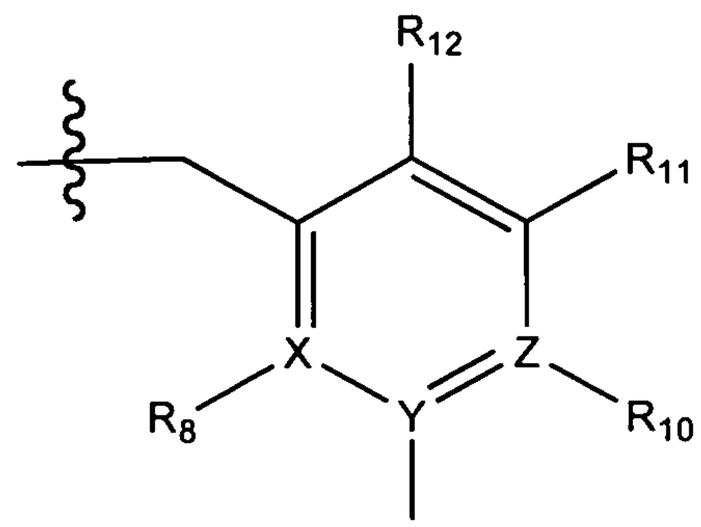
F is H, aryl (e.g., phenyl), heteroaryl (e.g., pyridyl, diazolyl, triazolyl, for example, pyrid-2-yl, imidazol-1-yl, 1,2,4-

triazol-1-yl), halo (e.g., F, Br, Cl), haloC_{1-4}alkyl (e.g., trifluoromethyl), -C(O)-R_{15}, -N(R_{16})(R_{17}), -$S(O)_2R_{21}$ or C_{3-7}cycloalkyl optionally containing at least one atom selected from a group consisting of N or O (e.g., cyclopentyl, cyclohexyl, pyrrolidinyl (e.g., pyrrolidin-3-yl), tetrahydro-*2H*-pyran-4-yl, or morpholinyl);

wherein D, E and F are independently and optionally substituted with one or more halo (e.g., F, Cl or Br), C_{1-4}alkyl (e.g., methyl), haloC_{1-4}alkyl (e.g., trifluoromethyl), for example, F is heteroaryl, e.g., pyridyl substituted with one or more halo (e.g., 6-fluoropyrid-2-yl, 5-fluoropyrid-2-yl, 6-fluoropyrid-2-yl, 3-fluoropyrid-2-yl, 4-fluoropyrid-2-yl, 4,6-dichloropyrid-2-yl), haloC_{1-4}alkyl (e.g., 5-trifluoromethylpyrid-2-yl) or C_{1-4}alkyl (e.g., 5-methylpyrid-2-yl), or F is aryl, e.g., phenyl, substituted with one or more halo (e.g., 4-fluorophenyl) or F is a C_{3-7}heterocycloalkyl (e.g., pyrrolidinyl) optionally substituted with a C_{1-6}alkyl (e.g., 1-methylpyrrolidin-3-yl); or

b) a substituted heteroarylalkyl, e.g., substituted with haloalkyl;

c) 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_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}haloalkyl (e.g., trifluoromethyl), aryl (e.g., phenyl), heteroaryl (e.g., pyridyl (for example pyrid-2-yl), or thiadiazolyl (e.g., 1,2,3-thiadiazol-

4-yl)), diazolyl, triazolyl, tetrazolyl, arylcarbonyl (e.g., benzoyl), alkylsulfonyl (e.g., methylsulfonyl), heteroarylcarbonyl, or alkoxycarbonyl; provided that when X, Y, or Z is nitrogen, R_8, R_9, or R_{10}, respectively, is not present;

