TITLE: PARTIAL OR FULL A_1 AGONISTS - N^6 HETEROCYCLIC 5'-THIO SUBSTITUTED ADENOSINE DERIVATIVES

BACKGROUND OF THE INVENTION

(1) Field of the Invention

This invention includes stable and useful drugs and pro-drugs that are N^6 heterocyclic 5'-thio modified adenosine derivatives. The compositions of this invention are selective, partial or full adenosine A_1 receptor agonists, and as such, are useful for modifying cardiac activity, modifying adipocyte function, treating central nervous system disorders, and treating diabetic disorders and obesity in mammals, and especially in humans.

(2) Description of the Art

There are at least two subtypes of adenosine receptors in the heart: A_1 and A_{2A}. Each subtype affects different physiological functions. The A_1 adenosine receptor mediates two distinct physiological responses. Inhibition of the cardiostimulatory effects of catecholamine are mediated via the inhibition of adenylate cyclase, whereas the direct effects to slow the heart rate (HR) and to prolong impulse propagation through the AV node are due in great part to activation of I_{KAdo}. (B. Lerman and L. Belardinelli Circulation, Vol. 83 (1991), P 1499-1509 and J. C. Shryock and L. Belardinelli The Am. J. Cardiology, Vol. 79 (1997) P 2-10). Both, the anti-β-adrenergic action and direct depressant effects on SA and AV nodal function are mediated by the A_1 receptor; there is no role for the A_{2A} receptor in this response to adenosine. A_{2A} receptors mediate the coronary vasodilatation caused by adenosine. Stimulation of the A_1 adenosine receptor accordingly shortens the duration and decreases the amplitude of the action potential of AV nodal cells, and hence prolongs the refractory period of the AV nodal cell. The consequence of these effects is to limit the number of impulses conducted from the atria to the ventricles. This forms the basis of the clinical utility of A_1 receptor agonists for the treatment of supraventricular tachycardias, including termination of nodal re-entrant tachycardias, and control of ventricular rate during atrial fibrillation and flutter.

A clinical utility of A_1 agonists therefore is in the treatment of acute and chronic disorders of heart rhythm, especially those diseases characterized by rapid heart rate where the rate is driven by abnormalities in the sinoatrial, atria, and AV nodal tissues. Such disorders include but are not limited to atrial fibrillation, supraventricular tachycardia and atrial flutter.

Exposure to A_1 agonists causes a reduction in the heart rate and a regularization of the abnormal rhythm thereby improving cardiovascular function.

A_1 agonists, through their ability to inhibit the effects of catecholamines, decrease cellular cAMP, and thus, should have beneficial effects in the failing heart where increased sympathetic tone increases cellular cAMP levels. The latter has been shown to be associated with increased likelihood of ventricular arrhythmias and sudden death. All of the above concepts are discussed in reviews regarding the effects of adenosine on cardiac electrophysiology (see B. Lennan and L. Belardinelli Circulation, Vol. 83 (1991), P 1499-1509 and J. C. Shryock and L. Belardinelli, Am. J. Cardiology, Vol. 79 (1997) P 2-10).

A controversial area in the field of A_1 adenosine agonism is that the benefit of preconditioning of the heart prior to ischemia may be due to binding of adenosine to the A_1 receptor. Evidence for this hypothesis comes from a rabbit ischemia model wherein 2-chloro N6-cyclopentyladenosine (CCPA) and R-PIA were administered prior to ischemia providing protection with respect to infarct size (J. D. Thornton et al. Circulation Vol. 85 (1992) 659-665).

A_1 agonists, as a result of their inhibitory action on cyclic AMP generation, have antilipolytic effects in adipocytes that leads to a decreased release of nonesterified fatty acids (NEFA) (E. A. van Schaick et al J. Pharmacokinetics and Biopharmaceutics, Vol. 25 (1997) p 673-694 and P. Strong Clinical Science Vol. 84 (1993) p. 663-669). Non-insulin-dependent diabetes mellitus (NIDDM) is characterized by an insulin resistance that results in hyperglycemia. Factors contributing to the observed hyperglycemia are a lack of normal glucose uptake and activation of skeletal muscle glycogen synthase (GS). Elevated levels of NEFA have been shown to inhibit insulin-stimulated glucose uptake and glycogen synthesis (D. Thiebaud et al Metab. Clin. Exp. Vol. 31 (1982) p 1128-1136 and G. Boden et al J. Clin. Invest. Vol. 93 (1994) p 2438-2446). The hypothesis of a glucose fatty acid cycle was proposed by P. J. Randle as early as 1963 (P. J. Randle et al Lancet (1963) p. 785-789). A tenet of this hypothesis would be that limiting the supply of fatty acids to the peripheral tissues should promote carbohydrate utilization (P. Strong et al Clinical Science Vol. 84 (1993) p. 663-669).

The benefit of an A_1 agonist in central nervous disorders has been reviewed and the

content are included herein by reference (L. J. S. Knutsen and T. F. Murray In Purinergic Approaches in Experimental Therapeutics, Eds. K. A. Jacobson and M. F. Jarvis (1997) Wiley-Liss, N. Y., P –423-470). Briefly, based on experimental models of epilepsy, a mixed A_{2A}: A_1 agonist, metrifudil, has been shown to be a potent anticonvulsant against seizures induced by the inverse benzodiazepine agonist methyl 6,7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate (DMCM, H. Klitgaard Eur. J. Pharmacol. (1993) Vol. 224 p. 221-228). In other studies using CGS 21680, an A_{2A} agonist, it was concluded that the anticonvulsant activity was attributed to activation of the A_1 receptor (G. Zhang et al. Eur. J. Pharmacol. Vol. 255 (1994) p. 239-243). Furthermore, A_1 adenosine selective agonists have been shown to have anticonvulsant activity in the DMCM model (L. J. S. Knutsen In Adenosine and Adenne Nucleotides: From Molecular Biology to Integrative Physiology; eds. L. Belardinelli and A. Pelleg, Kluwer: Boston, 1995, pp 479-487). A second area where an A_1 adenosine agonist has a benefit is in animal models of forebrain ishemia as demonstrated by Knutsen et al (J. Med. Chem. Vol. 42 (1999) p. 3463-3477). The benefit in neuroprotection is believed to be in part due to the inhibition of the release of excitatory amino acids (ibid).

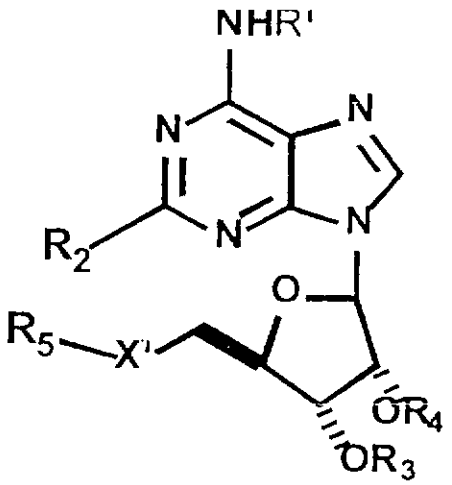
There are a number of full A_1 agonists disclosed in the prior art. However, the agonists disclosed are generally in the forms that are not useful in the mammalian body. Because useful forms of A_1 agonists may not always be stable, soluble or they may have other properties that make their incorporation into therapeutic dosage forms difficult, it is often necessary to identify compositions that are more easily incorporated into therapeutic dosage forms in order to provide the desired therapeutic effect. Also, these agonists fail as useful therapeutics due to side effects caused by the non-selective stimulation of the A_1 adenosine receptor in all biologically available tissues and the desensitization of the desired response preempting their use as chronic agents. Therefore, there remains a need for specific and selective A_1 agonists, precursors and/or pro-drugs that are converted in the body into useful therapeutic compositions.

SUMMARY OF THE INVENTION

In one aspect, this invention includes heterocyclic 5'-thio modified adenosine derivative compositions that are useful partial or full adenosine A_1 receptor agonists.

In another aspect, this invention includes pharmaceutical compositions including one or more heterocyclic 5'-thio modified adenosine derivative compositions that are well tolerated with few side effects.

In still another embodiment, this invention includes heterocyclic 5'-thio modified adenosine derivatives having the formula:

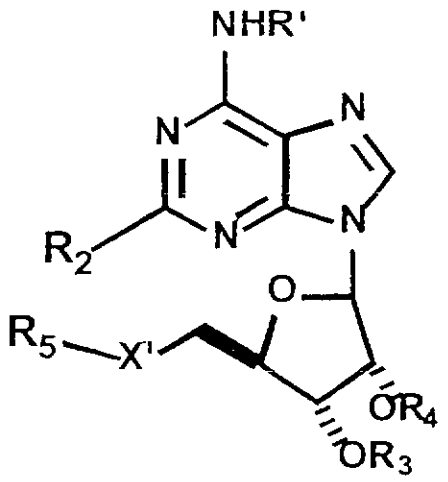


In yet another embodiment, this invention includes methods for administering compositions of this invention to mammals, and especially to humans, to stimulate coronary activity, to modify adipocyte function, to treat central nervous system disorders, and to treat diabetic disorders.

In a further embodiment, this invention is pharmaceutical compositions of matte. comprising at least one composition of this invention and one or more pharmaceutical excipients.

DESCRIPTION OF THE CURRENT EMBODIMENT

This invention includes a class of heterocyclic 5'-thio modified adenosine derivatives having the formula having the formula:



wherein X^1 = S, S(O), S(O2);

wherein R^1 is a monocyclic or polycyclic heterocyclic group containing from 3 to 15 carbon atoms wherein at least one carbon atom is substituted with an atom or molecule selected from the group consisting of N, 0, P and $S\text{-}(O)_{0\text{-}2}$ and wherein R^1 does not contain an epoxide group, and wherein R_2 is selected from the group consisting of hydrogen, halo, CF_3, and cyano; wherein R_3 and R_4 are independently selected from the group consisting of hydrogen, and –(CO)-R' and –(CO)-R'' wherein R' and R'' are independently selected from the group consisting of $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group of halo, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and each optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, NO_2, alkyl, CF_3, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NR^{20}COR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$,

$OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, or OR^{20};

wherein R_5 is selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, alkyl, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $S(O)_3R^{20}$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $P(O)(OR^{20})_2$, $N(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and wherein optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, NO_2, alkyl, CF_3, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NR^{20}COR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})$, CN, or OR^{20};

wherein R^{20} is a member selected from the group consisting of H, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C1-C6 alkyl, CF3, aryl, and heteroaryl; and

R^{22} is a member selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, and heteroaryl.

