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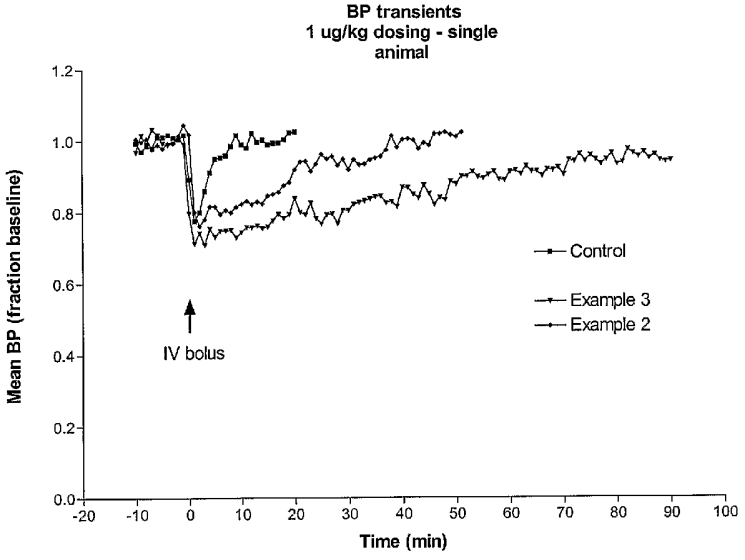
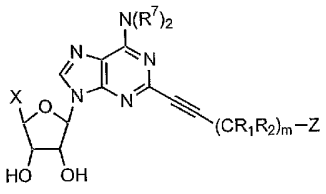
(54) Title: 2-PROPYNYL ADENOSINE ANALOGS WITH MODIFIED 5'-RIBOSE GROUPS HAVING A2A AGONIST ACTIVITY

(57) Abstract: The invention provides compounds having the following general formula (I): wherein X, R^1, R^2, R^7 and Z are as described herein.





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2-PROPYNYL ADENOSINE ANALOGS WITH MODIFED 5'-RIBOSE GROUPS HAVING A_{2A} AGONIST ACTIVITY

Related Applications

This application claims priority from a provisional application entitled: "2-PROPYNYL ADENOSINE ANALOGS and COMPOSITIONS WITH MODIFED 5'-RIBOSE GROUPS HAVING A2A AGONIST ACTIVITY", filed on August 2, 2004, serial number 60/598,018, the entire contents of which is included herein by reference.

Government Funding

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Background of the Invention

The inflammatory response serves the purpose of eliminating harmful agents from the body. There is a wide range of pathogenic insults that can initiate an inflammatory response including infection, allergens, autoimmune stimuli, immune response to transplanted tissue, noxious chemicals, and toxins, ischemia/reperfusion, hypoxia, mechanical and thermal trauma. Inflammation normally is a very localized action, which serves in expulsion, attenuation by dilution, and isolation of the damaging agent and injured tissue. The body's response becomes an agent of disease when it results in inappropriate injury to host tissues in the process of eliminating the targeted agent, or responding to a traumatic insult.

As examples, inflammation is a component of pathogenesis in several vascular diseases or injuries. Examples include: ischemia/reperfusion injury (N. G. Frangogiannis et al., in Myocardial Ischemia: Mechanisms, Reperfusion, Protection, M. Karmazyn, ed., Birkhuser Verlag (1996) at 236-284; H. S. Sharma et al., Med. of Inflamm., 6, 175 (1987)), atherosclerosis (R. Ross, Nature, 362, 801 (1993)), inflammatory aortic aneurysms (N. Girardi et al., Ann.

Thor. Surg., 64, 251 (1997); D. I. Walker et al., Brit. J. Surg., 59, 609 (1972); R. L. Pennell et al., J. Vasc. Surg., 2, 859 (1985)), and restenosis following balloon angioplasty (see, R. Ross cited above). The cells involved with inflammation include leukocytes (i.e., the immune system cells – neutrophils, eosinophils, lymphocytes, monocytes, basophils, macrophages, dendritic cells, and mast cells), the vascular endothelium, vascular smooth muscle cells, fibroblasts, and myocytes.

The release of inflammatory cytokines such as tumor necrosis factor-alpha (TNFα) by leukocytes is a means by which the immune system combats pathogenic invasions, including infections. TNFα stimulates the expression and activation of adherence factors on leukocytes and endothelial cells, primes neutrophils for an enhanced inflammatory response to secondary stimuli and enhances adherent neutrophil oxidative activity. See, Sharma et al., cited herein. In addition, macrophages/dendritic cells act as accessory cells processing antigen for presentation to lymphocytes. The lymphocytes, in turn, become stimulated to act as pro-inflammatory cytotoxic cells.

Generally, cytokines stimulate neutrophils to enhance oxidative (*e.g.*, superoxide and secondary products) and non-oxidative (*e.g.*, myeloperoxidase and other enzymes) inflammatory activity. Inappropriate and over-release of cytokines can produce counterproductive exaggerated pathogenic effects through the release of tissue-damaging oxidative and non-oxidative products (K. G. Tracey et al., J. Exp. Med., 167, 1211 (1988); and D. N. Männel et al., Rev. Infect. Dis., 9 (suppl. 5), S602-S606 (1987)). For example, TNFα can induce neutrophils to adhere to the blood vessel wall and then to migrate through the vessel to the site of injury and release their oxidative and non-oxidative inflammatory products.

Although monocytes collect slowly at inflammatory foci, given favorable conditions, the monocytes develop into long-term resident accessory cells and macrophages. Upon stimulation with an inflammation trigger, monocytes/macrophages also produce and secrete an array of cytokines (including TNFα), complement, lipids, reactive oxygen species, proteases and growth factors that remodel tissue and regulate surrounding tissue functions.

For example, inflammatory cytokines have been shown to be pathogenic in: arthritis (C. A. Dinarello, Semin. Immunol., 4, 133 (1992)); ischemia (A. Seekamp et al., Agents-Actions-Supp., 41, 137 (1993)); septic shock (D. N. Männel et al., Rev. Infect. Dis., 9 (suppl. 5), S602-S606 (1987)); asthma (N. M. Cembrzynska et al., Am. Rev. Respir. Dis., 147, 291 (1993)); organ transplant rejection (D. K. Imagawa et al., Transplantation, 51, 57 (1991); multiple sclerosis (H. P. Hartung, Ann. Neurol., 33, 591 (1993)); AIDS (T. Matsuyama et al., AIDS, 5, 1405 (1991)); and in alkali-burned eyes (F. Miyamoto et al., Opthalmic Res., 30, 168 (1997)). In addition, superoxide formation in leukocytes has been implicated in promoting replication of the human immunodeficiency virus (HIV) (S. Legrand-Poels et al., AIDS Res. Hum. Retroviruses, 6, 1389 (1990)).

It is well known that adenosine and some analogs of adenosine that non-selectively activate adenosine receptor subtypes decrease neutrophil production of inflammatory oxidative products (B. N. Cronstein et al., Ann. N.Y. Acad. Sci., 451, 291 (1985); P. A. Roberts et al., Biochem. J., 227, 669 (1985); D. J. Schrier et al., J. Immunol., 137, 3284 (1986); B. N. Cronstein et al., Clinical Immunol. and Immunopath., 42, 76 (1987); M. A. Iannone et al., in Topics and Perspective in Adenosine Research, E. Gerlach et al., eds., Springer-Verlag, Berlin, p. 286 (1987); S. T. McGarrity et al., J. Leukocyte Biol., 44, 411421 (1988); J. De La Harpe et al., J. Immunol., 143, 596 (1989); S. T. McGarrity et al., J. Immunol., 142, 1986 (1989); and C. P. Nielson et al., Br. J. Pharmacol., 97, 882 (1989)). For example, adenosine has been shown to inhibit superoxide release from neutrophils stimulated by chemoattractants such as the synthetic mimic of bacterial peptides, f-met-leu-phe (fMLP), and the complement component C_5a (B. N. Cronstein et al., J. Immunol., 135, 1366 (1985)). Adenosine can decrease the greatly enhanced oxidative burst of PMN (neutrophil) first primed with TNF-α and then stimulated by a second stimulus such as f-met-leu-phe (G. W. Sullivan et al., Clin. Res., 41, 172A (1993)). Additionally, it has been reported that adenosine can decrease the rate of HIV replication in a T-cell line (S. Sipka et al., Acta. Biochim. Biopys. Hung., 23, 75 (1988)). However, there is no evidence that in vivo adenosine has anti-

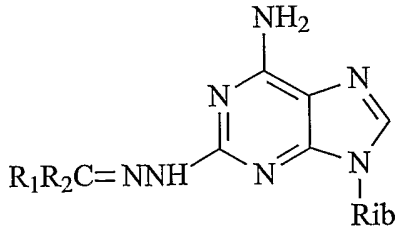
inflammatory activity (G. S. Firestein et al., Clin. Res., 41, 170A (1993); and B. N. Cronstein et al., Clin. Res., 41, 244A (1993)).

It has been suggested that there is more than one subtype of adenosine receptor on neutrophils that can have opposite effects on superoxide release (B. N. Cronstein et al., J. Clin. Invest., 85, 1150 (1990)). The existence of A_{2A} receptor on neutrophils was originally demonstrated by Van Calker et al. (D. Van Calker et al., Eur. J. Pharmacology, 206, 285 (1991)).

There has been progressive development of compounds that are more and more potent and/or selective as agonists of A_{2A} adenosine receptors (AR) based on radioligand binding assays and physiological responses. Initially, compounds with little or no selectivity for A_{2A} receptors were developed, such as adenosine itself or 5′-carboxamides of adenosine, such as 5′-N-ethylcarboxamidoadenosine (NECA) (B. N. Cronstein et al., J. Immunol., 135, 1366 (1985)). Later, it was shown that addition of 2-alkylamino substituents increased potency and selectivity, *e.g.*, CV1808 and CGS21680 (M. F. Jarvis et al., J. Pharmacol. Exp. Ther., 251, 888 (1989)). 2-Alkoxy-substituted adenosine derivatives such as WRC-0090 are even more potent and selective as agonists at the coronary artery A_{2A} receptor (M. Ueeda et al., J. Med. Chem., 34, 1334 (1991)). The 2-alklylhydrazino adenosine derivatives, *e.g.*, SHA 211 (also called WRC-0474) have also been evaluated as agonists at the coronary artery A_{2A} receptor (K. Niiya et al., J. Med. Chem., 35, 4557 (1992)).

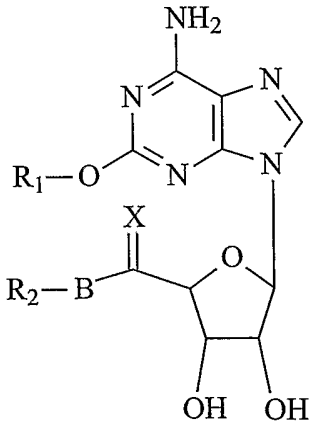
There is one report of the combination of relatively nonspecific adenosine analogs, R-phenylisopropyladenosine (R-PIA) and 2-chloroadenosine (Cl-Ado) with a phosphodiesterase (PDE) inhibitor resulting in a lowering of neutrophil oxidative activity (M. A. Iannone et al., Topics and Perspectives in Adenosine Research, E. Garlach et al., eds., Springer-Verlag, Berlin, pp. 286-298 (1987)). However, R-PIA and Cl-Ado analogs are actually more potent activators of A_1 adenosine receptors than of A_{2A} adenosine receptors and, thus, are likely to cause side effects due to activation of A_1 receptors on cardiac muscle and other tissues causing effects such as "heart block."

R. A. Olsson et al. (U.S. Pat. No. 5,278,150) disclose selective adenosine A_2 receptor agonists of the formula:



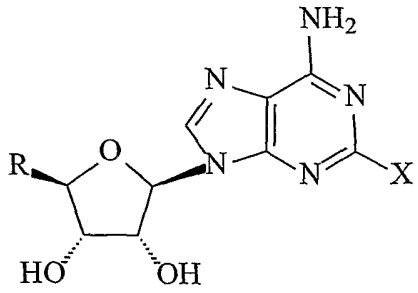
wherein Rib is ribosyl, R_1 can be H and R_2 can be cycloalkyl. The compounds are disclosed to be useful for treating hypertension, atherosclerosis and as vasodilators.

Olsson et al. (U.S. Pat. No. 5,140,015) disclose certain adenosine A_2 receptor agonists of formula:



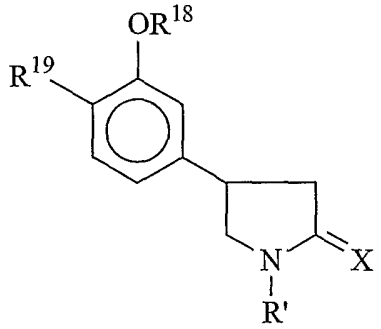
wherein $C(X)BR_2$ can be CH_2OH and R_1 can be alkyl- or alkoxyalkyl. The compounds are disclosed to be useful as vasodilators or an antihypertensives.

Linden et al. (U.S. Pat. No. 5,877,180) is based on the discovery that certain inflammatory diseases, such as arthritis and asthma, may be effectively treated by the administration of compounds which are selective agonists of A_{2A} adenosine receptors, preferably in combination with a Type IV phosphodiesterase inhibitor. An embodiment of the Linden et al. invention provides a method for treating inflammatory diseases by administering an effective amount of an A_{2A} adenosine receptor of the following formula:



wherein R and X are as described in the patent.

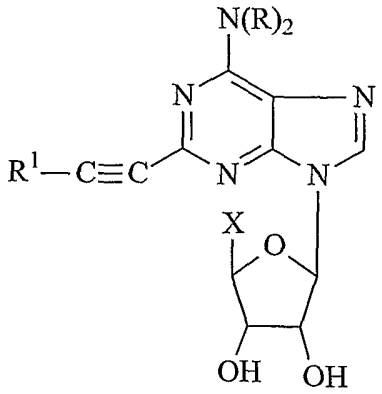
In one embodiment, the Linden et al. invention involves the administration of a Type IV phosphodiesterase (PDE) inhibitor in combination with the A_{2A} adenosine receptor agonist. The Type IV phosphodiesterase (PDE) inhibitor includes racemic and optically active 4-(polyalkoxyphenyl)-2-pyrrolidones of the following formula:



wherein R', R^{18}, R^{19} and X are as disclosed and described in U.S. Pat. No. 4,193,926. Rolipram is an example of a suitable Type IV PDE inhibitor included within the above formula.

G. Cristalli (U.S. Pat. No. 5,593,975) discloses 2-arylethynyl, 2-cycloalkylethynyl or 2-hydroxyalkylethynyl derivatives, wherein the riboside residue is substituted by carboxy amino, or substituted carboxy amino ($R_3HNC(O)$-). 2-Alkynylpurine derivatives have been disclosed in Miyasaka et al. (U.S. Pat. No. 4,956,345), wherein the 2-alkynyl group is substituted with (C_3-C_{16})alkyl. The '975 compounds are disclosed to be vasodilators and to inhibit platelet aggregation, and thus to be useful as anti-ischemic, anti-atherosclerosis and anti-hypertensive agents.

Recently, U.S. Patent 6,232,297 to Linden, et al. disclosed compounds having the general formula:



wherein each R is H, X is ethylaminocarbonyl and R^1 is 4-carboxycyclohexylmethyl (DWH-146a), R^1 is 4-methoxycarbonylcyclohexylmethyl (DWH-146e) or R^1 is 4-acetoxymethyl-cyclohexylmethyl (JMR-193). These compounds are reported to be A_{2A} agonists.

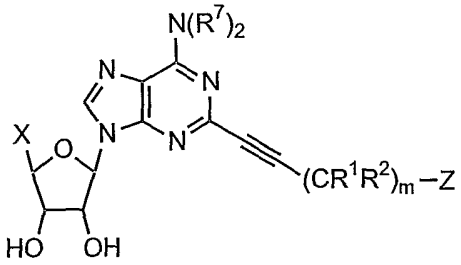
However, a continuing need exists for selective A_2 adenosine receptor agonists useful for therapeutic applications, which have reduced side effects. In addition, a continuing need exists for selective A2 adenosine receptor agonists useful for use as pharmacological stressors in stress imaging or in other ventricular function imaging techniques, that preferably have reduced side effects, while being chemically stable and short-acting.

Summary of the Invention

The present invention comprises compounds and methods of their use for the treatment of inflammatory activity in mammalian tissue. The inflammatory tissue activity can be due to pathological agents or can be due to physical, chemical or thermal trauma, or the trauma of medical procedures, such as organ, tissue or cell transplantation, angioplasty (PCTA), inflammation following ischemia/reperfusion, or grafting. The present compounds comprise a novel class of 2-alkynyladenosine derivatives, substituted at the ethyn-2-yl position by substituted cycloalkyl and heterocycle (heterocyclic) moieties. Preferably, the riboside residue is modified at the 5'-position by substituting an N-(cycloalkyl)carboxyamino ("aminocarbonyl") moiety ("X") or a 5- or 6-membered heterocyclic ring. Thus, the present invention provides a method for

inhibiting the inflammatory response in a mammal, such as a human subject, and protecting the tissue subject to the response, by administering an effective amount of one or more compounds of the invention.

The compounds of the invention have general formula (I):



(I)

wherein

Z is $CR^3R^4R^5$ or NR^4R^5;

each R^1 is independently hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{3-8}cycloalkyl, heterocycle, heterocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-N=NR^a$, or $-OPO_2R^a$;

each R^2 is independently hydrogen, halo, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, heterocycle, heterocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, or heteroaryl(C_1-C_8)alkylene-; or

R^1 and R^2 and the atom to which they are attached is C=O, C=S or $C=NR^c$.

R^4 and R^5 together with the atoms to which they are attached form a saturated or partially unsaturated, or aromatic ring having 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms optionally comprising 1, 2, 3, or 4 heteroatoms selected from non-peroxide oxy (-O-), thio (-S-), sulfinyl (-SO-), sulfonyl $(-S(O)_2-)$ or amine $(-NR^a-)$ in the ring;

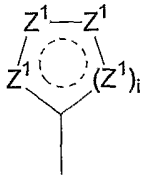
wherein any ring comprising R^4 and R^5 is substituted with from 1 to 14 R^6 groups;

wherein each R^6 is independently hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_8)cycloalkyl, (C_1-C_8)cycloalkyl(C_1-C_8)alkylene-, (C_6-C_{12})bicycloalkyl, heterocycle or heterocycle (C_1-C_8)alkylene-, aryl, aryl (C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $-NNR^a$,$-OPO_2R^a$, or two R^6 groups and the atom to which they are attached is C=O, or C=S; or two R^6 groups together with the atom or atoms to which they are attached can form a carbocyclic or a heterocyclic ring comprising from 1 to 6 carbon atoms and 1, 2, 3, or 4 heteroatoms selected from non-peroxide oxy (-O-), thio (-S-), sulfinyl (-SO-), sulfonyl $(-S(O)_2-)$, phosphine $(-OP(O)_2-)$, or amine $(-NR^a-)$ in the ring;

R^3 is hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, (C_1-C_8)cycloalkyl-(C_1-C_8)alkylene-, heterocycle, heterocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-NNR^a$, $-OPO_2R^a$; or if the ring formed from CR^4R^5 is aryl or heteroaryl or partially unsaturated then R^3 can be absent;

each R^7 is independently hydrogen, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_1-C_8)cycloalkyl(C_1-C_8)alkylene-, heterocycle, heterocycle (C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene-;

X is $-CH_2OR^e$, $-CO_2R^e$, $-CH_2OC(O)R^e$, $-C(O)NR^eR^f$, $-CH_2SR^e$, $-C(S)OR^e$, $-CH_2OC(S)R^e$ or $C(S)NR^eR^f$ $-CH_2N(R^e)(R^f)$, or a group having the formula



wherein each Z^1 is non-peroxide -O-, $-S(O)_p-$, $-C(R^8)_j-$, or $-N(R^8)-$; provided that at least one Z^1 is non-peroxide -O-, $-S(O)_p-$, or $-N(R^8)-$;

each R^8 is independently hydrogen, (C_1-C_8)alkyl, (C_1-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_1-C_8)alkyl(C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkenyl, (C_1-C_8)alkyl(C_3-C_8)cycloalkenyl, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene-; wherein any of the alkyl or alkenyl groups of R^8 are optionally interrupted by -O-, -S-, or $-N(R^a)-$;

R^e is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl;

R^f is hydrogen, (C_1-C_8)alkyl, or (C_1-C_8)alkyl substituted with 1-3 (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_1-C_8)alkylthio, amino acid, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene; and

wherein any of the alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, aryl, or heteroaryl, groups of R^1, R^2, R^3, R^6, R^7 and R^8 is optionally substituted on carbon with one or more (*e.g.* 1, 2, 3, or 4) substituents selected from the group consisting of halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle or heterocycle(C_1-C_8)alkylene-, aryl, aryloxy, aryl (C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)_p-$, $R^aR^bNS(O)_p-$, $N=NR^a$, and $-OPO_2R^a$;

wherein any (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, (C_1-C_8)alkoxy, (C_1-C_8)alkanoyl, (C_1-C_8)alkylene, or heterocycle, is optionally partially unsaturated;

R^a and R^b are each independently hydrogen, (C_1-C_{18})alkyl, or (C_1-C_{18})alkyl substituted with 1-3 (C_1-C_{18})alkoxy, (C_3-C_8)cycloalkyl, (C_1-C_{18})alkylthio, amino acid, aryl, aryl(C_1-C_{18})alkylene, heteroaryl, or

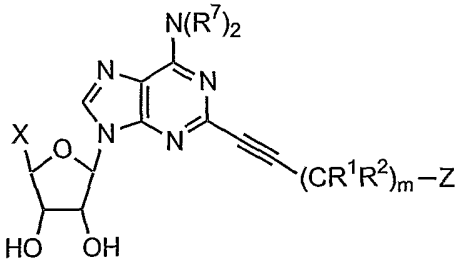
heteroaryl(C_1-C_{18})alkylene; or R^a and R^b, together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring; and

R^c is hydrogen or (C_1-C_6)alkyl;

m is 0, 1, 2, 3, 4, 5, 6, 7, or 8; i is 1, or 2; each j is independently 1, or 2; and each p is independently 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the compounds of the invention have general formula (I):



(I)

wherein

Z is $CR^3R^4R^5$ or NR^4R^5;

each R^1 is independently hydrogen, halo, -OR^a, -SR^a, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{3-8}cycloalkyl, heterocycle, heterocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, $R^aS(=O)_2$-, -$N=NR^a$, or -OPO_2R^a;

each R^2 is independently hydrogen, halo, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, heterocycle, heterocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, or heteroaryl(C_1-C_8)alkylene-; or

R^1 and R^2 and the atom to which they are attached is C=O, C=S or $C=NR^c$.

R^4 and R^5 together with the atoms to which they are attached form a saturated or partially unsaturated, or aromatic ring having 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms optionally comprising 1, 2, 3, or 4 heteroatoms selected from non-peroxide oxy (-O-), thio (-S-), sulfinyl (-SO-), sulfonyl (-$S(O)_2$-) or amine (-NR^a-) in the ring;

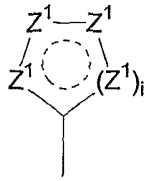
wherein any ring comprising R^4 and R^5 is substituted with from 1 to 14 R^6 groups;

wherein each R^6 is independently hydrogen, halo, -OR^a, -SR^a, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_8)cycloalkyl, (C_1-C_8)cycloalkyl(C_1-C_8)alkylene-, (C_6-C_{12})bicycloalkyl, heterocycle or heterocycle (C_1-C_8)alkylene-, aryl, aryl (C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, -NNR^a,-OPO_2R^a, or two R^6 groups and the atom to which they are attached is C=O, or C=S; or two R^6 groups together with the atom or atoms to which they are attached can form a carbocyclic or a heterocyclic ring comprising from 1 to 6 carbon atoms and 1, 2, 3, or 4 heteroatoms selected from non-peroxide oxy (-O-), thio (-S-), sulfinyl (-SO-), sulfonyl (-$S(O)_2$-), phosphine (-$OP(O)_2$-, or amine (-NR^a-) in the ring;

R^3 is hydrogen, halo, -OR^a, -SR^a, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, (C_1-C_8)cycloalkyl-(C_1-C_8)alkylene-, heterocycle, heterocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, $R^aS(=O)_2$-, -NNR^a, -OPO_2R^a; or if the ring formed from CR^4R^5 is aryl or heteroaryl or partially unsaturated then R^3 can be absent;

each R^7 is independently hydrogen, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_1-C_8)cycloalkyl(C_1-C_8)alkylene-, heterocycle, heterocycle (C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene-;

X is $-CH_2OR^e$, $-CO_2R^e$, $-CH_2OC(O)R^e$, $-C(O)NR^eR^f$, $-CH_2SR^e$, $-C(S)OR^e$, $-CH_2OC(S)R^e$ or $C(S)NR^eR^f$ $-CH_2N(R^e)(R^f)$, or a group having the formula



wherein each Z^1 is non-peroxide -O-, $-S(O)_p-$, $-C(R^8)_j-$, or $-N(R^8)-$; provided that at least one Z^1 is non-peroxide -O-, $-S(O)_p-$, or $-N(R^8)-$;

each R^8 is independently hydrogen, (C_1-C_8)alkyl, (C_1-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_1-C_8)alkyl(C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkenyl, (C_1-C_8)alkyl(C_3-C_8)cycloalkenyl, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene-; wherein any of the alkyl or alkenyl groups of R^8 are optionally interrupted by -O-, -S-, or $-N(R^a)-$;

R^e is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl;

R^f is hydrogen, (C_1-C_8)alkyl, or (C_1-C_8)alkyl substituted with 1-3 (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_1-C_8)alkylthio, amino acid, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene; and

wherein any of the alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, aryl, or heteroaryl, groups of R^1, R^2, R^3, R^6, R^7 and R^8 is optionally substituted on carbon with one or more (*e.g.* 1, 2, 3, or 4) substituents selected from the group consisting of halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle or heterocycle(C_1-C_8)alkylene-, aryl, aryloxy, aryl (C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)_p-$, $R^aR^bNS(O)_p-$, $N=NR^a$, and $-OPO_2R^a$;

wherein any (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, (C_1-C_8)alkoxy, (C_1-C_8)alkanoyl, (C_1-C_8)alkylene, or heterocycle, is optionally partially unsaturated;

R^a and R^b are each independently hydrogen, $(C_1$-$C_8)$alkyl, or $(C_1$-$C_8)$alkyl substituted with 1-3 $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_1$-$C_8)$alkylthio, amino acid, aryl, aryl$(C_1$-$C_8)$alkylene, heteroaryl, or heteroaryl$(C_1$-$C_8)$alkylene; or R^a and R^b, together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring; and

R^c is hydrogen or $(C_1$-$C_6)$alkyl;

m is 0, 1, 2, 3, 4, 5, 6, 7, or 8; i is 1, or 2; each j is independently 1, or 2; and each p is independently 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound of formula I for use in medical therapy, preferably for use in treating inflammation or protecting mammalian tissue from inflammation such as an inflammatory response, *e.g.*, resulting from allergy, trauma or ischemia/reperfusion injury, as well as the use of a compound of formula I for the manufacture of a medicament for the treatment of an inflammatory response due to a pathological condition or symptom in a mammal, such as a human, which is associated with inflammation.