(v) R_6 is

H,

C_{1-4}alkyl,

C_{3-7}cycloalkyl (e.g., cyclopentyl),

aryl (e.g., phenyl),

heteroaryl (e.g., pyridyl, for example, pyrid-4-yl),

arylC_{1-4}alkyl (e.g., benzyl),

arylamino (e.g., phenylamino),

heterarylamino,

N,N-diC_{1-4}alkylamino,

N,N-diarylamino,

N-aryl-N-(arylC_{1-4}alkyl)amino (e.g., N-phenyl-N-(1,1'-biphen-4-ylmethyl)amino), or

$-N(R_{18})(R_{19})$;

wherein the aryl or heteroaryl is optionally substituted with one or more halo (e.g., F, Cl), hydroxy or C_{1-6}alkoxy (e.g., methoxy), for example, R_6 is 4-hydroxyphenyl or 4-fluorophenyl,

(vi) n = 0 or 1;

(vii) when n=1, **A** is $-C(R_{13}R_{14})-$, wherein R_{13} and R_{14}, are, independently, H or C_{1-4}alkyl, aryl, heteroaryl, (optionally hetero)arylC_{1-4}alkoxy or (optionally hetero)arylC_{1-4}alkyl;

(viii) R_{15} is C_{1-4}alkyl, haloC_{1-4}alkyl, -OH or $-OC_{1-4}$alkyl (e.g., $-OCH_3$)

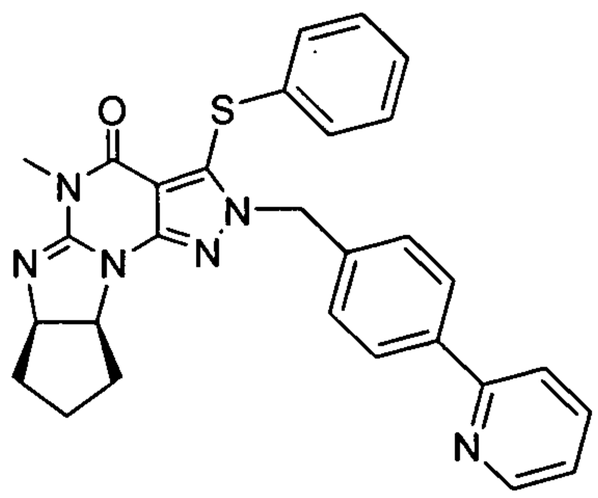
(ix) R_{16} and R_{17} are independently H or C_{1-4}alkyl;

(x) R_{18} and R_{19} are independently H, C_{1-4}alky or aryl (e.g., phenyl) wherein said aryl is optionally substituted with one or more halo (e.g., fluorophenyl, e.g., 4-fluorophenyl) or hydroxy (e.g., hydroxyphenyl, e.g., 4-hydroxyphenyl or 2-hydroxyphenyl)

(xi) R_{20} is H, C_{1-4}alkyl (e.g., methyl) or C_{3-7}cycloalkyl,

(xii) R_{21} is C_{1-6}alkyl.