In preferred compositions, X^1=S or SO_2; R_2 is a hydrogen; R_3 and R_4 are each independently selected from the group consisting of hydrogen, –(CO)-R' and –(CO)-R" wherein R' and R'' are each independently selected from the group consisting of C_{1-6} alkyl and, more preferably, R_3 and R_4 are each hydrogen; R_5 is selected from the group consisting of C_{1-8} alkyl, and aryl wherein alkyl, and aryl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF_3, CN, OR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CON(R^{20})_2$, CO_2R^{20}, $CON(R^{20})_2$, and

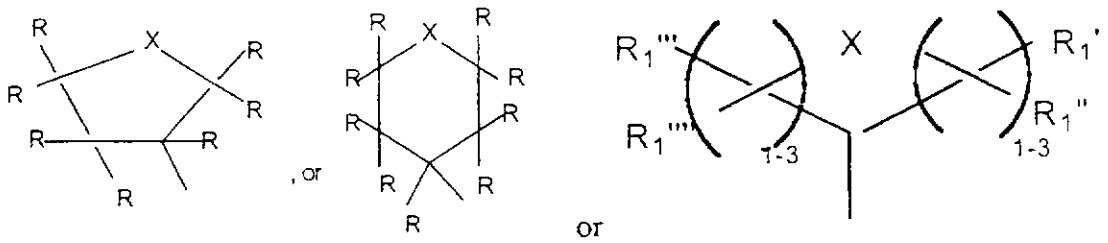
wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3, CO_2R^{20}, CN, and OR^{20}; R_{20} is selected from the group consisting of H, C_{1-6} alkyl; and R_{22} is selected from the group consisting of C_{1-6}. In the above compositions, R_5 is more preferably selected from the group consisting of C_{1-8} alkyl, and aryl wherein alkyl, and aryl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, CF_3, and OR^{20}.

In more preferred compositions, X^1=S or SO_2; R_2 is a hydrogen; R_3 and R_4 are independently selected from the group consisting of hydrogen, –(CO)-R' and –(CO)-R'' wherein R' and R'' are each independently selected from the group consisting of C_{1-6} alkyl which alkyl are optionally substituted with 1 substituent selected from the group consisting of aryl, CF_3, CN, OR^{20}, $N(R^{20})_2$, and wherein each optional aryl substituent is further optionally substituted with halo, NO_2, alkyl, CF_3; R_5 is C_{1-8} alkyl, wherein alkyl, is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF_3, CN, OR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CON(R^{20})_2$, CO_2R^{20}, $CON(R^{20})_2$, wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3, CO_2R^{20}, CN, and OR^{20}; R^{20} is selected from the group consisting of H, C_{1-6} alkyl; and R_{22} is selected from the group consisting of C_{1-6}. In the above compositions, R_5 is more preferably C_{1-8} alkyl that is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of aryl, heteroaryl, OR^{20}, $S(O)R^{22}$, CO_2R^{20}, $CON(R^{20})_2$, and wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3, CO_2R^{20}, CN, and OR^{20}, and R_5 is even more preferably C_{1-8} alkyl that is optionally substituted with 1 substituent selected from the group consisting of CO_2R^{20}, and $CON(R^{20})_2$, and R_5 is even more preferably C_{1-6} alkyl and most preferably methyl or ethyl or isopropyl. Also in the above compositions, R_3 and R_4 are more preferably each hydrogen and R_{20} is more preferably selected from the group consisting of H, and methyl.

In another class of preferred compositions, R_2 is a hydrogen; R_3 and R_4 are each independently selected from the group consisting of hydrogen, –(CO)-R' and –(CO)-R'' wherein each R' and R'' are independently selected from the group consisting of C_{1-6} alkyl, and aryl, which alkyl and aryl are optionally substituted with from 1 to 2 substituents

independently selected from the group of halo, NO_2, aryl, CF_3, CN, OR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, and wherein each optional aryl substituent is further optionally substituted with halo, NO_2, alkyl, CF_3; R_5 is selected from the group consisting of, aryl, and heteroaryl, wherein aryl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, CO_2R^{20}, $CON(R^{20})_2$, and wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3, CO_2R^{20}, $CON(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, or OR^{20}; R^{20} is selected from the group consisting of H, C_{1-6} alkyl, and aryl, which alkyl and aryl are optionally substituted with 1 substituent selected from halo, alkyl, mono- or dialkylamino, CN, O-C_{1-6} alkyl, CF_3; and R^{22} is selected from the group consisting of C_{1-6} alkyl and aryl, which alkyl and aryl are optionally substituted with 1 substituent selected from halo, alkyl or CN, O-C_{1-6} alkyl, and CF_3. In the above compositions, X^1 is preferably S; R_3 and R_4 are more preferably hydrogen; R_5 is more preferably selected from the group consisting of, aryl, and heteroaryl, wherein aryl, and heteroaryl are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, CF_3, CN, OR^{20}, SR^{20}, CO_2R^{20}, $CON(R^{20})_2$. Even more preferably R_5 is aryl that is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, alkyl, CF_3, OR^{20}, CO_2R^{20}, $CON(R^{20})_2$. And most preferably, R_5 is phenyl that is optionally substituted with a substituent selected from the group consisting of methoxy, chloro, fluoro, methyl, and trifluoromethyl. In the compounds above, R^{20} is preferably selected from the group consisting of H, C_{1-3} alkyl and most preferably H or methyl while R_{22} is preferably selected from the group consisting of C_{1-6} alkyl.

In the compositions of this invention, R_1 is preferably mono or polysubstituted with one or more compounds selected from the group consisting of halogen, oxo, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, cyano and mixtures thereof. More preferably, R_1 is a monocyclic, bicyclic, or tricyclic cycloalkyl group containing from 3 to 15 carbon atoms wherein at least one carbon atom is substituted with an atom or molecule selected from the group consisting of O or S-$(O)_{0-2}$. Some examples of preferred R_1 moieties include:



wherein R_1', R_1'', R_1''', and R_1'''' may each individually be selected from the group halogen, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, and cyano, and X is O, or S $(-O)_{0-2}$, alternately, R_1''' and R_1'''' may be a single oxygen atom. More preferably, R_1', R_1'', R_1''', and R_1'''' are each individually selected from the group hydrogen, lower alkyl, and substituted lower alkyl. In the compositions above, each R is individually selected from the group consisting of H, lower alkyl, and substituted lower alkyl and wherein X is O, or S $(-O)_{0-2}$.

Most preferred compounds of this invention include, 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(methylthiomethyl)oxolane-3,4-diol ; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(Ethylthio)methyl]oxolane-3,4-diol; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(Methylethylthio)methyl]oxolane-3,4-diol; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(phenylthiomethyl)oxolane-3,4-diol; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-Methoxyphenylthio)methyl]oxolane-3,4-diol; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-chlorophenylthio)methyl]oxolane-3,4-diol; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-fluorophenylthio)methyl]oxolane-3,4-diol; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-methylphenylthio)methyl]oxolane-3,4-diol; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-(trifluoromethyl)phenylthio)methyl]oxolane-3,4-diol; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(2-Methoxyphenylthio)methyl]oxolane-3,4-diol; (5-{6-[((3R)oxolan-3-yl)amino]purinyl-9-yl}(2S,3S,4R,5R)-3,4-dihydroxyoxolan-2-yl)(ethylsulfonyl)methane; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(2,4-difluorophenylthio)methyl]oxolane-3,4-diol; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(2,6-

dichlorophenylthio)methyl]oxolane-3,4-diol; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(3-fluorophenylthio)methyl]oxolane-3,4-diol; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(2-fluorophenylthio)methyl]oxolane-3,4-diol; 5-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(2S,3R,4R,5R)-4-acetyloxy-2-[(fluorophenylthio)methyl]oxolan-3-yl acetate; Methyl 2[(5-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(2S,3S,4R,5R)-3,4-dihydroxyoxolan-2-yl)methylthio]benzoate; {2[(5-{6-[((3R)oxolan-3-yl)amino]purin-9-yl} (2S,3S,4R,5R)-3,4-dihydroxyoxolan-2-yl) methylthio]phenyl}-N-methylcarboxamidebenzoate; 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(benzoxazol-2-ylthiomethyl)oxolane-3,4-diol; 2-{6-[((3S)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(1-methylimidazol-2-yl-thio)methyl]oxolane-3,4-diol; 2-{6-[((3S)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(pyrimidine-2-ylthiomethyl)oxolane-3,4-diol; 2-{6-[((3S)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(2 pyridylthiomethyl)oxolane-3,4-diol; 2-{6-[((3S)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(4-pyridylthiomethyl)oxolane-3,4-diol; and 5-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(2S,3R,4R,5R)-4-acetyloxy-2-[(4-fluorophenylthio)methyl]oxolan-3-yl]acetate.

The following definitions apply to terms as used herein.

"Halo" or "Halogen" - alone or in combination means all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), iodo (I).

"Hydroxyl" refers to the group -OH.

"Thiol" or "mercapto" refers to the group -SH.

"Alkyl" - alone or in combination means an alkane-derived radical containing from 1 to 20, preferably 1 to 15, carbon atoms (unless specifically defined). It is a straight chain alkyl, branched alkyl or cycloalkyl. Preferably, straight or branched alkyl groups containing from 1-15, more preferably 1 to 8, even more preferably 1-6, yet more preferably 1-4 and most preferably 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl and the like. The term "lower alkyl" is used herein to describe the straight chain alkyl groups described immediately above. Preferably, cycloalkyl groups are monocyclic, bicyclic or tricyclic ring systems of 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl and the like. Alkyl also includes a straight chain or branched alkyl group that contains or is interrupted by a cycloalkyl portion. The straight

chain or branched alkyl group is attached at any available point to produce a stable compound. Examples of this include, but are not limited to, 4-(isopropyl)-cyclohexylethyl or 2-methyl-cyclopropylpentyl. A substituted alkyl is a straight chain alkyl, branched alkyl, or cycloalkyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Alkenyl" - alone or in combination means a straight, branched, or cyclic hydrocarbon containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most preferably 2-4, carbon atoms and at least one, preferably 1-3, more preferably 1-2, most preferably one, carbon to carbon double bond. In the case of a cycloalkyl group, conjugation of more than one carbon to carbon double bond is not such as to confer aromaticity to the ring. Carbon to carbon double bonds may be either contained within a cycloalkyl portion, with the exception of cyclopropyl, or within a straight chain or branched portion. Examples of alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, cyclohexenyl, cyclohexenylalkyl and the like. A substituted alkenyl is the straight chain alkenyl, branched alkenyl or cycloalkenyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, or the like attached at any available point to produce a stable compound.

"Alkynyl" - alone or in combination means a straight or branched hydrocarbon containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most

preferably 2-4, carbon atoms containing at least one, preferably one, carbon to carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl and the like. A substituted alkynyl refers to the straight chain alkynyl or branched alkenyl defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like attached at any available point to produce a stable compound.

"Alkyl alkenyl" refers to a group -R-CR'=CR''' R'''', where R is lower alkyl, c substituted lower alkyl, R', R''', R'''' may independently be hydrogen, halogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

"Alkyl alkynyl" refers to a groups -RC CR' where R is lower alkyl or substituted lower alkyl, R' is hydrogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

"Alkoxy" denotes the group -OR, where R is lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroalkyl, heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or substituted cycloheteroalkyl as defined.