The invention also includes the use of a combination of these compounds with type IV phosphodiesterase inhibitors to preferably cause synergistic decreases in the inflammatory response mediated by leukocytes.

The invention also provides a pharmaceutical composition comprising an effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier, and optionally, in combination with a Type IV phosphodiesterase (PDE) inhibitor. Preferably, the composition is presented as a unit dosage form.

Additionally, the invention provides a therapeutic method for preventing or treating a pathological condition or symptom in a mammal, such as a human, wherein the activity of A_{2A} adenosine receptors is implicated and agonism of said receptors is desired, comprising administering to a mammal in need of such therapy, an effective amount of a compound of formula I, or a

pharmaceutically acceptable salt thereof. It is believed that activation of A_{2A} adenosine receptors inhibits inflammation by affecting neutrophils, mast cells, monocytes/macrophages, platelets T-cells and/or eosinophils. Inhibition of these inflammatory cells results in tissue protection following tissue insults.

In addition, the present invention provides a therapeutic method for treating biological diseases that includes the administration of an effective amount of a suitable antibiotic agent, antifungal agent or antiviral agent in conjunction with an A_{2A} adenosine receptor agonist. If no anti-pathogenic agent is known the A_{2A} agonist can be used alone to reduce inflammation, as may occur during infection with antibiotic resistant bacteria, or certain viruses such as those that cause SARS or Ebola. Optionally, the method includes administration of a type IV PDE inhibitor. The A_{2A} adenosine receptor agonist can provide adjunctive therapy for treatment conditions such as, the inflammation, caused by sepsis, for example, *human uremic syndrome* when administered with antibiotics in the treatment of bio-terrorism weapons, such as anthrax, tularemia, Escherichia coli, plague and the like. The present invention also provides adjunctive therapy for treatment of lethal bacterial, fungal and viral infections such as anthrax, tularemia, escherichia and plague comprising administration of an antibacterial agent, an antifungal agent or an antiviral agent in conjunction with selective, A_{2A} adenosine receptor agonists.

The present invention provides a therapeutic method for treating biological diseases that provoke inflammation either alone or in combination with a disease killing medicine. These include bacteria in combination with antibiotics, including but not limited to bacteria that cause anthrax, tularemia, plague, lyme disease and anthrax. Also included are viruses including but not limited to those that cause RSV, severe acute respiratory syndrome (SARS), influenza and Ebola with or without anti-viral therapy. Also included are yeast and fungal infections with or without anti-yeast or anti-fungal agents.

The antibacterial agent, antifungal agent or antiviral agent can be co-administered (*e.g.*, simultaneously) with the A_{2A} adenosine receptor agonist or they can be can be administered either simultaneously or as a mixture or they can be administered subsequently. The subsequent administration of the A_{2A}

adenosine receptor agonists can be prior to the agent, within minutes or up to about 48 hours after the administration of the agent. Preferably the administration of the A_{2A} adenosine receptor agonists will be within about 24 hours and more preferably within about 12 hours.

The method of the invention will also be useful for treating patients with sepsis, severe sepsis, and potentially, the systemic inflammatory response syndrome, in addition to septic shock. The A_{2A}AR agonists exert multiple anti-inflammatory effects early in the inflammatory cascade, and thus a short course of an A_{2A}AR agonists could produce profound benefit in serious, life-threatening infectious and inflammatory disorders of humans, including inhalational anthrax, tularemia, escherichia and plague.

The anti-inflammatory effect of A_{2A}AR agonists has been documented *in vivo*, in experimental models of meningitis, peritonitis and arthritis. The potentially fatal syndrome of bacterial sepsis is an increasingly common problem in acute care units. Sepsis and septic shock, now the eleventh leading cause of death in the United States, are increasing in frequency. Current estimates indicate that about 900,000 new cases of sepsis (approximately 60% Gram negative) occur in the United States annually with an estimated crude mortality rate of 35%. Furthermore, the mortality rate, as assessed in recent clinical trials, is approximately 25%, while approximately 10 % of patients die from their underlying disease. Shock develops in approximately 200,000 cases annually with an attributable mortality rate of 46 % (92,000 deaths). Sepsis accounts for an estimated $ 5-10 billion annually in health care expenditures. It is now widely appreciated that among hospitalized patients in non-coronary intensive care units, sepsis is the most common cause of death. Sepsis syndrome is a public-health problem of major importance. A_{2A}AR agonists are anticipated to have use as a new and unique adjunctive therapeutic approach to reduce morbidity and mortality. It is believed that this treatment will improve the outcome in systemic anthrax, tularemia, escherichia and plague.

The agonists of A_{2A} adenosine receptors of the invention can inhibit neutrophil, macrophage and T cell activation and thereby reduce inflammation caused by bacterial and viral infections. The compounds, in conjunction with

antibiotics or antiviral agents can prevent or reduce mortality caused by sepsis or hemolytic uremic syndrome or other inflammatory conditions. The effects of adenosine A_{2A} agonists are enhanced by type IV phosphodiesterase inhibitors such as rolipram.

The invention also provides a pharmaceutical composition comprising an effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier. Preferably, the composition is presented as a unit dosage form, and can be adapted for parenteral, *e.g.*, intravenous infusion.

The invention also provides a compound of formula I for use in medical therapy (*e.g.*, for use as an adjunct in the treatment of potentially lethal bacterial infections, such as, anthrax, tularemia, Escherichia, plague, or other bacterial or viral infections, and treatment of systemic intoxification caused by bacterial and/or viral infections, as well as the use of a compound of formula I for the manufacture of a medicament for reducing inflammation caused by the bacteria or virus or the treatment thereof in a mammal, such as a human. The compounds of the invention are also useful for treatment of treating systemic intoxification wherein the bacterial or viral agents cause inflammation either directly or as a result of treatment, *e.g.*, with an antibiotic or antiviral agent.

Sepsis is a severe illness caused by overwhelming infection of the bloodstream by toxin-producing bacteria or viruses. The infection, which can manifest as inflammation, can be caused by the bacteria or virus pathogens directly or from the treatment thereof, *i.e.*, the death of the pathogens due to treatment with antibacterial or antiviral agents. Sepsis can be also be viewed as the body's response to an infection. The infection can be caused by micro-organisms or "germs" (usually bacteria) invade the body, can be limited to a particular body region (*e.g.*, a tooth abscess) or can be widespread in the bloodstream (often referred to as "septicemia" or "blood poisoning")

The systemic intoxification or inflammatory shock is often referred to as Septic shock; Bacteremic shock; Endotoxic shock; Septicemic shock; or Warm shock.

Septic shock is a serious, abnormal condition that occurs when an overwhelming infection leads to low blood pressure and low blood flow. Vital organs, such as the brain, heart, kidneys, and liver may not function properly or may fail. Septic shock occurs most often in the very old and the very young. It also occurs in people with underlying illnesses. Any bacterial organism can cause septic shock. Fungi and viruses may also cause this condition. Toxins released by the bacteria, fungi or viruses may cause direct tissue damage, and may lead to low blood pressure and/or poor organ function. These toxins can also produce a vigorous inflammatory response from the body, which contributes to septic shock.

In another aspect, the present invention also provides a method to treat severe acute respiratory syndrome (SARS), comprising administering to a mammal in need of said therapy, an effective anti-inflammatory amount of an agonists of A_{2A} adenosine receptor, optionally with a PDE-IV inhibitor, such as, rolipram.

The present invention provides compounds and methods of their use for detecting the presence of, and assessing the severity of, coronary artery stenoses in a mammal, such as a human or domestic animal. Preferably, the compounds of the invention are used as pharmacological stress-inducing agents or stressors that are useful in pharmacological stress imaging for the detection and assessment of coronary artery disease. The specific compounds of the invention useful as stress-inducing agents are potent and selective at A_{2A} adenosine receptors, but are also short-acting, so that they are rapidly cleared by the body following the imaging process.

Thus, the present invention provides a method for detecting the presence and severity of coronary artery stenoses in a mammal, such as a human subject, comprising (1) administering an amount of one or more compounds of the general formula (I) and (2) performing a technique on said mammal to detect and/or determine the severity of said coronary artery stenoses.

The invention provides a compound of formula (I) for use in medical diagnostic procedures, preferably for use in detecting the presence of, and assessing the severity of, coronary artery stenoses in a human subject. The

present invention provides the use of a compound of formula (I) for the manufacture of a pharmacologic vasodilator agent which could be used with clinical perfusion imaging techniques for diagnosing and assessing the extent of coronary artery disease. Preferred perfusion imaging techniques are planar or single photon emission computed tomography (SPECT) gamma camera scintigraphy, positron emission tomography (PET), nuclear magnetic resonance (NMR) imaging, magnetic resonance inaging (MRI) imaging, perfusion contrast echocardiography, digital subtraction angiography (DSA) and ultrafast X-ray computed tomography (CINE CT).

The invention also provides a pharmaceutical composition comprising an effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier. Preferably, the composition is presented as a unit dosage form, and can be adapted for parenteral, *e.g.*, intravenous infusion.

Brief Description of the Figures

Figure 1 is an illustration of the duration of action of A_{2A} agonists by monitoring the reduction of blood pressure in rats after administration of compounds of the present invention compared with other A_{2A} agonists.

Figure 2 is an illustration of the duration of action of A_{2A} agonists by monitoring the reduction of blood pressure in rats after administration of compounds of the present invention orally compared with other A_{2A} agonists.

Detailed Description of the Invention

The following definitions are used, unless otherwise described. Halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, aralkyl, alkylaryl, etc. denote both straight and branched alkyl groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Aryl includes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical attached

via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, (C_1-C_4)alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

It will be appreciated by those skilled in the art that the compounds of formula (I) have more than one chiral center and may be isolated in optically active and racemic forms. Preferably, the riboside moiety of formula (I) is derived from D-ribose. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, or enzymatic techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine adenosine agonist activity using the tests described herein, or using other similar tests which are well known in the art.

Among the inflammatory responses that can be treated (including treated prophylactically) with a compound of formula I, optionally with a Type IV PDE inhibitor, are inflammation due to:

(a) autoimmune stimulation (autoimmune diseases), such as lupus erythematosus, multiple sclerosis, infertility from endometriosis, type I diabetes mellitus including the destruction of pancreatic islets leading to diabetes and the inflammatory consequences of diabetes, including leg ulcers, Crohn's disease, ulcerative colitis, inflammatory bowel disease, osteoporosis and rheumatoid arthritis;

(b) allergic diseases such as asthma, hay fever, rhinitis, poison ivy, vernal conjunctivitis and other eosinophil-mediated conditions;

(c) skin diseases such as psoriasis, contact dermatitis, eczema, infectious skin ulcers, healing of open wounds, cellulitis;

(d) infectious diseases including sepsis, septic shock, encephalitis, infectious arthritis, endotoxic shock, gram negative shock, Jarisch-Herxheimer reaction, anthrax, plague, tularemia, ebola, shingles, toxic shock, cerebral malaria, bacterial meningitis, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), lyme disease, HIV infection, (TNFα-enhanced HIV replication, TNFα inhibition of reverse transcriptase inhibitor activity);

(e) wasting diseases: cachexia secondary to cancer and HIV;

(f) organ, tissue or cell transplantation (e.g., bone marrow, cornea, kidney, lung, liver, heart, skin, pancreatic islets) including transplant rejection, and graft versus host disease;

(g) adverse effects from drug therapy, including adverse effects from amphotericin B treatment, adverse effects from immunosuppressive therapy, e.g., interleukin-2 treatment, adverse effects from OKT3 treatment, contrast dyes, antibiotics, adverse effects from GM-CSF treatment, adverse effects of cyclosporine treatment, and adverse effects of aminoglycoside treatment, stomatitis and mucositis due to immunosuppression;

(h) cardiovascular conditions including circulatory diseases induced or exasperated by an inflammatory response, such as ischemia, atherosclerosis, peripheral vascular disease, restenosis following angioplasty, inflammatory aortic aneurysm, vasculitis, stroke, spinal cord injury, congestive heart failure, hemorrhagic shock, ischemia/reperfusion injury, vasospasm following subarachnoid hemorrhage, vasospasm following cerebrovascular accident, pleuritis, pericarditis, and the cardiovascular complications of diabetes;

(i) dialysis, including pericarditis, due to peritoneal dialysis;

(j) gout; and

(k) chemical or thermal trauma due to burns, acid, alkali and the like.

Of particular interest and efficacy is the use of the present compounds to limit inflammatory responses where the ischemia/reperfusion injury is caused

by angioplasty or throbolysis. Also of particular interest and efficacy is the use of the present compounds to limit inflammatory responses due to organ, tissue or cell transplantation, i.e., the transplantation of allogeneic or xenogeneic tissue into a mammalian recipient, autoimmune diseases and inflammatory conditions due to circulatory pathologies and the treatment thereof, including angioplasty, stent placement, shunt placement or grafting. Unexpectedly, it was found that administration of one or more compounds of formula (I) was effective after the onset of the inflammatory response, e.g., after the subject was afflicted with the pathology or trauma that initiates the inflammatory response.

Tissue or cells comprising ligand bound receptor sites can be used to measure the selectively of test compounds for specific receptor subtypes, the amount of bioactive compound in blood or other physiological fluids, or can be used as a tool to identify potential therapeutic agents for the treatment of diseases or conditions associated with receptor site activation, by contacting said agents with said ligand-receptor complexes, and measuring the extent of displacement of the ligand and/or binding of the agent, or the cellular response to said agent (*e.g.*, cAMP accumulation).

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, (C_1-C_8)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, hexyl, heptyl, octyl and the like. As used herein, the term "(C_1-C_8)alkoxy" can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, hexyloxy, 1-methylhexyloxy, heptyloxy and the like.

As used herein, the term "cycloalkyl" can be bicycloalkyl (norbornyl, 2.2.2-bicyclooctyl, etc.) and tricycloalkyl (adamantyl, etc.), optionally including 1-2 N, O or S. Cycloalkyl also encompasses (cycloalkyl)alkyl. Thus, (C_3-C_6)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. Specifically, (C_6-C_{12})bicycloalkyl includes norbornyl, 2.2.2-bicyclooctyl and the like.

As used herein, the term "(C_1-C_8)alkoxy" can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, hexyloxy; and the like.

As used herein, the term "(C_2-C_6)alkenyl" can be vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, and the like

As used herein, the term "(C_2-C_6)alkynyl" can be ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, and the like.

As used herein, the term "(C_1-C_8)alkanoyl" can be acetyl, propanoyl, butanoyl, and the like.

As used herein, the term "halo(C_1-C_8)alkyl" can be iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, and the like.

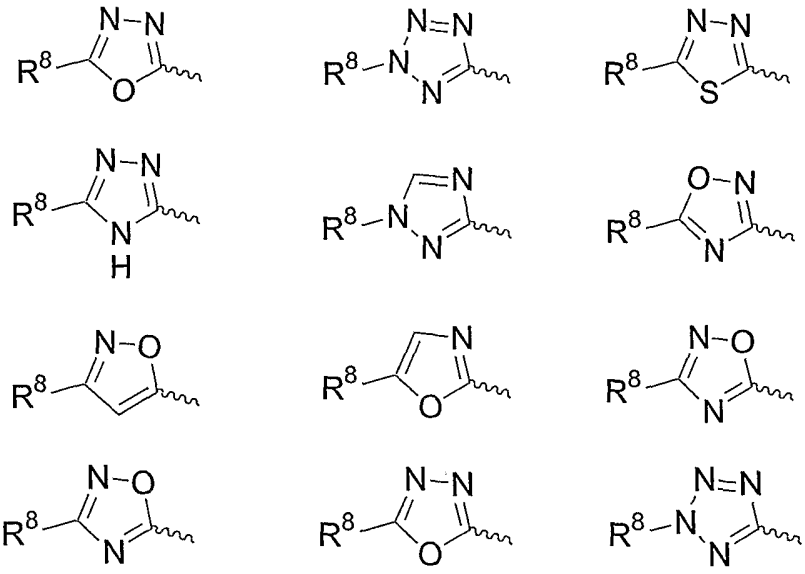
As used herein, the term "hydroxy(C_1-C_6)alkyl" can be hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxybutyl, 4-hydroxybutyl, 1-hydroxypentyl, 5-hydroxypentyl, 1-hydroxyhexyl, 6-hydroxyhexyl, and the like.

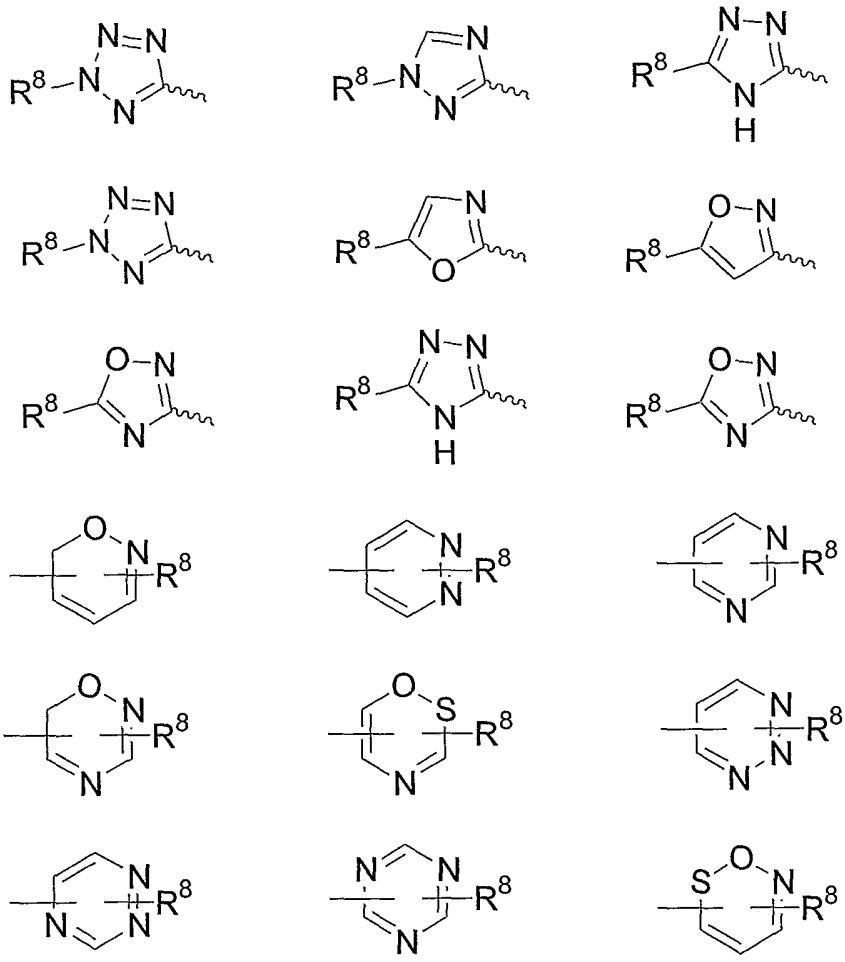
As used herein, the term "(C_1-C_8)alkylthio" can be methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, hexylthio, and the like.

As used herein, the term " aryl includes phenyl, indenyl, indanyl, naphthyl, and the like. In addition, aryl includes ortho-fused bicyclic carbocyclic radicals having about nine to ten ring atoms in which at least one ring is aromatic. The term "aryl" can include radicals of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

As used herein, the term "heteroaryl" can be a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and 1, 2, 3, or 4 heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) where Y is absent or is H, O, (C_1-C_8)alkyl, phenyl or benzyl. Non-limiting examples of heteroaryl groups include furyl, imidazolyl, triazolyl, triazinyl, oxazoyl, isoxazoyl, thiazolyl, isothiazoyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide), quinolyl (or its N-oxide) and the like. The term "heteroaryl" can include radicals of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto. Examples of heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazoyl, isoxazoyl, thiazolyl, isothiazoyl, pyraxolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl (or its N-oxide), thientyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide), quinolyl (or its N-oxide), and the like.

As used herein, the  symbol in the heterocyclic X ring denotes that the ring can have one or two double bonds and may be aromatic. Non-limiting examples of X rings include:





and the like.

The term "heterocycle" generally represents a non aromatic heterocyclic group, having from 3 to about 10 ring atoms, which can be saturated or partially unsaturated, containing at least one heteroatom (*e.g.*, 1, 2, or 3) selected from the group consisting of oxygen, nitrogen, and sulfur. Specific, "heterocycle" groups include monocyclic, bicyclic, or tricyclic groups containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. A "heterocycle" group also can include one or more oxo groups (=O) attached to a ring atom. Non-limiting examples of heterocycle groups include 1,3-dioxolane, 1,4-dioxane, 1,4-dithiane, 2H-pyran, 2-pyrazoline, 4H-pyran, chromanyl, imidazolidinyl, imidazolinyl, indolinyl, isochromanyl, isoindolinyl, morpholine, piperazinyl, piperidine, piperidyl, pyrazolidine, pyrazolidinyl, pyrazolinyl, pyrrolidine, pyrroline, quinuelidine, thiomorpholine, and the like.

The term "alkylene" refers to a divalent straight or branched hydrocarbon chain (*e.g.* ethylene $-CH_2-CH_2-$).

The term "aryl(C_1-C_8)alkylene" for example includes benzyl, phenethyl, naphthylmethyl and the like.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_i-C_j indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, (C_1-C_8)alkyl refers to alkyl of one to eight carbon atoms, inclusive.

The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (*e.g.*, "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours and "rt" for room temperature).

A specific value for R^1 is hydrogen, -OH, halo, $-CH_2OH$, -OMe, -OAc, $-NH_2$, -NHMe, $-NMe_2$ or -NHAc.

Another specific value for R^1 is hydrogen, -OH, -F, -OMe, -OAc, $-NH_2$, -NHMe, $-NMe_2$ or -NHAc.

Another specific value for R^1 is hydrogen, -OH, -F, -OMe, or $-NH_2$.

Another specific value for R^1 is hydrogen, -OH, -F, or $-NH_2$.

A more specific value for R^1 is hydrogen or -OH.

A specific value for R^2 is hydrogen, halo, or (C_1-C_8)alkyl, cyclopropyl, cyclohexyl or benzyl.

Another specific value for R^2 is hydrogen, -F, methyl, ethyl or propyl.

Another specific value for R^2 is hydrogen or methyl.

A more specific value for R^2 is hydrogen.

A specific value for R^1, R^2 and the carbon atom to which they are attached is carbonyl (C=O).

A specific value for R^3 is hydrogen, OH, OMe, OAc, NH_2, NHMe, NMe_2 or NHAc.

Another specific value for R^3 is hydrogen, OH, OMe, or NH_2.

Another specific value for R^3 is hydrogen, OH, or NH_2.

A more specific value for R^3 is hydrogen or OH.

A specific value for the ring comprising R^4, R^5 and the atom to which they are connected is cyclopentane, cyclohexane, piperidine, dihydro-pyridine, tetrahydro-pyridine, pyridine, piperazine, decaline, tetrahydro-pyrazine, dihydro-pyrazine, pyrazine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine, pyrazine, imidazole, dihydro-imidazole, imidazolidine, pyrazole, dihydro-pyrazole, and. pyrazolidine.

A more specific value for the ring comprising R^4 and R^5 and the atom to which they are connected is, cyclohexane, piperidine or piperazine.

A specific value for R^6 is $(C_1\text{-}C_8)$alkyl, substituted $(C_1\text{-}C_8)$alkyl, halo, $-OR^a$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)R^a$, $-OC(=O)R^a$, $-NR^aR^b$, $-C(=O)NR^aR^b$, $-OC(=O)NR^aR^b$, or aryl.

Another specific value for R^6 is $(C_1\text{-}C_4)$alkyl, chloro, fluoro, phenyl, $-OR^a$, $-CH_2OR^a$, $-CO_2R^a$, $-CH_2CO_2R^a$, $-OCO_2R^a$, $-CH_2OCO_2R^a$, $-C(=O)R^a$, $-CH_2C(=O)R^a$, $-OC(=O)R^a$, $-CH_2OC(=O)R^a$, $-NR^aR^b$, $-CH_2NR^aR^b$, $-C(=O)NR^aR^b$, $-CH_2C(=O)NR^aR^b$, $-OC(=O)NR^aR^b$, or $-CH_2OC(=O)NR^aR^b$.

Another specific value for R^6 is OH, OMe, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, $-CH_2OH$, phenyl, -OAc, $-CH_2OAc$, $-CO_2H$, $-CO_2Me$, $-CO_2Et$, $-CO_2i$-Pr, $-CO_2i$-Bu, $-CO_2t$-Bu, $-OCO_2Me$, $-OCO_2Et$, $-C(=O)CH_3$, $-CONH_2$, -CONHMe, $-CONMe_2$, -CONMeEt, $-NH_2$, -NHMe, $-NMe_2$, -NHEt, $-N(Et)_2$, or $-CH_2N(CH_3)_2$.

Another specific value for R^6 is OH, OMe, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, $-CH_2OH$, phenyl, -OAc, $-CH_2OAc$, $-CO_2Me$, $-CO_2Et$, $-CO_2i$-Pr, $-CO_2i$-Bu, $-CO_2t$-Bu, $-OCO_2Me$, $-OCO_2Et$, $-CONMe_2$, -CONMeEt.

A specific number of R^6 groups substituted on the Z ring is an integer from 1 to about 4.

A specific value for R^a is hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, phenyl or benzyl.

A specific value for R^b is hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, phenyl or benzyl.

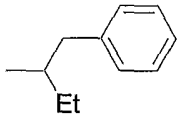
Another specific value for R^a is hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, *sec*-butyl, isobutyl, or *tert*-butyl and R^b is hydrogen, or methyl.

Another specific value for R^a and R^b together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring.

Another specific value for R^a and R^b together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, or morpholino, ring.

A specific value for R^7 is hydrogen, $(C_1\text{-}C_4)$alkyl, aryl, aryl$(C_1\text{-}C_8)$alkylene, diaryl$(C_1\text{-}C_8)$alkylene, heteroaryl$(C_1\text{-}C_8)$alkylene, or diheteroaryl$(C_1\text{-}C_8)$alkylene.

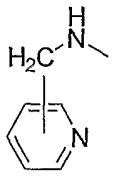
Another specific value for R^7 is hydrogen, methyl, ethyl, 3-pentyl, phenylCH_2CH_2-, (phenyl)$_2$CHCH_2-, pyridylCH_2-, benzyl, or



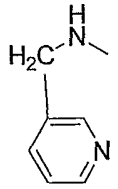
.

Another specific value for R^7 is hydrogen, 3-pentyl, pyridylmethyl, or benzyl.

A specific value for -N$(R^7)_2$ is amino, methylamino, dimethylamino, ethylamino, diethylamino, pentylamino, diphenylethylamino, benzylamino, or

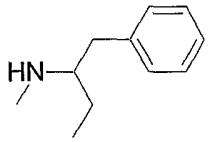


(pyridylmethylamino).

A specific pyridylmethylamino Group is 

A more specific value for R^7 is H.