4. The compound according to claim 1,2 or 3, selected from any of the following: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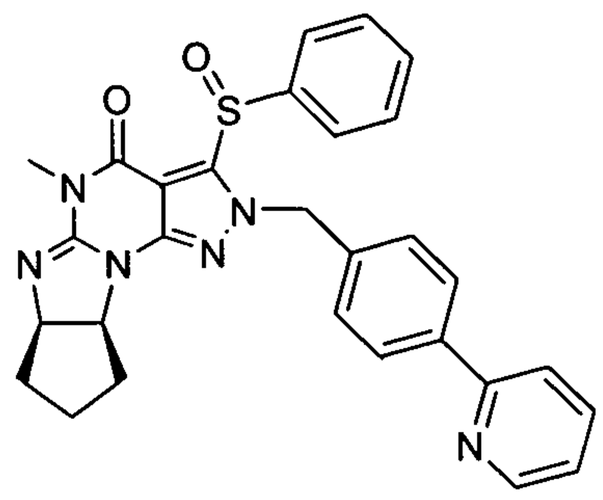
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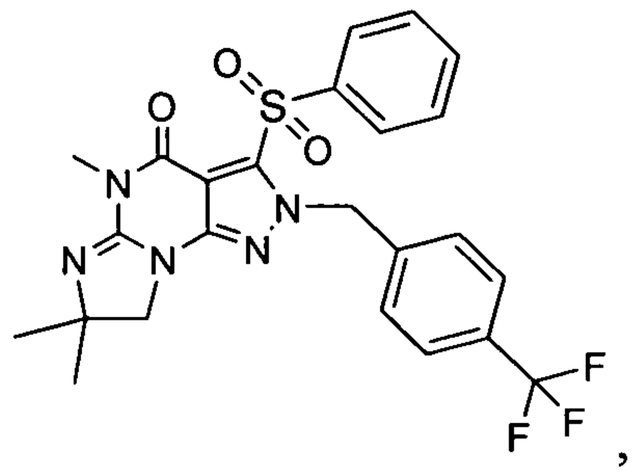
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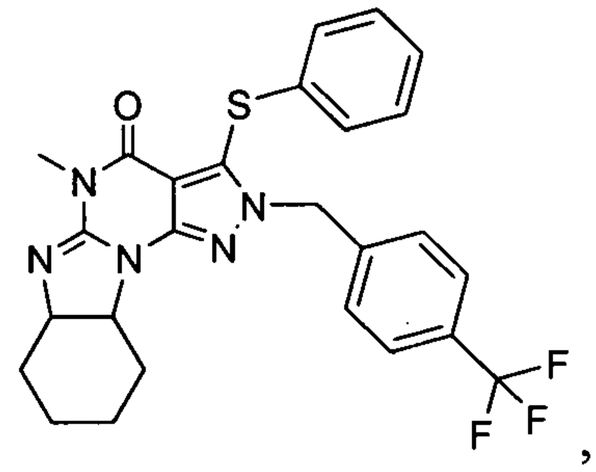
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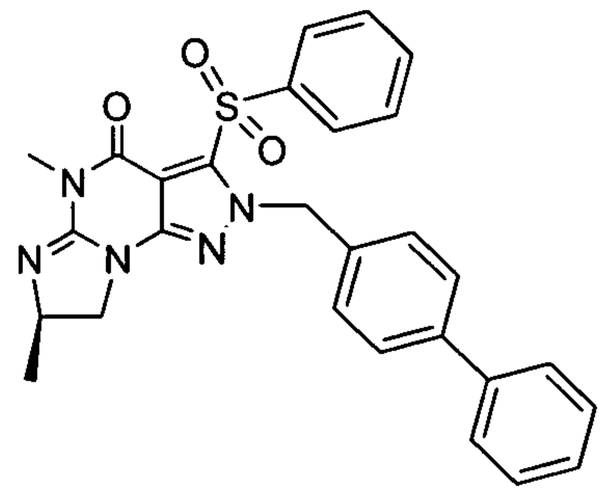
