PC01089

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 June 2001 (07.06.2001)

PCT

(10) International Publication Number
WO 01/40246 A1

(51) International Patent Classification[7]: C07H 19/16, A61K 31/7076, A61P 9/00, 25/00

(21) International Application Number: PCT/US00/32721

(22) International Filing Date: 1 December 2000 (01.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/454,136 3 December 1999 (03.12.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/454,136 (CON)
Filed on 3 December 1999 (03.12.1999)

(71) Applicant *(for all designated States except US)*: **CV THERAPEUTICS, INC.** [US/US]; 3172 Porter Drive, Palo Alto, CA 94304 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZABLOCKI, Jeff, A.** [US/US]; 580 Sleeper Avenue, Mountain View, CA 94040 (US). **PALLE, Venkata, P.** [IN/US]; 200 E. Dana Street, #F122, Mountain View, CA 94041 (US). **VARKHEDKAR, Vaibhav** [IN/US]; 142 S. Bernado Avenue #2, Sunnyvale, CA 94086 (US). **BELARDINELLI, Luiz** [US/US]; 704 University Drive, Menlo Park, CA 94025 (US).

(74) Agent: **HUGHES, A., Blair**; McDonnell Boehnen Hulbert & Berghoff, 300 South Wacker Drive, Suite 3200, Chicago, IL 60606 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/40246 A1

(54) Title: PARTIAL OR FULL A_1 AGONISTS - N^6 HETEROCYCLIC 5'-THIO SUBSTITUTED ADENOSINE DERIVATIVES

(57) Abstract: N^6 heterocyclic 5' modified adenosine derivatives that are adenosine A_1 receptor partial or full 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.

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. Lerman 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).

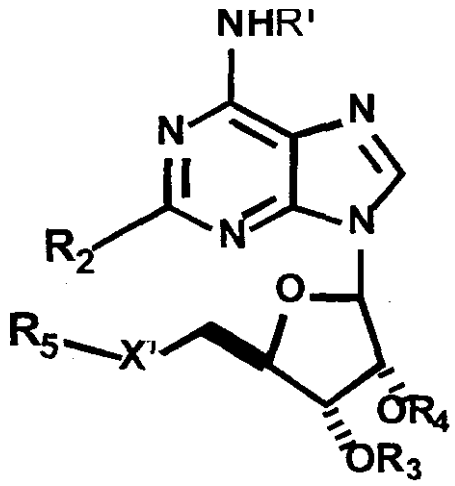
There are a number of full A_1 agonists disclosed in the prior art. However, the agonists disclosed are generally in the forms that are not useful in the mammalian body. Because useful forms of A_1 agonists may not always be stable, soluble or they may have other properties that make their incorporation 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:

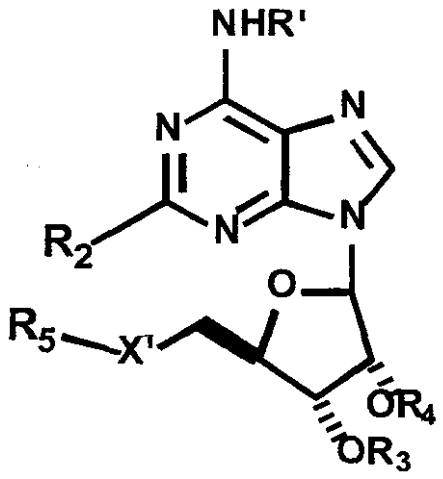


In yet another embodiment, this invention includes methods for administering compositions of this invention to mammals, and especially to humans, to stimulate coronary activity, to modify adipocyte function, to treat central nervous system disorders, and to treat diabetic disorders.

In a further embodiment, this invention is pharmaceutical compositions of matter 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-$(O)_{0-2}$ 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_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} 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}, $SO_2N(R^{20})_2$, 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

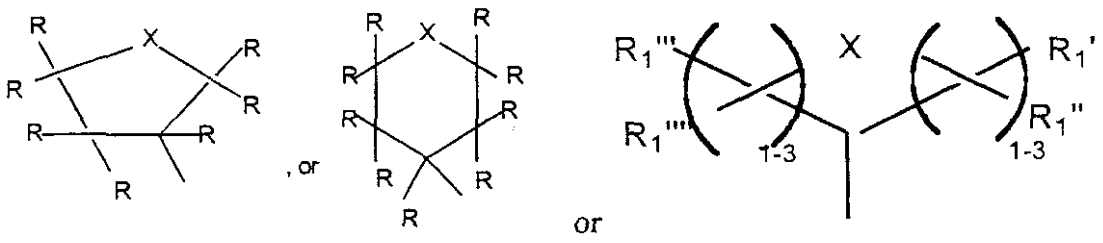
wherein each optional heteroaryl, and aryl substituent is further optionally substituted with halo, alkyl, CF_3, CO_2R^{20}, CN, and OR^{20} ; R_{20} is selected from the group consisting of H, C_{1-6} alkyl; and R_{22} is selected from the group consisting of C_{1-6}. In the above compositions, R_5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

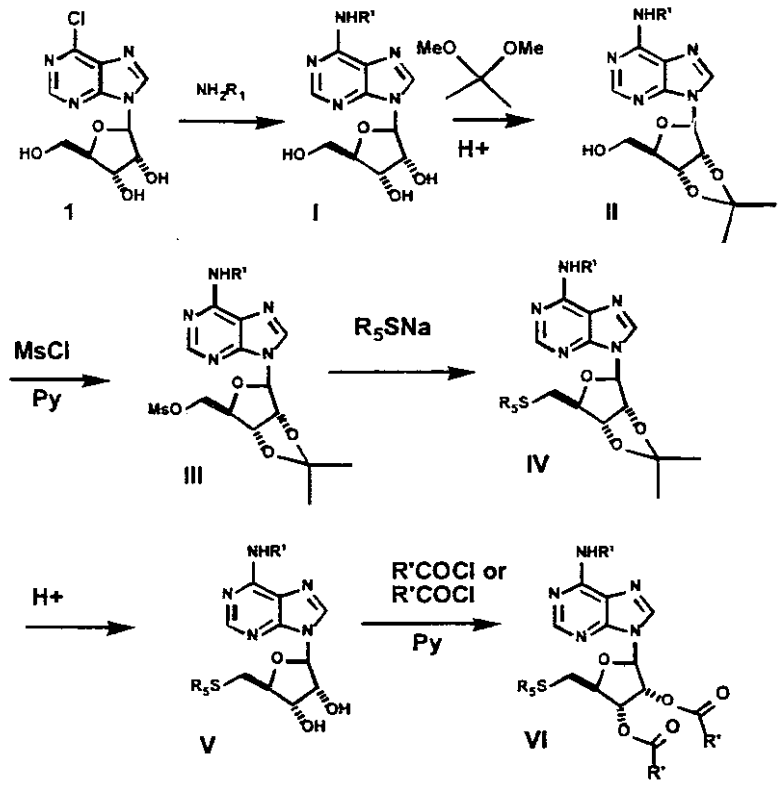
"Alkyl cycloalkyl" denotes the group -R-cycloalkyl where cycloalkyl is a cycloalkyl group and R is a lower alkyl or substituted lower alkyl. Cycloalkyl groups can optionally be unsubstituted or substituted with *e.g.* halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl,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