Another specific value for $N(R^7)_2$ is amino (NH_2), 3-pentylamino, diphenylethylamino, pyridylmethylamino, benzylamino, or a group having the formula:



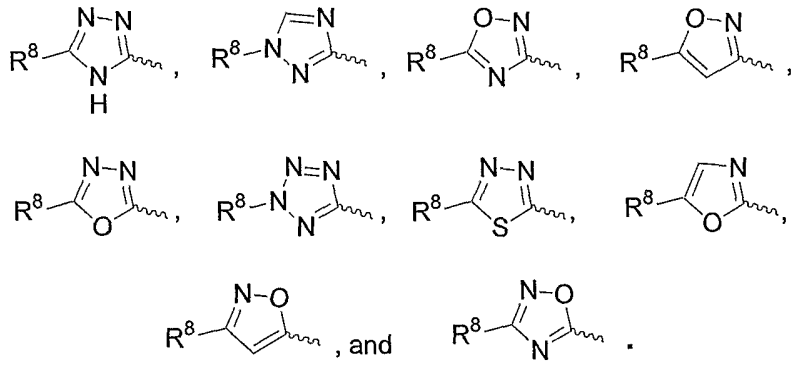
Another specific value for $-N(R^7)_2$ is amino, diphenylethylamino, pentylamino or benzylamino.

A more specific value for $N(R^7)_2$ is amino.

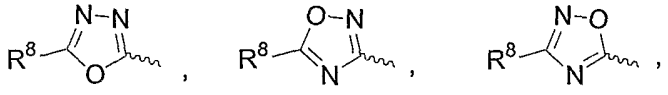
A specific value for X is $-CH_2OR^e$, $-CO_2R^e$, $-CH_2OC(O)R^e$, $-C(O)NR^eR^f$, or $-CH_2N(R^e)(R^f)$.

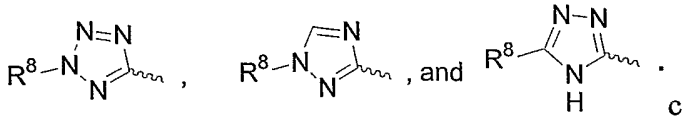
Another specific value for X is $-CH_2OR^e$ or $-C(O)NR^eR^f$.

Another specific value for X is

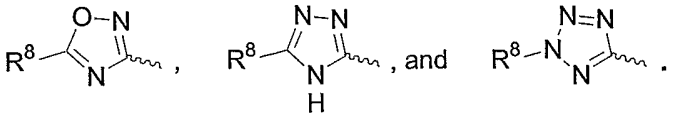


Another specific value for X is





Another specific value for X is



A specific value for R^8 is methyl, ethyl, isopropyl, isopropenyl, -$CH{=}CH_2$, CH_2OH, propyl, -CH_2-$CH{=}CH_2$, -$CH{=}CH$-CH_3, cyclopropyl, cyclopropenyl, cyclopropylmethyl, cyclopropenylmethyl, cyclobutyl, cyclobutenyl, -$(CH_2)Y(CH_2)_nH$, -$(CH_2)_nCOOCH_3$, -$(CH_2)_nCO(CH_2)_nH$, where Y is O, S, $N(CH_2)_n$.

Another specific value for R^8 is $(C_1$-$C_3)$alkyl, CH_2OH, cyclopropyl, cyclobutyl, cyclopropylmethyl, -$(CH_2)_2CO_2CH_3$, -$(CH_2)_{2\text{-}3}OH$, -$(CH_2)_2$halogen.

A more specific value for R^8 is methyl, ethyl, propyl, 2-propenyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, -$(CH_2)_2CO_2CH_3$, -$(CH_2)_{2\text{-}3}OH$

A more specific value for R^8 is methyl, ethyl, cyclopropyl.

A specific value for R^e is cyclopropyl, or cyclobutyl.

A specific value for R^e is cyclopropyl.

A specific value for R^e is cyclobutyl.

A specific value for R^f is hydrogen, or $(C_1$-$C_8)$alkyl.

Another specific value for R^f is hydrogen, methyl, ethyl, or propyl.

Another specific value for R^f is hydrogen, or methyl.

Another specific value for R^f is hydrogen.

A specific value for i is 1.

Another specific value for i is 2.

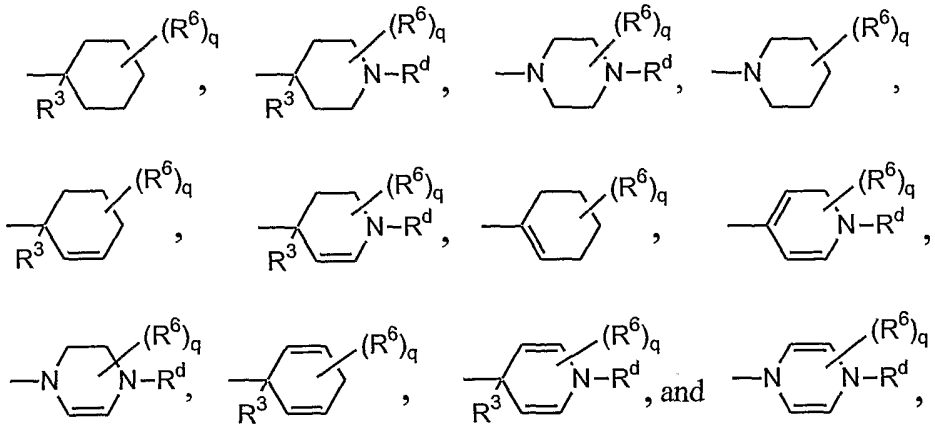
A specific value for j is 1.

Another specific value for j is 2.

A specific value for m is 0, 1, or 2.

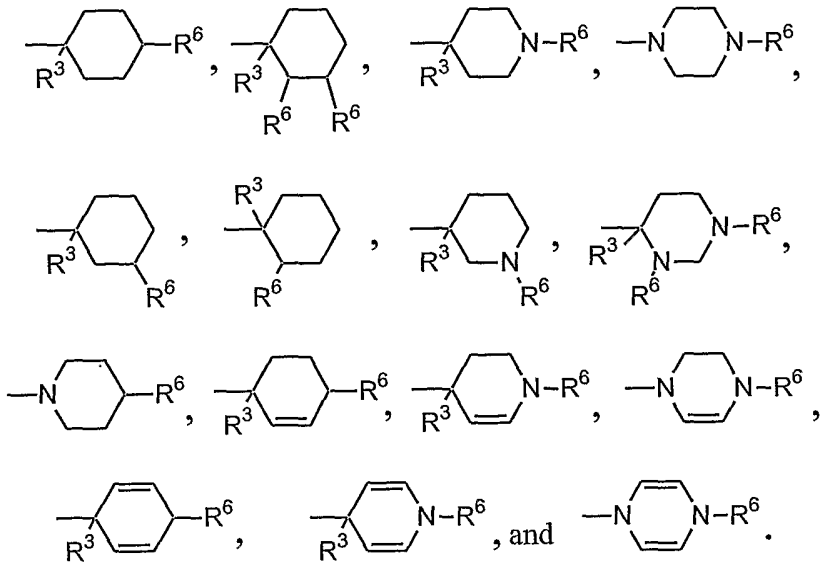
A more specific value for m is 0, or 1.

Specific examples of rings comprising R^4, R^5 and the atom to which they are connected include:



where q is from 1 to 14 and R^d is hydrogen, provided that when q is zero then R^d is not hydrogen.

More specific examples of rings comprising R^4, R^5 and the atom to which they are connected include:



A specific value for the ring comprising $-C(R^3)R^4R^5$ is 2-methyl cyclohexane, 2,2-dimethylcyclohexane, 2-phenylcyclohexane, 2-ethylcyclohexane, 2,2-diethylcyclohexane, 2-tert-butyl cyclohexane, 3-methyl cyclohexane, 3,3-dimethylcyclohexane, 4-methyl cyclohexane,

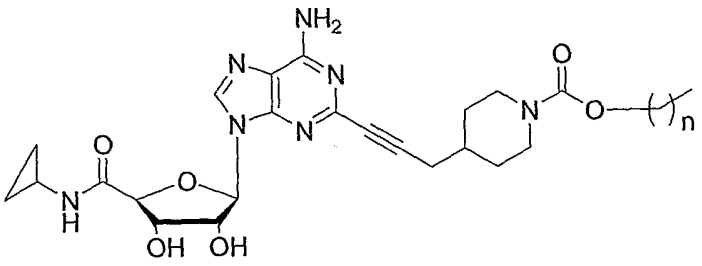
4-ethylcyclohexane, 4-phenyl cyclohexane, 4-tert-butyl cyclohexane, 4-carboxymethyl cyclohexane, 4-carboxyethyl cyclohexane, 3,3,5,5-tetramethyl cyclohexane, 2,4-dimethyl cyclopentane. 4-cyclohexanecarboxyic acid, 4-cyclohexanecarboxyic acid esters, or 4-methyloxyalkanoyl-cyclohexane.

A specific value for the ring comprising $-C(R^3)R^4R^5$ is 4-piperidine, 4-piperidene-1-carboxylic acid, 4-piperidine-1-carboxylic acid methyl ester, 4-piperidine-1-carboxylic acid ethyl ester, 4-piperidine-1-carboxylic acid propyl ester, 4-piperidine-1-carboxylic acid tert-butyl ester, 1-piperidine, 1-piperidine-4-carboxylic acid methyl ester, 1-piperidine-4-carboxylic acid ethyl ester, 1-piperidine-4-carboxylic acid propyl ester, 1-piperidine-4-caboxylic acid tert-butyl ester, 1-piperidine-4-carboxylic acid methyl ester, 3-piperidine, 3-piperidene-1-carboxylic acid, 3-piperidine-1-carboxylic acid methyl ester, 3-piperidine-1-carboxylic acid tert-butyl ester, 1,4-piperazine, 4-piperazine-1-carboxylic acid, 4-piperazine-1-carboxylic acid methyl ester, 4-piperazine-1-carboxylic acid ethyl ester, 4-piperazine-1-carboxylic acid propyl ester, 4-piperazine-1-carboxylic acid tert-butylester, 1,3-piperazine, 3-piperazine-1-carboxylic acid, 3-piperazine-1-carboxylic acid methyl ester, 3-piperazine-1-carboxylic acid ethyl ester, 3-piperazine-1-carboxylic acid propyl ester, 3-piperidine-1-carboxylic acid tert-butylester, 1-piperidine-3-carboxylic acid methyl ester, 1-piperidine-3-carboxylic acid ethyl ester, 1-piperidine-3-carboxylic acid propyl ester or 1-piperidine-3-caboxylic acid tert-butyl ester.

A specific value for the ring comprising R^4 and R^5 is 2-methyl cyclohexane, 2,2-dimethylcyclohexane, 2-phenyl cyclohexane, 2-ethylcyclohexane, 2,2-diethylcyclohexane, 2-tert-butyl cyclohexane, 3-methyl cyclohexane, 3,3-dimethylcyclohexane, 4-methyl cyclohexane, 4-ethylcyclohexane, 4-phenyl cyclohexane, 4-tert-butyl cyclohexane, 4-carboxymethyl cyclohexane, 4-carboxyethyl cyclohexane, 3,3,5,5-tetramethyl cyclohexane, 2,4-dimethyl cyclopentane, 4-piperidine-1-carboxylic acid methyl ester, 4-piperidine-1-carboxylic acid tert-butyl ester 4-piperidine, 4-piperazine-1-carboxylic acid methyl ester, 4-piperidine-1-carboxylic acid tert-butylester, 1-piperidine-4-carboxylic acid methyl ester, 1-piperidine-4-caboxylic

acid tert-butyl ester, tert-butylester, 1-piperidine-4-carboxylic acid methyl ester, or 1-piperidine-4-caboxylic acid tert-butyl ester, 3-piperidine-1-carboxylic acid methyl ester, 3-piperidine-1-carboxylic acid tert-butyl ester, 3-piperidine, 3-piperazine-1-carboxylic acid methyl ester, 3-piperidine-1-carboxylic acid tert-butylester, 1-piperidine-3-carboxylic acid methyl ester, 1-piperidine-3-caboxylic acid tert-butyl ester.

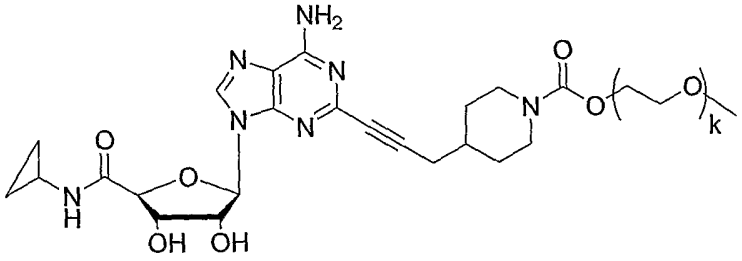
Specific compounds of the invention include formula (IA)



(IA)

In formuila (IA) n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18. In another group of specific compounds n is, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18.

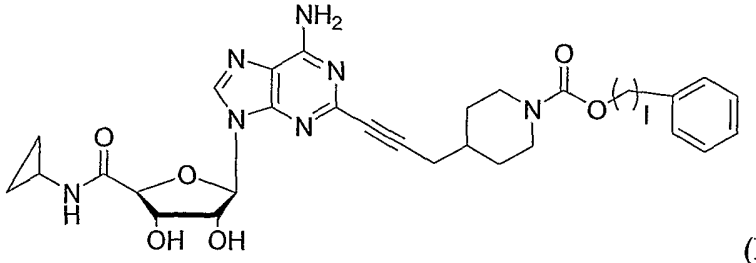
Specific compounds of the invention include formula (IB)



(IB)

In formuila (IB) k is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18.

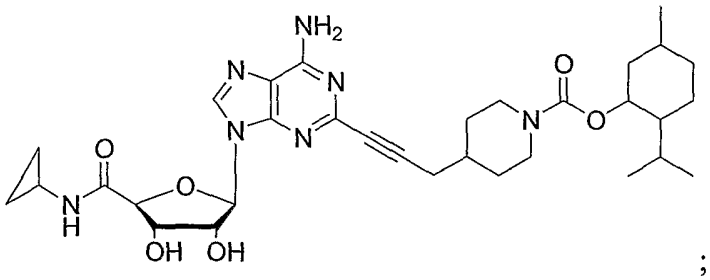
Specific compounds of the invention include formula (IC)



(IC)

In formuila (IC) l is 0, 1, 2, 3, or 4.

Other specific compounds of the invention include



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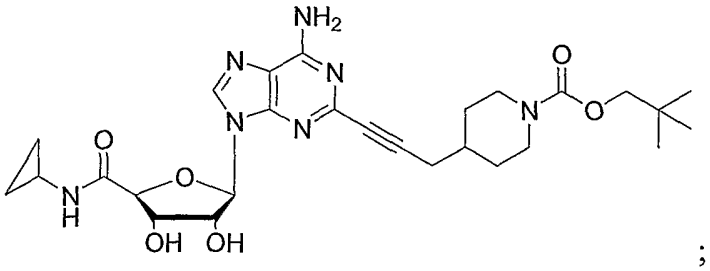

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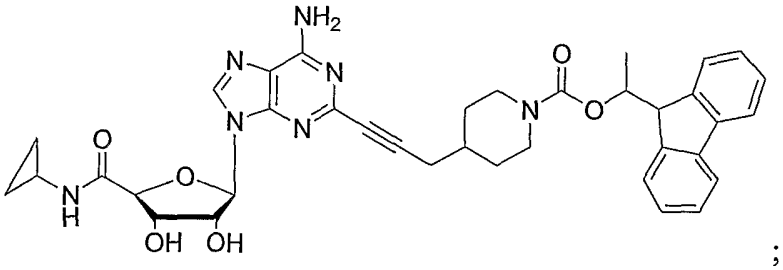

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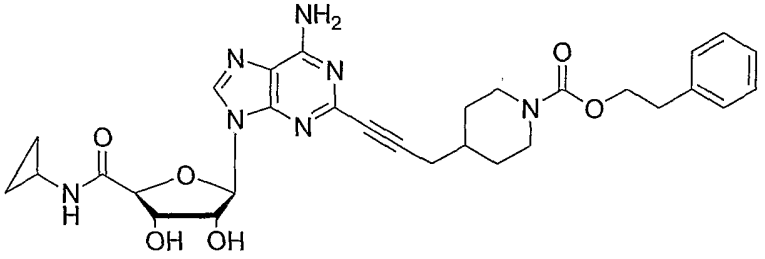
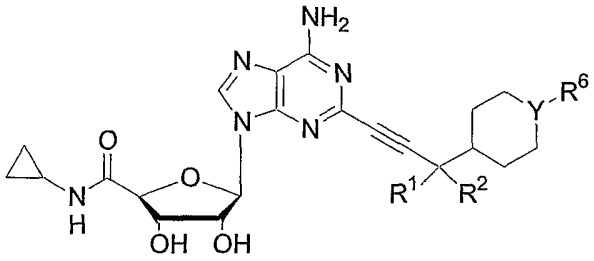


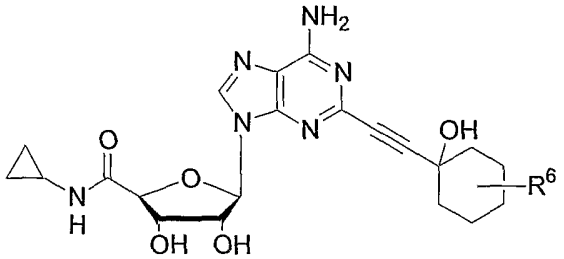
Additional compounds of the invention are depicted in Table 1, below:

Table 1



Compound	R^1	R^2	Y	R^6
101	H	H	CH	CO_2Me
102	H	H	CH	CO_2Et
103	H	H	CH	CO_2iPr
104	H	H	CH	CO_2tBu
105	H	H	CH	CO_2iBu
106	H	H	CH	CH_2OH
107	H	H	CH	CH_2OAc
108	H	H	N	CO_2Me
109	H	H	N	CO_2Et
110	H	H	N	CO_2iPr
111	H	H	N	CO_2tBu
112	H	H	N	CO_2iBu

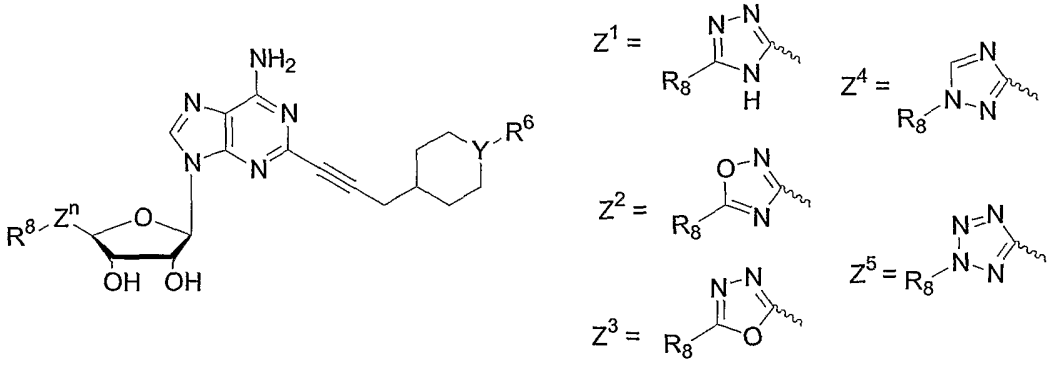
Table 2



Compound #	R^6
201	2-CH_3
202	3-CH_3 (R)

203	3-CH_3 (S)
204	3-Et (R)
205	3-Et (S)
206	4-Me
207	4-Et
208	4-Pr
209	4-tBu
210	4-Phenyl

Table 3



$R^1 = R^2 = H$, $R^7 = NH_2$

Compound	R^8	Z	Y	R^6
301	Methyl	Z1	CH	CO_2Me
302	Methyl	Z1	CH	CO_2Et
303	Methyl	Z1	CH	CO_2iPr
304	Methyl	Z1	CH	CO_2tBu
305	Methyl	Z1	CH	CO_2iBu
306	Methyl	Z1	CH	CH_2OH
307	Methyl	Z1	CH	CH_2OAc
308	Methyl	Z1	N	CO_2Me
309	Methyl	Z1	N	CO_2Et
310	Methyl	Z1	N	CO_2iPr
311	Methyl	Z1	N	CO_2tBu
312	Methyl	Z1	N	CO_2iBu
313	Ethyl	Z1	CH	CO_2Me
314	Ethyl	Z1	CH	CO_2Et
315	Ethyl	Z1	CH	CO_2iPr
316	Ethyl	Z1	CH	CO_2tBu
317	Ethyl	Z1	CH	CO_2iBu
318	Ethyl	Z1	CH	CH_2OH
319	Ethyl	Z1	CH	CH_2OAc
320	Ethyl	Z1	N	CO_2Me
321	Ethyl	Z1	N	CO_2Et
322	Ethyl	Z1	N	CO_2iPr
323	Ethyl	Z1	N	CO_2tBu
324	Ethyl	Z1	N	CO_2iBu
325	Cyclopropyl	Z1	CH	CO_2Me
326	Cyclopropyl	Z1	CH	CO_2Et
327	Cyclopropyl	Z1	CH	CO_2iPr
328	Cyclopropyl	Z1	CH	CO_2tBu
329	Cyclopropyl	Z1	CH	CO_2iBu
330	Cyclopropyl	Z1	CH	CH_2OH
331	Cyclopropyl	Z1	CH	CH_2OAc
332	Cyclopropyl	Z1	N	CO_2Me

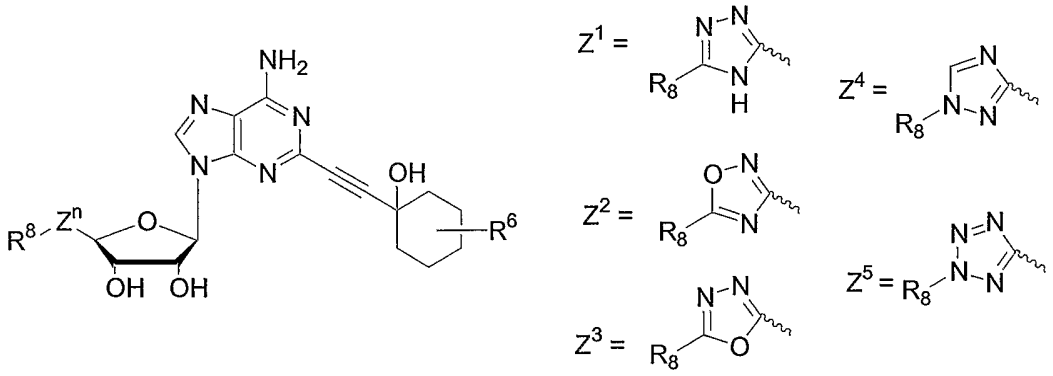
333	Cyclopropyl	Z1	N	CO_2Et
334	Cyclopropyl	Z1	N	CO_2iPr
335	Cyclopropyl	Z1	N	CO_2tBu
336	Cyclopropyl	Z1	N	CO_2iBu
337	Methyl	Z2	CH	CO_2Me
338	Methyl	Z2	CH	CO_2Et
339	Methyl	Z2	CH	CO_2iPr
340	Methyl	Z2	CH	CO_2tBu
341	Methyl	Z2	CH	CO_2iBu
342	Methyl	Z2	CH	CH_2OH
343	Methyl	Z2	CH	CH_2OAc
344	Methyl	Z2	N	CO_2Me
345	Methyl	Z2	N	CO_2Et
346	Methyl	Z2	N	CO_2iPr
347	Methyl	Z2	N	CO_2tBu
348	Methyl	Z2	N	CO_2iBu
349	Ethyl	Z2	CH	CO_2Me
350	Ethyl	Z2	CH	CO_2Et
351	Ethyl	Z2	CH	CO_2iPr
352	Ethyl	Z2	CH	CO_2tBu
353	Ethyl	Z2	CH	CO_2iBu
354	Ethyl	Z2	CH	CH_2OH
355	Ethyl	Z2	CH	CH_2OAc
356	Ethyl	Z2	N	CO_2Me
357	Ethyl	Z2	N	CO_2Et
358	Ethyl	Z2	N	CO_2iPr
359	Ethyl	Z2	N	CO_2tBu
360	Ethyl	Z2	N	CO_2iBu
361	Cyclopropyl	Z2	CH	CO_2Me
362	Cyclopropyl	Z2	CH	CO_2Et
363	Cyclopropyl	Z2	CH	CO_2iPr
364	Cyclopropyl	Z2	CH	CO_2tBu
365	Cyclopropyl	Z2	CH	CO_2iBu
366	Cyclopropyl	Z2	CH	CH_2OH
367	Cyclopropyl	Z2	CH	CH_2OAc
368	Cyclopropyl	Z2	N	CO_2Me
369	Cyclopropyl	Z2	N	CO_2Et
370	Cyclopropyl	Z2	N	CO_2iPr
371	Cyclopropyl	Z2	N	CO_2tBu
372	Methyl	Z3	CH	CO_2Me
373	Methyl	Z3	CH	CO_2Et
374	Methyl	Z3	CH	CO_2iPr
375	Methyl	Z3	CH	CO_2tBu
376	Methyl	Z3	CH	CO_2iBu
377	Methyl	Z3	CH	CH_2OH
378	Methyl	Z3	CH	CH_2OAc
379	Methyl	Z3	N	CO_2Me

380	Methyl	Z3	N	CO_2Et
381	Methyl	Z3	N	CO_2iPr
382	Methyl	Z3	N	CO_2tBu
383	Methyl	Z3	N	CO_2iBu
384	Ethyl	Z3	CH	CO_2Me
385	Ethyl	Z3	CH	CO_2Et
386	Ethyl	Z3	CH	CO_2iPr
387	Ethyl	Z3	CH	CO_2tBu
388	Ethyl	Z3	CH	CO_2iBu
389	Ethyl	Z3	CH	CH_2OH
390	Ethyl	Z3	CH	CH_2OAc
391	Ethyl	Z3	N	CO_2Me
392	Ethyl	Z3	N	CO_2Et
393	Ethyl	Z3	N	CO_2iPr
394	Ethyl	Z3	N	CO_2tBu
395	Ethyl	Z3	N	CO_2iBu
396	Cyclopropyl	Z3	CH	CO_2Me
397	Cyclopropyl	Z3	CH	CO_2Et
398	Cyclopropyl	Z3	CH	CO_2iPr
399	Cyclopropyl	Z3	CH	CO_2tBu
400	Cyclopropyl	Z3	CH	CO_2iBu
401	Cyclopropyl	Z3	CH	CH_2OH
402	Cyclopropyl	Z3	CH	CH_2OAc
403	Cyclopropyl	Z3	N	CO_2Me
404	Cyclopropyl	Z3	N	CO_2Et
405	Cyclopropyl	Z3	N	CO_2iPr
406	Cyclopropyl	Z3	N	CO_2tBu
407	Cyclopropyl	Z3	N	CO_2iBu
408	Methyl	Z4	CH	CO_2Me
409	Methyl	Z4	CH	CO_2Et
410	Methyl	Z4	CH	CO_2iPr
411	Methyl	Z4	CH	CO_2tBu
412	Methyl	Z4	CH	CO_2iBu
413	Methyl	Z4	CH	CH_2OH
414	Methyl	Z4	CH	CH_2OAc
415	Methyl	Z4	N	CO_2Me
416	Methyl	Z4	N	CO_2Et
417	Methyl	Z4	N	CO_2iPr
418	Methyl	Z4	N	CO_2tBu
419	Methyl	Z4	N	CO_2iBu
420	Ethyl	Z4	CH	CO_2Me
421	Ethyl	Z4	CH	CO_2Et
422	Ethyl	Z4	CH	CO_2iPr
423	Ethyl	Z4	CH	CO_2tBu
424	Ethyl	Z4	CH	CO_2iBu
425	Ethyl	Z4	CH	CH_2OH
426	Ethyl	Z4	CH	CH_2OAc