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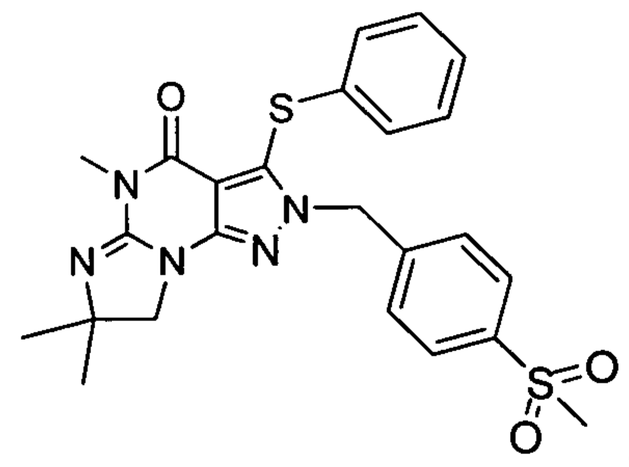
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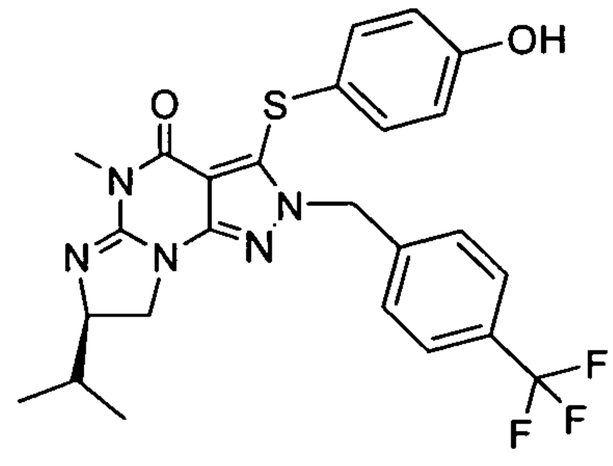
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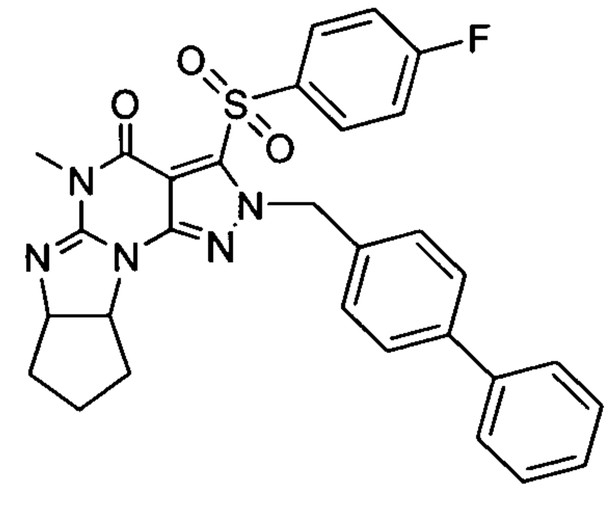
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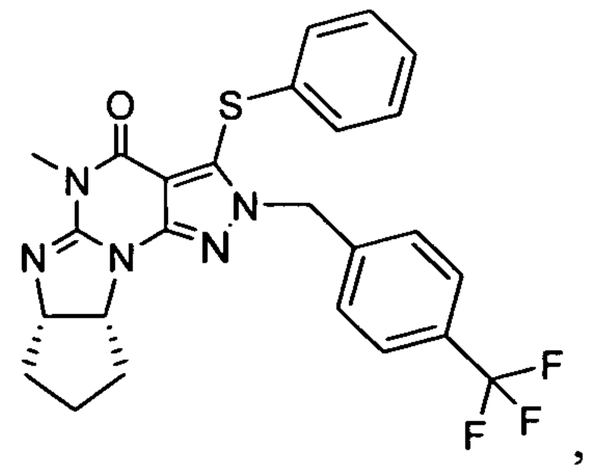
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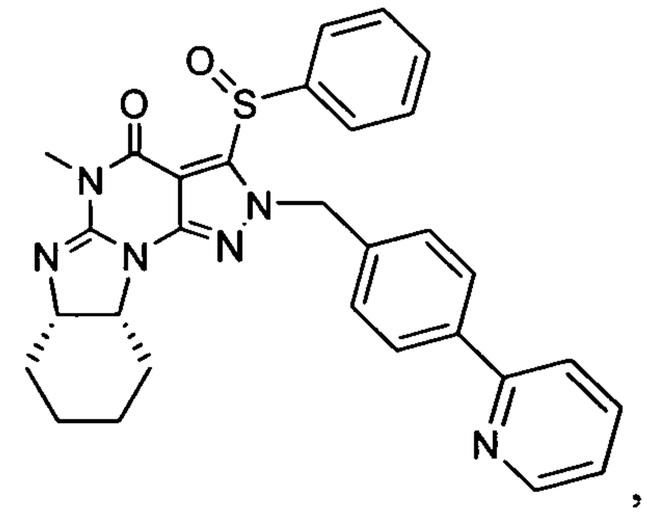
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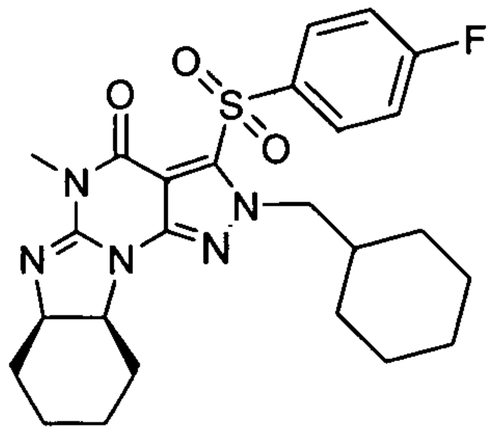