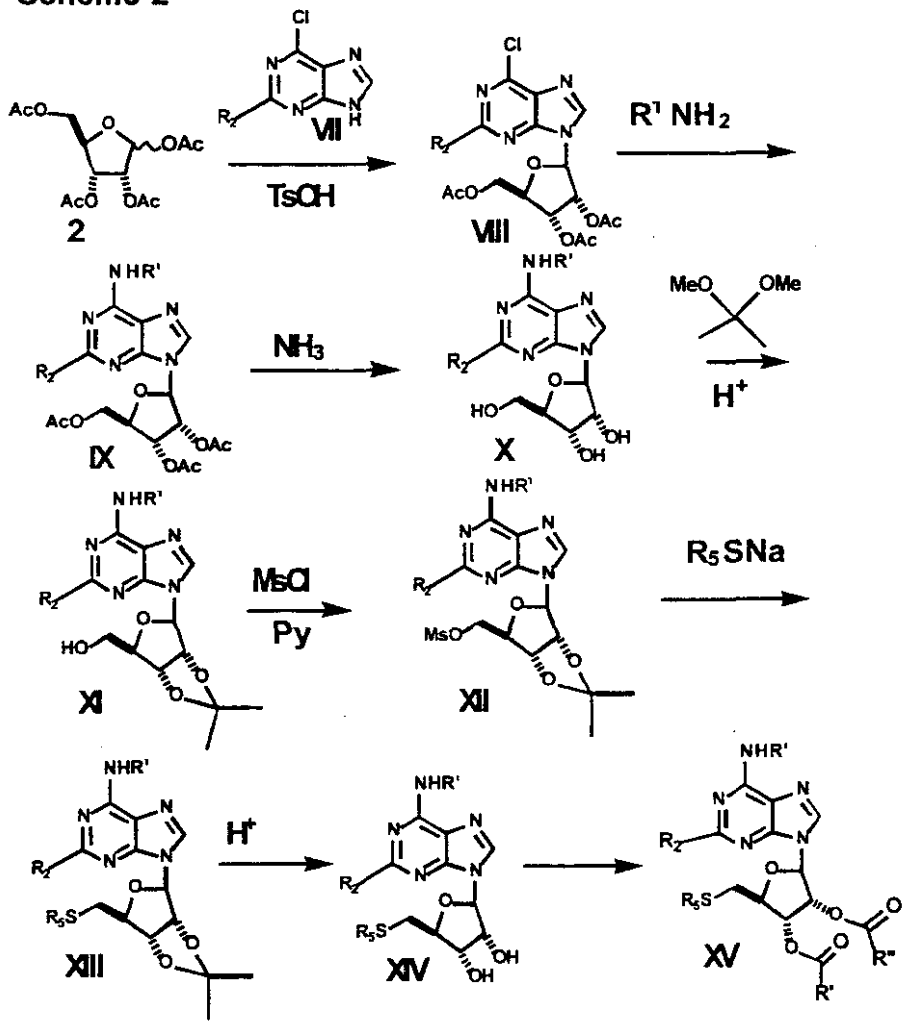
The compounds of this invention can be prepared as outlined in the schemes 1-5 below. A general outline for the preparation of **V** and **VI** is shown in Scheme 1. Compound **I** can be prepared, following the procedures reported earlier (U.S. Patent No. 5,789,416, the specification of which is incorporated 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
NH2R1
NHR'
MeO
OMe
H+
HO
OH
1
I
II
MsCl
Py
MsO
III
R5SNa
R5S
IV
H+
V
R'COCl or
R'COCl
Py
VI
R'

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

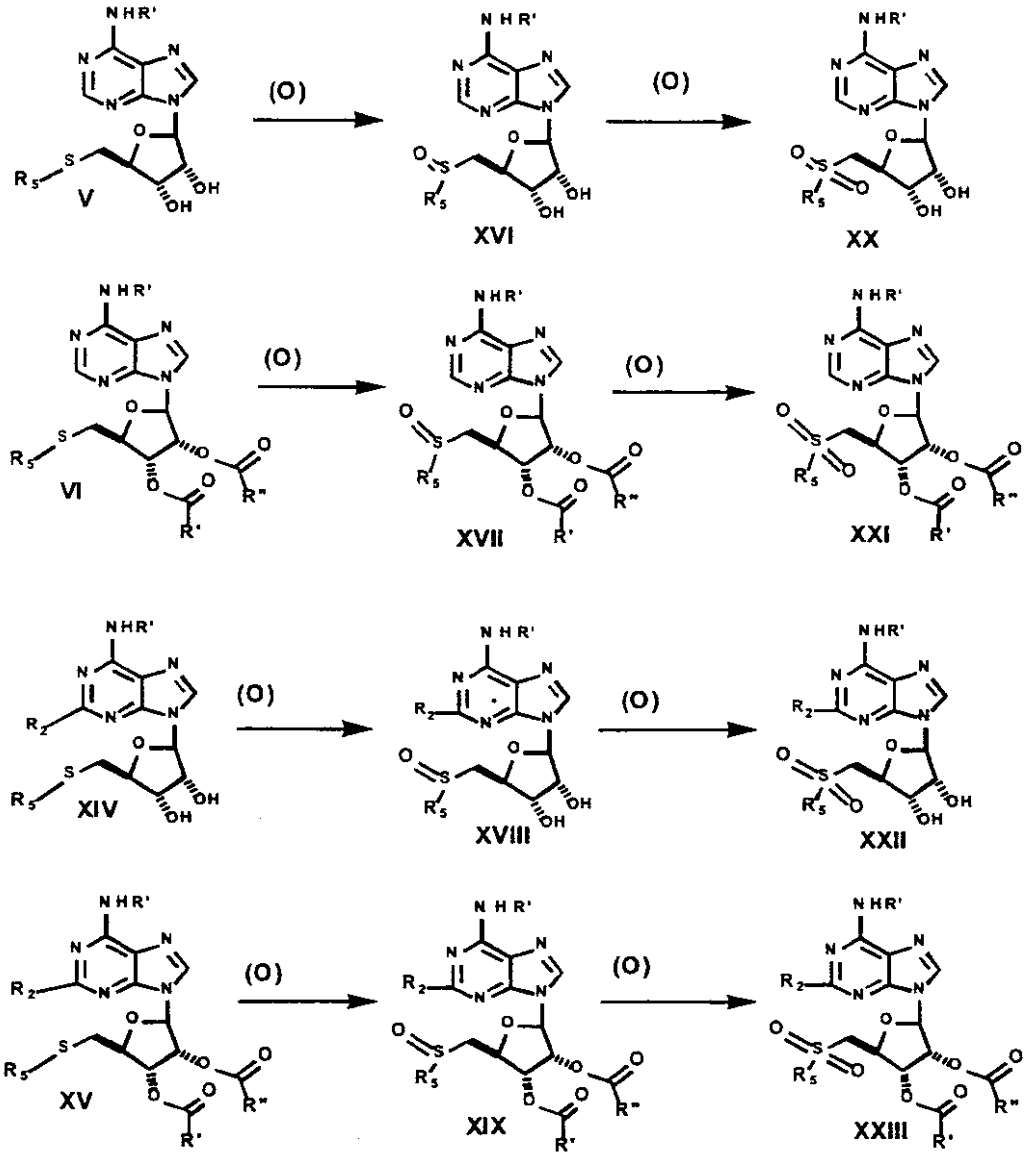


formula **XIII** that can be deprotected to give sulfides with general formula **XIV**. Esterification at the 2', 3' positions can afford the 2', 3' diesters with the general formula **XV**.