"Alkylthio" denotes the group -SR, $-S(O)_{n=1-2}-R$, where R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl as defined herein.

"Acyl" denotes groups -C(O)R, where R is hydrogen, lower alkyl substituted lower alkyl, aryl, substituted aryl and the like as defined herein.

"Aryloxy" denotes groups -OAr, where Ar is an aryl, substituted aryl, heteroaryl, or substituted heteroaryl group as defined herein.

"Amino" denotes the group NRR', where R and R' may independently by hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined herein or acyl.

"Amido" denotes the group -C(O)NRR', where R and R' may independently by hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, substituted hetaryl as defined herein.

"Carboxyl" denotes the group -C(O)OR, where R is hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, and substituted hetaryl as defined herein.

"Aryl" - alone or in combination means phenyl or naphthyl optionally carbocyclic fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members and/or optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Substituted aryl" refers to aryl optionally substituted with one or more functional groups, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring (*e.g.*, morpholino, pyridyl or furyl) or multiple condensed rings (*e.g.*, naphthpyridyl, quinoxalyl, quinolinyl, indolizinyl or benzo[b]thienyl) and having at least one hetero atom, such as N, O or S, within the ring, which can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroaryl" - alone or in combination means a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group O, S, and N, and optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl,

acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable aromatic ring is retained. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrazinyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, indolyl and the like. A substituted heteroaryl contains a substituent attached at an available carbon or nitrogen to produce a stabl compound.

"Heterocyclyl" - alone or in combination means a non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally benzo fused or fused heteroaryl of 5-6 ring members and/or are optionally substituted as in the case of cycloalkyl. Heterocycyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. The point of attachment is at a carbon or nitrogen atom. Examples of heterocyclyl groups are tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, piperazinyl, dihydrobenzofuryl, dihydroindolyl, and the like. A substituted hetercyclyl contains a substituent nitrogen attached at an available carbon or nitrogen to produce a stable compound.

"Substituted heteroaryl" refers to a heterocycle optionally mono or poly substituted with one or more functional groups, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Aralkyl" refers to the group -R-Ar where Ar is an aryl group and R is lower alkyl or substituted lower alkyl group. Aryl groups can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano,

thiol, sulfamido and the like.

"Heteroalkyl" refers to the group -R-Het where Het is a heterocycle group and R is a lower alkyl group. Heteroalkyl groups can optionally be unsubstituted or substituted with *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroarylalkyl" refers to the group -R-HetAr where HetAr is an heteroaryl group and R lower alkyl or substituted lower alkyl. Heteroarylalkyl groups can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Cycloalkyl" refers to a divalent cyclic or polycyclic alkyl group containing 3 to 15 carbon atoms.

"Substituted cycloalkyl" refers to a cycloalkyl group comprising one or more substituents with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Cycloheteroalkyl" refers to a cycloalkyl group wherein one or more of the ring carbon atoms is replaced with a heteroatom (*e.g.*, N, O, S or P).

Substituted cycloheteroalkyl" refers to a cycloheteroalkyl group as herein defined which contains one or more substituents, such as halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

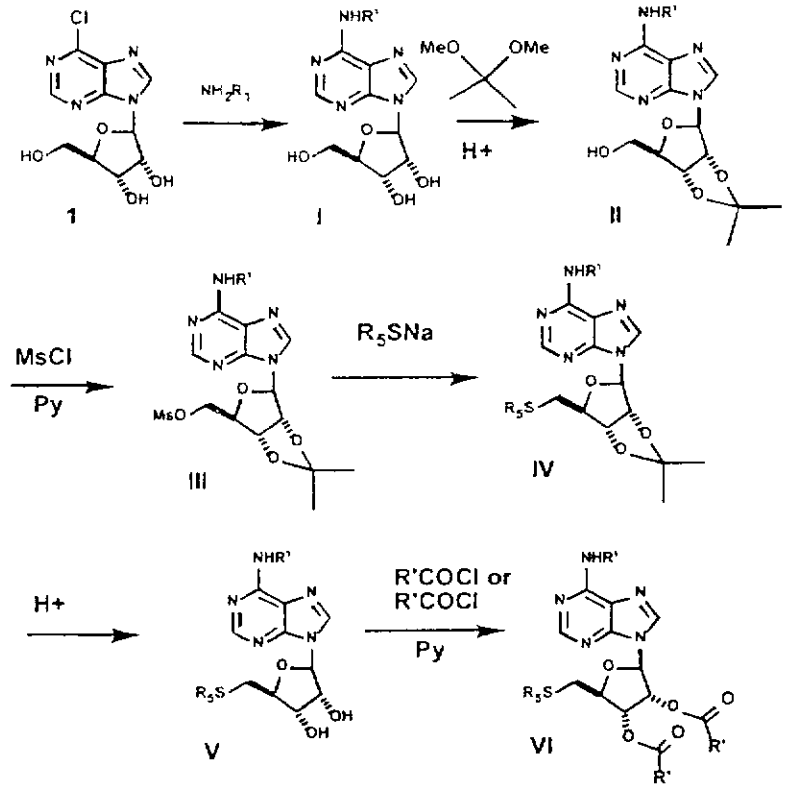
"Alkyl cycloalkyl" denotes the group -R-cycloalkyl where cycloalkyl is a cycloalkyl group and R is a lower alkyl or substituted lower alkyl. Cycloalkyl groups can optionally be unsubstituted or substituted with *e.g.* halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Alkyl cycloheteroalkyl" denotes the group -R-cycloheteroalkyl where R is a lower alkyl or substituted lower alkyl. Cycloheteroalkyl groups can optionally be unsubstituted or

substituted with *e.g.* halogen, lower alkyl, lower alkoxy, alkylthio, amino, amido, carboxyl, acetylene, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

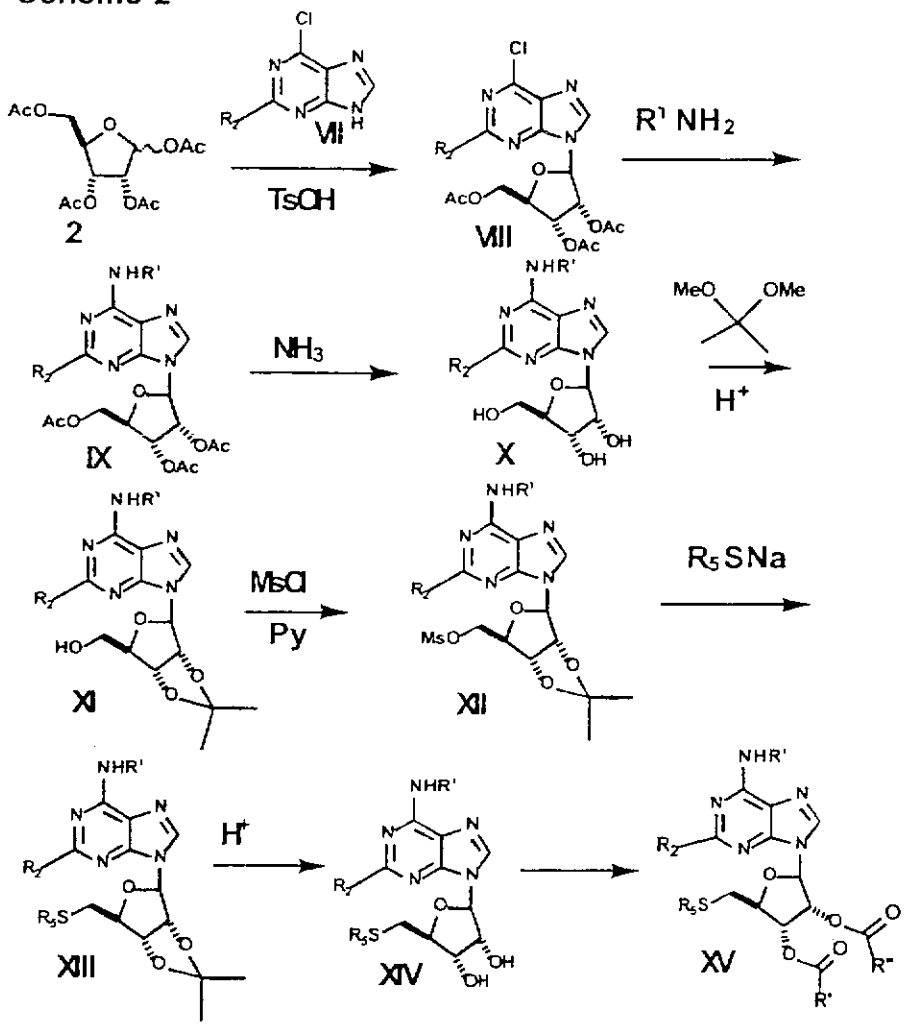
The compounds of this invention can be prepared as outlined in the schemes 1-5 below. A general outline for the preparation of **V** and **VI** is shown in Scheme 1. Compound **I** can be prepared, following the procedures reported earlier (U.S. Patent No. 5,789,416, the specification of which is incorporated herein by reference), by reacting 6-chloropurine riboside **1** with a primary amine R^1NH_2. The 2', 3' hydroxy groups can be protected as acetonide by reacting **I** with 2,2'-dimethoxypropane in the presence of a catalytic amount of TsOH [Evans, Parrish and Long Carbohydrat. Res., 3, 453 (1967)] to give **II**. Activation of the 5'-hydroxyl of **II** with MsCl in pyridine can give the 5'-mesylate **III**. Displacement of the 5'-mesylate with R^5SNa can give sulfides with the general formula **IV**. Treatment of **IV** with an acid can free the 2', 3' hydroxyl groups to give sulfide derivatives with the general formula **V**. Esterification of **V** can afford 2', 3' diesters with the general formula **VI**.