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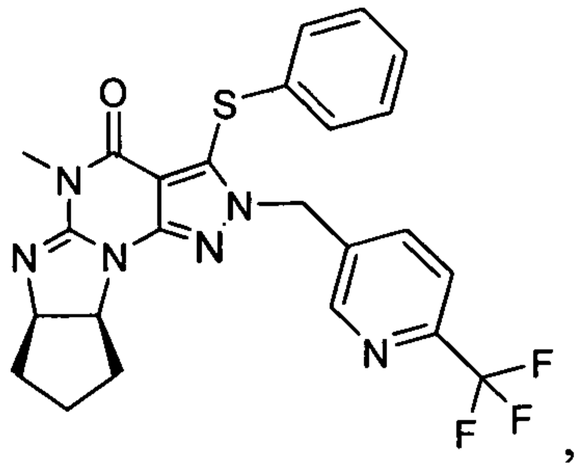
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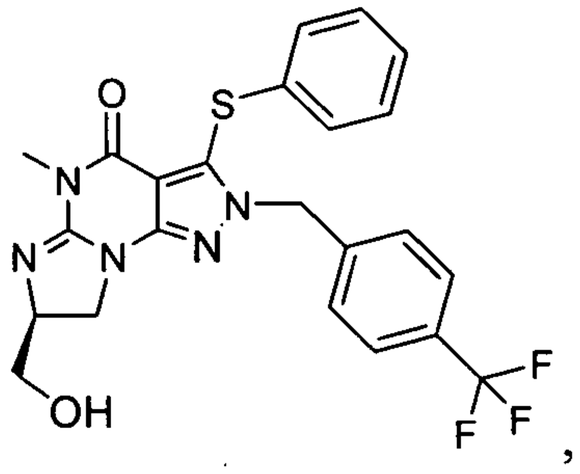
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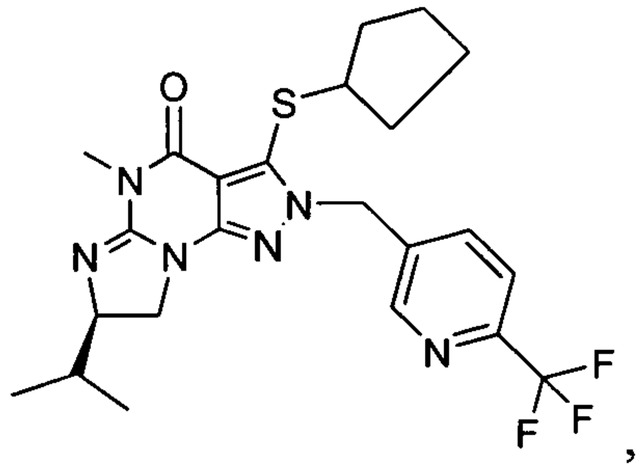
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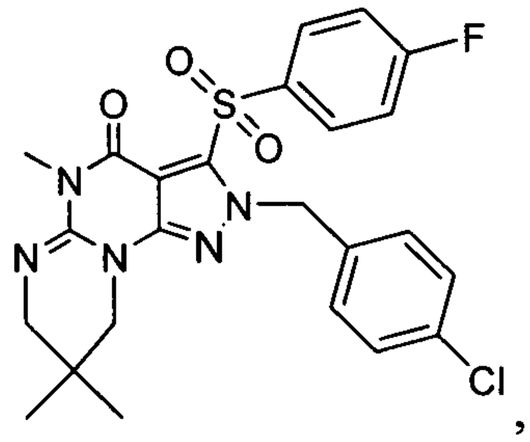
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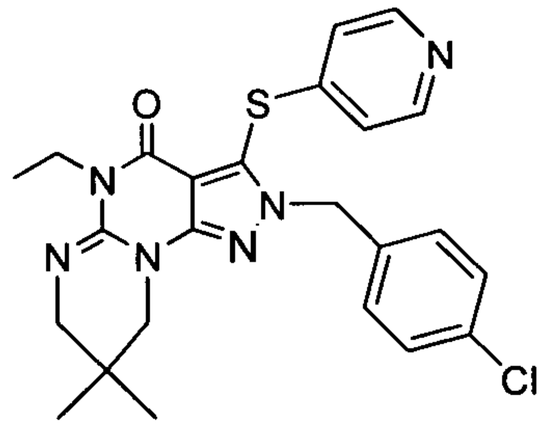