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.**

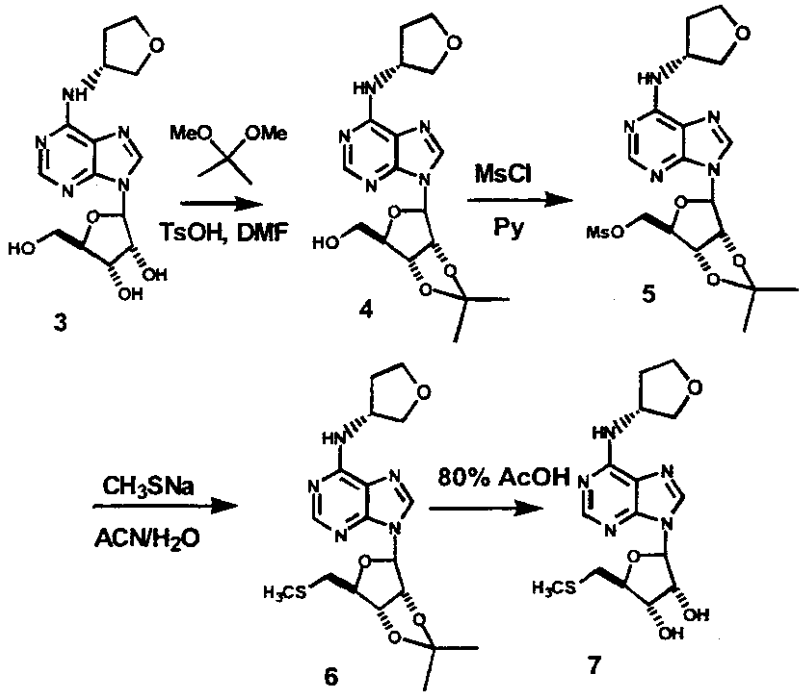
Scheme 3



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

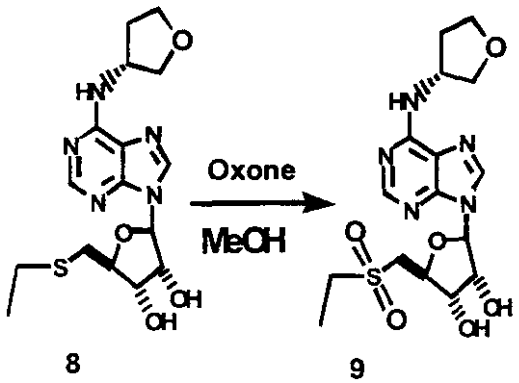
the 2' and 3' hydroxyls with dimethoxypropane in the presence of TsOH(cat.) gave acetonide **4**. Reaction of **4** with MsCl in pyridine at 0 °C gave mesylate **5** which on displacement with sodium methanethiolate in an acetonitrile/water mixture gave sulfide **6**. Deprotection of **6** with 80% acetic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

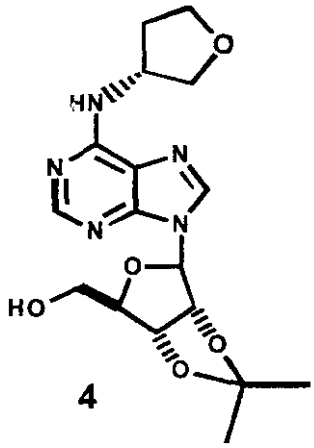
The compositions of this invention may be administered orally, intravenously, through the epidermis, bolus, nasally, by inhalation or by any other means known in the art for administering a therapeutic agents. The method of treatment comprises the administration of an effective quantity of the chosen 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.

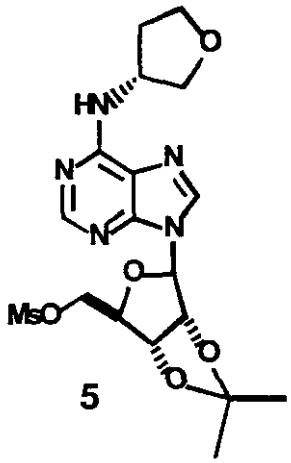
Example 1



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)

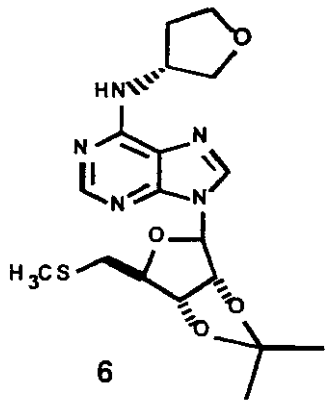
To a solution of compound **3** (2.0 g, 6.0 mmol) and 2,2-dimethoxypropane (1.2 g, 11.8 mmol) in dimethylformamide (20 mL) was added p-toluenesulfonic acid (50 mg, 0.26 mmol) at 70°C. After 48 h at 70°C, the reaction was concentrated in vacuo to afford a solid. The solid was dissolved in methanol (3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



5

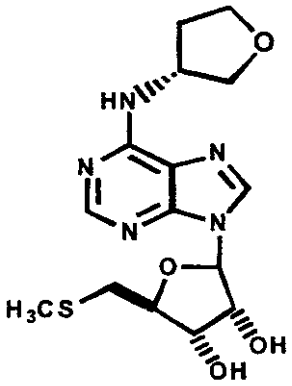
To a solution of **4** (190 mg, 0.5 mmol) in anhydrous pyridine (5mL), was added MsCl (80 microL, 1 mmol) at 0°C. The reaction mixture was stirred at the same temperature for 2h. Pyridine was removed under reduced pressure, residue was taken in dichloromethane (50mL),

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

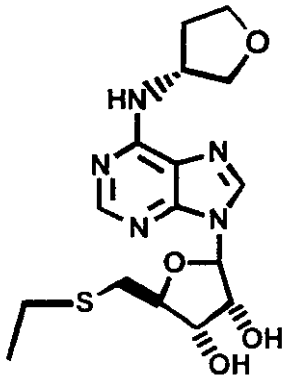
A mixture of mesylate **5** (150 mg) and methanethiolate(150mg) in acetonitrile (2mL) and water (1mL) was heated at 70 C for 24h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC [methanol-dichloromethane (1:19)] to afford product **6**: ^{1}H NMR (CDCl3) 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)