427	Ethyl	Z4	N	CO_2Me
428	Ethyl	Z4	N	CO_2Et
429	Ethyl	Z4	N	CO_2iPr
430	Ethyl	Z4	N	CO_2tBu
431	Ethyl	Z4	N	CO_2iBu
432	Cyclopropyl	Z4	CH	CO_2Me
433	Cyclopropyl	Z4	CH	CO_2Et
434	Cyclopropyl	Z4	CH	CO_2iPr
435	Cyclopropyl	Z4	CH	CO_2tBu
436	Cyclopropyl	Z4	CH	CO_2iBu
437	Cyclopropyl	Z4	CH	CH_2OH
438	Cyclopropyl	Z4	CH	CH_2OAc
439	Cyclopropyl	Z4	N	CO_2Me
440	Cyclopropyl	Z4	N	CO_2Et
441	Cyclopropyl	Z4	N	CO_2iPr
442	Cyclopropyl	Z4	N	CO_2tBu
443	Methyl	Z5	CH	CO_2Me
444	Methyl	Z5	CH	CO_2Et
445	Methyl	Z5	CH	CO_2iPr
446	Methyl	Z5	CH	CO_2tBu
447	Methyl	Z5	CH	CO_2iBu
448	Methyl	Z5	CH	CH_2OH
449	Methyl	Z5	CH	CH_2OAc
450	Methyl	Z5	N	CO_2Me
451	Methyl	Z5	N	CO_2Et
452	Methyl	Z5	N	CO_2iPr
453	Methyl	Z5	N	CO_2tBu
454	Methyl	Z5	N	CO_2iBu
455	Ethyl	Z5	CH	CO_2Me
456	Ethyl	Z5	CH	CO_2Et
457	Ethyl	Z5	CH	CO_2iPr
458	Ethyl	Z5	CH	CO_2tBu
459	Ethyl	Z5	CH	CO_2iBu
460	Ethyl	Z5	CH	CH_2OH
461	Ethyl	Z5	CH	CH_2OAc
462	Ethyl	Z5	N	CO_2Me
463	Ethyl	Z5	N	CO_2Et
464	Ethyl	Z5	N	CO_2iPr
465	Ethyl	Z5	N	CO_2tBu
466	Ethyl	Z5	N	CO_2iBu
467	Cyclopropyl	Z5	CH	CO_2Me
468	Cyclopropyl	Z5	CH	CO_2Et
469	Cyclopropyl	Z5	CH	CO_2iPr
470	Cyclopropyl	Z5	CH	CO_2tBu
471	Cyclopropyl	Z5	CH	CO_2iBu
472	Cyclopropyl	Z5	CH	CH_2OH
473	Cyclopropyl	Z5	CH	CH_2OAc

474	Cyclopropyl	Z5	N	CO_2Me
475	Cyclopropyl	Z5	N	CO_2Et
476	Cyclopropyl	Z5	N	CO_2iPr
477	Cyclopropyl	Z5	N	CO_2tBu
478	Cyclopropyl	Z5	N	CO_2iBu

Table 4



5

Compound	R^8	Z	R^6
501	Methyl	Z1	2-CH_3
502	Methyl	Z1	3-CH_3 (R)
503	Methyl	Z1	3-CH_3 (S)
504	Methyl	Z1	3-Et (R)
505	Methyl	Z1	3-Et (S)
506	Methyl	Z1	4-Me
507	Methyl	Z1	4-Et
508	Methyl	Z1	4-Pr
509	Methyl	Z1	4-tBu
510	Methyl	Z1	4-Phenyl
511	Ethyl	Z1	2-CH_3
512	Ethyl	Z1	3-CH_3 (R)
513	Ethyl	Z1	3-CH_3 (S)
514	Ethyl	Z1	3-Et (R)
515	Ethyl	Z1	3-Et (S)
516	Ethyl	Z1	4-Me
517	Ethyl	Z1	4-Et
518	Ethyl	Z1	4-Pr
519	Ethyl	Z1	4-tBu
520	Ethyl	Z1	4-Phenyl

521	Cyclopropyl	Z1	2-CH_3
522	Cyclopropyl	Z1	3-CH_3 (R)
523	Cyclopropyl	Z1	3-CH_3 (S)
524	Cyclopropyl	Z1	3-Et (R)
525	Cyclopropyl	Z1	3-Et (S)
526	Cyclopropyl	Z1	4-Me
527	Cyclopropyl	Z1	4-Et
528	Cyclopropyl	Z1	4-Pr
529	Cyclopropyl	Z1	4-tBu
530	Cyclopropyl	Z1	4-Phenyl
531	Methyl	Z2	2-CH_3
532	Methyl	Z2	3-CH_3 (R)
533	Methyl	Z2	3-CH_3 (S)
534	Methyl	Z2	3-Et (R)
535	Methyl	Z2	3-Et (S)
536	Methyl	Z2	4-Me
537	Methyl	Z2	4-Et
538	Methyl	Z2	4-Pr
539	Methyl	Z2	4-tBu
540	Methyl	Z2	4-Phenyl
541	Ethyl	Z2	2-CH_3
542	Ethyl	Z2	3-CH_3 (R)
543	Ethyl	Z2	3-CH_3 (S)
544	Ethyl	Z2	3-Et (R)
545	Ethyl	Z2	3-Et (S)
546	Ethyl	Z2	4-Me
547	Ethyl	Z2	4-Et
548	Ethyl	Z2	4-Pr
549	Ethyl	Z2	4-tBu
550	Ethyl	Z2	4-Phenyl
551	Cyclopropyl	Z2	2-CH_3
552	Cyclopropyl	Z2	3-CH_3 (R)
553	Cyclopropyl	Z2	3-CH_3 (S)
554	Cyclopropyl	Z2	3-Et (R)
555	Cyclopropyl	Z2	3-Et (S)
556	Cyclopropyl	Z2	4-Me
557	Cyclopropyl	Z2	4-Et
558	Cyclopropyl	Z2	4-Pr

559	Cyclopropyl	Z2	4-tBu
560	Cyclopropyl	Z2	4-Phenyl
561	Methyl	Z3	2-CH_3
562	Methyl	Z3	3-CH_3 (R)
563	Methyl	Z3	3-CH_3 (S)
564	Methyl	Z3	3-Et (R)
565	Methyl	Z3	3-Et (S)
566	Methyl	Z3	4-Me
567	Methyl	Z3	4-Et
568	Methyl	Z3	4-Pr
569	Methyl	Z3	4-tBu
570	Methyl	Z3	4-Phenyl
571	Ethyl	Z3	2-CH_3
572	Ethyl	Z3	3-CH_3 (R)
573	Ethyl	Z3	3-CH_3 (S)
574	Ethyl	Z3	3-Et (R)
575	Ethyl	Z3	3-Et (S)
576	Ethyl	Z3	4-Me
577	Ethyl	Z3	4-Et
578	Ethyl	Z3	4-Pr
579	Ethyl	Z3	4-tBu
580	Ethyl	Z3	4-Phenyl
581	Cyclopropyl	Z3	2-CH_3
582	Cyclopropyl	Z3	3-CH_3 (R)
583	Cyclopropyl	Z3	3-CH_3 (S)
584	Cyclopropyl	Z3	3-Et (R)
585	Cyclopropyl	Z3	3-Et (S)
586	Cyclopropyl	Z3	4-Me
587	Cyclopropyl	Z3	4-Et
588	Cyclopropyl	Z3	4-Pr
589	Cyclopropyl	Z3	4-tBu
590	Cyclopropyl	Z3	4-Phenyl
591	Methyl	Z4	2-CH_3
592	Methyl	Z4	3-CH_3 (R)
593	Methyl	Z4	3-CH_3 (S)
594	Methyl	Z4	3-Et (R)
595	Methyl	Z4	3-Et (S)
596	Methyl	Z4	4-Me

597	Methyl	Z4	4-Et
598	Methyl	Z4	4-Pr
599	Methyl	Z4	4-tBu
600	Methyl	Z4	4-Phenyl
601	Ethyl	Z4	2-CH_3
602	Ethyl	Z4	3-CH_3 (R)
603	Ethyl	Z4	3-CH_3 (S)
604	Ethyl	Z4	3-Et (R)
605	Ethyl	Z4	3-Et (S)
606	Ethyl	Z4	4-Me
607	Ethyl	Z4	4-Et
608	Ethyl	Z4	4-Pr
609	Ethyl	Z4	4-tBu
610	Ethyl	Z4	4-Phenyl
611	Cyclopropyl	Z4	2-CH_3
612	Cyclopropyl	Z4	3-CH_3 (R)
613	Cyclopropyl	Z4	3-CH_3 (S)
614	Cyclopropyl	Z4	3-Et (R)
615	Cyclopropyl	Z4	3-Et (S)
616	Cyclopropyl	Z4	4-Me
617	Cyclopropyl	Z4	4-Et
618	Cyclopropyl	Z4	4-Pr
619	Cyclopropyl	Z4	4-tBu
620	Cyclopropyl	Z4	4-Phenyl
621	Methyl	Z5	2-CH_3
622	Methyl	Z5	3-CH_3 (R)
623	Methyl	Z5	3-CH_3 (S)
624	Methyl	Z5	3-Et (R)
625	Methyl	Z5	3-Et (S)
626	Methyl	Z5	4-Me
627	Methyl	Z5	4-Et
628	Methyl	Z5	4-Pr
629	Methyl	Z5	4-tBu
630	Methyl	Z5	4-Phenyl
631	Ethyl	Z5	2-CH_3
632	Ethyl	Z5	3-CH_3 (R)
633	Ethyl	Z5	3-CH_3 (S)
634	Ethyl	Z5	3-Et (R)

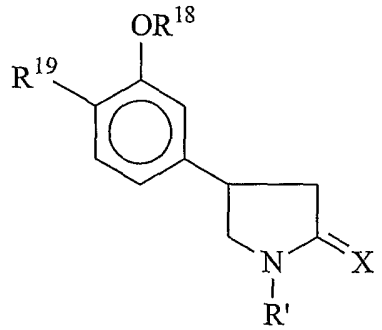
635	Ethyl	Z5	3-Et (S)
636	Ethyl	Z5	4-Me
637	Ethyl	Z5	4-Et
638	Ethyl	Z5	4-Pr
639	Ethyl	Z5	4-tBu
640	Ethyl	Z5	4-Phenyl
641	Cyclopropyl	Z5	2-CH_3
642	Cyclopropyl	Z5	3-CH_3 (R)
643	Cyclopropyl	Z5	3-CH_3 (S)
644	Cyclopropyl	Z5	3-Et (R)
645	Cyclopropyl	Z5	3-Et (S)
646	Cyclopropyl	Z5	4-Me
647	Cyclopropyl	Z5	4-Et
648	Cyclopropyl	Z5	4-Pr
649	Cyclopropyl	Z5	4-tBu
650	Cyclopropyl	Z5	4-Phenyl

The following abbreviations have been used herein:

2-Aas	2-alkynyladenosines;
^{125}I-ABA	N^6-(4-amino-3-^{125}iodo-benzyl)adenosine
APCI	Atmospheric pressure chemical ionization
ATL146e	4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxy-tetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}cyclo-hexanecarboxylic acid methyl ester;
CCPA	2-chloro-N^6-cyclopentyladenosine;
CGS21680	2-[4-(2-carboxyethyl)phenethylamino]-5'-*N*-ethyl-carboxamidoadenosine;
Cl-IB-MECA	N^6-3-iodo-2-chlorobenzyladenosine-5'-*N*-methylur onamide;
CPA	N^6-cyclopentyladenosine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
EtOAc	ethyl acetate
eq	equivalent
GPCR	G protein coupled receptor; hA_{2A}AR, Recombinant human A_{2A} adenosine receptor;
IADO	2-Iodoadenosine
^{125}I-APE,	2-[2-(4-amino-3-[^{125}I]iodophenyl)ethylamino]adenosine;
	NECA, 5'-*N*-ethylcarboxamidoadenosine;
IB-MECA	N^6-3-iodobenzyladenosine-5'-*N*-methyluronamide;

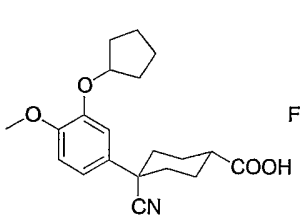
2-Iodoadenosine	5-(6-amino-2-iodo-purin-9-yl)-3,4-dihydroxytetra-hydro-furan-2carboxylic acid ethylamide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
^{125}I-ZM241385,	^{125}I-4-(2-[7-amino-2-[2-furyl][1,2,4]triazolo[2,3-*a*][1,3,5]-triazin-5-yl-amino]ethyl)phenol;
INECA	2-iodo-N-ethylcarboxamidoadenosine
LC/MS	liquid chromatography/mass spectrometry
m.p.	melting point
MHz	megahertz
MRS 1220,	N-(9-chloro-2-furan-2-yl-[1,2,4]triazolo[1,5-c]-quinazolin-5-yl)-2-phenylacetamide;
MS	mass spectrometry
NECA	N-ethylcarboxamidoadenosine
NMR	nuclear magnetic resonance
RP-HPLC	reverse phase high-performance liquid chromatography
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
TBDMSCl	tert-butyldimethylsilylchloride
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuan
TLC	thin layer chromatography
p-TSOH	para-toluenesulfonic acid
XAC	8-(4-((2-a-minoethyl)aminocarbonyl-methyloxy)-phenyl)-1-3-dipropylxanthine;

Specific Type IV phosphodiesterase (PDE) inhibitors useful in practicing the instant invention include racemic and optically active 4-(polyalkoxyphenyl)-2-pyrrolidones of the following formula:

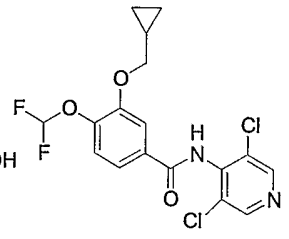


wherein R′, R^{18}, R^{19} and X are as disclosed and described in U.S. Pat. No. 4,193,926. Rolipram is an example of a suitable Type IV PDE inhibitor included within the above formula.

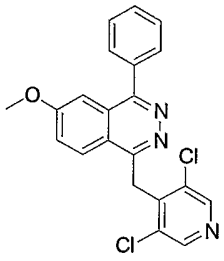
Additional non-limiting examples of PDE IV inhibitors useful in practicing the instant invention include but are not limited to compounds having the following formulas and variations thereof.

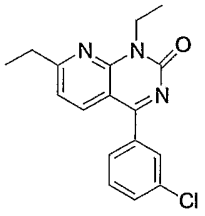


cilomilast
(SB 207499 Ariflo™)

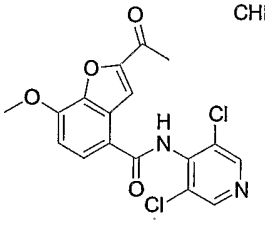


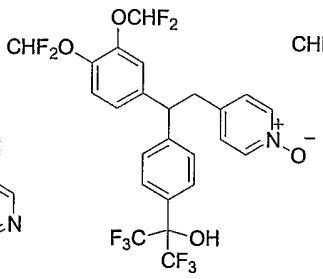
roflumilast



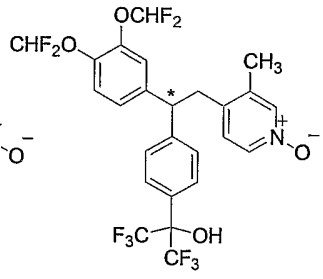


YM976

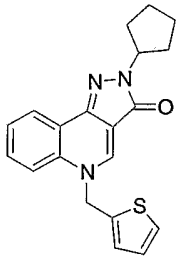


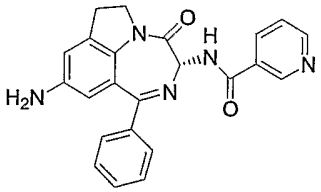


L-791,943

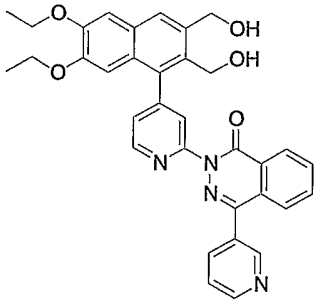


L-826,141



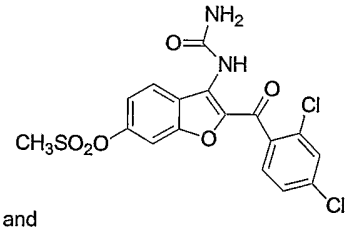


CI-1004



T-2585

and



BAY 19-8004

The present invention further provides pharmaceutical compositions that include a compound of Formula (I) in combination with one of more members selected from the group consisting of the following: (a) Leukotriene biosynthesis inhibitors, 5-lipoxygenase (5-LO) inhibitors, and 5-lipoxygenase activating protein (FLAP) antagonists selected from the group consisting of zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; N-(5-

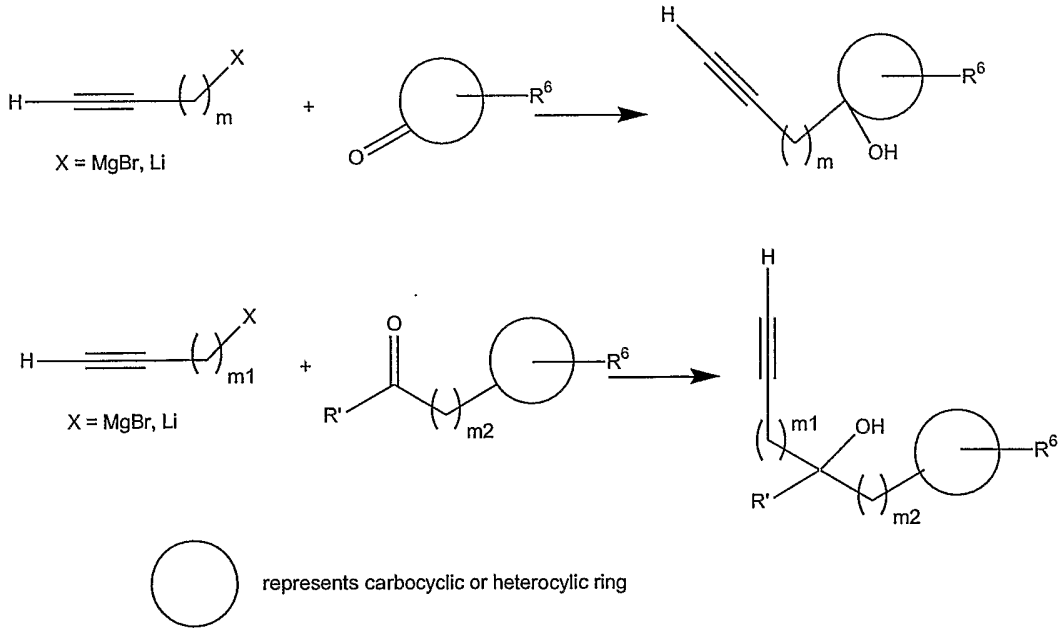
substituted)-thiophene-2-alkylsulfonamides of Formula (5.2.8); 2,6-di-tert-butylphenol hydrazones of Formula (5.2.10); Zeneca ZD-2138 of Formula (5.2.11); SB-210661 of Formula (5.2.12); pyridinyl-substituted 2-cyanonaphthalene compound L-739,010; 2-cyanoquinoline compound L-746,530; indole and quinoline compounds MK-591, MK-886, and BAY x 1005; (b) Receptor antagonists for leukotrienes LTB4, LTC4, LTD4, and LTE4 selected from the group consisting of phenothiazin-3-one compound L-651,392; amidino compound CGS-25019c; benzoxazolamine compound ontazolast; benzenecarboximidamide compound BIIL 284/260; compounds zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195; (d) 5-Lipoxygenase (5-LO) inhibitors; and 5-lipoxygenase activating protein (FLAP) antagonists; (e) Dual inhibitors of 5-lipoxygenase (5-LO) and antagonists of platelet activating factor (PAF); (f) Theophylline and aminophylline; (g) COX-1 inhibitors (NSAIDs); and nitric oxide NSAIDs; (h) COX-2 selective inhibitor rofecoxib; (i) Inhaled glucocorticoids with reduced systemic side effects selected from the group consisting of prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate; (j) Platelet activating factor (PAF) antagonists; (k) Monoclonal antibodies active against endogenous inflammatory entities; (l) Anti-tumor necrosis factor (TNFα) agents selected from the group consisting of etanercept, infliximab, and D2E7; (m) Adhesion molecule inhibitors including VLA-4 antagonists; (n) Immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine, and methotrexate; or (o) anti-gout agents selected from the group consisting of colchicines.

Compounds of the invention can generally be prepared as illustrated in Schemes 1A and 1B below. Starting materials can be prepared by procedures described in these schemes, procedures described in the General methods below or by procedures that would be well known to one of ordinary skill in organic chemistry. The variables used in Schemes 1A and Scheme 1B are as defined herein or as in the claims.

The preparation of alkynyl cycloalkanols is illustrated in Scheme 1A. A solution of an appropriate cycloalkanone (where j is from 0-5) is prepared in a solvent such as THF. A solution of a suitable ethynylmagnesium halide compound in a solvent is added to the cycloalkanone. After addition, the solution is allowed to stir at about 20°C for about 20 hours. The reaction is monitored via TLC until the starting material is consumed. The reaction is quenched with water, filtered over a plug of sand and silica, washed with a solvent, such as EtOAc, and evaporated to provide the product. Typically, two products are formed, the isomers formed by the axial/equatorial addition of the alkyne (where m is as defined above, and the sum of m1 and m2 is from 0 to about 7) to the ketone. The compounds are purified via flash chromatography using EtOAc/Hexanes to provide the product.

Scheme 1A

General Route to Synthesis of Alkyne Precursors

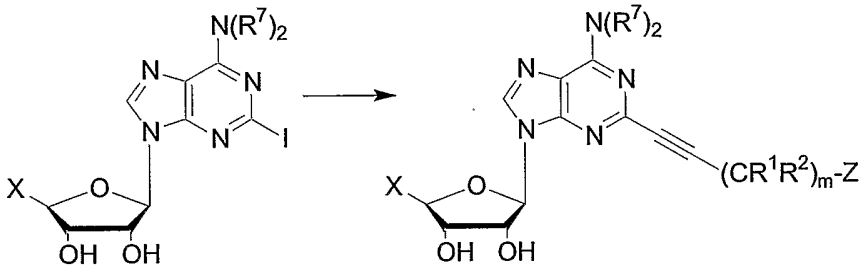


The preparation of 2-alkynyladenosines is illustrated in Scheme 1B. A flame-dried round bottom under nitrogen is charged with 5-(6-Amino-2-iodo-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (NECA 2-Iodoadenosine) and a solvent such as DMF. The appropriate alkyne, wherein

R is a $-(CR^1R^2)_m Z$ group, is dissolved in acetonitrile followed by TEA, 5 mole % $Pd(PPh_3)_4$, and CuI. All solvents are thoroughly degassed.

The solution is allowed to stir for about 24 hours at room temperature, and monitored until complete by HPLC. If the reaction is not complete after this time, additional catalyst, CuI, and TEA are added. After the reaction is complete, the solvents are removed under high-vacuum and the residue taken up in a small amount of DMF. This product is isolated using preparative silica TLC. The product is purified by RP-HPLC.

Scheme 1B



Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids that form a physiological acceptable anion, for example, tosylate, methanesulfonate, malate, acetate, citrate, malonate, tart rate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

The compounds of formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, *e.g.*, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or

its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to

administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid, a liquid or in a dermatological patch.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions, which can be used to deliver the compounds of formula I to the skin are disclosed in Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by comparing their in vitro activity, and in vivo activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949. Useful dosages of Type IV PDE inhibitors are known to the art. For example, see, U.S. Pat. No. 5,877,180, Col. 12.

Generally, the concentration of the compound(s) of formula (I) in a liquid composition, such as a lotion, will be from about 0.1-25% wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 μg/kg, *e.g.*, from about 10 to about 75 μg/kg of body weight per day, such as 3 to about 50 μg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 μg/kg/day, most preferably in the range of 15 to 60 μg/kg/day.

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 μg, conveniently 10 to 750 μg, most conveniently, 50 to 500 μg of active ingredient per unit dosage form.

Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.1 to about 10 nM, preferably, about 0.2 to 10 nM, most preferably, about 0.5 to about 5 nM. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1-100 μg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 μg/kg/hr or by intermittent infusions containing about 0.4-15 μg/kg of the active ingredient(s).

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye. For example, it is desirable to administer the present compositions intravenously over an extended period of time following the insult that gives rise to inflammation.

The ability of a given compound of the invention to act as an A_{2A} adenosine receptor agonist (or antagonist) may be determined using pharmacological models which are well known to the art, or using tests described below.

The present compounds and compositions containing them are administered as pharmacological stressors and used in conjunction with any one of several noninvasive diagnostic procedures to measure aspects of myocardial perfusion. For example, intravenous adenosine may be used in conjunction with thallium-201 myocardial perfusion imaging to assess the severity of myocardial ischemia. In this case, any one of several different radiopharmaceuticals may be substituted for thallium-201 (e.g., technetium-99m-labeled radiopharmaceuticals (ie: Tc-99m-sestamibi, Tc-99m-teboroxime), iodine-123-labeled radiopharmaceuticals such as I-123-IPPA or BMIPP, rubidium-82, nitrogen-13, etc...). Similarly, one of the present compounds may be administered as a pharmacological stressor in conjunction with radionuclide ventriculography to assess the severity of myocardial contractile dysfunction. In this case, radionuclide ventriculographic studies may be first pass or gated equilibrium studies of the right and/or left ventricle. Similarly, a compound of formula (I) may be administered as a pharmacological stressor in conjunction with echocardiography to assess the presence of regional wall motion abnormalities. Similarly, the active compound may be administered as a pharmacological stressor in conjunction with invasive measurements of coronary blood flow such as by intracardiac catheter to assess the functional significance of stenotic coronary vessels.

The method typically involves the administration of one or more compounds of formula (I) by intravenous infusion in doses which are effective to provide coronary artery dilation (approximately 0.25-500, preferably 1-250 mcg/kg/min). However, its use in the invasive setting may involve the intracoronary administration of the drug in bolus doses of 0.5-50 mcg.

Preferred methods comprise the use of a compound of formula (I) as a substitute for exercise in conjunction with myocardial perfusion imaging to detect the presence and/or assess the severity of coronary artery disease in

humans wherein myocardial perfusion imaging is performed by any one of several techniques including radiopharmaceutical myocardial perfusion imaging using planar scintigraphy or single photon emission computed tomography (SPECT), positron emission tomograph (PET), nuclear magnetic resonance (NMR) imaging, perfusion contrast echocardiography, digital subtraction angiography (DSA), or ultrafast X-ray computed tomography (CINE CT).

A method is also provided comprising the use of a compound of formula (I) as a substitute for exercise in conjunction with imaging to detect the presence and/or assess the severity of ischemic ventricular dysfunction in humans wherein ischemic ventricular dysfunction is measured by any one of several imaging techniques including echocardiography, contrast ventriculography, or radionuclide ventriculography. The myocardial dysfunction can be coronary artery disease, ventricular dysfunction, differences in blood flow through disease-free coronary vessels and stenotic coronary vessels and the like

A method is also provided comprising the use of a compound of formula (I) as a coronary hyperemic agent in conjunction with means for measuring coronary blood flow velocity to assess the vasodilatory capacity (reserve capacity) of coronary arteries in humans wherein coronary blood flow velocity is measured by any one of several techniques including Doppler flow catheter or digital subtraction angiography.