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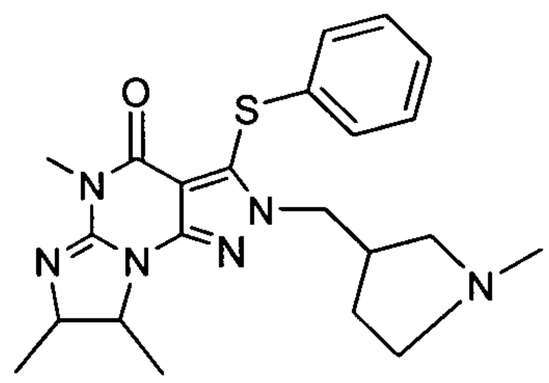
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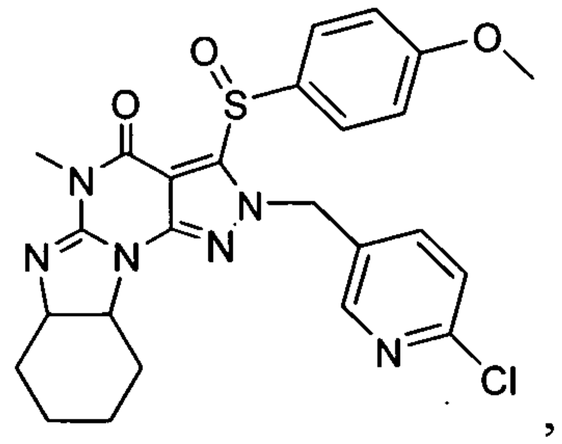
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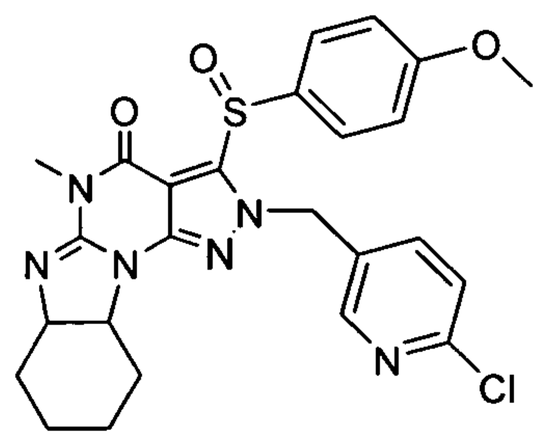
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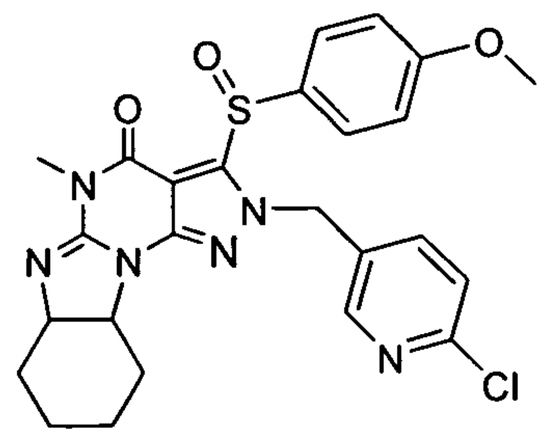
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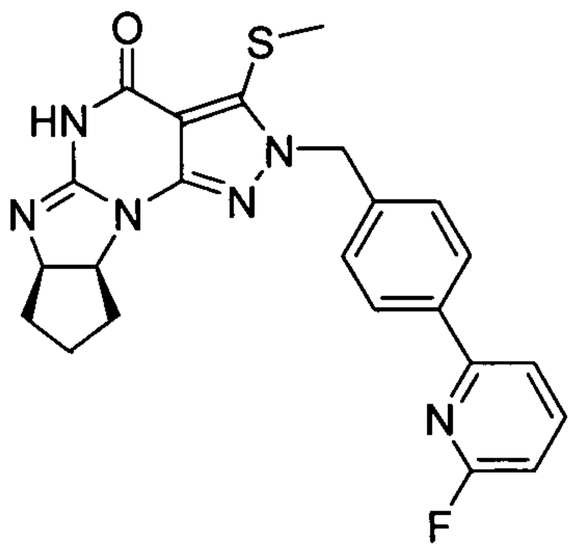
in free or salt form.