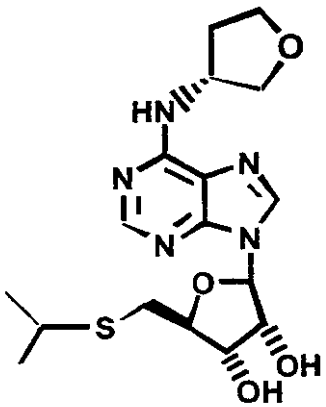
Compound **6** (50mg) was dissolved in a mixture of acetic acid (8 mL) and water (2 mL) and heated at 90°C for 16 h. Solvents were removed under reduced pressure, and the residue was purified by preparative TLC [methanol-dichloromethane (1:9)] to afford compound **7**: 1H NMR ($CDCl_3$) δ 1.90-2.05 (m, 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)

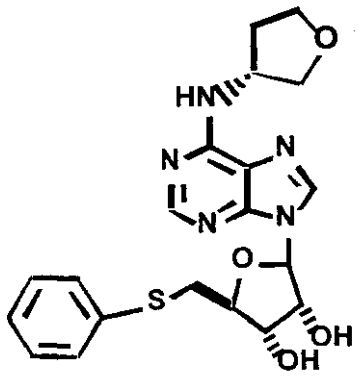
Compound 8 was prepared in the manner similar to that of 7 substituting ethane thiolate for methane thiolate. (M+1) = 382.30



10

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

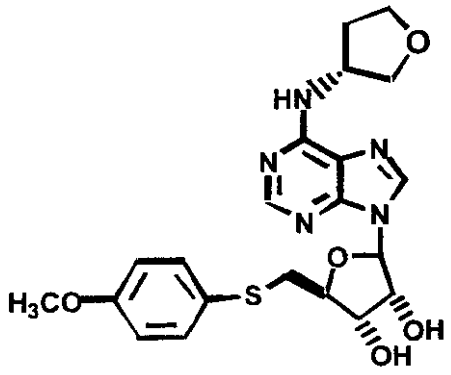
Compound **10** was prepared in the manner similar to that of **7** substituting i-propane thiolate for methane thiolate. ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 6H), 1.90-2.05 (m, 1H), 2.15 (s, 3H), 2.30-2.40 (m, 1H), 2.85-2.87 (d, 2H), 2.95 (septet, 1H), 3.80-3.90 (m, 2H), 3.95-4.05 (m, 2H), 4.35-4.40 (m,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

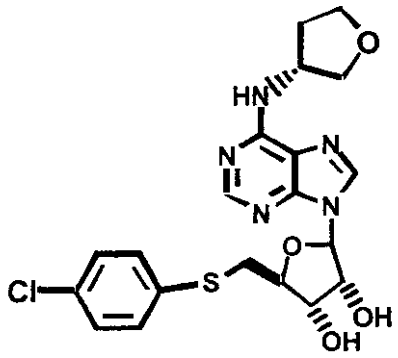
Compound **11** was prepared in the manner similar to that of **7** substituting phenyl thiolate for methane thiolate. ^{1}H NMR ($CDCl_3$) 1.95-2.05 (m, 1H), 2.30-2.40 (m, 1H), 3.2 (d, 2H), 3.80-3.90 (m, 2H), 3.95-4.10 (m, 2H), 4.35-4.40 (d, 1H), 4.45 (t, 1H), 4.50-4.55 (m, 1H), 4.80-4.90 (m, 1H), 5.85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

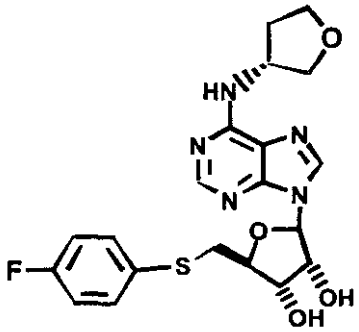
This compound was prepared in the manner similar to that of 7 substituting 4-methoxyphenyl thiolate for methane thiolate. (M+1) = 460.4



13

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

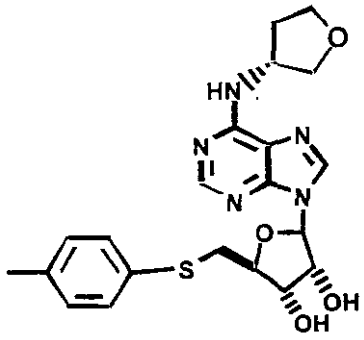
This compound was prepared in a manner similar to that of 7 substituting 4-chlorophenyl thiolate for methane thiolate. (M+1) = 464.3



14

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

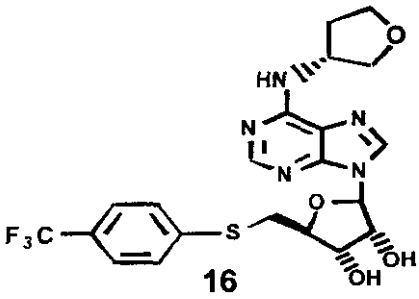
This compound was prepared in a manner similar to that of 7 substituting 4-fluorophenyl thiolate for methane thiolate. (M+1) = 448.3



15

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

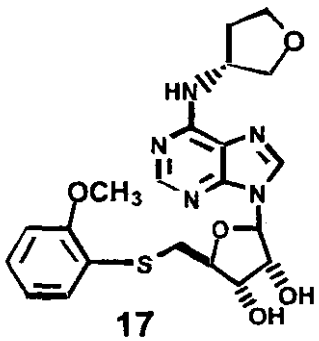
This compound was prepared in a manner similar to that of 7 substituting 4-methylphenyl thiolate for methane thiolate. (M+1) = 444.38



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)

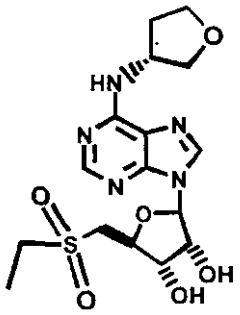
This compound was prepared in a manner similar to that of 7 substituting 4-trifluoromethylphenyl thiolate for methane thiolate. (M+1) = 488.36



17

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

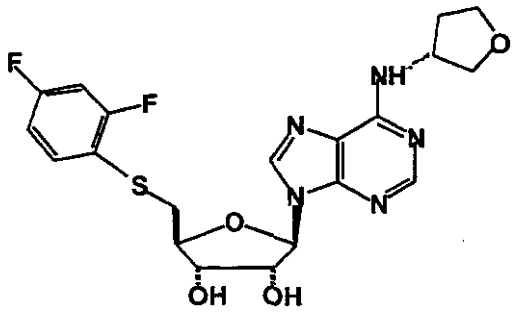
This compound was prepared in a manner similar to that of 7 substituting 2-methoxyphenyl thiolate for methane thiolate. (M+1) = 460.4