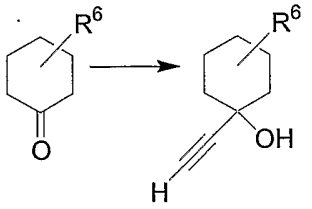
The invention will be further described by reference to the following detailed examples, which are given for illustration of the invention, and are not intended to be limiting thereof.

Description of Preffered Embodiments

All melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra for proton (^{1}H NMR) were recorded on a 300 MHz GE spectrophotometer. The chemical shift values are expressed in ppm (parts per million) relative to tetramethylsilane. For data reporting, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectra were measured

on a Finnigan LcQ Classic. High resolution mass spectrometry (HRMS) data was provided by the Nebraska Center for Mass Spectrometry. Analytical HPLC was done on a Waters 2690 Separation Module with a Waters Symmetry C8 (2.1 x 150 mm) column operated at room temperature. Compounds were eluted at 200 μL/min with 70:30 acetonitrile:water, containing 0.5% acetic acid, with UV detection at 214 nm using a Waters 486 Tunable Detector. Preparative HPLC was performed on a Shimadzu Discovery HPLC with a Shim-pack VP-ODS C_{18} (20 x 100 mm) column operated at room temperature. Compounds were eluted at 30mL/min with a gradient 20-80% of water (containing 0.1% TFA) to methanol over 15 minutes with UV detection at 214 nm using a SPD10A VP Tunable detector. All final compounds presented here were determined to be greater than 98% pure by HPLC. Flash chromatography was performed on Silicyle 60A gel (230-400 mesh) or using reusable chromatography columns and system from RT Scientific, Manchester NH. Analytical thin-layer chromatography was done on Merck Kieselgel 60 F254 aluminum sheets. Preparative thin-layer chromatography was done using 1000 micron Analtech Uniplate with silica gel. All reactions were done under a nitrogen atmosphere in flame-dried glassware unless otherwise stated.

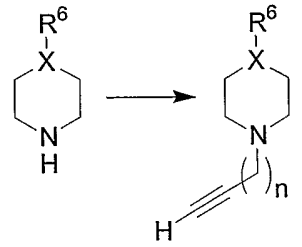
General method 1: Preparation of alkynyl cyclohexanols



To a solution of 10 mmol of the appropriate cyclohexanone in 50 mL of THF was added 60 mL (30 mmol) of 0.5 M ethynylmagnesium bromide in THF. The solution was allowed to stir at 20°C for 20 h, at which time TLC indicated that all the starting material had been consumed. The reaction was quenched with 5 mL of water, filtered over a plug of sand and silica, washed with EtOAc, and evaporated to yield a yellow oil usually containing two spots on TLC w/ 20% EtOAc/Hexanes which were visualized with Vanillin. These two products were usually the different isomers formed by the axial/equatorial addition of the

alkyne to the ketone. The compounds were purified via flash chromatography using 10% EtOAc/Hexanes to yield clear oils or white solids in 50-80% yields.

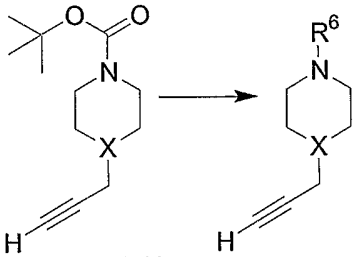
General method 2: Preparation of propargyl piperadines and piperazines.



X=CH, N

To a solution of 10.0 mmol of the appropriate piperazine or piperadine in 20mL acetonitrile were added 12.0 mmol of propargyl bromide (80% stabilized in toluene) and 50.0 mmol of anhydrous potassium carbonate. The reaction mixture was filtered, and evaporated to dryness. The residue was taken up in 50 mL of dichloromethane/water and the organic removed. The aqueous was washed with an additional 3 x 25 mL dichloromethane. The organic was then dried using anhydrous sodium sulfate, filtered, and concentrated to yield crude product which was purified using column chromatography.

General method 3: Preparation of modified piperadines and piperazines.

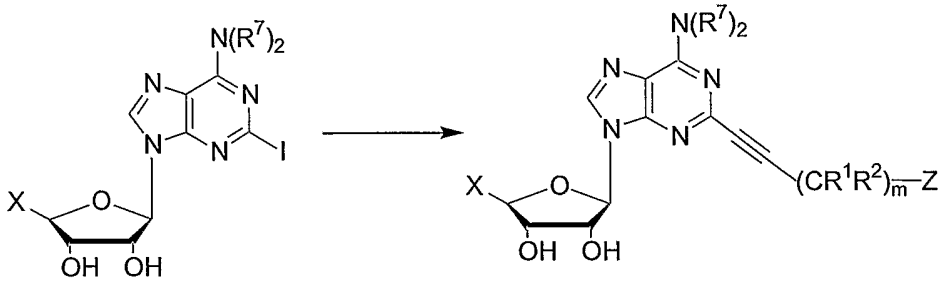


X=CH, N

To 100 mg of the appropriate Boc-protected piperazine or piperadine, JR3275/JR3255 respectively, was added 2-4 mL of neat TFA. The solution was allowed to stir for 6 hours, after which time the TFA was removed under reduced pressure to yield a yellow oil. This oil was taken up in 10 mL of dichloromethane to which was added 10-fold excess of TEA and 3 equivalents of the appropriate electrophile. The yellow solution was allowed to stir at r.t. for

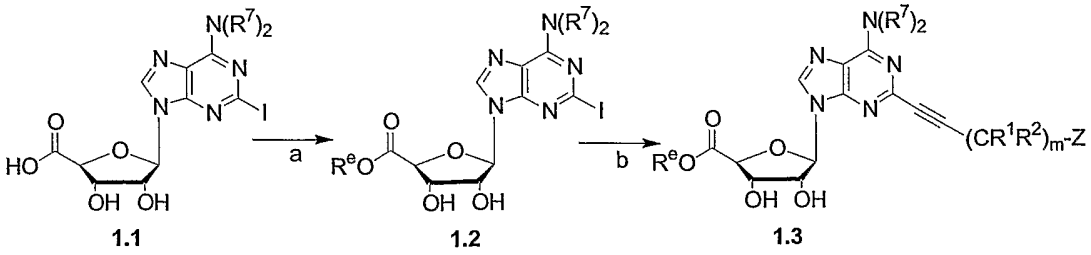
12 hours, after which time the solvents were removed and the product purified using a 1.1x30cm 14 g RTSI column with a 5%-30% gradient of ethyl acetate/hexanes.

General method 4: Preparation of 2-AAs (2-alkynyladenosines).



A flame dried 25 mL round bottom under nitrogen was charged with 2-Iodo adenosine analog (40 mg) and dissolved in 2 mL of DMF. The appropriate alkyne (approx 0.1mL) was then added followed by 4mL of acetonitrile and 0.1mL of TEA. All three solvents had been degassed with nitrogen for at least 24 hours. To this solution was added 5 mole percent $Pd(PPh_3)_4$ and 6 mole % copper iodide. The yellowish solution was allowed to stir for 24 hours at room temperature, or until complete by HPLC. If the reaction was not complete at this time, additional catalyst, CuI, and TEA were added. After the reaction was complete, the solvents were removed under high-vacuum and the red/black residue taken back up in a small amount of DMF. This solution was added to a preparative silica TLC plate (Analtech 1000 microns, 20cm x 20cm) and eluted first with 120 mL of 40% Hexanes/CH_2Cl_2, and then again after addition of 40 mL of MeOH. The UV active band (usually yellow in color) in the middle of the plate is collected, slowly washed with 4 x 25 mL 20% MeOH/CH_2Cl_2, and concentrated. This product is then purified by RP-HPLC to yield solids after trituration with anhydrous ethyl ether.

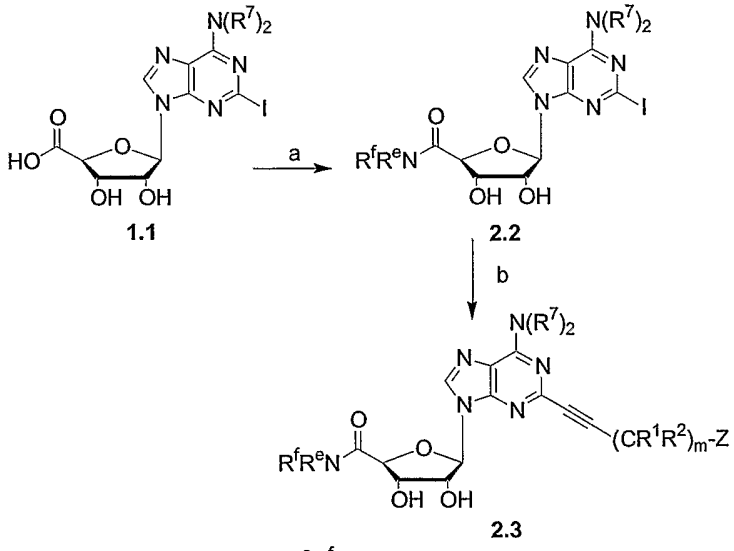
Scheme 1: Preparation of 5′ ester analogs:



a) $SOCl_2$, R^eOH b)$Pd(PPH_3)_4$, CuI, TEA, DMF, CH_3CN, alkyne

To a cooled solution of compound 1.1 in alcohol is added about 5 equivalents of ice-cooled thionyl chloride. This solution is allowed to stir, gradually coming to room temperature for about 12 hours. The solvent is then removed *en vacuo* to yield 1.2 as a white solid. This solid is then treated according to general method 4 to yield compound 1.3.

Scheme 2: Preparation of 5' amide analogs:



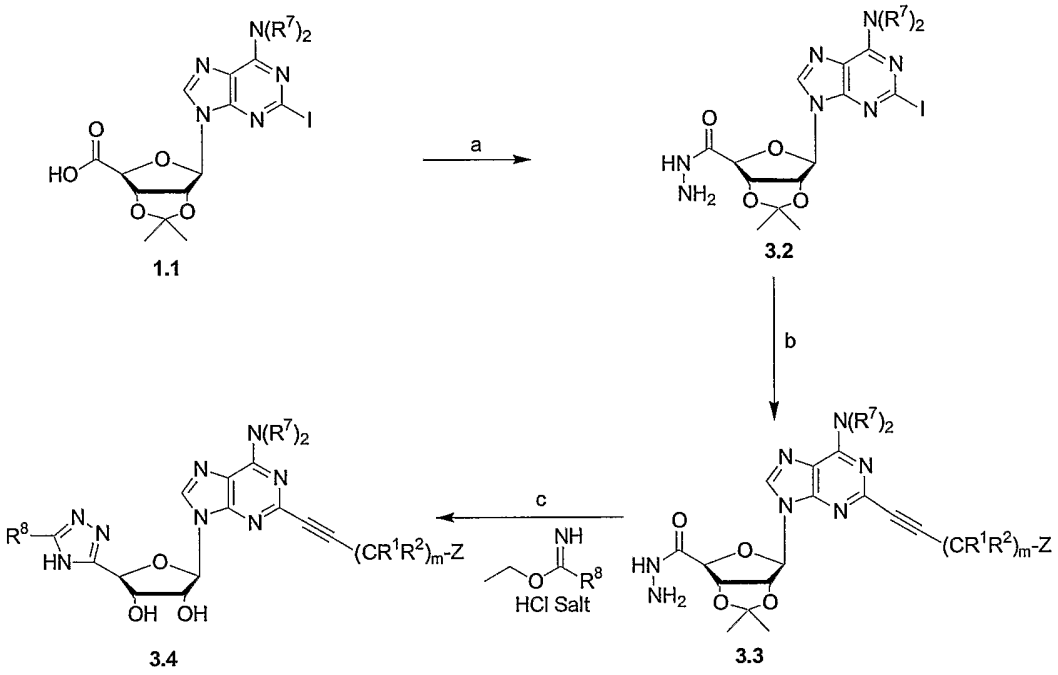
a) 1) $SOCl_2$, MeOH; 2) NHR^eR^f (neat)

b) $Pd(PPH_3)_4$, CuI, TEA, DMF, CH_3CN, alkyne

To a cooled solution of compound 1.1 in methanol is added about 5 equivalents of ice-cooled thionyl chloride. This solution is allowed to stir, gradually coming to r.t for about 12 hours. The solvent is then removed en vacuo to yield compound 1.2, which is dissolved in the appropriate amine (NHR_aR_b) at 0C and allowed to stir for several hours or until complete. The

solvent is then removed under vacuum and the product purified via crystallization or chromatography using a gradient of methanol and dichloromethane to afford 2.2 as a white solid. This solid is then treated according to general method 4 to yield compound 2.3.

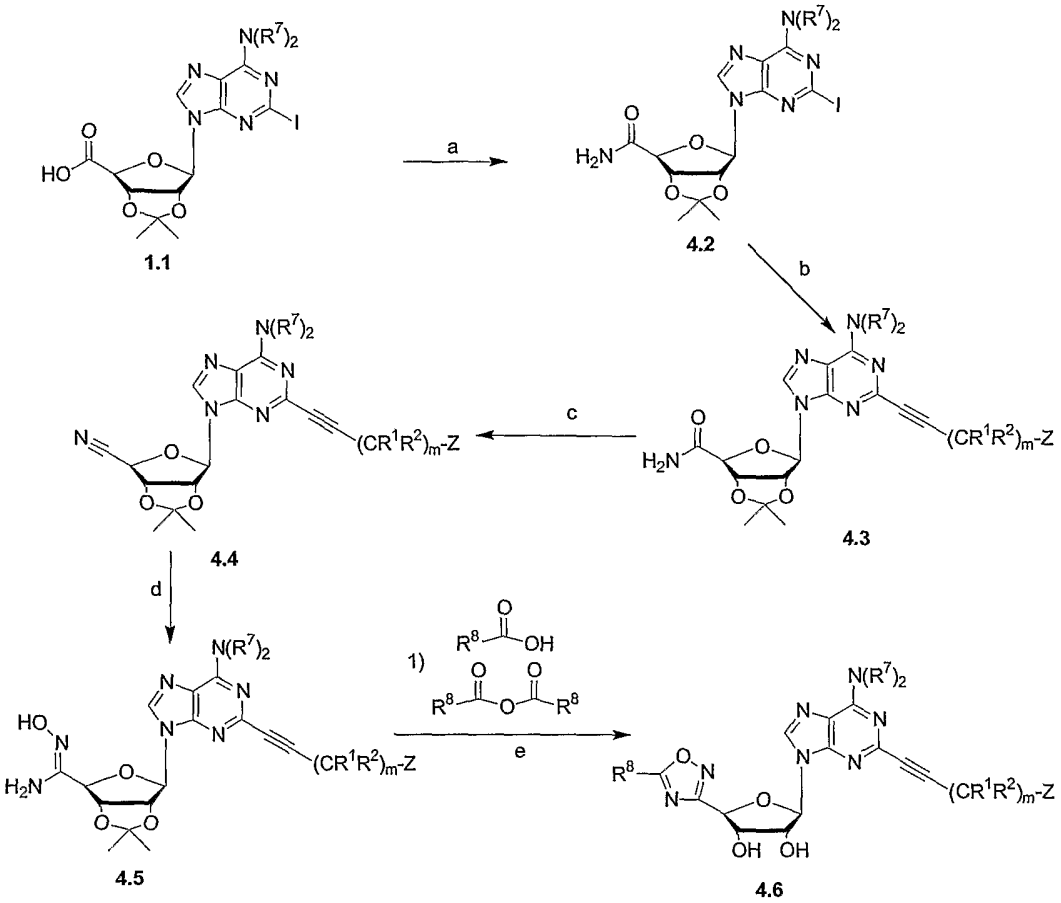
Scheme 3: Preparation of 4' triazoles:



a) HBTU, DIPEA, DMF, H_2NNNH_2 H_2O b) $Pd(PPH_3)_4$, CuI, TEA, DMF, CH_3CN, alkyne c) 1)EtOH, 80C ; 2) Formic Acid, 50%

Hydrazine hydrate (1 equiv) is added to a stirred solution of 1.1 (1 equiv) in dry DMF, HBTU (1 equiv) and DIEA (2.5 equiv) and the solution is allowed to stir for about 24 hours. After extractive work-up, 3.2 can be isolated. 3.2 can be treated according to general method 4 to afford 3.3 which can then be dissolved in EtOH and treated with ethylacetimidate hydrochloride and TEA and refluxed for about 16h to yield 3.4 after chromatography and deprotection using 50 % formic acid for 6 h.

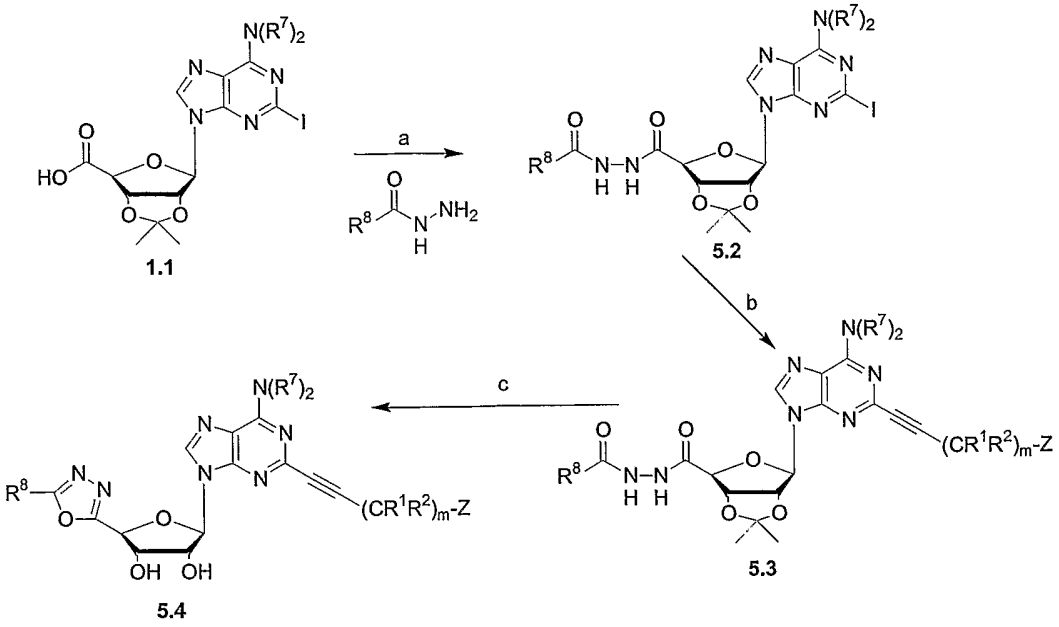
Scheme 4: Preparation of 4'-1,2,4-oxadiazoles



a) 1) TEA, CH_2Cl_2, pivaloyl chloride, 0 C; 2) ammonia b) $Pd(PPH_3)_4$, CuI, TEA, DMF, CH_3CN, alkyne c) TEA, DMAP, CH_3CN, DMF, $POCl_3$ d) NH_2OH HCl, K_2CO_3, EtOH, 80 C e) 1) 90 C 2) 50% formic acid, 60 C

Pivaloyl chloride is added to a cooled solution of 1.1 in DCM and TEA and allowed to stir for several hours. Ammonia gas is the bubbled through the solution to afford 4.2 after isolation and purification. 4.2 can be treated according to general method 4 to afford 4.3 which is then taken up in anhydrous acetonitrile and TEA and DMAP are added. To the ice-cooled solution is cautiously added $POCl_3$. After stirring for about 30 minutes, DMF is added to the solution and the mixture heated to 95C for about 24 h. Purification affords 4.4, to which is added potassium carbonate and hydroxylamine hydrochloride after dissolution in EtOH. This solution is refluxed for about 24 h to yield 4.5 after purification. Treatment of 4.5 with the appropriate carboxylic acid/anhydride pair affords 4.6 after reflux and deprotection using 50% formic acid.

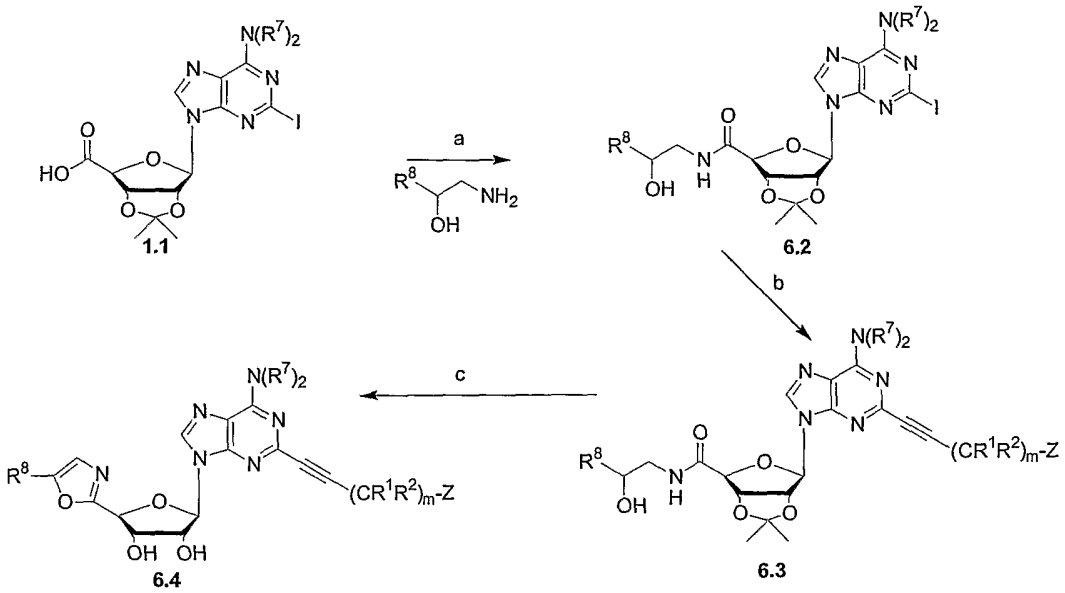
Scheme 5: Preparation of 4'-1,3,4 oxadiazoles



a) 1) DIEA, THF, pivaloyl chloride, 0 C; 2) THF, 3 days b) $Pd(PPH_3)_4$, CuI, TEA, DMF, CH_3CN, alkyne c) 1) DMF, $POCl_3$ 2) 50% formic acid, 60 C

Pivaloyl chloride is added to a solution of 1.1 in THF and DIEA at 0 C. After stirring for several hours the appropriate hydrazide is added and the mixture allowed to stir for about 3 days to yield 5.2. This product can be treated according to general method 4 to afford 5.3 which is dissolved in DMF and treated with $POCl_3$ at 0 C for several hours to yield 5.4 after purification and deprotection with 50% formic acid.

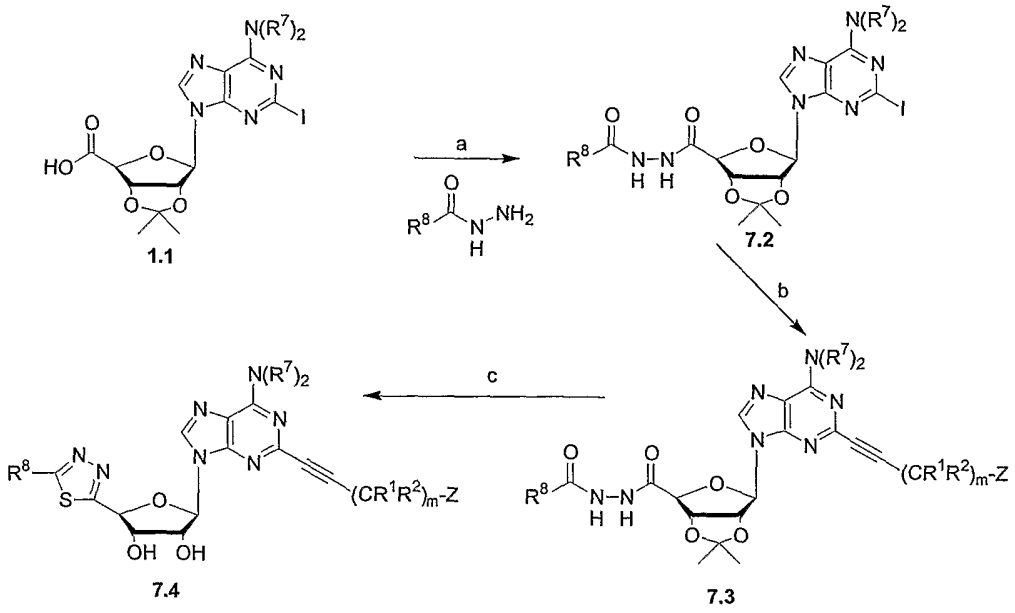
Scheme 6: Preparation of 4'-1,3 oxazole



a) 1) DIEA, DCM, pivaloyl chloride, 0 C; 2) THF b) $Pd(PPH_3)_4$, CuI, TEA, DMF, CH_3CN, alkyne c) 1) PDC, DCM, 4A sieves, AcOH; 2) $POCl_3$, Toluene, Reflux; 3) 50% formic acid, 60 C

Pivaloyl chloride is added to a solution of 1.1 in DCM and DIEA at 0 C. After stirring for several hours the appropriate 1,2-hydroxyl amine is added and the mixture allowed to stir for about 24 h to yield 6.2. This product can be treated according to general method 4 to afford 6.3. This product is dissolved in DCM and treated with PDC, 4Å molecular sieves, and AcOH to convert the alcohol to the ketone. This intermediate is then converted to 6.4 by reflux in toluene after treatment with $POCl_3$ and subsequent heating in 50 % formic acid for 6 h

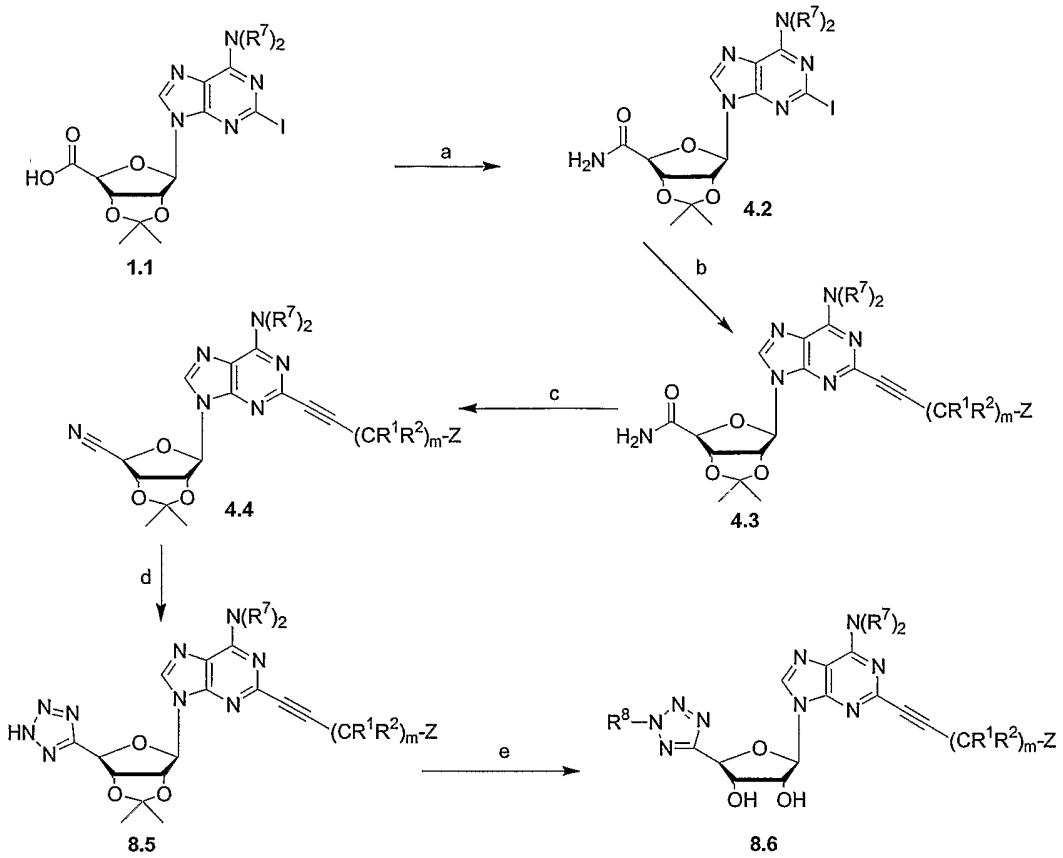
Scheme 7: Preparation of 4'-1,3,4 thiadiazole



a) 1) DIEA, THF, pivaloyl chloride, 0 C; 2) DMF, r.t. 3h b) $Pd(PPH_3)_4$, CuI, TEA, DMF, CH_3CN, alkyne c) 1) Lawessons reagent, CH_3CN, 50 C, 18h; 2) 50% formic acid, 60 C

Pivaloyl chloride is added to a solution of 1.1 in THF and DIEA at 0 C. After stirring for several hours the appropriate hydrazide is added and the mixture is allowed to stir for several additional hours to yield 7.2. This product can be treated according to general method 4 to afford 7.3 which is dissolved in acetonitrile and treated with Lawessons reagent at 50 C for about 1 day to yield 7.4 after purification and deprotection with 50 % formic acid for 6 hours.