Scheme 1


Cl
NHR'
MeO
OMe
NH_2R_1
H+
HO
OH
1
I
II
MsCl
Py
MsO
III
R_5SNa
R_5S
IV
H+
V
R'COCl or
R'COCl
Py
VI

The 2-substituted derivatives with the general formula XV can be prepared as shown in Scheme 2. Condensation of 1,2,3,5-tetraacetylribofuranaside 2 with 2-substituted-6-chloropurine VII can give 2-substituted–6-chloropurineriboside triacetate VIII which on reaction with a primary amine R^1NH_2 can give 2-substituted-6-alkylamino derivatives IX. Hydrolysis of the acetates followed by protection of the 2', 3' hydroxy groups as an acetonide can give XI. Activation of the 5'-hydroxyl of XI with MsCl in pyridine can give the 5'-mesylate XII. Displacement of the 5'-mesylate with R^5SNa can give sulfides with the general

Scheme 2

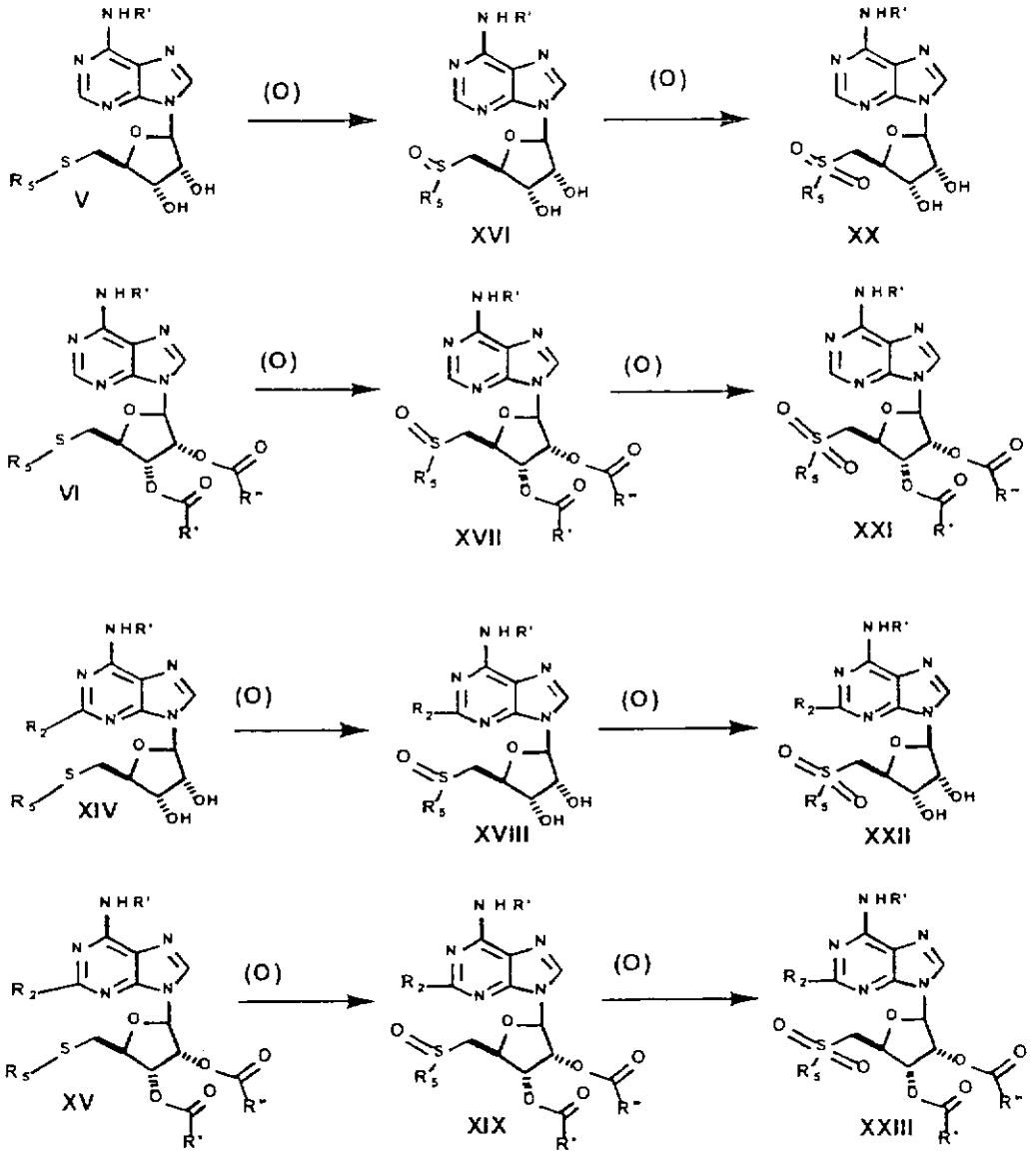


formula XIII that can be deprotected to give sulfides with general formula XIV. Esterification at the 2', 3' positions can afford the 2', 3' diesters with the general formula XV.

Oxidation of sulfides with the general formula V, VI, XIV, XV (Scheme 3) with an oxidizing agent (Drabowicz, et.al. The chemistry of sulfones and sulfoxides, Wiley, New

York, 1988, 233-378) can afford corresponding sulfoxides with the general formula **XVI, XVII, XVIII, XIX**. These sulfoxides on further oxidation can afford sulfones with the general **formula XX, XXI, XXII, XXIII.**

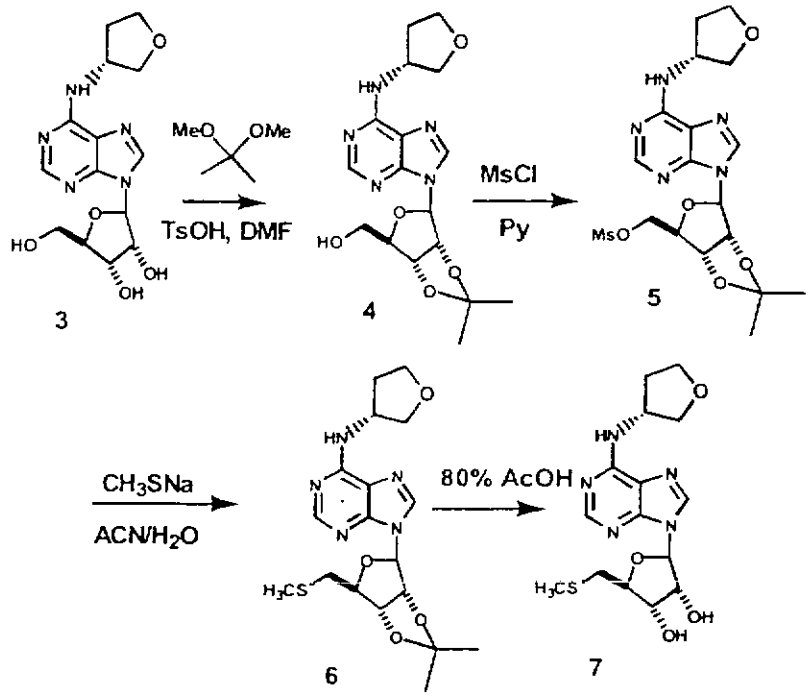
Scheme 3



An example of a specific synthesis of one of the compounds of this invention is shown in Scheme 4. Preparation of compound 7 starting from compound 3 is shown in scheme 3. Compound 3 was prepared from 6-chloropurineriboside **1** and 3-(R)-aminotetrahydrofuran following the procedure reported previously (See U.S. Patent No. 5,789,164). Protection of

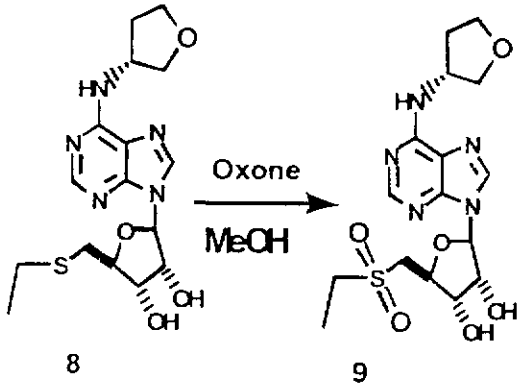
the 2' and 3' hydroxyls with dimethoxypropane in the presence of TsOH(cat.) gave acetonide **4**. Reaction of **4** with MsCl in pyridine at 0 °C gave mesylate **5** which on displacement with sodium methanethiolate in an acetonitrile/water mixture gave sulfide **6**. Deprotection of **6** with 80% acetic acid /water gave the target compound **7**.

Scheme 4



Oxidation of the ethyl sulfide **8** with oxone (Trost, B.M.; Curran, D.P. Tetrahedron Letters 1981, 22, 1287) in MeOH gave sulfone **9** (Scheme 5).

Scheme 5



This invention also includes pro-drugs of the A_1 agonist compositions of this invention A pro-drug is a drug which has been chemically modified and may be biologically inactive at its site of action, but which will be degraded or modified by one or more enzymatic or *in vivo* processes to the bioactive form. The pro-drugs of this invention should have a different pharmacokinetic profile to the parent enabling improved absorption across the mucosal epithelium, better salt formulation and/or solubility and improved systemic stability. The compounds of this invention may be preferably modified at one or more of the hydroxyl groups to form pro-drugs. The modifications may be (1) ester or carbamate derivatives which may be cleaved by esterases or lipases, for example; (2) peptides which may be recognized by specific or non specific proteinase; or (3) derivatives that accumulate at a site of action through membrane selection or a pro-drug form or modified pro-drug form, or any combination of (1) to (3) above.

If a compound of this invention contains a basic group, then corresponding acid addition salt may be prepared. Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic, or methanesulfonic. The hydrochloric salt form is especially useful. If a compound of this invention contains an acidic group, then corresponding cationic salts may be prepared. Typically the parent compound is treated with an excess of an alkaline reagent, such as hydroxide, carbonate or alkoxide, containing the appropriate cation. Cations such as Na^+, K^+, Ca^{+2} and NH_4^+ are examples of cations present in pharmaceutically acceptable salts. Certain of the compounds form inner salts or zwitterions which may also be acceptable.

The compositions of this invention are useful for treating a variety of mammalian disorders and preferably human disorders that are mediated by an A_1 adenosine receptor. For example, the compositions of this invention are useful for modifying cardiac activity in mammals experiencing a coronary electrical disorder that can be treated by stimulating an A_1 adenosine receptor. Examples of coronary electrical disorders that can be treated by the compositions of this invention include supraventricular tachycardias, atrial fibrillation, atrial flutter, and AV nodal re-entrant tachycardia. Furthermore, orally active A_1 agonists of this invention that demonstrate an excellent safety profile in treating supraventricular arrhythmias

may also be used as a prophylactic for those at high risk of a myocardial ischemia.

The compositions of this invention are also useful for modifying adipocyte function by stimulating an A_1 adenosine receptor that leads to diminished release of NEFA and increased release of leptin. Disease states related to adipocyte function that can be modified using compositions of this invention include diabetes, and obesity.

In skeletal muscle cells, A_1 AdoR agonists mediate a synergistic stimulation of glucose uptake and transport by insulin (Vergauwen, L. *et al*, *J. Clin. Invest.* 1994, *93*, 974-81; Challiss, R.A. *et al*, *Eur.J.Pharacol.*, 1992, *226*, 121-8). Another therapeutic utility of compositions of this invention is more efficient regulation of glucose and a decrease of circulating insulin in patients afflicted with diabetes.

The A_1 receptor agonist, R-PIA, has been shown to increase the leptin released from white adipocytes and augment insulin-stimulated leptin production (M. Ozeck Master' Thesis Univ. of Florida 1999 with L. Belardinelli). Evidence suggests that catecholamines inhibit the production of leptin from adipocytes through activation of β-adrenergic receptors. The anti-β-adrenergic effects of A_1 agonists on the adipocytes are believed to play a role in the increased release of leptin. The functional role of leptin is multifaceted including decreased appetite, stimulated energy utilization, and increased fertility.