9

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

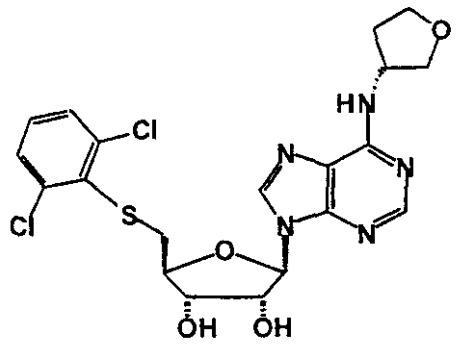
To a cooled solution of sulfide **8** in methanol at 0°C under nitrogen was added 3 eq. of Oxone (Potassium peroxy monosulfate) and the reaction mixture was allowed to stir at the same temperature for 1hour. After the starting material consumed (by TLC), the reaction mixture was concentrated and filtered 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)

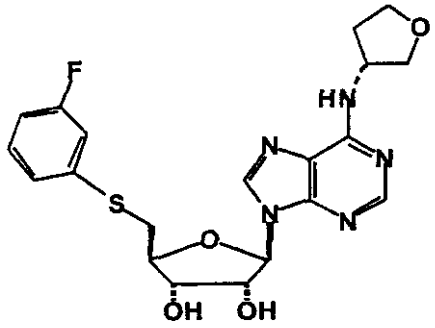
This compound was prepared in a manner similar to that of 7 substituting 2,4-difluorophenyl thiolate for methane thiolate. (M+1) = 466.23



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)

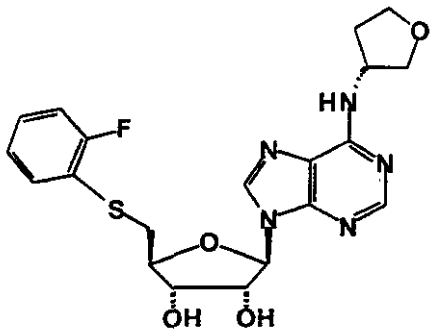
This compound was prepared in a manner similar to that of 7 substituting 2,6-dichlorophenyl thiolate for methane thiolate. (M+1) = 498.18



20

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

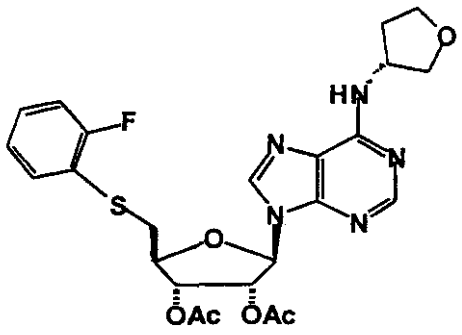
This compound was prepared in a manner similar to that of 7 substituting 3-fluorophenyl thiolate for methane thiolate. (M+1) = 448.26



21

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

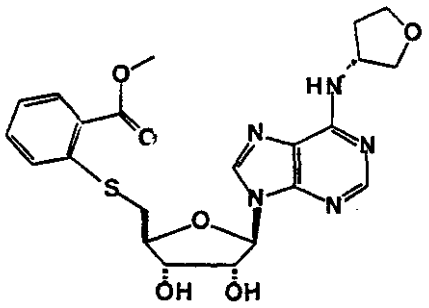
This compound was prepared in a manner similar to that of 7 substituting 2-fluorophenyl thiolate for methane thiolate. (M+1) = 448.24



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)

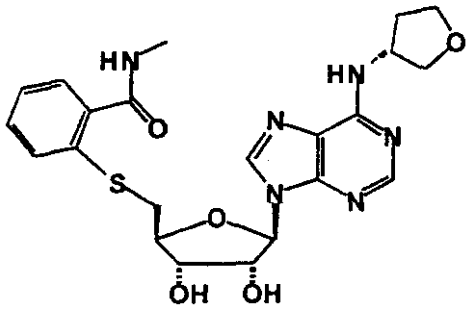
To a solution of compound 21 (139 mg) in pyridine (2 mL) at 23 °C was added acetic anhydride (0.1 mL). After 3 h at 23 °C, the reaction was concentrated *in vacuo* . The residue was dissolved in methylene chloride (50 mL), washed with water (3 x 10 mL), and dried (Na_2SO_4). After concentration *in vacuo*, 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)

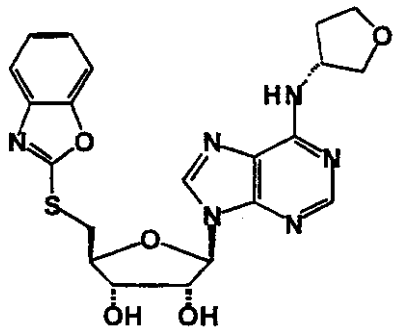
To a solution of Compound 4 (0.377g, 1 mmol) in 5mL of THF, was added Triphenylphosphine (0.524g, 2 mmol), DEAD (0.40 mL, 2 mmoles), let stir for 5 minutes before adding 2-carbomethoxythiophenol (0.5mL). Reaction was allowed to stir under reflux. After 72 h of reflux, the reaction was concentrated in 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)

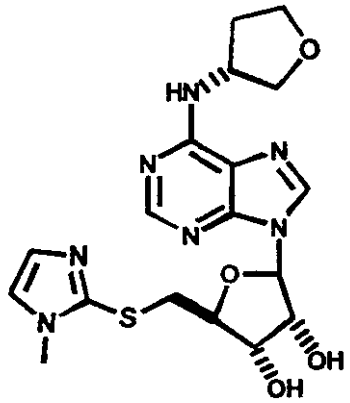
Compound 23 was taken into 40% aq.methylamine (2 mL) and l-propanol (2 mL) and heated at 70 C for 16h. Solvents were removed in vacuo and the residue was purified by prep TLC TLC [methanol-dichloromethane (1:9)] to give compound 24. (M+1) =487.5



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

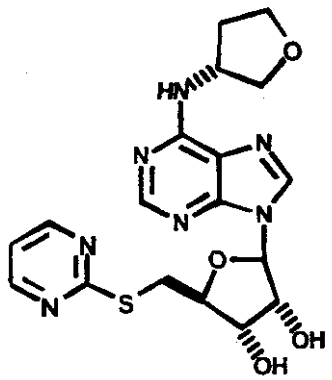


26

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)].

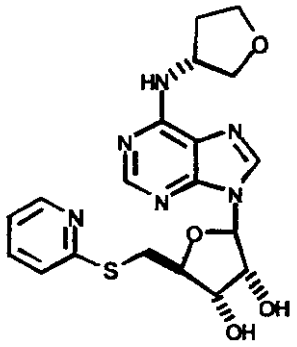
2-{6-[((3S)oxolan-3-yl)amino]purin-9-yl}(4S,5S,2R,3R)-5-(pyrimidine-2-



27

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

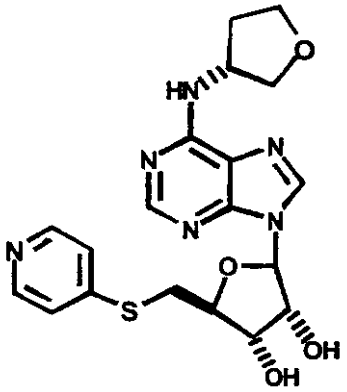
Compound **27** was prepared in the manner of compound **23** substituting 2-mercaptopyrimidine for 2-carbomethoxythiophenol [MS 432.4 (M+1)].