5. The compound according to claim 1,2 or 3, selected from any of the following: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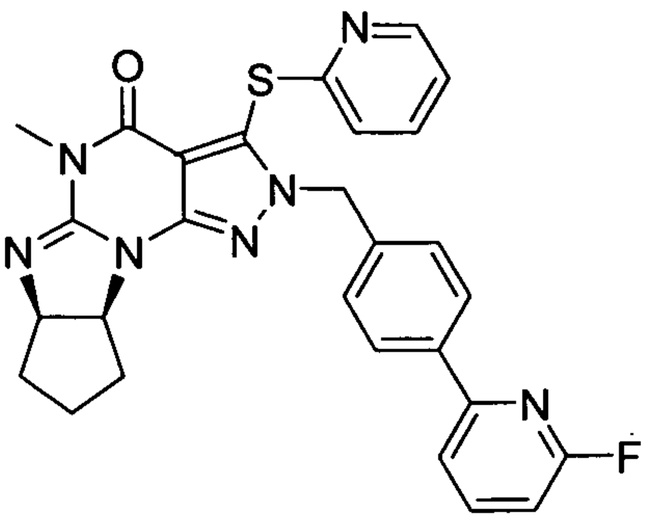
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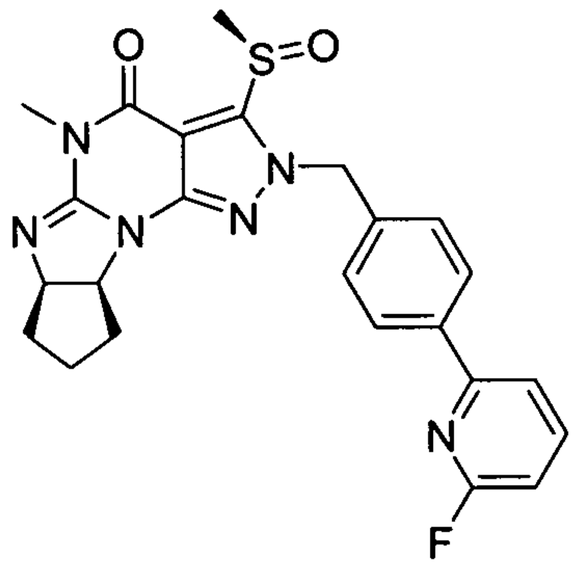
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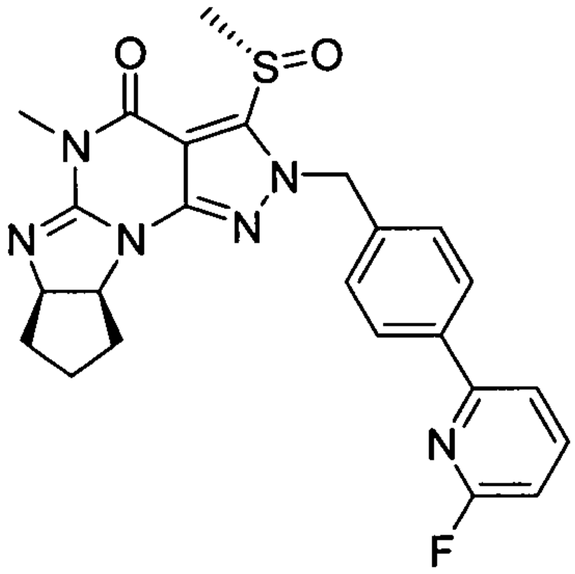
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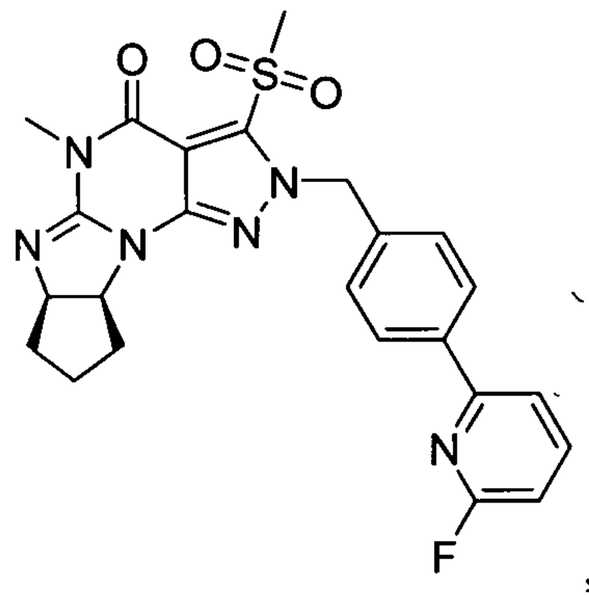
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in free or salt form.