The compositions of this invention may also be used to provide central nervous system neuroprotection by stimulating an A_1 adenosine receptor. Central nervous system disorders that may be treated using the compositions of this invention include epilepsy, and stroke.

In the kidney, there is evidence that stimulation of the A_1 AdoR promotes sodium retention, promotes exchange of sodium in urine for potassium, and reduces glomerular filtration rate as sodium excretion increases (Gellai, M. *et al*, *JPET*, 1998, *286*, 1191-6; Wilcox, C.S. *et al*, *J.Am.Soc.Nephrol.*, 1999, *10*, 714-720). It is believed that these responses are elicited by chronic local production of adenosine. That is, in the kidney there is a tonic effect of adenosine to stimulate the A_1 AdoR. Another clinical utility of compositions of this invention, therefore, is the selective antagonism of the A_1 AdoR in the kidney to inhibit sodium retention, inhibit the exchange of sodium for potassium, and preserve kidney glomerular filtration rate when sodium excretion rises to yield a potassium sparring diuretic that preserves renal function.

The compositions of this invention are further useful for providing cardiomyocyte protection from ischemic events by stimulating an A_1 adenosine receptor. Ischemic events treatable using the compositions of this invention include stable angina, unstable angina, cardiac transplant, and myocardial infarction.

An important aspect of compounds of this invention is that each compound has an intrinsic efficacy associated with it (for a discussion see T. P. Kenakin Stimulus Response Mechanisms. In Pharmacological Analysis of Drug-Receptor Interaction, Ed. Kenakin, T.P. New York: Raven Press, p 39-68). This intrinsic efficacy is not defined by it's affinity for the receptor, but it is defined as the quantitative effect of the compound to activate a given effector system (eg. cAMP production) in a given cell type. The intrinsic efficacy of a given compound may vary from cell type to cell type and/or from effector system to effector system. When a compound has an intrinsic efficacy lower than a full agonist (i.e. submaximal) than the agonist is called a partial agonist. Thus, a partial agonist is a molecule that binds to a receptor and elicits a response that is smaller than that of a full agonist (submaximal), but also competitively antagonizes the response(s) elicited by a full agonist. The tonic action of adenosine with respect to kidney function is a prime example where a partial A_1 agonist be expected to act as antagonists (e.g. adenosine). The tonic action of adenosine with respect to kidney function is a prime example where a partial A_1 agonist could be expected to act as an antagonist. The compounds of this invention are believed to have therapeutically useful affinities for the adenosine A_1 receptor, and they will have a range of intrinsic efficacies from full agonist to partial agonist. That is, some compounds may have no effect with respect to a given effector system in a given cell type, but be a full agonist in another cell type and/or effector system. The reason for such variable pharmacological behavior relates to the magnitude of the receptor reserve for the A_1 adenosine receptor in any given cell type (eg. AV nodal cells vs. adipocytes) and for a given response. The receptor reserve (spare receptor capacity) is the total number of receptors minus the fraction of receptors that is required to induce the maximal response using a full agonist (L. E. Limbird, Cell Surface Receptors: A Short Course on Theory and Methods, Kluwer Acad. Pub. 1996, Boston, Mass.). Therefore, the agonist could be a full agonist at eliciting a response, and a partial agonist for eliciting another response in other tissue or cells and still be an antagonist or lack activity for a third

response in another tissue or cell. Consequently, a partial agonist targeted to a selected target is likely to cause fewer side effects than a full agonist. As a corollary, a full agonist elicits all the effects mediated by the respective receptor, whereas this is not necessarily the case of a partial agonist. The compounds of this invention based on their affinity for the A_1 receptor and their potency and selectivity to elicit A_1 receptor mediated responses have the potential for therapeutic intervention in the multiple disease states described above.

Partial A_1 agonists may have an added benefit for chronic therapy because they will be less likely to induce desensitization of the A_1 receptor (R. B. Clark, B. J. Knoll, R. Barber TiPS, Vol. 20 (1999) p. 279-286) and to cause side effects. Chronic administration of a full agonist (R-N6-phenylisopropyladenosine, R-PIA) for 7 days led to a desensitization of the A_1 receptor in terms of the dromotropic response in guinea pigs (note: a decrease in receptor number was observed – D. M. Dennis, J. C. Shryock, L. Belardinelli JPET, Vol. 272 (1995) p 1024-1035). The A_1 agonist induced inhibitory effect on the production of cAMP by adenylate cyclase in adipocytes has been shown to desensitize upon chronic treatment with an A_1 agonist as well (W. J. Parsons and G. L. Stiles J. Biol. Chem. Vol. 262 (1987) p. 841-847).

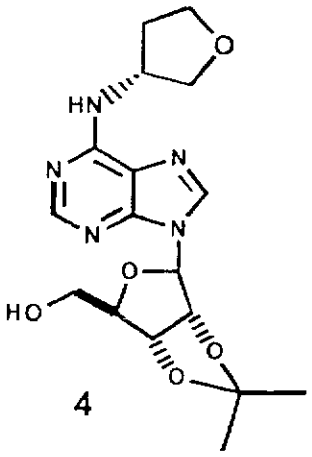
The compositions of this invention may be administered orally, intravenously, through the epidermis, bolus, nasally, by inhalation or by any other means known in the art for administering a therapeutic agents. The method of treatment comprises the administration of an effective quantity of the chosen compound, preferably dispersed in a pharmaceutical carrier. Dosage units of the active ingredient are generally selected from the range of 0.01 to 100 mg/kg, but will be readily determined by one skilled in the art depending upon the route of administration, age and condition of the patient.

Pharmaceutical compositions including the compounds of this invention, and/or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. If used in liquid form the compositions of this invention are preferably incorporated into a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water and buffered sodium or ammonium acetate solution. Such liquid formulations are suitable for parenteral administration, but may also be used for oral administration. It may be

desirable to add excipients such as polyvinylpyrrolidinone, gelatin, hydroxycellulose, acacia, polyethylene glycol, mannitol, sodium chloride, sodium citrate or any other excipient known to one of skill in the art to pharmaceutical compositions including compounds of this invention. Alternatively, the pharmaceutical compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, alcohols and water. Solid carriers include starch, lactose, calcium sulfate, dihydrate, teffa alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glycerol monostearate or glycerol distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 gram per dosage unit. The pharmaceutical dosages are made using conventional techniques such as milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly or filled into a soft gelatin capsule.

The Examples which follow serve to illustrate this invention. The Examples are not intended to limit the scope of this invention, but are provided to show how to make and use the compounds of this invention.

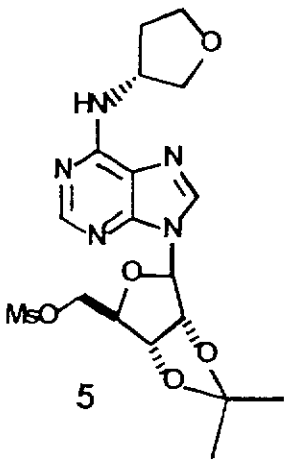
Example 1



4

Intermediate – (4-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(1R, 2R, 5R)-7,7-dimethyl-3,6,8-trioxabicyclo[3.3.0]oct-2-yl)methan-1-ol (4)

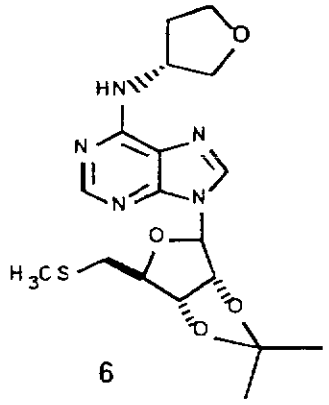
To a solution of compound 3 (2.0 g, 6.0 mmol) and 2,2-dimethoxypropane (1.2 g, 11.8 mmol) in dimethylformamide (20 mL) was added p-toluenesulfonic acid (50 mg, 0.26 mmol) at 70°C. After 48 h at 70°C, the reaction was concentrated in vacuo to afford a solid. The solid was dissolved in methanol (3 mL), then triturated with ethyl ether (50 mL). The resultant crystals were collected by vacuum filtration to afford the intermediate **4**.



5

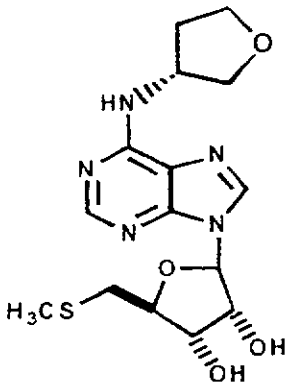
To a solution of **4** (190 mg, 0.5 mmol) in anhydrous pyridine (5mL), was added MsCl (80 microL, 1 mmol) at 0°C. The reaction mixture was stirred at the same temperature for 2h. Pyridine was removed under reduced pressure, residue was taken in dichloromethane (50mL),

washed with water (3 x 20mL) and dried (Na_2SO_4). Evaporation of the solvent gave product 5 as a white foam: ^{1}H NMR ($CDCl_3$) δ1.4 (s,3H), 1.6(s, 3H), 2.0-2.2(m, 1H), 2.3-2.5(m, 1H), 2.9(s, 3H), 3.7-4.2(m, 4H), 4.4-4.6(m, 3H), 4.8-5.0(bs, 1H), 5.1-5.2(bs, 1H), 5.4-5.5(bs, 1H), 6.1(s, 1H), 6.4-6.6(bs, 1H), 8.1 (s, 1H), 8.4(s, 1H)



6

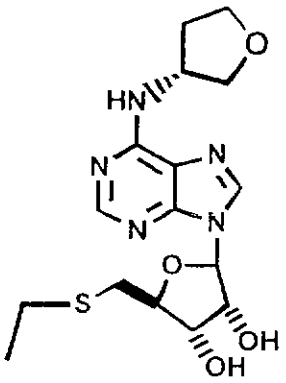
A mixture of mesylate 5 (150 mg) and methanethiolate(150mg) in acetonitrile (2mL) and water (1mL) was heated at 70 C for 24h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC [methanol-dichloromethane (1:19)] to afford product 6: ^{1}H NMR (CDCl3) δ 1.35 (s, 3H), 1.60 (s, 3H), 1.90-2.05 (m, 1H), 2.05 (s, 3H), 2.30-2.40 (m, 1H), 2.70 (doublet of AB quartet, 2H), 3.75-3.90 (m, 2H), 3.95-4.00 (m, 2H), 4.3-4.4 (m, 1H), 4.8-4.95 (m, 1H), 5.00-5.05 (m, 1H), 5.45-5.50 (d, 1H), 6.00-6.10 (m, 2H), 7.85 (s, 1H), 8.3 (s, 1H).