28

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

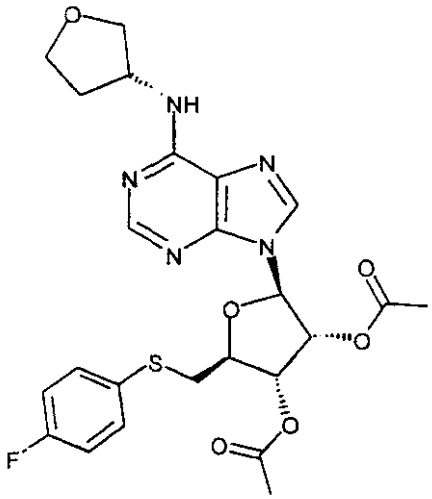
Compound **28** was prepared in the manner of compound **23** substituting 2-mercaptopyridine for 2-carbomethoxythiophenol [MS 431.4 (M+1)].



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

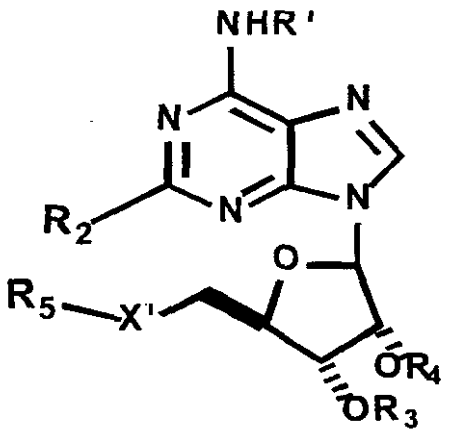
A scintillation proximity assay (SPA) using rabbit antibodies directed at cAMP using an added tracer of adenosine 3',5'-cyclic phosphoric acid 2'-O-succinyl-3-[^{125}I]iodotyrosine methyl ester and fluoromicrospheres containing anti-rabbit specific antibodies as described by Amersham Pharmacia Biotech (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 composition of matter having the formula:



wherein X^1= S, S(O), $S(O)_2$;

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, O, P and S-$(O)_{0-2}$ wherein R_1 does not contain an epoxide group;

R_2 is selected from the group consisting of hydrogen, halo, CF_3, and cyano;

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_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with from 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 wherein each optional heteroaryl, aryl, and heterocyclyl substituent is further 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};

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 each alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with from 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 the optional heteroaryl, aryl, and heterocyclyl substituent are each further 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};

R^{20} is selected from the group consisting of H, 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 from 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, aryl, and heteroaryl; and

R^{22} is 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 from 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.

2. The composition of claim 1 wherein R_2 is selected from the group consisting of hydrogen, and halo;

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_{1-15} alkyl, heterocyclyl, aryl, and heteroaryl, which alkyl, aryl, heterocyclyl, and heteroaryl are each optionally substituted with from 1 to 2 substituents independently selected from the group of halo, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, $S(O)R^{22}$, SO_2R^{22},

$SO_2N(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$ and wherein each optional heteroaryl, aryl, and heterocyclyl substituent is further optionally substituted with halo, NO_2, alkyl, CF_3, amino, mono- or di- alkylamino, CN, or OR^{20};

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 from 1 to 3 substituents independently selected from the group of halo, alkyl, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, $S(O)_3R^{20}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, and wherein each optional heteroaryl, and aryl substituent is optionally substituted with halo, alkyl, CF_3, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, or OR^{20};

R^{20} is selected from the group consisting of H, C_{1-15} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are each optionally substituted with from 1 to 2 substituents independently 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_{1-15} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are each optionally substituted with from 1 to 2 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or CN, O-C_{1-6} alkyl, and CF_3.

3. The composition of claim 1 wherein 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_{1-10} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with from 1 to 2 substituents independently selected from the group of halo, NO_2, aryl, heteroaryl, CF_3, CN, OR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $NR^{20}COR^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}SO_2R^{22}$, and wherein each optional heteroaryl, aryl, and heterocyclyl substituent is further optionally substituted with halo, NO_2, alkyl, CF_3;

R_5 is selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, heterocyclyl, aryl, and heteroaryl, wherein each alkyl, alkenyl, aryl, heterocyclyl, 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}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, COR^{20}, 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}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and 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 independently selected from halo, alkyl, mono- or dialkylamino, alkyl or CN, O-C_{1-6} alkyl, and CF_3.

4. The composition of claim 1 wherein 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 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}, $N(R^{20})_2$, and wherein each optional aryl substituent is optionally substituted with halo, NO_2, alkyl, CF_3;

R_5 is selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, aryl, and heteroaryl, wherein alkyl, alkenyl, 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.

5. The composition of claim 1 wherein 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 which alkyl are optionally substituted with 1 substituent selected from the group 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 selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and aryl wherein alkyl, alkenyl, 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}.

6. The composition of claim 1 wherein 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;

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}.

7. The composition of claim 1 wherein X^1=S or SO_2;

R_2 is a hydrogen;

R_3 and R_4 are 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, CF_3, CN, OR^{20}, CO_2R^{20}; and

R^{20} is selected from the group consisting of H, C_{1-6} alkyl.

8. The composition of claim 1 wherein X^1=S or SO_2;

R_2 is a hydrogen;

R_3 and R_4 are 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, CF_3, OR^{20}; and

R^{20} is selected from the group consisting of H, C_{1-6} alkyl.

9. The composition of claim 1 wherein 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}.

10. The composition of claim 1 wherein 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;

R_5 is 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};

R^{20} is selected from the group consisting of H, C_{1-3} alkyl; and

R^{22} is selected from the group consisting of C_{1-6}.

11. The composition of claim 1 wherein =S or SO_2;

R_2 is a hydrogen;

R_3 and R_4 are hydrogen;

R_5 is 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^{20} is selected from the group consisting of H, and methyl.

12. The composition of claim 11 wherein R_5 is C_{1-6} alkyl.

13. The composition of claim 11 wherein R_5 is selected from the group consisting of methyl and ethyl and isopropyl.

14. The composition of claim 1 wherein 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}, $N(R^{20})_2$, 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.

15. The composition of claim 1 wherein X^1=S;

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;

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, CF_3, CN, OR^{20}, SR^{20}, CO_2R^{20}, $CON(R^{20})_2$; and

R^{20} is selected from the group consisting of H, C_{1-3} alkyl.

16. The composition of claim 1 wherein X^1=S;

R_2 is a hydrogen;

R_3 and R_4 are hydrogen;

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}, $CON(R^{20})_2$;

R^{20} is selected from the group consisting of H, and methyl; and

R^{22} is selected from the group consisting of C_{1-6} alkyl.