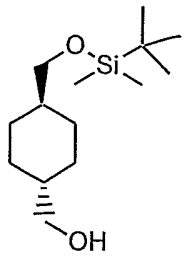
Scheme 8: Preparation of 4'-tetrazole



a) 1) TEA, CH_2Cl_2, pivaloyl chloride, 0 C; 2) ammonia b) $Pd(PPH_3)_4$, CuI, TEA, DMF, CH_3CN, alkyne c) TEA, DMAP,CH_3CN, DMF, $POCl_3$ d) $TMSN_3$, toluene e) 1) R_aI, K_2CO_3, DMF; 2) 50% formic acid, 60 C

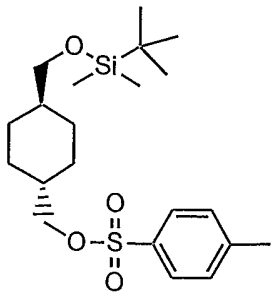
Pivaloyl chloride is added to a cooled solution of 1.1 in DCM and TEA and allowed to stir for several hours. Ammonia gas is the bubbled through the solution to afford 4.2 after isolation and purification. 4.2 is then taken up in anhydrous acetonitrile and TEA and DMAP are added. To the ice-cooled solution is cautiously added $POCl_3$. After stirring for about 30 minutes, DMF is added to the solution and the mixture heated to 95C for about 24 h. Purification affords 4.4, to which is added toluene, azidotrimethylsilane, and dibutyltin oxide and the mixture is heated to 60C for about 15 hours to afford 8.5. Treatment of 8.5 with the appropriate alkyl halide and potassium carbonate affords 8.6 after reflux and deprotection with 50 % formic acid for 6 h.

Preparation 1: [4-(tert-Butyl-dimethyl-silanyloxymethyl)-cyclohexyl]-methanol (83).



To a 100 mL-flask containing 79 (4.0 g, 27.8 mmol) in DMF (40 mL) was added TBDMSCl (3.56 g, 23.6 mmol) and imidazole (3.79 g, 55.6 mmol). The reaction was allowed to stir at 25 °C for 16hoursafter which time saturated aqueous LiBr (50 mL) was added and the reaction extracted with ether (2 x 50 mL). The ether layers were pooled and extracted again with LiBr (2 x 35 mL). The ether layer became clear. The ether layer was then concentrated in vacuo and the product purified by flash chromatography, on a silica gel column, eluting with 1:2 ether/petroleum ether to yield 83 (3.80 g, 62%) as a homogenous oil. ^{1}H NMR ($CDCl_3$) δ 3.46 (d, J = 6.2 Hz, 2 H), 3.39 (d, J = 6.2 Hz, 2 H), 1.95-1.72 (m, 4 H), 1.65 (m, 1 H), 1.40 (m, 1 H), 1.03 – 0.89 (m, 4 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 69.2, 69.1, 41.2, 41.1, 29.5, 26.5, 18.9, -4.8;. APCI m/z (rel intensity) 259 (MH^+, 100).

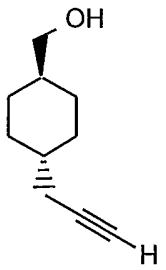
Preparation 2: Toluene-4-sulfonic acid 4-(tert-butyl-dimethyl-silanyloxymethyl)-cyclohexylmethyl ester (84).



To a 100 mL-flask containing 83 (3.4 g, 13.2 mmol) in $CHCl_3$ (30 mL) was added tosyl chloride (3.26 g, 17.1 mmol) and pyridine (3.2 mL, 39.6 mmol). The reaction was allowed to stir at 25 °C for 14hoursafter which time the

reaction was concentrated in vacuo to yield a wet white solid. To this solid was added ether (50 mL) and the solid was filtered and subsequently washed with additional ether (2 x 50 mL). The ether layers were pooled, concentrated in vacuo to yield a clear oil which was purified by flash chromatography, on a silica gel column, eluting with 1:4 ether/petroleum ether to yield 84 (4.5 g, 83 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 7.7, 2 H), 7.33 (d, J = 7.7 Hz, 2 H), 3,81 (d, J = 6.2 Hz, 2H), 3.37 (d, J = 6.2, 2 H), 2.44 (s, 3 H), 1.95-1.72 (m, 4 H), 1.65 (m, 1 H), 1.40 (m, 1 H), 1.03 – 0.89 (m, 4 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 145.1, 133.7, 130.3, 128.4, 75.8, 68.9, 40.7, 38.0, 29.1, 26.5, 22.1, 18.9, -4.9; APCI m/z (rel intensity) 413 (MH^+, 100).

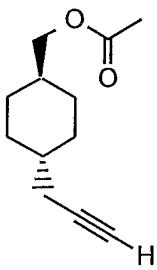
Preparation 3: (4-Prop-2-ynyl-cyclohexyl)-methanol (86).



A 3-neck 250 mL-flask equipped with a gas inlet tube and dry-ice condenser was cooled to –78 °C and charged with liquid ammonia (40 mL). To the reaction mixture was added lithium wire (600 mg, 86.4 mmol) generating a deep blue solution. The mixture was allowed to stir for 1hour. Acetylene, passed through a charcoal drying tube, was added to the ammonia until all the lithium had reacted and the solution turned colorless, at which time the flow of acetylene was stopped, the acetylene-inlet tube and condenser removed and the flask outfitted with a thermometer. DMSO (20 mL) was added and the ammonia evaporated with a warm water bath until the mixture reached a temperature of 30 °C. The solution was stirred at this temperature for 2 hours until the solution stopped bubbling. The mixture was cooled to 5 °C and compound 84 (11.25 g, 27.3 mmol), in DMSO (10 mL), was added. The temperature was maintained at 5 °C. The mixture was allowed to stir at 5 °C for 0.5 hours. Then the solution was gradually warmed to room temperature and stirred for an additional 18

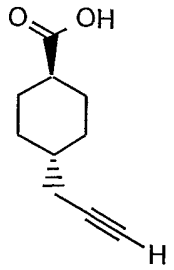
hours. The brown/black reaction mixture was poured slowly over ice (300 g) and extracted with ether (4 x 100 mL), dried with anhydrous sodium sulfate, and concentrated in vacuo to yield a yellow oil. The oil was subsequently dissolved in THF (200 mL) and changed to a brownish color upon addition of TBAF hydrate (11.20 g, 35.5mmol). The solution was allowed to stir for 24 hours 2under N_2 atmosphere. After stirring, the reaction was quenched with water (200 mL) and extracted with ether (3 x 100 mL). The ether extracts were combined and concentrated in vacuo. The crude product was purified by chromatography, on a silica gel column, eluting with 1:1 ether/petroleum ether to yield 86 (3.91 g, 93%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.45 (d, J = 6.2, 2 H), 2.10 (d, J = 6.2, 2 H), 1.9 (s, 1 H), 1.94 – 1.69 (m, 4 H), 1.52 – 1.34 (m, 2 H), 1.16 – 0.83 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 83.8, 69.5, 69.0, 40.8, 37.7, 32.3, 29.7, 26.5.

Preparation 4: (4-prop-2-ynylcyclohexyl)methyl acetate (87).



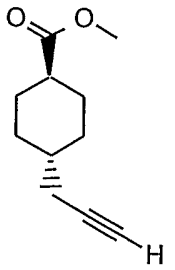
To a solution of 960 mg (6.31 mmol) of 86 in 6 mL DMF was added 0.62 mL (7.57 mmol) pyridine and 0.78 mL (8.27mmol) acetic anhydride. The reaction was allowed to stir overnight at room temperature. After 16 hours, starting material still remained. The reaction mixture was heated at 75 °C for 3 hours. The solvent was removed under reduced pressure to yield a yellow oil which was purified by flash chromatography, on silica gel, eluting with 1:3 ether/petroleum ether to yield 1.12 g (91%) of 87 as an oil. ^{1}H NMR ($CDCl_3$) δ3.87 (d, J = 6.2 Hz, 2 H), 2.06 (d, J = 4.3 Hz, 2 H), 2.03 (s, 3 H), 1.98 – 1.93 (m, 1 H), 1.92 – 1.83 (m, 2 H), 1.83 – 1.74 (m, 2 H), 1.63 – 1.36 (m, 2 H), 1.12 – 0.90 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 171.7, 83.7, 69.9, 69.6, 37.4, 37.3, 32.1, 29.7, 26.5, 21.4; APCI m/z (rel intensity) 195 (M^+, 30), 153 (M^+, 70), 135 (M^+, 100).

Preparation 5: 4-prop-2-ynyl-cyclohexanecarboxylic acid (88).



A solution of chromium trioxide (600 mg, 6.0 mmol) in 1.5 M H_2SO_4 (2.6 mL, 150 mmol) was cooled to 5 °C and added to a solution of 86 (280 mg, 1.84 mmol) in acetone (15 mL). The mixture was allowed to warm to room temperature and allowed to stir overnight. Isopropanol (4 mL) was added to the green/black solution, which turned light blue after 1hr. After adding water (15 mL), the solution was extracted with $CHCl_3$ (6 x 25 mL). The organic layers were pooled and concentrated in vacuo to yield a white solid. The solid was dissolved in ether (50 mL) and extracted with 1 M NaOH (2 x 30 mL). The basic extracts were pooled, acidified w/ 10% HCl, and re-extracted with ether (3 x 30mL). The ether layers were combined, dried with sodium sulfate and concentrated in vacuo to yield a white solid. The product was recrystallized from acetone/water to yield 88 (222 mg, 73%) as white needles: mp 84-85 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 –2.23 (m, 1 H), 2.17 – 2.11 (m, 2 H), 2.07-2.03 (m, 2 H), 1.97 – 1.91 (m, 3H), 1.51-1.39 (m, 3 H), 1.13- 1.01 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 182.5, 83.8, 69.6, 40.7, 37.7, 32.3, 29.6, 26.5; APCI m/z (rel intensity) 165 (M^-, 100).

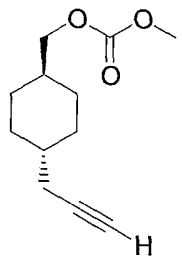
Preparation 6: Methyl 4-prop-2-ynylcyclohexanecarboxylate (89).



To a solution of 88 (240 mg, 1.45mmol) in 7:3 CH_2Cl_2:MeOH (10 mL) was added TMS Diazomethane (2.0 M in hexanes) (0.9 mL, 1.8 mmol) in 0.2 ml

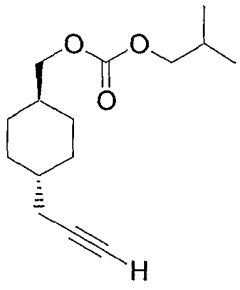
aliquots until the color remained yellow. The reaction was allowed to stir for an additional 0.25 hours at room temperature. After stirring, glacial acetic acid was added dropwise until the solution became colorless. The reaction was concentrated in vacuo to an oil which was purified by flash chromatography on silica gel using ether:petroleum ether (1:9) to yield 89 (210 mg, 80%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 3H), 2.25 – 2.13 (m, 1 H), 2.08 – 1.94 (m, 3 H), 1.95 – 1.90 (m, 2 H), 1.49 – 1.31 (m, 3 H), 1.10 – 0.93 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 176.7, 83.3, 69.8, 51.9, 43.4, 36.7, 31.9, 29.2, 26.3; APCI m/z (rel intensity) 181 (MH^+, 100).

Preparation 7: Trans[4-(1-Propargyl)cyclohexylmethyl] methyl carbonate (90).



Yield: 345 mg, 81%. ^{1}H NMR ($CDCl_3$) δ 0.98-1.07, 1.40-1.52, 1.57-1.70, 1.78-1.93 (4 x m, 10H, cyclohexyl), 1.96 (t, 1H, acetylene), 2.10 (dd, 2H, -$C_6H_{10}CH_2CCH$), 3.78 (s, 3H, -OCH_3), 3.96 (d, -$C_6H_{10}CH_2O$-).

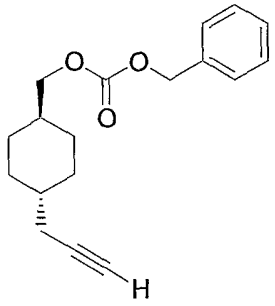
Preparation 8: Trans[4-(1-Propargyl)cyclohexylmethyl] *iso*-butyl carbonate (91).



Yield: 433 mg, 83%. ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 4H, -$OCH_2CH(CH_3)_2$), 0.98-1.09, 1.40-1.51, 1.57-1.70, 1.78-1.93 (4 x m, 10H, cyclohexyl), 1.94-2.04 (m, 1H, -$OCH_2CH(CH_3)_2$), 1.96 (t, 1H, acetylene), 2.10

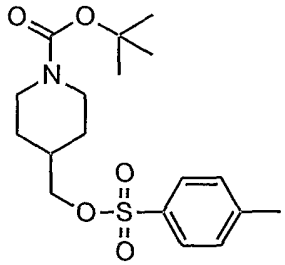
(dd, 2H, -$C_6H_{10}CH_2CCH$), 3.91, 3.95 (2 x d, 4H, -$OCH_2CH(CH_3)_2$, -$C_6H_{10}CH_2O$-).

Preparation 9: Trans[4-(1-Propargyl)cyclohexylmethyl] benzyl carbonate (92).



Yield: 340 mg, 69%. ^1H NMR ($CDCl_3$) δ 0.97-1.08, 1.40-1.49, 1.55-1.69, 1.77-1.93 (4 x m, 10H, cyclohexyl), 1.96 (t, 1H, acetylene), 2.10 (dd, 2H, -$C_6H_{10}CH_2CCH$), 3.98 (d, -$C_6H_{10}CH_2O$-), 5.15 (s, 2H, -OCH_2Ph), 7.33-7.40 (m, 5H, Ar).

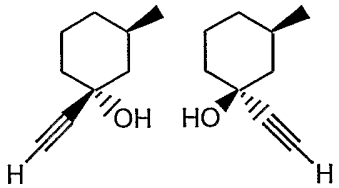
Preparation 10: 4-(Toluene-4-sulfonyloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester (JR3215).



JR3215

A solution of N-Boc-4-piperidinemethanol, 5.0 g (23.2 mmol) in chloroform, 50 mL, was prepared. Toluene sulfonyl chloride, 5.75 g (30.2 mmol), in 5.6 mL of pyridine (69.6 mmol) was added. The solution was stirred under nitrogen allowed to stir for 24 hours. Standard workup and chromatographic purification provided the title compound. Yield 6.0g

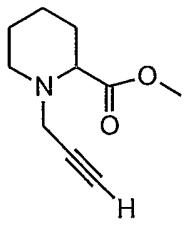
Preparation 11: (R)-1-Ethynyl-(R)-3-methyl-cyclohexanol (JR3217A), (S)-1-Ethynyl-(R)-3-methyl-cyclohexanol (JR3217B).



JR3217A JR3217B

To a solution of 1.0 g (8.9 mmol) (R)-(+)-3-methyl-cyclohexanone in 50 mL of THF was added 54 mL (26.7 mmol) of 0.5 M ethynylmagnesium bromide in THF. The solution was allowed to stir at 20 °C for 20 hours. Analysis by TLC indicated that the starting material had been consumed. The reaction was quenched with 5 mL of water, filtered over a plug of sand and silica, washed with EtOAc, and evaporated to yield 1.15 g of a yellow oil containing two spots (r.f.'s 0.33 (minor, JR3217A) and 0.25 (major, JR3217B), 20% EtOAc/Hexanes) which were visualized with Vanillin. The compound was purified via flash chromatography using 10% EtOAc/Hexanes (225 mL silica) to provide JR3217A and JR3217B.

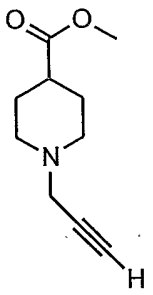
Preparation 12: 1-Prop-2-ynyl-piperidine-2-carboxylic acid methyl ester (JR3249).



JR3249

The title compound was prepared starting with 4.0g (22.3 mmol) of methylpipecolinate hydrochloride according to general method 2.

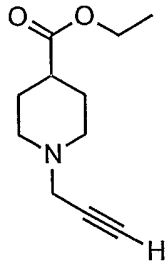
Preparation 13: 1-Prop-2-ynyl-piperidine-4-carboxylic acid methyl ester (JR3245).



JR3245

To a solution of methyl isonipecotate 3.5g (24.4 mmol, 3.30 mL) in 100 mL dichloromethane was added TEA (1.5 eq, 36.6 mmol, 5.1 mL), propargyl bromide (3.0eq, 73.2 mmol, 6.5 ml), at room temperature for 36 hrs. The reaction was quenched with 35 mL water to yield to provide a clear solution. The solution was extracted with dichloromethane 2x25 mL, dried with Na2SO4, and the solvent evaporated to provide a yellow oil. r.f. (40% EtOAc/Hexanes) 0.26 stains faint white with Vanillin, starting material r.f. 0.05 stains yellow with Vanillin. The product appeared pure after extraction.

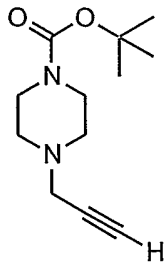
Preparation 14: 1-Prop-2-ynyl-piperidine-4-carboxylic acid ethyl ester (JR3271).



JR3271

The title compound was prepared starting with 2.0g (12.7 mmol) of ethyl isonipecotate according to general method 2.

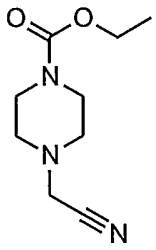
Preparation 15: 4-Prop-2-ynyl-piperazine-1-carboxylic acid tert-butyl ester (JR3275).



JR3275

To a solution of 10.0 g (54.8 mmol) of tert-butyl-1-piperazine carboxylate in 60 mL acetonitile was added 5.20 mL (60.4 mmol) propargyl bromide and 37.9 g (274 mmol) anhydrous potassium carbonate. Additional propargyl bromide, 1.5mL, was added after stirring for 36 hours at room temperature. The residue was evaporated to dryness. Dichloromethane, 50 mL, and water, 50 mL, were added. The reaction mixture was extracted with CH_2Cl_2, 4 x 40 mL, dried over magnesium sulfate, and evaporate to provide a brown oil. The oil was dissolved in dichloromethane and purify with a RT Scientific system using hexane/ethyl acetate gradient to yield 5.5 g (46%) of yellow oil, which ultimately crystallized upon standing.

Preparation 16: 4-Cyanomethyl-piperazine-1-carboxylic acid ethyl ester (JR3287).

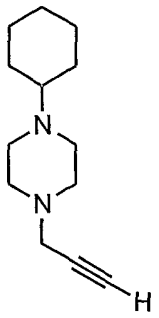


JR3287

To a solution of 3g (19.0 mmol) of ethyl N-piperazinecarboxylate in 25 mL of CH_3CN was added 1.57g (1.32 mL 20.1mmol) of 2-chloroacetonitrile and 15.6g (95mmol) $K_2CO_3 \bullet 1\frac{1}{2}H_2O$. The suspension was stirred at room temperature for 16 hours. The reaction was analyzed using TLC (35% Ethyl

acetate/Hexanes, product r.f. 0.38 vs. s.m. r.f. of 0.02). The analysis indicated the reaction was complete. The golden yellow solution was evaporated to dryness. The residue was extracted with CH_2Cl_2/H_2O, dried with $MgSO_4$, and concentrated.

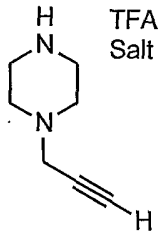
Preparation 17: 1-Cyclohexyl-4-prop-2-ynyl-piperazine (JR4019).



JR4019

The title compound was prepared starting with 3g (17.9 mmol) of 1-cyclohexylpiperazine according to general method 2

Preparation 18: 1-Prop-2-ynyl-piperazine (JR4029).

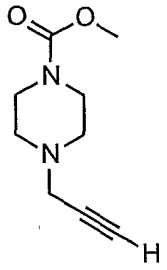


JR4029

To a flame-dried 25 mL round bottom flask under nitrogen was added 2.1 g of 4-Prop-2-ynyl-piperazine-1-carboxylic acid tert-butyl ester. To this solid was added 5 mL of 98% TFA in 1 mL portions. The solution turned wine red, bubbled and smoked. The additional portions of TFA were added when this activity subsided. After the third portion of TFA had been added only minimal bubbling occurred. The solution was allowed to stir under nitrogen at room temperature for an additional hour and evaporated under reduced pressure to yield the product as a thick red syrup. Assumed quantitative yield of 1.16 g. The residue was suspended in 20 mL dichloromethane and used immediately

without further purification for the preparation of compounds JR4031, JR4033, and JR4035.

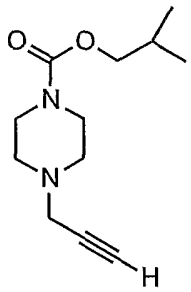
Preparation 19: 4-Prop-2-ynyl-piperazine-1-carboxylic acid methyl ester (JR4031).



JR4031

The title compound was prepared starting with 385 mg (3.1 mmol) of JR4029 and using methylchloroformate according to general method 3.

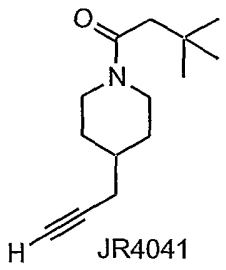
Preparation 20: 4-Prop-2-ynyl-piperazine-1-carboxylic acid isobutyl ester (JR4035).



JR4035

The title compound was prepared starting with 385 mg (3.1 mmol) of JR4029 and using isobutylchloroformate according to general method 3.

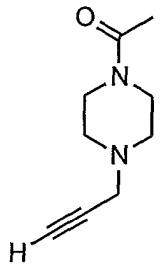
Preparation 21: 3,3-Dimethyl-1-(4-prop-2-ynyl-piperidin-1-yl)-butan-1-one (JR4041).



JR4041

The title compound was prepared starting with *tert*-butyl ester (JR3257) and using *tert*-butylacetylchloride according to general method 3.

Preparation 22: 1-(4-Prop-2-ynyl-piperazin-1-yl)-ethanone (JR4043).

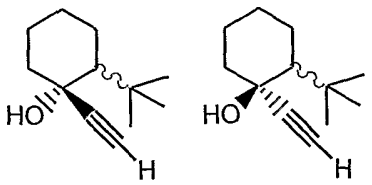


JR4043

The title compound was prepared starting with 385 mg (3.1 mmol) of JR4029 and using acetyl chloride according to general method 3.

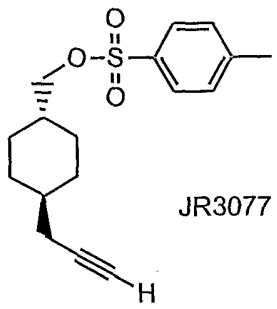
The following intermediate compounds are prepared using the general method 1 described herein and the appropriate starting materials.

(R)-1-Ethynyl-3-*tert*-butyl-cyclohexanol (JR3255A), (S)-1-Ethynyl-3-*tert*-butyl-cyclohexanol (JR3255B).



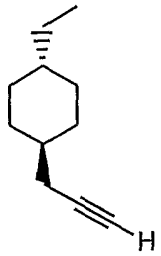
JR3225A JR3225B

Toluene-4-sulfonic acid 4-prop-2-ynyl-cyclohexylmethyl ester (JR3077).



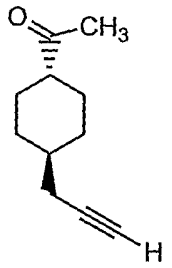
JR3077

1-Ethyl-4-prop-2-ynyl-cyclohexane (JR3083).



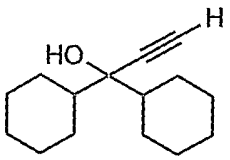
JR3083

1-(4-Prop-2-ynyl-cyclohexyl)-ethanone (JR3115).



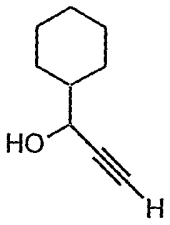
JR3115

1,1-Dicyclohexyl-prop-2-yn-1-ol (JR3127).



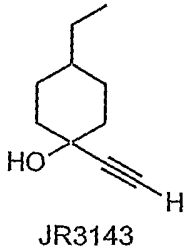
JR3127

1-Cyclohexyl-prop-2-yn-1-ol (JR3129).



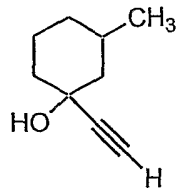
JR3129

4-Ethyl-1-ethynyl-cyclohexanol (JR3143).



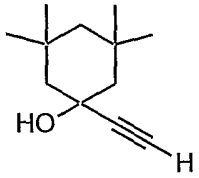
JR3143

1-Ethynyl-3-methyl-cyclohexanol.



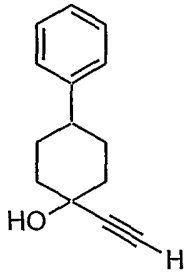
JR3147B

1-Ethynyl-3,3,5,5-tetramethyl-cyclohexanol (JR3151).



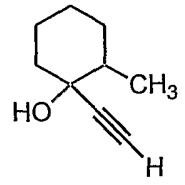
JR3151

1-Ethynyl-4-phenyl-cyclohexanol (JR3153).



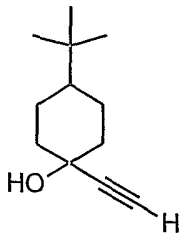
JR3153

1-Ethynyl-2-methyl-cyclohexanol (JR3167B)



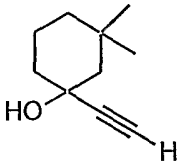
JR3167B

4-tert-Butyl-1-ethynyl-cyclohexanol (JR3191).



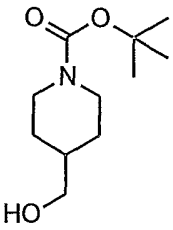
JR3191

1-Ethynyl-3,3-dimethyl-cyclohexanol (JR3193).