7

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(methylthiomethyl)oxolane-3,4-diol (7)

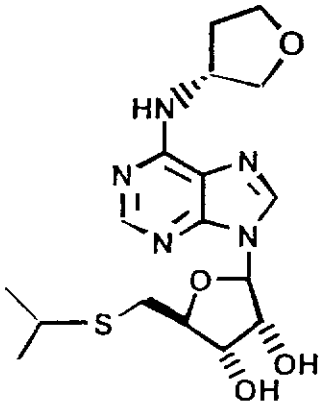
Compound 6 (50mg) was dissolved in a mixture of acetic acid (8 mL) and water (2 mL) and heated at 90°C for 16 h. Solvents were removed under reduced pressure, and the residue was purified by preparative TLC [methanol-dichloromethane (1:9)] to afford compound 7: 1H NMR ($CDCl_3$) δ 1.90-2.05 (m, 1H), 2.15 (s, 3H), 2.30-2.40 (m, 1H), 2.75-2.85 (m, 2H), 3.80-3.90 (m, 2H), 3.90-4.00 (m, 2H), 4.30-4.45 (m, 2H), 4.50-4.55 (m, 1H), 4.75-4.95 (m, 1H), 5.90-5.95 (m, 1H), 6.30-6.60 (m, 1H), 7.95 (s, 1H), 8.25 (s, 1H).



8

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(Ethylthio)methyl]oxolane-3,4-diol(8)

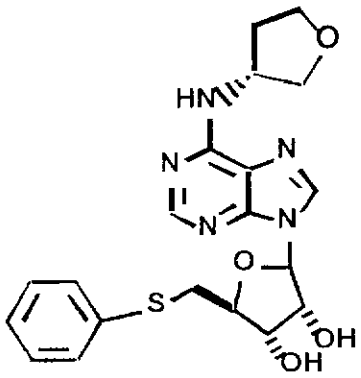
Compound 8 was prepared in the manner similar to that of 7 substituting ethane thiolate for methane thiolate. (M+1) = 382.30



10

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(Methylethylthio)methyl]oxolane-3,4-diol(10)

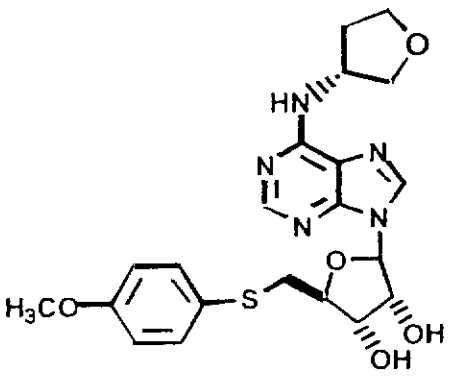
Compound **10** was prepared in the manner similar to that of 7 substituting i-propane thiolate for methane thiolate. ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 6H), 1.90-2.05 (m, 1H), 2.15 (s, 3H), 2.30-2.40 (m, 1H), 2.85-2.87 (d, 2H), 2.95 (septet, 1H), 3.80-3.90 (m, 2H), 3.95-4.05 (m, 2H), 4.35-4.40 (m, 2H), 4.50-4.55 (m, 1H), 4.75-4.85 (m, 1H), 5.90-5.95 (d, 1H), 6.85-6.95 (m, 1H), 7.95 (s, 1H), 8.25 (s, 1H).



11

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(phenylthiomethyl)oxolane-3,4-diol(11)

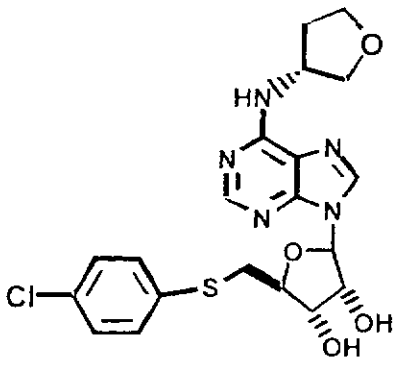
Compound **11** was prepared in the manner similar to that of 7 substituting phenyl thiolate for methane thiolate. ^{1}H NMR ($CDCl_3$) 1.95-2.05 (m, 1H), 2.30-2.40 (m, 1H), 3.2 (d, 2H), 3.80-3.90 (m, 2H), 3.95-4.10 (m, 2H), 4.35-4.40 (d, 1H), 4.45 (t, 1H), 4.50-4.55 (m, 1H), 4.80-4.90 (m, 1H), 5.85 (d, 1H), 6.70-6.80 (m, 1H), 7.15-7.30 (m, 3H), 7.35 (d, 2H), 7.75 (s, 1H), 8.25 (s, 1H).



12

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-Methoxyphenylthio)methyl]oxolane-3,4-diol(12)

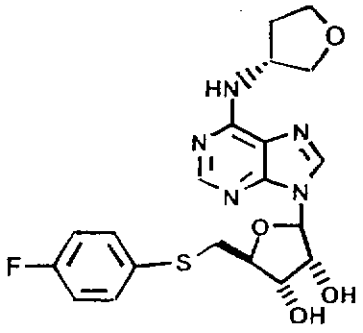
This compound was prepared in the manner similar to that of 7 substituting 4-methoxyphenyl thiolate for methane thiolate. (M+1) = 460.4



13

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-chlorophenylthio)methyl]oxolane-3,4-diol(13)

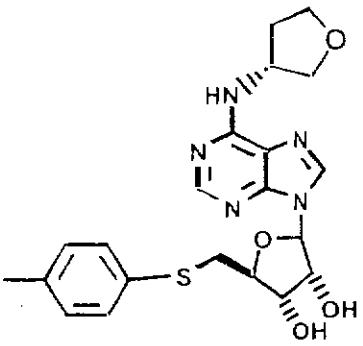
This compound was prepared in a manner similar to that of 7 substituting 4-chlorophenyl thiolate for methane thiolate. (M+1) = 464.3



14

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-fluorophenylthio)methyl]oxolane-3,4-diol(14)

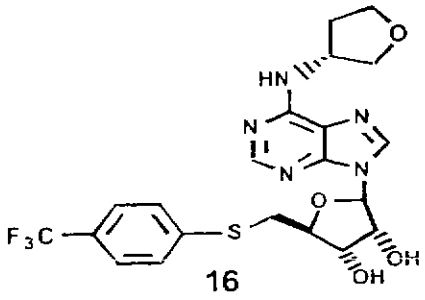
This compound was prepared in a manner similar to that of 7 substituting 4-fluorophenyl thiolate for methane thiolate. (M+1) = 448.3



15

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-methylphenylthio)methyl]oxolane-3,4-diol(15)

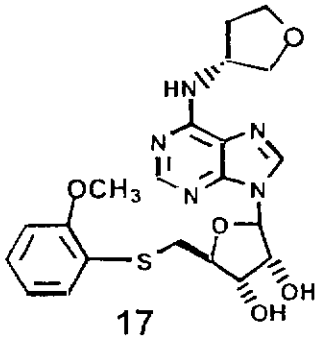
This compound was prepared in a manner similar to that of 7 substituting 4-methylphenyl thiolate for methane thiolate. (M+1) = 444.38



16

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-(trifluoromethyl)phenylthio)methyl]oxolane-3,4-diol(16)

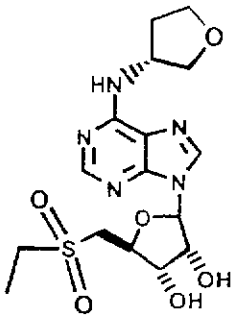
This compound was prepared in a manner similar to that of 7 substituting 4-trifluoromethylphenyl thiolate for methane thiolate. (M+1) = 488.36



17

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(2-Methoxyphenylthio)methyl]oxolane-3,4-diol(17)

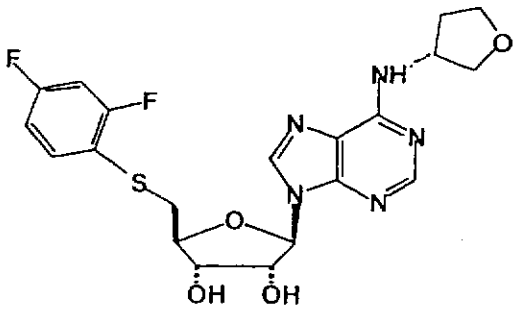
This compound was prepared in a manner similar to that of 7 substituting 2-methoxyphenyl thiolate for methane thiolate. (M+1) = 460.4



9

(5-{6-[((3R)oxolan-3-yl)amino]purinyl-9-yl}(2S,3S,4R,5R)-3,4-dihydroxyoxolan-2-yl)(ethylsulfonyl)methane(9)

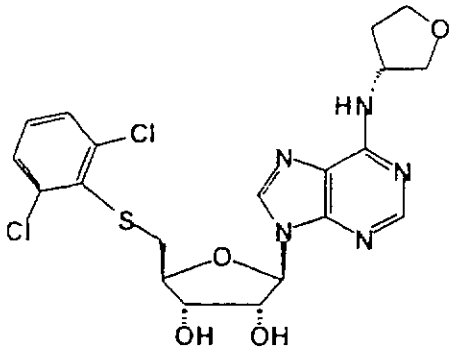
To a cooled solution of sulfide 8 in methanol at 0°C under nitrogen was added 3 eq. of Oxone (Potassium peroxy monosulfate) and the reaction mixture was allowed to stir at the same temperature for 1hour. After the starting material consumed (by TLC), the reaction mixture was concentrated and filtered through a small plug of silica gel. Purification by preparative TLC [methanol-dichloromethane (1:19)] afforded 9 as an off-white hygroscopic solid. (M+1) = 414.28



18

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(2,4-difluorophenylthio)methyl]oxolane-3,4-diol(18)

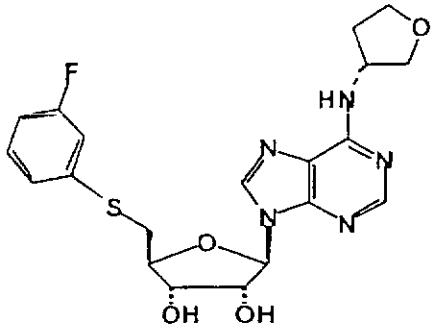
This compound was prepared in a manner similar to that of 7 substituting 2,4-difluorophenyl thiolate for methane thiolate. (M+1) = 466.23



19

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(2,6-dichlorophenylthio)methyl]oxolane-3,4-diol(19)

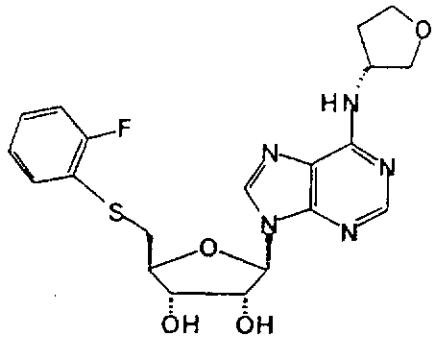
This compound was prepared in a manner similar to that of 7 substituting 2,6-dichlorophenyl thiolate for methane thiolate. (M+1) = 498.18