17. The composition of claim 16 wherein R_5 is phenyl that is optionally substituted with a substituent selected from the group consisting of methoxy, chloro, fluoro, methyl, and trifluoromethyl.

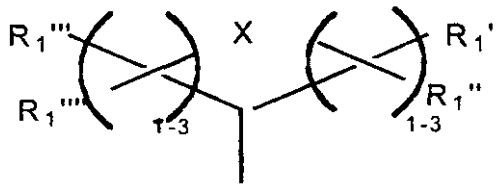
18. The composition of claim 1 wherein R^1 is mono or polysubstituted with one or more compounds selected from the group consisting of halogen, oxo, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, cyano and mixtures thereof.

19. The composition of matter of claim 1 wherein 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 0 or S-

$(O)_{0-2}$.

20. The composition of claim 19 wherein R^1 is 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.

21. The composition of claim 1 wherein R^1 is:



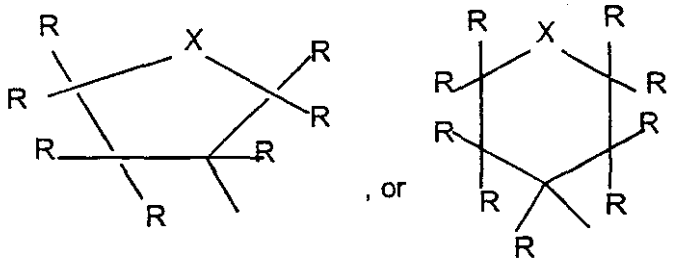
wherein R_1`, R_1``, R_1```, and R_1````` are each independently selected from the group halogen, hydroxyl, lower alkyl, substituted lower alkyl, alkoxy, aryl, acyl, aryloxy, carboxyl, substituted aryl, heterocycle, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, nitro, cyano and mixtures thereof and X is O, or S $(-O)_{0-2}$.

22. The composition of claim 21 wherein R_1``` and R_1````` can together be a single oxygen atom.

23. The composition of claim 21 wherein R_1`, R_1``, R_1```, and R_1````` are each individually selected from the group H, lower alkyl, substitute lower alkyl, alkoxy, aryl, and substituted aryl.

24. The composition of claim 21 wherein R_1`, R_1``, R_1```, and R_1````` are each individually selected from the group H, lower alkyl, and substitute lower alkyl.

25. The composition of claim 1 wherein R^1 is selected from the group consisting of:



wherein each R may be independently selected from the group consisting of H, lower alkyl, and substituted lower alkyl and wherein X is O, or S $(-O)_{0-2}$.

26. The composition of claims 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 wherein R_1 is selected from the group consisting of 3-tetrahydrofuranyl, 3-tetrahydrothiofuranyl, 4-pyranyl, and 4 thiopyranyl.

27. The composition of claims 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 wherein R_1 is 3-tetrahydrofuranyl.

28. The composition of claim 1 wherein the compound is selected from the group of compounds consisting of 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.

29. A method for modifying cardiac activity in a mammal experiencing a heart electrical disorder that can be treated by stimulating an A_1 adenosine receptor comprising the administration of a therapeutically effective amount of the composition of claim 1 to the mammal.

30. A method for modifying mammalian adipocyte function by stimulating an A_1 adenosine receptor comprising administering a therapeutically effective amount of the composition of claim 1 to the mammal.

31. A method to restore sensitivity and efficacy of insulin in a mammal by stimulating an A_1 adenosine receptor comprising the administration of a therapeutically effective amount of a composition of claim 1 to the mammal.

32. A method for providing a mammal with central nervous system neuroprotection by stimulating an A_1 adenosine receptor comprising administering a therapeutically effective amount of the composition of claim 1 to the mammal.

33. A method for providing a mammal with cardiomyocyte protection from ischemia by stimulating an A_1 adenosine receptor comprising administering a therapeutically effective amount of the composition of claim 1 to the mammal.

34. The method of claim 29 or 30 or 31 or 32 or 33 wherein the therapeutically effective amount ranges from about 0.01 to about 100 mg/kg weight of the mammal.

35. The method of claim 29 wherein the composition is administered to the mammal experiencing a heart electrical disorder selected from the group consisting of supraventricular tachycardias, atrial fibrillation, atrial flutter, and AV nodal re-entrant tachycardia.

36. The method of claim 30 or 31 wherein the composition is administered to a mammal experiencing a disorder selected from the group consisting of diabetes and obesity.

37. The method of claim 32 wherein the composition is administered to a mammal experiencing an central nervous system disorder selected from the group consisting of epilepsy, and stroke.

38. The method of claim 33 wherein the composition is administered 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.

39. The method of claim 29 or 30 or 31 or 32 or 33 wherein the mammal is a human.

40. A pharmaceutical composition of matter comprising the composition of claim 1 and one or more pharmaceutical excipients.

41. The pharmaceutical composition of matter of claim 40 wherein the pharmaceutical composition is in the form of a solution.

42. The pharmaceutical composition of matter of claim 40 wherein the pharmaceutical composition is in the form of a tablet.

INTERNATIONAL SEARCH REPORT

.national Application No
PCT/US 00/32721

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/16 A61K31/7076 A61P9/00 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 589 467 A (LAU JESPER ET AL) 31 December 1996 (1996-12-31) claims example 21 ---	1,2,29, 40
A	US 5 789 416 A (LUM ROBERT T ET AL) 4 August 1998 (1998-08-04) the whole document ---	1,29,40
A	US 4 373 097 A (STRAMENTINOLI GIORGIO ET AL) 8 February 1983 (1983-02-08) abstract ---	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	*Date of mailing of the international search report*
27 March 2001	05/04/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	de Nooy, A

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

.national Application No
PCT/US 00/32721

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	S. SNOWDY ET AL.: "A comparison of an A1 adenosine receptor agonist (CVT-510) with diltiazem for slowing of AV nodal conduction in guinea-pig" BRITISH JOURNAL OF PHARMACOLOGY, vol. 126, 1999, pages 137-146, XP000992136 abstract figure 1 ----	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

/national Application No
PCT/US 00/32721

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[19]中华人民共和国国家知识产权局

[51]Int. Cl[7]
C07H 19/16
A61K 31/7076 A61P 9/00
A61P 25/00

[12]发明专利申请公开说明书

[21]申请号 00813933.4

[43]公开日 2002年11月6日

[11]公开号 CN 1378550A

[22]申请日 2000.12.1 [21]申请号 00813933.4
[30]优先权
[32]1999.12.3 [33]US [31]09/454,136
[86]国际申请 PCT/US00/32721 2000.12.1
[87]国际公布 WO01/40246 英 2001.6.7
[85]进入国家阶段日期 2002.4.5
[71]申请人 CV治疗公司
地址 美国加里福尼亚州
[72]发明人 杰弗里·A·扎布沃茨基
文卡塔·P·帕勒
维布哈夫·瓦尔科赫德卡尔
路易斯·贝拉尔迪内利
卜拉布罕·N·易卜拉欣