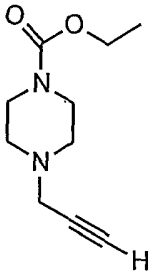
JR3193

4-Hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (JR3199).



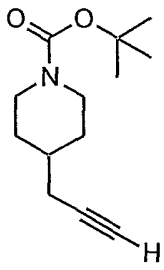
JR3199

4-Prop-2-ynyl-piperazine-1-carboxylic acid ethyl ester (JR3211).



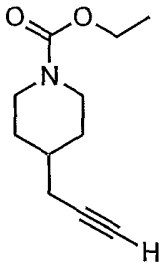
JR3211

4-Prop-2-ynyl-piperidine-1-carboxylic acid tert-butyl ester (JR3257).



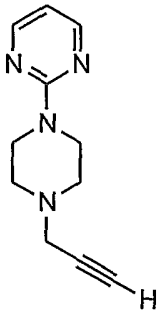
JR3257

4-Prop-2-ynyl-piperidine-1-carboxylic acid ethyl ester (JR3267B).



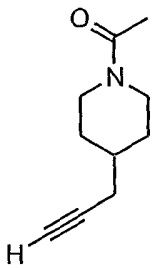
JR3267B

2-(4-Prop-2-ynyl-piperazin-1-yl)-pyrimidine (JR3277).



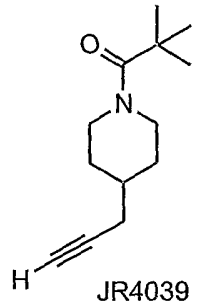
JR3277

1-(4-Prop-2-ynyl-piperidin-1-yl)-ethanone (JR4037).



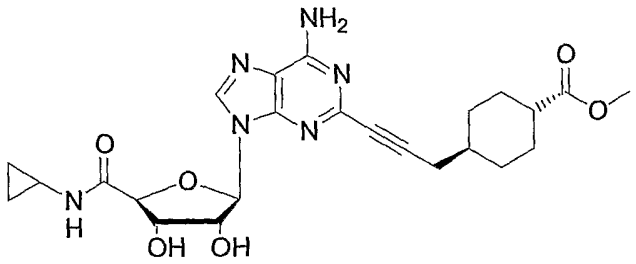
JR4037

2,2-Dimethyl-1-(4-prop-2-ynyl-piperidin-1-yl)-propan-1-one (JR4039).



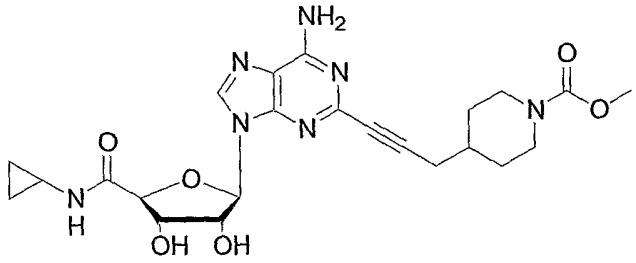
JR4039

Example 1: 4-{3-[6-Amino-9-(5-cyclopropylcarbamoyl-3,4-dihydroxy-tetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-cyclohexanecarboxylic acid methyl ester.



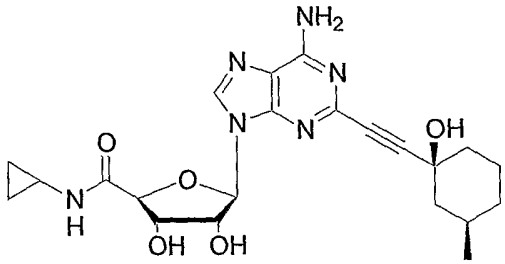
MS: m/z 499.3 $(M+H)^+$.

Example 2: 4-{3-[6-Amino-9-(5-cyclopropylcarbamoyl-3,4-dihydroxy-tetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-1-carboxylic acid methyl ester.



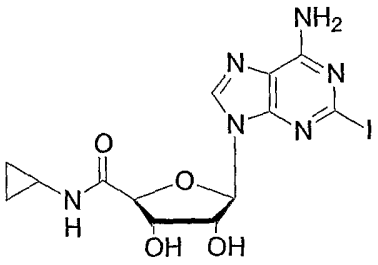
MS: m/z 500.4 (M+H)+.

Example 3: 5-[6-Amino-2-(1-hydroxy-3-methyl-cyclohexylethynyl)-purin-9-yl]-3,4-dihydroxy-tetrahydro-furan-2-carboxylic acid cyclopropylamide.



MS: m/z 457.4 (M+H)+.

Example 4: 5-(6-Amino-2-iodo-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-carboxylic acid cyclopropylamide.



Example 5: Cell culture and membrane preparation.

Sf9 cells were cultured in Grace's medium supplemented with 10% fetal bovine serum, 2.5 μg/ml amphotericin B and 50 μg/ml gentamycin in an atmosphere of 50% N_2/50% O_2. Viral infection was performed at a density of $2.5x10^6$ cells/mL with a multiplicity of infection of two for each virus used. Infected cells were harvested 3 days post-infection and washed twice in insect PBS (PBS pH 6.3). Cells were then resuspended in lysis buffer (20 mM HEPES pH 7.5, 150 mM NaCl, 3mM $MgCl_2$, 1mM β-mercaptoethanol (BME), 5μg/mL leupeptin, 5μg/mL pepstatin A, 1 μg/mL aprotinin, and 0.1mM PMSF) and snap frozen for storage at - 80°C. Cells were thawed on ice, brought to 30 mL total volume in lysis buffer, and burst by N_2 cavitation (600 psi for 20 minutes). A low-speed centrifugation was performed to remove any unlysed cells (1000 x *g* for 10 minutes), followed by a high-speed centrifugation (17,000 x *g* for 30 minutes). The pellet from the final centrifugation was homogenized in buffer containing 20 mM HEPES pH 8, 100mM NaCl, 1% glycerol, 2 μg/mL leupeptin, 2 μg/mL pepstatin A, 2 μg/mL Aprotinin, 0.1 mM PMSF, and 10 μM GDP using a small glass homogenizer followed by passage through a 26 gauge needle. Membranes were aliquoted, snap frozen in liquid N_2, and stored at -80°C. Membranes from cells stably expressing the human A_1 AR (CHO K1 cells) or A_3 AR (HEK 293 cells) were prepared as described (Robeva *et al.*, 1996).

Example 6:Radioligand Binding Assays.

Radioligand binding to recombinant human A_{2A} receptors in Sf9 cell membranes was performed using either the radio labeled agonist, ^{125}I-APE (Luthin et al., 1995) or the radio labeled antagonist, ^{125}I-ZM241385 (^{125}I-ZM). To detect the high affinity, GTPγS-sensitive state of A_1 and A_3AR, we used the agonist, ^{125}I-ABA (Linden et al., 1985;Linden et al., 1993). Binding experiments were performed in triplicate with 5 μg (A_{2A}) or 25 μg (A_1 and A_3) membrane protein in a total volume of 0.1mL HE buffer (20 mM HEPES and 1

mM EDTA) with1 U/mL adenosine deaminase and 5 mM $MgCl_2$ with or without 50 μM GTPγS. Membranes were incubated with radioligands at room temperature for three hours (for agonists) or two hours (for antagonists) in Millipore Multiscreen® 96-well GF/C filter plates and assays were terminated by rapid filtration on a cell harvester (Brandel, Gaithersburg, MD) followed by 4 × 150 μl washes over 30 seconds with ice cold 10 mM Tris-HCl, pH 7.4, 10 mM $MgCl_2$. Nonspecific binding was measured in the presence of 50 μM NECA. Competition binding assays were performed as described (Robeva et al., 1996) using 0.5-1 nM ^{125}I-APE, ^{125}I-ZM241385, or ^{125}I-ABA. We found that it was sometimes important to change pipette tips following each serial dilution to prevent transfer on tips of potent hydrophobic compounds. The Ki values for competing compound binding to a single site were derived from IC_{50} values with correction for radioligand and competing compound depletion as described previously (Linden, 1982).

Linden J (1982) Calculating the Dissociation Constant of an Unlabeled Compound From the Concentration Required to Displace Radiolabel Binding by 50%. J Cycl Nucl Res 8: 163-172.

Linden J, Patel A and Sadek S (1985) [^{125}I]Aminobenzyladenosine, a New Radioligand With Improved Specific Binding to Adenosine Receptors in Heart. Circ Res 56: 279-284.

Linden J, Taylor HE, Robeva AS, Tucker AL, Stehle JH, Rivkees SA, Fink JS and Reppert SM (1993) Molecular Cloning and Functional Expression of a Sheep A_3 Adenosine Receptor With Widespread Tissue Distribution. Mol Pharmacol 44: 524-532.

Luthin DR, Olsson RA, Thompson RD, Sawmiller DR and Linden J (1995) Characterization of Two Affinity States of Adenosine A_{2A} Receptors With a New Radioligand, 2-[2-(4-Amino-3-[^{125}I]Iodophenyl)Ethylamino]Adenosine. Mol Pharmacol 47: 307-313.

Robeva AS, Woodard R, Luthin DR, Taylor HE and Linden J (1996) Double Tagging Recombinant A_1- and A_{2A}-Adenosine Receptors With

Hexahistidine and the FLAG Epitope. Development of an Efficient Generic Protein Purification Procedure. Biochem Pharmacol 51: 545-555.

Chemiluminescence Methods: Luminol enhanced chemiluminescence, a measure of neutrophil oxidative activity, is dependent upon both superoxide production and mobilization of the granule enzyme myeloperoxidase. The light is emitted from unstable high-energy oxygen species such as hypochlorous acid and singlet oxygen generated by activated neutrophils.

Purified human neutrophils (2 X 106/ml) suspended in Hanks balanced salt solution containing 0.1% human serum albumin (HA), adenosine deaminase (1U/mL) and rolipram (100 nM) were incubated (37°C) in a water bath for 15 min with or without rhTNF(10U/ml). Following incubation 100 L aliquots of the PMN were transferred to wells (White walled clear bottom 96 well tissue culture plates Costar #3670; 2 wells /condition) containing 50l HA and luminol (final concentration 100 M) with or without adenosine agonist (final agonist concentrations 0.01-1000 nM). The plate was incubated 5 min (37°C) and then fMLP (50 l in HA; final concentration 1M) was added to all wells.

Peak chemiluminescence was determined with a Victor 1420 Multilabel Counter in the chemiluminescence mode using the Wallace Workstation software. Data are presented as peak chemiluminescence as percent of activity in the absence of an adenosine agonist. The EC_{50} was determined using PRISM software. All compounds were tested with PMNs from three separate donors. The results are summarized in Table 5.

Table 5

Binding Affinity And Selectivity For A_{2A} Agonists

Compound	A_1 (nM)	A_{2A} (nM)	A_3 (nM)	Functional (nM)[1]	Functional + Roli (nM)[2]
Example 1	32	.58	34	2.0	0.20
Example 2	57	.7	247	2.0	0.20
Example 3	1.5	.5	3	0.3	0.04
Example 4	33	0.6	45	2.0	0.20

1 - Human neutrophil experiment as described in Example 7 without Rolipram.

2 - Human neutrophil experiment as described in Example 7 with Rolipram.

Example 7: Effect of A_{2A} Agonists on Neutrophil Oxidative Activity

A. Materials.

f-met-leu-phe (fMLP), luminol, superoxide dismutase, cytochrome C, fibrinogen, adenosine deaminase, and trypan blue were obtained from Sigma Chemical. Ficoll-hypaque was purchased from ICN (Aurora, OH), and Cardinal Scientific (Santa Fe, NM) and Accurate Chemicals and Scientific (Westerbury, NY). Endotoxin (lipopolysaccharide; *E. coli* K235) was from List Biologicals (Campbell, CA). Hanks balanced salt solution (HBSS), and limulus amebocyte lysate assay kit were from BioWittaker (Walkersville, MD). Human serum albumin (HSA) was from Cutter Biological (Elkhart, IN). Recombinant human tumor necrosis factor-alpha was supplied by Dianippon Pharmaceutical Co. Ltd. (Osaka, Japan). ZM241385 (4-(2-[7-amino-2-(2-furyl)[1,2,4]-triazolo[2,3-a][1,3,5]triazin-5-yl amino]ethyl)phenol) was a gift from Simon Poucher, Zeneca Pharmaceuticals, Cheshire, UK. Stock solutions (1 mM and 10 mM in DMSO) were made and stored at -20°C.

B. Human neutrophil preparation

Purified neutrophils (~98% neutrophils and >95% viable by trypan blue exclusion) containing <1 platelet per 5 neutrophils and < 50 pg/ml endotoxin (limulus amebocyte lysate assay) were obtained from normal heparinized (10 U/ml) venous blood by a one step Ficoll-hypaque separation procedure (A. Ferrante et al., J. Immunol. Meth., 36, 109 (1980)).

C. Release of inflammatory reactive oxygen species from primed and stimulated human neutrophils Chemiluminescence

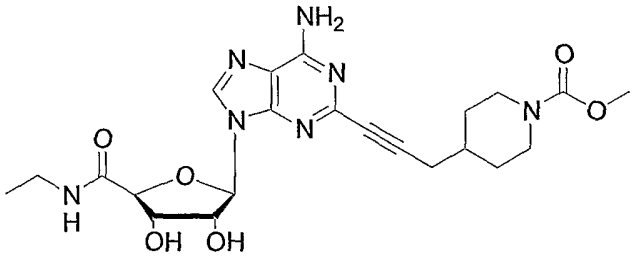
Luminol-enhanced chemiluminescence, a measure of neutrophil oxidative activity, is dependent upon both superoxide production and mobilization of the lysosomal granule enzyme myeloperoxidase. The light is emitted from unstable high-energy oxygen species generated by activated neutrophils. Purified neutrophils ($5\text{-}10 \times 10^5$/ml) were incubated in Hanks

balanced salt solution containing 0.1% human serum albumin (1 ml) with the tested A_{2A} agonist with or without rolipram and with or without tumor necrosis factor-alpha (1 U/ml) for 30 minutes at 37°C in a shaking water bath. Then luminol (1×10^{-4} M) enhanced f-met-leu-phe (1 mcM) stimulated chemiluminescence was read with a Chronolog® Photometer (Crono-log Corp., Havertown, PA) at 37°C for 2-4 minutes. Chemiluminescence is reported as relative peak light emitted (= height of the curve) compared to samples with tumor necrosis factor-alpha and without agonist or rolipram.

Example 8. *In vivo* rat blood pressure experiments.

Sprague-Dawley rats (mean weights, 250-300 grams) were anthesthetized and jugular and carotid catheters are implanted ipsilaterally and the animals are allowed to recover 24-48 hours. Prior to each experiment a baseline blood pressure reading is established for 30 minutes with each drug injection being preceded by a vehicle control. Drugs are injected bolus I.V. through a jugular catheter in a 200 microliter volume of saline and the catheter is flushed with an additional 300 microliters of saline. To measure blood pressure, a central line from the carotid catheter is attached to the pressure transducer of a Digi-Med Blood Pressure Analyzer. Systolic pressure, diastolic pressure, mean pressure, and heart rate are all recorded in real time at 30-60 second intervals. Data is recorded until mean blood pressure has returned to baseline and remained constant for 20 minutes. The data is presented as a fraction of the mean blood pressure averaged over the 10 minutes immediately prior to drug injection. The blood pressures are recorded and plotted over time as a means of determining potency of the compounds as well as biological half-life.

The compounds of examples 1 and 2 were tested against a control compound, illustrated below:



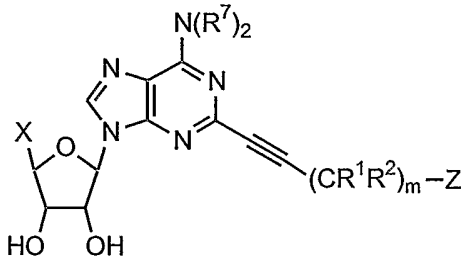
Control

The results are illustrated in Figures 1-2.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

Claims

1. A compound having formula (I):



(I)

wherein

Z is $CR^3R^4R^5$ or NR^4R^5;

each R^1 is independently hydrogen, halo, $-OR^a$, $-SR^a$, $(C_1\text{-}C_8)$alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, $C_{3\text{-}8}$cycloalkyl, heterocycle, heterocycle$(C_1\text{-}C_8)$alkylene-, aryl, aryl$(C_1\text{-}C_8)$alkylene-, heteroaryl, heteroaryl$(C_1\text{-}C_8)$alkylene-, $-CO_2R^a$, $R^aC(=O)O$-, $R^aC(=O)$-, $-OCO_2R^a$, $R^aR^bNC(=O)O$-, $R^bOC(=O)N(R^a)$-, R^aR^bN-, $R^aR^bNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^aR^bNC(=O)N(R^b)$-, $R^aR^bNC(=S)N(R^b)$-, $-OPO_3R^a$, $R^aOC(=S)$-, $R^aC(=S)$-, $-SSR^a$, $R^aS(=O)$-, $R^aS(=O)_2$-, $-N=NR^a$, or $-OPO_2R^a$;

each R^2 is independently hydrogen, halo, $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, heterocycle, heterocycle$(C_1\text{-}C_8)$alkylene-, aryl, aryl$(C_1\text{-}C_8)$alkylene-, heteroaryl, or heteroaryl$(C_1\text{-}C_8)$alkylene-; or

R^1 and R^2 and the atom to which they are attached is C=O, C=S or $C=NR^c$.

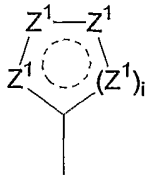
R^4 and R^5 together with the atoms to which they are attached form a saturated or partially unsaturated, or aromatic ring having 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms optionally comprising 1, 2, 3, or 4 heteroatoms selected from non-peroxide oxy (-O-), thio (-S-), sulfinyl (-SO-), sulfonyl $(-S(O)_2$-) or amine $(-NR^a$-) in the ring;

wherein any ring comprising R^4 and R^5 is substituted with from 1 to 14 R^6 groups; wherein each R^6 is independently hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_8)cycloalkyl, (C_1-C_8)cycloalkyl(C_1-C_8)alkylene-, (C_6-C_{12})bicycloalkyl, heterocycle or heterocycle (C_1-C_8)alkylene-, aryl, aryl (C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $-NNR^a$,$-OPO_2R^a$, or two R^6 groups and the atom to which they are attached is C=O, or C=S; or two R^6 groups together with the atom or atoms to which they are attached can form a carbocyclic or a heterocyclic ring comprising from 1 to 6 carbon atoms and 1, 2, 3, or 4 heteroatoms selected from non-peroxide oxy (-O-), thio (-S-), sulfinyl (-SO-), sulfonyl $(-S(O)_2-)$, phosphine $(-OP(O)_2-$, or amine $(-NR^a-)$ in the ring;

R^3 is hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, (C_1-C_8)cycloalkyl-(C_1-C_8)alkylene-, heterocycle, heterocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-NNR^a$, $-OPO_2R^a$; or if the ring formed from CR^4R^5 is aryl or heteroaryl or partially unsaturated then R^3 can be absent;

each R^7 is independently hydrogen, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_1-C_8)cycloalkyl(C_1-C_8)alkylene-, heterocycle, heterocycle (C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene-;

X is $-CH_2OR^e$, $-CO_2R^e$, $-CH_2OC(O)R^e$, $-C(O)NR^eR^f$, $-CH_2SR^e$, $-C(S)OR^e$, $-CH_2OC(S)R^e$ or $C(S)NR^eR^f$ $-CH_2N(R^e)(R^f)$, or a group having the formula



wherein each Z^1 is non-peroxide -O-, $-S(O)_p-$, $-C(R^8)_j-$, or $-N(R^8)-$; provided that at least one Z^1 is non-peroxide -O-, $-S(O)_p-$, or $-N(R^8)-$;

each R^8 is independently hydrogen, (C_1-C_8)alkyl, (C_1-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_1-C_8)alkyl(C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkenyl, (C_1-C_8)alkyl(C_3-C_8)cycloalkenyl, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene-; wherein any of the alkyl or alkenyl groups of R^8 are optionally interrupted by -O-, -S-, or $-N(R^a)-$;

R^e is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl;

R^f is hydrogen, (C_1-C_8)alkyl, or (C_1-C_8)alkyl substituted with 1-3 (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_1-C_8)alkylthio, amino acid, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene; and

wherein any of the alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, aryl, or heteroaryl, groups of R^1, R^2, R^3, R^6, R^7 and R^8 is optionally substituted on carbon with one or more (*e.g.* 1, 2, 3, or 4) substituents selected from the group consisting of halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle or heterocycle(C_1-C_8)alkylene-, aryl, aryloxy, aryl (C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^aR^bNC(=O)O-$, $R^bOC(=O)N(R^a)-$, R^aR^bN-, $R^aR^bNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^aR^bNC(=O)N(R^b)-$, $R^aR^bNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)_p-$, $R^aR^bNS(O)_p-$, $N=NR^a$, and $-OPO_2R^a$;

wherein any (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, (C_1-C_8)alkoxy, (C_1-C_8)alkanoyl, (C_1-C_8)alkylene, or heterocycle, is optionally partially unsaturated;

R^a and R^b are each independently hydrogen, $(C_1$-$C_{18})$alkyl, or $(C_1$-$C_8)$alkyl substituted with 1-3 $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_1$-$C_8)$alkylthio, amino acid, aryl, aryl$(C_1$-$C_8)$alkylene, heteroaryl, or heteroaryl$(C_1$-$C_8)$alkylene; or R^a and R^b, together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring; and

R^a and R^b are each independently hydrogen, $(C_1$-$C_8)$alkyl, or $(C_1$-$C_8)$alkyl substituted with 1-3 $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_1$-$C_8)$alkylthio, amino acid, aryl, aryl$(C_1$-$C_8)$alkylene, heteroaryl, or heteroaryl$(C_1$-$C_8)$alkylene; or R^a and R^b, together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring; and

R^c is hydrogen or $(C_1$-$C_6)$alkyl;

m is 0, 1, 2, 3, 4, 5, 6, 7, or 8; i is 1, or 2; each j is independently 1, or 2; and each p is independently 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

2. The compound of statement 1, wherein R^1 is hydrogen, -OH, halo, $-CH_2OH$, -OMe, -OAc, $-NH_2$, -NHMe, $-NMe_2$ or –NHAc.

3. The compound of claim 1 or 2, wherein R^1 is hydrogen, -OH, -OMe, fluoro, or $-NH_2$.

4. The compound of any of claims 1-3, wherein R^1 is hydrogen, -OH, fluoro, or $-NH_2$.

5. The compound any of claims 1-5, wherein R^1 is hydrogen or -OH.

6. The compound any of claims 1-6, wherein R^2 is hydrogen, halo, or $(C_1$-$C_8)$alkyl, cyclopropyl, cyclohexyl or benzyl.

7. The compound of any of claims 1-6, wherein R^2 is hydrogen, fluoro, methyl, ethyl or propyl.

8. The compound of any of claims 1-7, wherein R^2 is hydrogen or methyl.

9. The compound of any of claims 1-8, wherein R^2 is hydrogen.

10. The compound of claim 1, wherein R^1, R^2 and the carbon atom to which they are attached is carbonyl (C=O).

11. The compound of any of claims 1-10, wherein R^3 is hydrogen, OH, OMe, OAc, NH_2, NHMe, NMe_2 or NHAc.

12. The compound of any of claims 1-11, wherein R^3 is hydrogen, OH, OMe, or NH_2.

13. The compound of any of claims 1-12, wherein R^3 is hydrogen, OH, or NH_2.

14. The compound of any of claims 1-13, wherein R^3 is hydrogen or OH.

15. The compound of any of claims 1-14, wherein the ring comprising R^4, R^5 and the atom to which they are connected is cyclopentane, cyclohexane, piperidine, dihydro-pyridine, tetrahydro-pyridine, pyridine, piperazine, decaline, tetrahydro-pyrazine, dihydro-pyrazine, pyrazine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine, pyrazine, imidazole, dihydro-imidazole, imidazolidine, pyrazole, dihydro-pyrazole, or pyrazolidine.

16. The compound of any of claims 1-15, wherein the ring comprising R^4 and R^5 and the atom to which they are connected is, cyclohexane, piperidine, or piperazine.

17. The compound of any of claims 1-16, wherein R^6 is $(C_1\text{-}C_8)$alkyl, substituted $(C_1\text{-}C_8)$alkyl, halo, $-OR^a$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)R^a$, $-OC(=O)R^a$, $-NR^aR^b$, $-C(=O)NR^aR^b$, $-OC(=O)NR^aR^b$, or aryl. where substituted $(C_1\text{-}C_8)$alkyl is $(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_8)$alkylene-, halo$(C_1\text{-}C_8)$alkylene-, $-(CH_2)_{1\text{-}2}OR^a$, $-(CH_2)_{1\text{-}2}C(=O)OR^a$, $-(CH_2)_{1\text{-}2}OC(=O)R^a$, $-(CH_2)_{1\text{-}2}C(=O)R^a$, $-(CH_2)_{1\text{-}2}OCO_2R^a$, $-(CH_2)_{1\text{-}2}NR^aR^b$, or $-(CH_2)_{1\text{-}2}OC(=O)NR^aR^b$.

18. The compound of any of claims 1-17, wherein R^6 is $(C_1$-$C_4)$alkyl, chloro, fluoro, phenyl, $-OR^a$, $-CH_2OR^a$, $-CO_2R^a$, $-CH_2CO_2R^a$, $-OCO_2R^a$, $-CH_2OCO_2R^a$, $-C(=O)R^a$, $-CH_2C(=O)R^a$, $-OC(=O)R^a$, $-CH_2OC(=O)R^a$, $-NR^aR^b$, $-CH_2NR^aR^b$, $-C(=O)NR^aR^b$, $-CH_2C(=O)NR^aR^b$, $-OC(=O)NR^aR^b$, or $-CH_2OC(=O)NR^aR^b$.

19. The compound of any of claims 1-18, wherein R^6 is OH, OMe, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, $-CH_2OH$, phenyl, -OAc, $-CH_2OAc$, $-CO_2H$, $-CO_2Me$, $-CO_2Et$, $-CO_2$i-Pr, $-CO_2$i-Bu, $-CO_2$t-Bu, $-OCO_2Me$, $-OCO_2Et$, $-C(=O)CH_3$, $-CONH_2$, -CONHMe, $-CONMe_2$, -CONMeEt, $-NH_2$, -NHMe, $-NMe_2$, -NHEt, $-N(Et)_2$, or $-CH_2N(CH_3)_2$.

20. The compound of any of claims 1-19, wherein R^6 is OH, OMe, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, $-CH_2OH$, phenyl, -OAc, $-CH_2OAc$, $-CO_2Me$, $-CO_2Et$, $-CO_2$i-Pr, $-CO_2$i-Bu, $-CO_2$t-Bu, $-OCO_2Me$, $-OCO_2Et$, $-CONMe_2$, -CONMeEt.

21. The compound of any of claims 1-20, wherein the number of R^6 groups substituted on the Z ring is an integer from 1 to about 4.

22. The compound of any of claims 1-21, wherein R^a is hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, phenyl or benzyl.

23. The compound of any of claims 1-22, wherein R^b is hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, phenyl or benzyl.

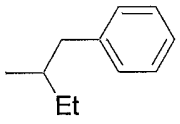
24. The compound of any of claims 1-23, wherein R^a is hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, *sec*-butyl, isobutyl, or *tert*-butyl and R^b is hydrogen, or methyl.