20

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(3-fluorophenylthio)methyl]oxolane-3,4-diol(20)

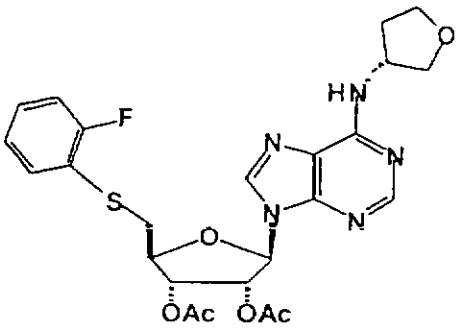
This compound was prepared in a manner similar to that of 7 substituting 3-fluorophenyl thiolate for methane thiolate. (M+1) = 448.26



21

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(2-fluorophenylthio)methyl]oxolane-3,4-diol(21)

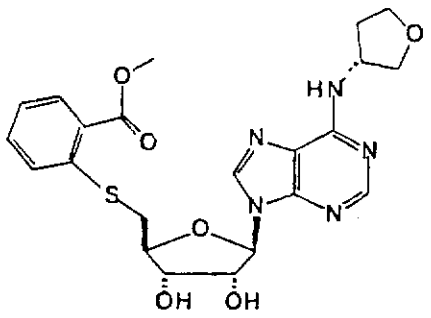
This compound was prepared in a manner similar to that of 7 substituting 2-fluorophenyl thiolate for methane thiolate. (M+1) = 448.24



22

5-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(2S,3R,4R,5R)-4-acetyloxy-2-[(fluorophenylthio)methyl]oxolan-3-yl acetate(22)

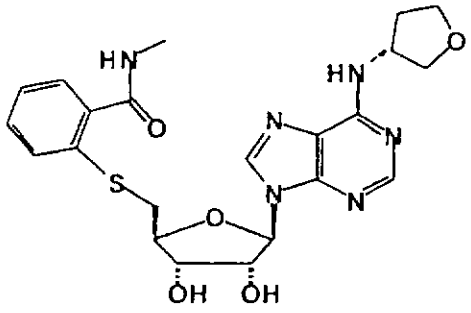
To a solution of compound 21 (139 mg) in pyridine (2 mL) at 23 °C was added acetic anhydride (0.1 mL). After 3 h at 23 °C, the reaction was concentrated *in vacuo* . The residue was dissolved in methylene chloride (50 mL), washed with water (3 x 10 mL), and dried (Na_2SO_4). After concentration *in vacuo*, the residue was purified by flash chromatography (methylene chloride: methanol 20:1 followed by 9:1) to afford compound 22 (170 mg):



23

Methyl 2[(5-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(2S,3S,4R,5R)-3,4-dihydroxyoxolan-2-yl)methylthio]benzoate (23)

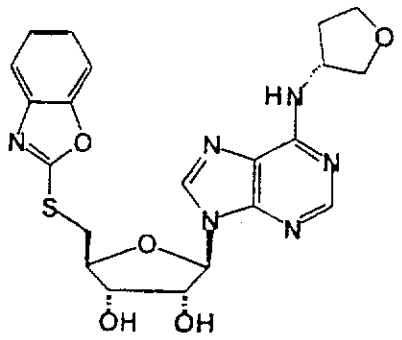
To a solution of Compound 4 (0.377g, 1 mmol) in 5mL of THF, was added Triphenylphosphine (0.524g, 2 mmol), DEAD (0.40 mL, 2 mmoles), let stir for 5 minutes before adding 2-carbomethoxythiophenol (0.5mL). Reaction was allowed to stir under reflux. After 72 h of reflux, the reaction was concentrated in vacuo and the residue purified by flash column chromatography (20%EtOAc/Hexanes) to give a clear viscous oil. It was taken into a mixture of aceticacid (8mL) and water (2mL) and heated at 80 C for 16h. Solvents were removed in vacuo and the residue was purified by prep TLC [methanol-dichloromethane (1:9)] to give compound 23. (M+1) = 488.5



24

{2[(5-{6-[((3R)oxolan-3-yl)amino]purin-9-yl} (2S,3S,4R,5R)-3,4-dihydroxyoxolan-2-yl) methylthio]phenyl}-N-methylcarboxamidebenzoate (24)

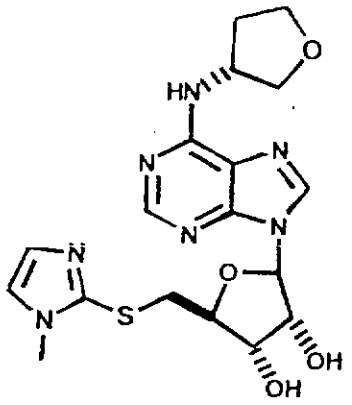
Compound 23 was taken into 40% aq.methylamine (2 mL) and 1-propanol (2 mL) and heated at 70 C for 16h. Solvents were removed in vacuo and the residue was purified by prep TLC TLC [methanol-dichloromethane (1:9)] to give compound 24. (M+1) =487.5



25

2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(benzoxazol-2-ylthiomethyl)oxolane-3,4-diol (25)

This compound was prepared in a manner similar to that of 23 substituting 2-mercaptobenzoxazole for 2-carbmethoxy thiophenol (M+1) = 471.4

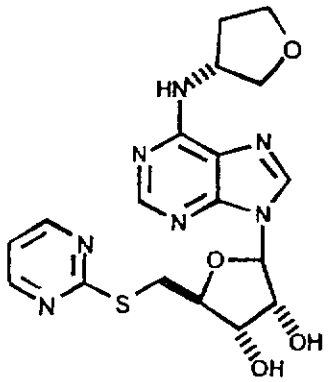


26

2-{6-[((3S)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(1-methylimidazol-2-yl-thio)methyl]oxolane-3,4-diol (26)

Compound 26 was prepared in the manner of compound 23 substituting 2-mercapto-1-methyl-imidazole for 2-carbomethoxythiophenol [MS 434.4 (M+1)].

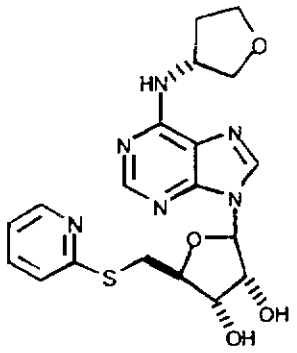
2-{6-[((3S)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(pyrimidine-2-



27

ylthiomethyl)oxolane-3,4-diol (27)

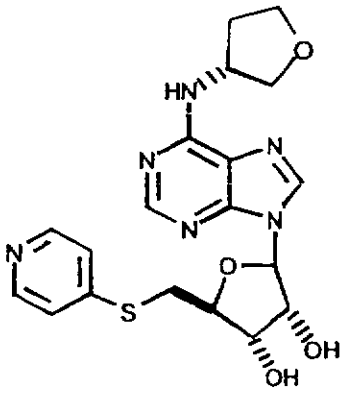
Compound **27** was prepared in the manner of compound **23** substituting 2-mercaptopyrimidine for 2-carbomethoxythiophenol [MS 432.4 (M+1)].



28

2-{6-[((3S)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(2-pyridylthiomethyl)oxolane-3,4-diol (28)

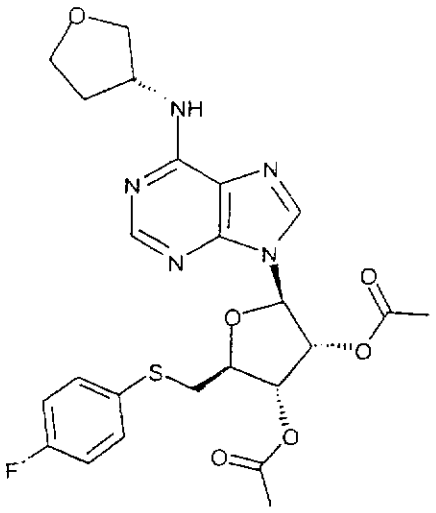
Compound **28** was prepared in the manner of compound **23** substituting 2-mercaptopyridine for 2-carbomethoxythiophenol [MS 431.4 (M+1)].



29

2-{6-[((3S)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(4-pyridylthiomethyl)oxolane-3,4-diol (29)

Compound **29** was prepared in the manner of compound **23** substituting 4-mercaptopyridine for 2-carbomethoxythiophenol [MS 431.4 (M+1)].



5-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(2S,3R,4R,5R)-4-acetyloxy-2-[(4-fluorophenylthio)methyl]oxolan-3-yl]acetate (30) (M+1) = 532.17.

EXAMPLE 2

Binding Assays – DDT$_1$ Cells

Cell Culture

DDT cells (hamster vas deferens smooth muscle cell line) were grown as monolayers in petri dishes using Dulbecco's Modified Eagle's Medium (DMEM) containing 2.5 g ml^{-1} amphotericin B, 100 U ml^{-1} penicillin G, 0.1 mg ml^{-1} streptomycin sulfate and 5% fetal bovine serum in a humidified atmosphere of 95% air and 5% CO_2. Cells were subcultured twice weekly by dispersion in Hank's Balanced Salt Solution (HBSS) without the divalent cations and containing 1 mM EDTA. The cells were then seeded in growth medium at a density of 1.2 x 10^5 cells per plate and experiments were performed 4 days later at approximately one day preconfluence.

Membrane Preparations

Attached cells were washed twice with HBSS (2 x 10 ml), scraped free of the plate with the aid of a rubber policeman in 5 ml of 50 mM Tris-HCl buffer pH 7.4 at 4 °C and the suspension homogenized for 10 s. The suspension was then centrifuged at 27,000 x g for 10 min. The pellet was resuspended in homogenization buffer by vortexing and centrifuged as described above. The final pellet was resuspended in 1 vol of 50 mM Tris-HCl buffer pH 7.4 containing 5 mM $MgCl_2$ for A_1 AdoR assays. For the [^{35}S]GTPγS binding assay the final

pellet was resuspended in 50 mM Tris-HCl pH 7.4 containing 5 mM $MgCl_2$, 100 mM NaCl and 1 mM dithiothreitol. This membrane suspension was then placed in liquid nitrogen for 10 min, thawed and used for assays. The protein content was determined with a Bradford™ Assay Kit using bovine serum albumin as standard.