6. A pharmaceutical composition comprising a compound according to any of claims 1-5, in admixture with a pharmaceutically acceptable diluent or carrier.

7. 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 1-5, or a pharmaceutical composition according to claim 6, to a patient in need of such treatment.

8. The method of claim 7, wherein the condition is Parkinson's disease.

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

10. The method of claim 7, wherein the condition is narcolepsy.

11. The method of claim 10 further comprising administering a compound or compounds selected from central nervous system stimulants, modafinil, antidepressants, and gamma hydroxybutyrate, to a patient in need thereof.

12. The method of claim 7, wherein said condition is female sexual dysfunction.

13. The method of claim 12, 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.

14. 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 1-5, in free or pharmaceutically

acceptable salt form, in an opthalmically compatible carrier to the eye of a patient in need thereof.

15. 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 1-5, in free or pharmaceutically acceptable salt form, to a patient in need thereof.

16. A method for the treatment of traumatic brain injury comprising admistering to a patient in need thereof, a compound according to any of claims 1-5, in free or pharmaceutically acceptable salt form.

17. 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 1-5, in free or salt form.

18. Use of the Compound according to any of claims 1-5, in free or pharmaceutically acceptable salt form, or a pharmaceutical composition according to claim 6 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..

19. Use of the Compound according to any of claims 1-5, in free or pharmaceutically acceptable salt form, or a pharmaceutical composition according to claim 6 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.

20. A pharmaceutical comprising a Compound according to any of claims 1-5, 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.