25. The compound of any of claims 1-24, wherein R^a and R^b together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring.

26. The compound of any of claims 1-25, wherein R^a and R^b together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, or morpholino, ring.

27. The compound of any of claims 1-26, wherein R^7 is hydrogen, $(C_1\text{-}C_4)$alkyl, aryl, aryl$(C_1\text{-}C_8)$alkylene, diaryl$(C_1\text{-}C_8)$alkylene, heteroaryl$(C_1\text{-}C_8)$alkylene, or diheteroaryl$(C_1\text{-}C_8)$alkylene.

28. The compound of any of claims 1-27, wherein R^7 is hydrogen, methyl, ethyl, 3-pentyl, phenylCH_2CH_2-, (phenyl)$_2CHCH_2$-, pyridylCH_2-, benzyl, or



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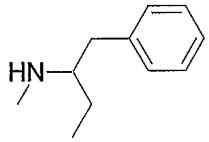
29. The compound of any of claims 1-28, wherein R^7 is hydrogen, 3-pentyl, pyridylmethyl, or benzyl.

30. The compound of any of claims 1-29, wherein R^7 is H.

31. The compound of any of claims 1-30, wherein $N(R^7)_2$ is amino (NH_2), 3-pentylamino, diphenylethylamino, pyridylmethylamino, benzylamino, or a group having the formula:



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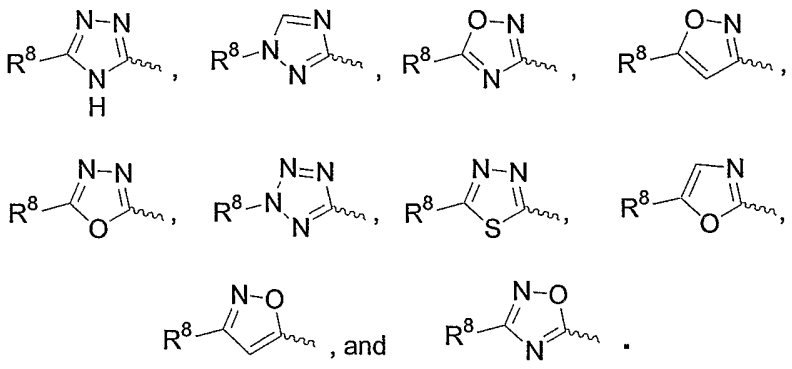
32. The compound of any of claims 1-31, wherein -$N(R^7)_2$ is amino, ethylamino, diethylamino, diphenylamino, pentylamino, or benzylamino.

33. The compound of any of claims 1-32, wherein $N(R^7)_2$ is amino.

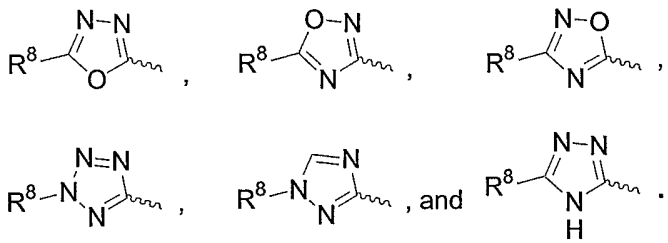
34. The compound of any of claims 1-33, wherein X is -CH_2OR^e, -CO_2R^e, -$CH_2OC(O)R^e$, -$C(O)NR^eR^f$, or -$CH_2N(R^e)(R^f)$.

35. The compound of any of claims 1-34, wherein X is -CH_2OR^e or -$C(O)NR^eR^f$.

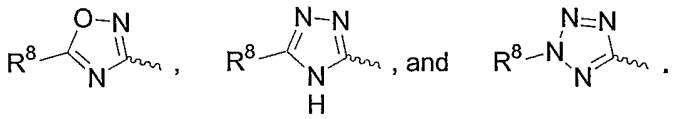
36. The compound of any of claims 1-35, wherein X is:



37. The compound of any of claims 1-36, wherein X is:



38. The compound of any of claims 1-37, wherein X is:



39. The compound of any of claims 1-38, wherein R^8 is methyl, ethyl, isopropyl, isopropenyl, -CH=CH_2, CH_2OH, propyl, -CH_2-CH=CH_2, -CH=CH-CH_3, cyclopropyl, cyclopropenyl, cyclopropylmethyl, cyclopropenylmethyl, cyclobutyl, cyclobutenyl, -$(CH_2)Y(CH_2)_nH$, -$(CH_2)_nCOOCH_3$, -$(CH_2)_nCO(CH_2)_nH$, where Y is O, S, $N(CH_2)_n$.

40. The compound of any of claims 1-39, wherein R^8 is $(C_1$-$C_3)$alkyl, CH_2OH, cyclopropyl, cyclobutyl, cyclopropylmethyl, -$(CH_2)_2CO_2CH_3$, -$(CH_2)_{2\text{-}3}OH$, -$(CH_2)_2$halogen.

41. The compound of any of claims 1-40, wherein R^8 is methyl, ethyl, propyl, 2-propenyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, -$(CH_2)_2CO_2CH_3$, -$(CH_2)_{2\text{-}3}OH$.

42. The compound of any of claims 1-41, wherein R^8 is methyl, ethyl, cyclopropyl.

43. The compound of any of claims 1-42, wherein R^e is cyclopropyl, or cyclobutyl.

44. The compound of any of claims 1-43, wherein R^e is cyclopropyl.

45. The compound of any of claims 1-44, wherein R^e is cyclobutyl.

46. The compound of any of claims 1-45, wherein R^f is hydrogen, or $(C_1\text{-}C_8)$alkyl.

47. The compound of any of claims 1-46, wherein R^f is hydrogen, methyl, ethyl, or propyl.

48. The compound of any of claims 1-47, wherein R^f is hydrogen, or methyl.

49. The compound of any of claims 1-48, wherein R^f is hydrogen.

50. The compound of any of claims 1-49, wherein i is 1.

51. The compound of any of claims 1-50, wherein i is 2.

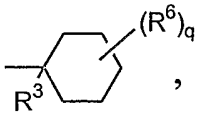
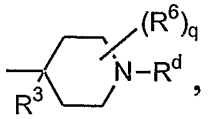
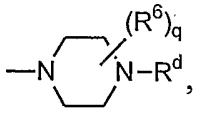
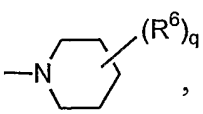
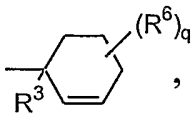
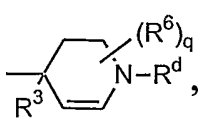
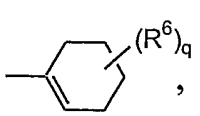
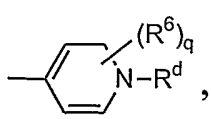
52. The compound of any of claims 1-51, wherein j is 1.

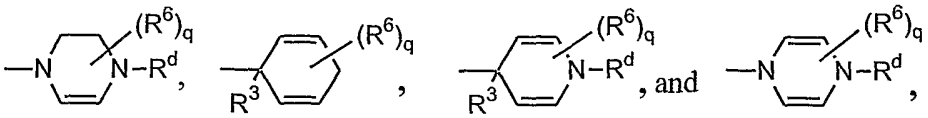
53. The compound of any of claims 1-52, wherein j is 2.

54. The compound of any of claims 1-53, wherein m is 0, 1, or 2.

55. The compound of any of claims 1-54, wherein m is 0, or 1.

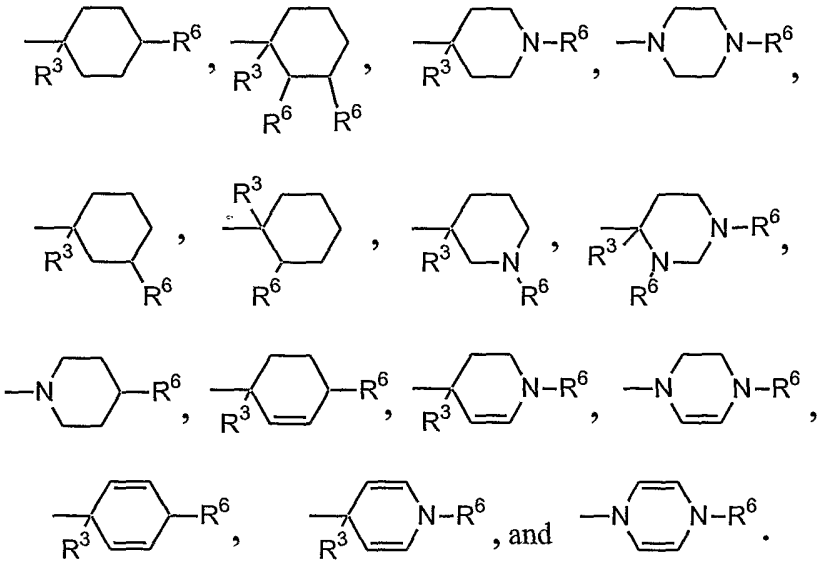
56. The compound of any of claims 1-55, wherein the ring comprising R^4, R^5 and the atom to which they are connected include:



where q is from 1 to 14 and R^d is hydrogen, provided that when q is zero then R^d is not hydrogen.

57. The compound of any of claims 1-56, wherein the ring comprising R^4, R^5 and the atom to which they are connected include:



58. The compound of any of claims 1-57, wherein the ring comprising – $C(R^3)R^4R^5$ is 2-methyl cyclohexane, 2,2-dimethylcyclohexane, 2-phenylcyclohexane, 2-ethylcyclohexane, 2,2-diethylcyclohexane, 2-tert-butyl cyclohexane, 3-methyl cyclohexane, 3,3-dimethylcyclohexane, 4-methyl cyclohexane, 4-ethylcyclohexane, 4-phenyl cyclohexane, 4-tert-butyl cyclohexane, 4-carboxymethyl cyclohexane, 4-carboxyethyl cyclohexane, 3,3,5,5-tetramethyl cyclohexane, 2,4-dimethyl cyclopentane. 4-cyclohexanecarboxyic acid, 4-cyclohexanecarboxyic acid esters, or 4-methyloxyalkanoyl-cyclohexane.

59. The compound of any of claims 1-58, wherein the ring comprising – $C(R^3)R^4R^5$ is 4-piperidine, 4-piperidene-1-carboxylic acid, 4-piperidine-1-carboxylic acid methyl ester, 4-piperidine-1-carboxylic acid ethyl ester, 4-piperidine-1-carboxylic

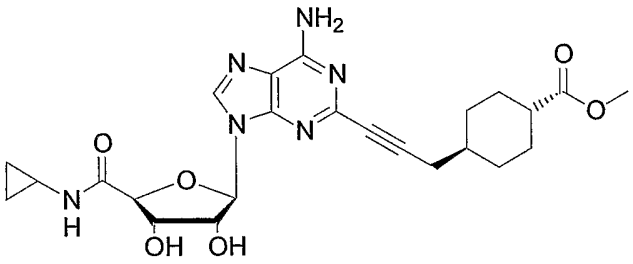
acid propyl ester, 4-piperidine-1-carboxylic acid tert-butyl ester, 1-piperidine, 1-piperidine-4-carboxylic acid methyl ester, 1-piperidine-4-carboxylic acid ethyl ester, 1-piperidine-4-carboxylic acid propyl ester, 1-piperidine-4-caboxylic acid tert-butyl ester, 1-piperidine-4-carboxylic acid methyl ester, 3-piperidine, 3-piperidene-1-carboxylic acid, 3-piperidine-1-carboxylic acid methyl ester, 3-piperidine-1-carboxylic acid tert-butyl ester, 1,4-piperazine, 4-piperazine-1-carboxylic acid, 4-piperazine-1-carboxylic acid methyl ester, 4-piperazine-1-carboxylic acid ethyl ester, 4-piperazine-1-carboxylic acid propyl ester, 4-piperazine-1-carboxylic acid tert-butylester, 1,3-piperazine, 3-piperazine-1-carboxylic acid, 3-piperazine-1-carboxylic acid methyl ester, 3-piperazine-1-carboxylic acid ethyl ester, 3-piperazine-1-carboxylic acid propyl ester, 3-piperidine-1-carboxylic acid tert-butylester, 1-piperidine-3-carboxylic acid methyl ester, 1-piperidine-3-carboxylic acid ethyl ester, 1-piperidine-3-carboxylic acid propyl ester or 1-piperidine-3-caboxylic acid tert-butyl ester.

60. The compound of any of claims 1-59, wherein the ring comprising R^4 and R^5 is 2-methyl cyclohexane, 2,2-dimethylcyclohexane, 2-phenyl cyclohexane, 2-ethylcyclohexane, 2,2-diethylcyclohexane, 2-tert-butyl cyclohexane, 3-methyl cyclohexane, 3,3-dimethylcyclohexane, 4-methyl cyclohexane, 4-ethylcyclohexane, 4-phenyl cyclohexane, 4-tert-butyl cyclohexane, 4-carboxymethyl cyclohexane, 4-carboxyethyl cyclohexane, 3,3,5,5-tetramethyl cyclohexane, 2,4-dimethyl cyclopentane, 4-piperidine-1-carboxylic acid methyl ester, 4-piperidine-1-carboxylic acid tert-butyl ester 4-piperidine, 4-piperazine-1-carboxylic acid methyl ester, 4-piperidine-1-carboxylic acid tert-butylester, 1-piperidine-4-carboxylic acid methyl ester, 1-piperidine-4-caboxylic acid tert-butyl ester, tert-butylester, 1-piperidine-4-carboxylic acid methyl ester, 1-piperidine-4-caboxylic acid tert-butyl ester,

3-piperidine-1-carboxylic acid methyl ester,
3-piperidine-1-carboxylic acid tert-butyl ester, 3-piperidine,
3-piperazine-1-carboxylic acid methyl ester,
3-piperidine-1-carboxylic acid tert-butylester,
1-piperidine-3-carboxylic acid methyl ester, or
1-piperidine-3-caboxylic acid tert-butyl ester.

61. The compound of claim 1, wherein R^a and R^b are each independently hydrogen, $(C_1\text{-}C_8)$alkyl, or $(C_1\text{-}C_8)$alkyl substituted with 1-3 $(C_1\text{-}C_8)$alkoxy, $(C_3\text{-}C_8)$cycloalkyl, $(C_1\text{-}C_8)$alkylthio, amino acid, aryl, aryl$(C_1\text{-}C_8)$alkylene, heteroaryl, or heteroaryl$(C_1\text{-}C_8)$alkylene; or R^a and R^b, together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring.

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



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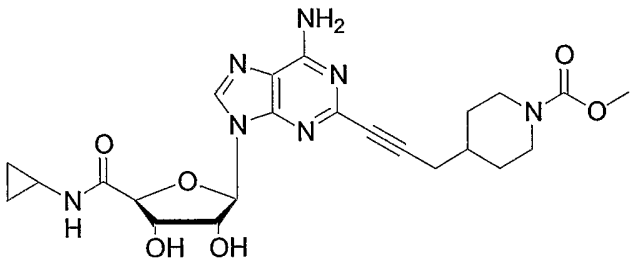

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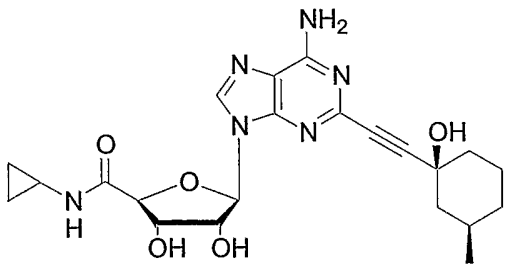


or a pharmaceutically acceptable salt thereof.

63. A therapeutic method to inhibit an inflammatory response comprising administering to a mammal in need of said therapy, an effective anti-inflammatory amount of a compound of any of claims 1-62.

64. A therapeutic composition comprising a compound of any of claims 1-62, in combination with a pharmaceutically acceptable carrier.

65. The composition of claim 64 further comprising a Type IV phosphodiesterase inhibitor.

66. The composition of claim 65 wherein the Type IV phosphodiesterase inhibitor is rolipram, cilomilast, or roflumilast.

67. The composition of any of claims 64-66, wherein the carrier is a liquid carrier.

68. The composition of any of claims 64-67, which is adapted for oral, intravenous, ocular, parenteral, aerosol or transdermal administration.

69. A method for preventing or treating a pathological condition or symptom in a mammal, wherein the activity of A_{2A} adenosine receptors is implicated and agonism of such activity is desired, comprising administering to said mammal an effective amount of a compound of any of claims 1-62.

70. The method of claim 69, wherein the mammal is a human or equine.

71. The method of claim 69 or 70, wherein the pathological condition or symptom is caused by autoimmune stimulation (autoimmune diseases), allergic diseases, skin diseases, infectious diseases, wasting diseases, organ transplantation, tissue or cell transplantation, open wounds, adverse effects from drug therapy, a cardiovascular condition, dialysis, gout; chemical trauma, or thermal trauma.

72. The method of claim 71, wherein the pathological condition is an open wound.

73. The method of claim 69, wherein the pathological condition or symptom is inflammation.

74. The method of claim 73, wherein the inflammation is caused by pathogenic organisms.

75. The method of claim 73, wherein the inflammation is caused by a viral organism.

76. The method of claim 73, further comprising administration of an effective amount of an anti-pathogenic agent.

77. The method of claim 74, wherein the pathogen is a bacteria and the anti-pathogenic agent is an antibiotic.

78. The method of claim 75, wherein the pathogen is a virus and the anti-pathogenic agent is an antiviral agent.

79. The method of claim 75, wherein the pathogen is yeast or fungus and the anti-pathogenic agent is an antifungal agent.

80. The method of claim 77, wherein the inflammation is caused by E. Coli.

81. The method of claim 77, wherein the bacteria causes hemolytic uremic syndrome.

82. A method to diagnose myocardial perfusion abnormalities in a mammal comprising:

(a) parenterally administering to said mammal an amount of a compound of any of claims 1-62; and

(b) performing a technique on said mammal to detect the presence of coronary artery stenoses, assess the severity of coronary artery stenoses or both.

83. The method of claim 82, wherein the mammal is a human or equine.

84. The method of claim 82 or 83, wherein said myocardial dysfunction is selected from the group consisting of coronary artery disease, ventricular dysfunction and differences in blood flow through disease-free coronary vessels and stenotic coronary vessels.

85. The method of claim 82 or 83, wherein said technique to detect the presence and assess the severity of coronary artery disease is selected from the group consisting of radiopharmaceutical myocardial perfusion imaging, ventricular function imaging, or techniques for measuring coronary blood flow velocity.

86. The method of claim 85, wherein said radiopharmaceutical myocardial perfusion imaging is selected from the group consisting of planar scintigraphy , single photon emission computed tomography (SPECT), positron emission tomography (PET), nuclear magnetic resonance (NMR) imaging, perfusion contrast echocardiography, digital subtraction angiography (DSA) and ultrafast X-ray computed tomography (CINE CT).

87. The method of claim 86, wherein a radiopharmaceutical agent is used in conjunction with said radiopharmaceutical myocardial perfusion imaging, and the radiopharmaceutical agent comprises a radionuclide selected from the group consisting of thallium-201, technetium-99m, nitrogen-13, rubidium-82, iodine-123 and oxygen-15.

88. The method of claim 87, wherein said radiopharmaceutical myocardial perfusion imaging is scintigraphy and said radiopharmaceutical agent is thallium-201.

89. The method of claim 85, wherein said ventricular function imaging technique is selected from the group consisting of echocardiography, contrast ventriculography and radionuclide ventriculography.

90. The method of claim 89, wherein said ventricular function imaging technique is echocardiography.

91. The method of claim 85, wherein said method for measuring coronary blood flow velocity is selected from the group consisting of doppler flow catheter, digital subtraction angiography and radiopharmaceutical imaging techniques.

92. The method of claim 86, wherein said method for measuring coronary blood flow velocity is doppler flow catheter.

93. The method of claim 83, comprising the steps of:

(a) administering to said human by intravenous infusion or by bolus injection an amount of a compound of formula I effective to provide coronary artery dilation;

(b) administering a radiopharmaceutical agent comprising thallium-201 or technetium-99m to said human; and

(c) performing the scintigraphy on said human in order to detect the presence and assess the severity of coronary artery disease.

94. The method of claim 93, wherein the agent is Tc-99m-sestamibi.

95. A method for preventing or treating a pathological condition or symptom in a mammal, wherein the activity of A_3 adenosine receptors is implicated and agonism of such activity is desired, comprising administering to said mammal an effective amount of a compound of any of claims 1-62.

96. A compound of any of claims 1-62, for use in medical therapy.

97. A compound of any of claims 1-62, wherein the medical therapy is inhibition of an inflammatory response.

98. The compound of claim 97, wherein the inflammatory response due to a pathological condition or symptom in a mammal, wherein the

activity of A_{2A} adenosine receptors is implicated and agonism of such activity is desired.

99. Use of a compound of claims 1-62, to prepare a medicament useful for treating an inflammatory response.

100. The use of claim 99, wherein the medicament comprises a Type IV phosphodiesterase inhibitor.

101. The use of claim 99, wherein the phosphodiesterase inhibitor is rolipram.

102. The use of claim 101, wherein the medicament comprises a liquid carrier.

103. The use of any of claims 99-102, wherein the medicament is adapted for parenteral, aerosol or transdermal administration.

Figure 1

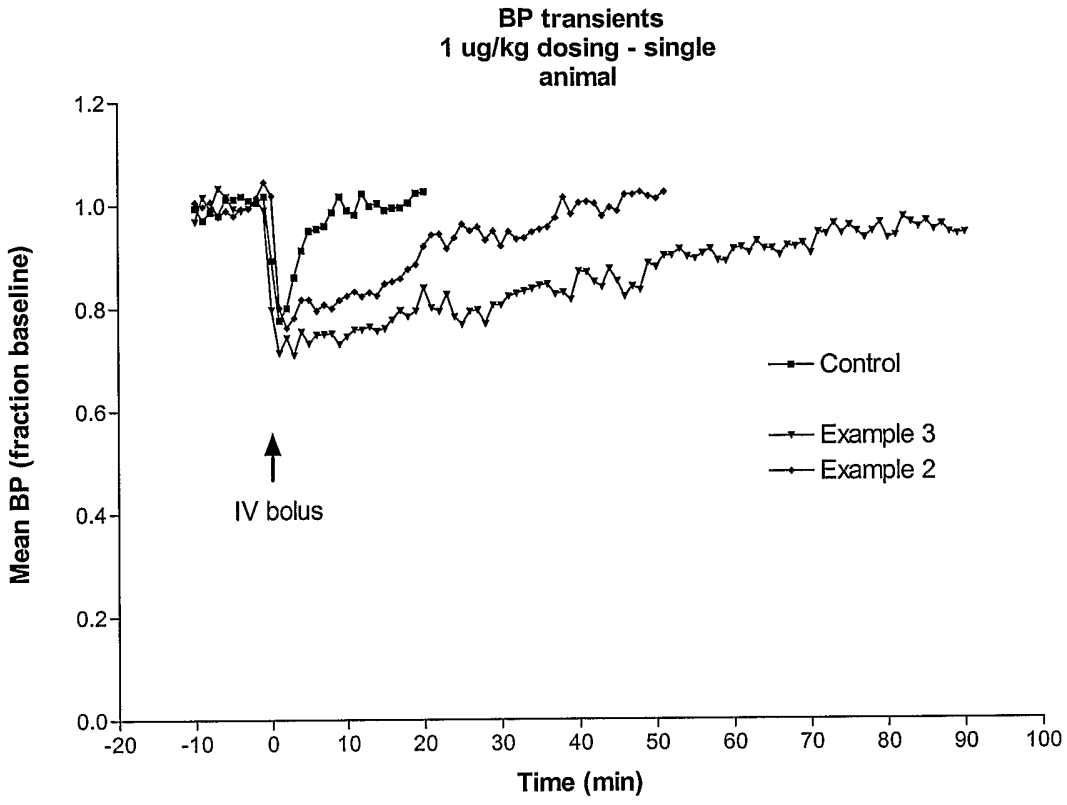
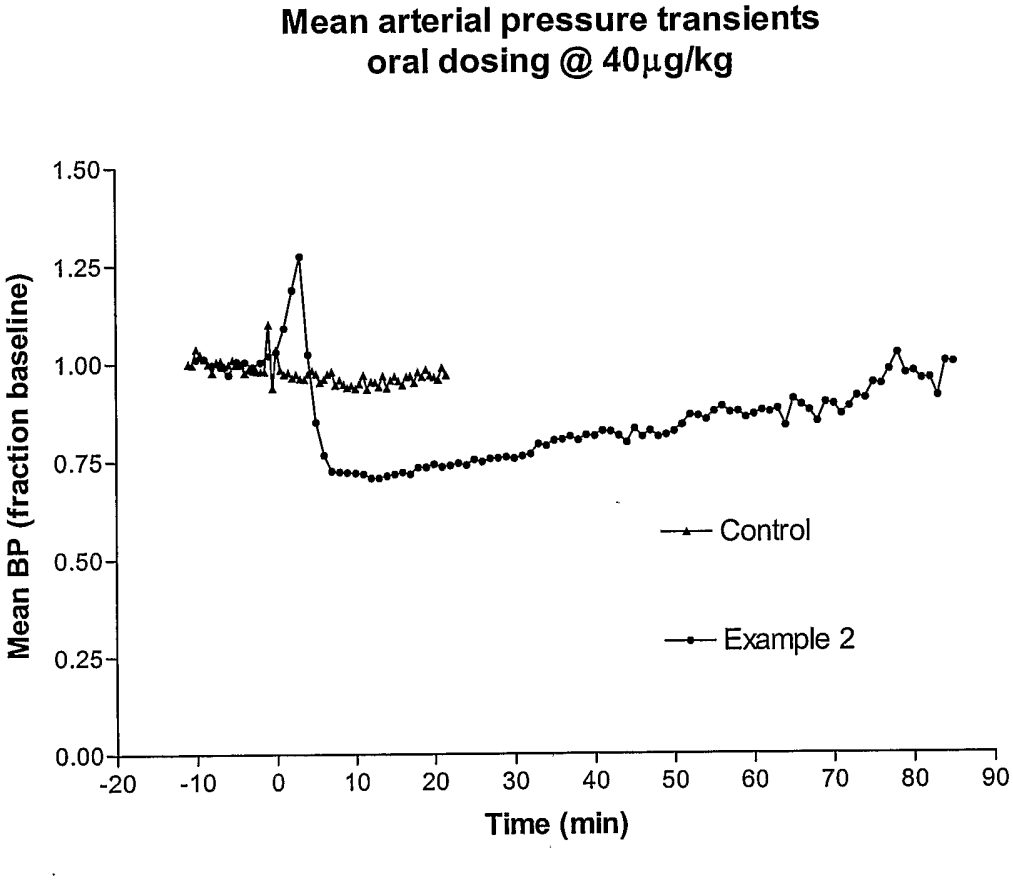

BP transients
1 ug/kg dosing - single animal
Mean BP (fraction baseline)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-20
-10
0
10
20
30
40
50
60
70
80
90
100
Time (min)
IV bolus
Control
Example 3
Example 2

Figure 2


Mean arterial pressure transients
oral dosing @ 40µg/kg
Mean BP (fraction baseline)
1.50
1.25
1.00
0.75
0.50
0.25
0.00
-20
-10
0
10
20
30
40
50
60
70
80
90
Time (min)
Control
Example 2