Competitive Binding Assay

Pig striatum were prepared by homogenation in 50 mM Tris buffer (5x volume of tissue mass pH = 7.4). After centrifugation at 19,000 rpm for 25 minutes at 4 °C, the supernatant was discarded, and the process was repeated twice. Compositions of this invention were assayed to determine their affinity for the A_1 receptor in a pig striatum membrane prep or a DDT_1 membrane prep. Briefly, 0.2 mg of pig striatal membranes or DDT_1 cell membranes were treated with adenosine deaminase and 50 mM Tris buffer (pH = 7.4) followed by mixing. To the pig membranes was added 2 µL of serially diluted DMSO stock solution of the compounds of this invention at concentrations ranging from 100 microM to 10 nM. The control received 2 microL of DMSO alone, then the antagonist [^{3}H] 8-cyclopentylxanthine (CPX) for pig striatum or the agonist [^{3}H] 2-chloro-6-cyclopentyladenosine (CCPA) for DDT_1 membranes in Tris buffer (50 mM, pH of 7.4) was added to achieve a final concentration of 2 nM. After incubation at 23 C for 2h, then the solutions were filtered using a membrane harvester using multiple washing of the membranes (3 x). The filter disks were counted in scintillation cocktail affording the amount of displacement of tritiated CPX or by the competitive binding compositions of this invention. Greater than a 5 point curve was used to generate Ki's and the number of experiments is indicated in the column marked in Table 1, below:

Table 1

Compound #	K_i – DDT_1 cell membrane	K_i – Pig Striatum
7	--	222 nM
10	--	188 nM
11	--	44 nM
12	820 nM	--
14	363 nM	--
15	922 nM	--
16	7701 nM	--
17	947 nM	--

EXAMPLE 3

[^{35}S]GTPγS Binding Assays

A_1-agonist stimulated [^{35}S] GTPγS binding was determined by a modification of the method described by Gierscikik et al. (1991) and Lorenzen et al. (1993). Membrane protein (30-50 μg) was incubated in a volume of 0.1 ml containing 50 mM Tris-HCl buffer pH 7.4, 5 mM $MgCl_2$, 100 mM NaCl, 1 mM dithiothreitol, 0.2 units ml^{-1} adenosine deaminase, 0.5% BSA, 1 mM EDTA, 10 mM GDP, 0.3 nM [^{35}S]GTPγS and with or without varying concentrations of CPA for 90 min at 30 °C. Nonspecific binding was determined by the addition of 10 μM GTPγS. Agonist stimulated binding was determined as the difference between total binding in the presence of CPA and basal binding determined in the absence of CPA. Previous reports have shown that agonist stimulated [^{35}S]GTPγS binding was dependent on the presence of GDP (Gierschik et al., 1991; Lorenzen et al., 1993; Traynor & Nahorski, 1995). In preliminary experiments, it was found that 10 μM GDP gave the optimal stimulation of CPA dependent [^{35}S]GTPγS binding and this concentration was therefore used in all studies. In saturation experiments, 0.5 nM [^{35}S]GTPγS was incubated with 0.5-1000 nM GTPγS. At the end of the incubation, each suspension was filtered and the retained radioactivity determined as described above. Results are presented normalized to the full agonist N-6-cyclopentyladenosine, CPA.

Table 2

Compound #	GTP□S
CPA	100 %
8	104%
12	52%
13	69%
14	61%
15	48%
16	31%
17	52%

EXAMPLE 4

cAMP Assay

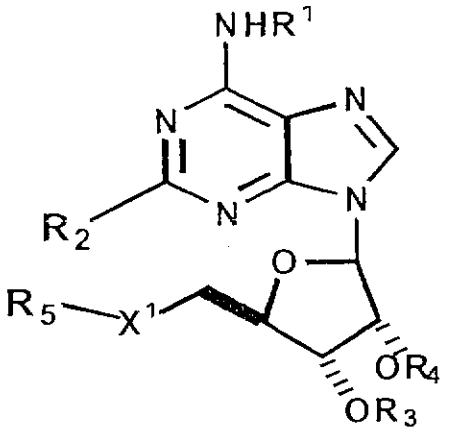
A scintillation proximity assay (SPA) using rabbit antibodies directed at cAMP using an added tracer of adenosine 3',5'-cyclic phosphoric acid 2'-O-succinyl-3-[^{125}I]iodotyrosine methyl ester and fluoromicrospheres containing anti-rabbit specific antibodies as described by Amersham Pharmacia Biotech (Biotrak cellular communication assays). Briefly, DDT_1 cells were cultured in clear bottomed 96 well microtiter plates with opaque wells at concentrations between 10^4 to 10^6 cells per well in 40 µl of HBSS at 37 °C (5% CO_2 and 95% humidity). The partial or full A_1 agonists (5 µl)of this invention were incubated at various concentrations with the DDT_1 cells in the presence of rolipram (50 µM), and 5 µM forskolin for 10 min at 37 °C. The cells were immediately lysed by treatment 5 µl of 10% dodecyltrimethylammonium bromide followed by shaking using microplate shaker. After incubation of the plate for 5 minutes, an immunoreagent solution (150 µl containing equal volumes of tracer, antiserum, and SPA fluorospheres) was added to each well followed by sealing the plate. After 15-20 h at 23 °C, the amount of bound [^{125}I] cAMP to the fluoromicrospheres was determined by counting in a microtitre plate scintillation counter for 2 minutes. Comparison of counts with standard curves generated for cAMP using a similar protocol afforded the cAMP present after cell lysis. Results are presented normalized to the full agonist N-6-cyclopentyladenosine, CPA. Thus, the full agonist CPA diminished the amount of forskolin induced cAMP generation back to basal levels.

Table 3

Compound #	Camp
CPA	107 %
8	37%
12	-9%
13	30%
14	47%
15	22%
16	22%
17	18%

What we claim is:

1. A compound of the formula:



wherein:

R^1 is an oxolanyl moiety attached at a carbon atom;

R_2, R_3, and R_4 are hydrogen;

R_5 is selected from the group consisting of C_{1-6} alkyl, optionally substituted phenyl, pyridyl, pyrimidinyl, methylimidazolyl, and benzoxazolyl, wherein the phenyl may be optionally substituted with a substituent selected from the group consisting of halogen, methyl, methoxy, CF_3, CO_2CH_3, and $CONHCH_3$; and

X^1 is S or $S(O)_2$;

or a pharmaceutically effective salt thereof.

2. The compound of claim 1, wherein X^1 is S.

3. The compound of claim 1, wherein X^1 is $S(O)_2$.

4. The compound of any one of claims 1 to 3, wherein R_5 is C_{1-6} alkyl.

5. The compound of claim 4, wherein R_5 is selected from the group consisting of methyl, ethyl, and isopropyl.

6. The compound of any one of claims 1 to 3, wherein R_5 is optionally substituted phenyl.

7. The compound of claim 1 wherein, R^1 is oxolan-3-yl, R_5 is methyl, and X^1 is S, namely 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(methylthiomethyl)oxolane-3,4-diol.

8. The compound of claim 1 wherein, R^1 is oxolan-3-yl, R_5 is ethyl, and X^1 is S, namely 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(ethylthio)methyl]oxolane-3,4-diol.

9. The compound of claim 1 wherein, R^1 is oxolan-3-yl, R_5 is isopropyl, and X^1 is S, namely 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(isopropylthio)methyl]oxolane-3,4-diol.

10. The compound of claim 1 wherein, R^1 is oxolan-3-yl, R_5 is phenyl, and X^1 is S, namely 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(phenylthiomethyl)oxolane-3,4-diol.

11. The compound of claim 1 wherein, R^1 is oxolan-3-yl, R_5 is 4-methoxyphenyl, and X^1 is S, namely 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-methoxyphenylthio)methyl]oxolane-3,4-diol.

12. The compound of claim 1 wherein, R^1 is oxolan-3-yl, R_5 is 4-chlorophenyl, and X^1 is S, namely 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-chlorophenylthio)methyl]oxolane-3,4-diol.

13. The compound of claim 1 wherein, R^1 is oxolan-3-yl, R_5 is 4-fluorophenyl, and X^1 is S, namely 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-fluorophenylthio)methyl]oxolane-3,4-diol.

14. The compound of claim 1 wherein, R^1 is oxolan-3-yl, R_5 is 4-methylphenyl, and X^1 is S, namely 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-methylphenylthio)methyl]oxolane-3,4-diol.

15. The compound of claim 1 wherein, R^1 is oxolan-3-yl, R_5 is 4-trifluorophenyl, and X^1 is S, namely 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(4-(trifluoromethyl)phenylthio)methyl]oxolane-3,4-diol.

16. The compound of claim 1 wherein, R^1 is oxolan-3-yl, R_5 is 2-methoxyphenyl, and X^1 is S, namely 2-{6-[((3R)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-[(2-methoxyphenylthio)methyl]oxolane-3,4-diol.

17. The compound of claim 1 wherein, R^1 is oxolan-3-yl, R_5 is ethyl, and X^1 is $S(O)_2$, namely (5-{6-[((3R)oxolan-3-yl)amino]purinyl-9-yl}(2S,3S,4R,5R)-3,4-dihydroxyoxolan-2-yl)(ethylsulfonyl)methane.

18. Use of a therapeutic amount of the composition of claim 1 in the preparation of a medicament for modifying cardiac activity in a mammal experiencing a heart electrical disorder that can be treated by stimulating an A_1 adenosine receptor.

19. Use of a therapeutic amount of the composition of claim 1 in the preparation of a medicament for modifying mammalian adipocyte function by stimulating an A_1 adenosine receptor.

20. Use of a therapeutic amount of the composition of claim 1 in the preparation of a medicament for restoring sensitivity and efficacy of insulin in a mammal by stimulating an A_1 adenosine receptor.

21. Use of a therapeutic amount of the composition of claim 1 in the preparation of a medicament for providing a mammal with central nervous system neuroprotection by stimulating an A_1 adenosine receptor.

22. Use of a therapeutic amount of the composition of claim 1 in the preparation of a medicament for providing a mammal with cardiomyocyte protection from ischemia by stimulating an A_1 adenosine receptor.

23. The use of any one of claims 18 to 22 wherein the therapeutically effective amount ranges from about 0.01 to about 100 mg/kg weight of the mammal.

24. The use of claim 18 wherein the medicament is suitable for administration to a mammal experiencing a heart electrical disorder selected from the group consisting of supraventricular tachycardias, atrial fibrillation, atrial flutter, and AV nodal re-entrant tachycardia.

25. The use of claim 19 or 20 wherein the medicament is suitable for administration to a mammal experiencing a disorder selected from the group consisting of diabetes and obesity.

26. The use of claim 21 wherein the medicament is suitable for administration to a mammal experiencing an central nervous system disorder selected from the group consisting of epilepsy, and stroke.

27. The use of claim 22 wherein the medicament is suitable for administration to a mammal experiencing an ischemic event in the heart selected from the group consisting of stable angina, unstable angina, cardiac transplant, and myocardial infarction.

28. The use of any one of claims 18 to 22 wherein the mammal is a human.

29. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and one or more pharmaceutical excipients.

30. The pharmaceutical composition of claim 29 wherein the pharmaceutical

composition is in the form of a solution.

31. The pharmaceutical composition of claim 29 wherein the pharmaceutical composition is in the form of a tablet.