[74]专利代理机构 隆天国际专利商标代理有限公司
代理人 楼仙英

权利要求书14页 说明书44页 附图0页

[54]发明名称 部分或完全A_1激动剂－N^6杂环5′硫代腺苷衍生物

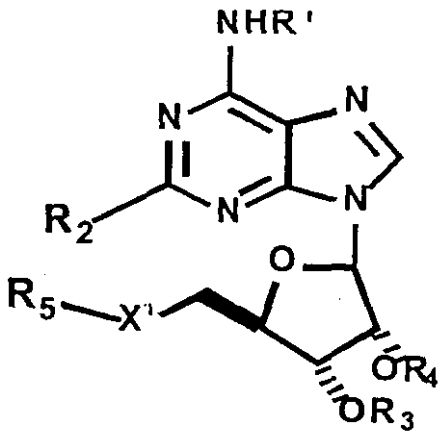
[57]摘要

N^6杂环5′改性腺苷衍生物，是腺苷A_1受体部分或完全激动剂，并且本身可用于改善哺乳动物尤其是人类的心脏活动，改善脂肪细胞功能，治疗中枢神经系统疾病，以及治疗糖尿病和肥胖症。

ISSN1008-4274

权 利 要 求 书

1. 一种具有如下结构式的物质成分：



其中 X^1=S、S(O)、$S(O_2)$；

其中 R^1 是含有 3 至 15 个碳原子的单环或多环杂环基，其中至少一个碳原子被选自 N、O、P 和 $S-(O)_{0-2}$ 的原子或分子取代，其中 R^1 不含有环氧基；

R_2 选自氢、卤素、CF3 和氰基；

R_3 和 R_4 每个独自选自氢、-(CO)-R'和-(CO)-R''，其中 R'和 R''每个独自选自 C_{1-15} 烷基、C_{2-15} 烯基、C_{2-15} 炔基、杂环基、芳基和杂芳基，这类烷基、烯基、炔基、芳基、杂环基和杂芳基以 1 至 3 个独自选自卤素、NO_2、杂环基、芳基、杂芳基、CF_3、CN、OR^{20}、SR^{20}、$S(O)R^{22}$、SO_2R^{22}、$SO_2N(R^{20})_2$、$SO_2NR^{20}COR^{22}$、$SO_2NR^{20}CO_2R^{22}$、$SO_2NR^{20}CON(R^{20})_2$、$N(R^{20})_2$、$NR^{20}COR^{22}$、$NR^{20}CO_2R^{22}$、$NR^{20}CON(R^{20})_2$、$NR^{20}C(NR^{20})NHR^{23}$、$COR^{20}$、$CO_2R^{20}$、$CON(R^{20})_2$、$CONR^{20}SO_2R^{22}$、$NR^{20}SO_2R^{22}$、$SO_2NR^{20}CO_2R^{22}$、$OCONR^{20}SO_2R^{22}$、$OC(O)R^{20}$、$C(O)OCH_2OC(O)R^{20}$ 和 $OCON(R^{20})_2$ 的取代基任选地取代，并且每个任选的杂芳基、芳基和杂环基

的取代基由卤素、NO_2、烷基、CF_3、氨基、单-或二-烷基氨基、烷基或芳基或杂芳基酰胺、$NR^{20}COR^{22}$、$NR^{20}SO_2R^{22}$、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 或 OR^{20} 进一步任选地取代；

R_5 选自 C_{1-15} 烷基、C_{2-15} 烯基、C_{2-15} 炔基、杂环基、芳基和杂芳基，这类烷基、烯基、炔基、芳基、杂环基和杂芳基以 1 至 3 个独自选自卤素、烷基、NO_2、杂环基、芳基、杂芳基、CF_3、CN、OR^{20}、SR^{20}、$S(O)_3R^{20}$、$S(O)R^{22}$、SO_2R^{22}、$SO_2N(R^{20})_2$、$SO_2NR^{20}COR^{22}$、$SO_2NR^{20}CO_2R^{22}$、$SO_2NR^{20}CON(R^{20})_2$、$P(O)(OR^{20})_2$、$N(R^{20})_2$、$NR^{20}COR^{22}$、$NR^{20}CO_2R^{22}$、$NR^{20}CON(R^{20})_2$、$NR^{20}C(NR^{20})NHR^{23}$、$COR^{20}$、$CO_2R^{20}$、$CON(R^{20})_2$、$CONR^{20}SO_2R^{22}$、$NR^{20}SO_2R^{22}$、$SO_2NR^{20}CO_2R^{22}$、$OCONR^{20}SO_2R^{22}$、$OC(O)R^{20}$、$C(O)OCH_2OC(O)R^{20}$ 和 $OCON(R^{20})_2$ 的取代基任选地取代，并且其中该任选的杂芳基、芳基和杂环基的取代基由卤素、NO_2、烷基、CF_3、氨基、单-或二-烷基氨基、烷基或芳基或杂芳基酰胺、$NR^{20}COR^{22}$、$NR^{20}SO_2R^{22}$、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 或 OR^{20} 进一步任选地取代；

R^{20} 选自 H、C_{1-15} 烷基、C_{2-15} 烯基、C_{2-15} 炔基、杂环基、芳基和杂芳基，这类烷基、烯基、炔基、杂环基、芳基和杂芳基由 1 至 3 个独自选自卤素、烷基、单-或二烷基氨基、烷基或芳基或杂芳基酰胺、CN、O-C_{1-6} 烷基、CF_3、芳基和杂芳基的取代任选地基取代；和

R^{22} 选自 C_{1-15} 烷基、C_{2-15} 烯基、C_{2-15} 炔基、杂环基、芳基和杂芳基，这类烷基、烯基、炔基、杂环基、芳基和杂芳基由 1 至 3 个独自选自卤素、烷基、单-或二烷基氨基、烷基或芳基或杂芳基酰胺、CN、O-C_{1-6} 烷基、CF_3 和杂芳基的取代基任选地取代。

2. 如权利要求 1 所述的成分，其中 R_2 选自氢和卤素；

R_3 和 R_4 各自独立地选自氢、-(CO)-R' 和-(CO)-R''，其中 R' 和 R'' 各

自独立地选自 C_{1-15} 烷基、杂环基、芳基和杂芳基，这类烷基、芳基、杂环基和杂芳基每个可任选地被 1 至 2 个独立地选自卤素、NO_2、杂环基、芳基、杂芳基、CF_3、CN、OR^{20}、$S(O)R^{22}$、SO_2R^{22}、$SO_2N(R^{20})_2$、$N(R^{20})_2NR^{20}COR^{22}$、$NR^{20}CO_2R^{22}$、$NR^{20}CON(R^{20})_2$、$NR^{20}C(NR^{20})NHR^{23}$、$COR^{20}$、$CO_2R^{20}$、$CON(R^{20})_2$、$CONR^{20}SO_2R^{22}$、$NR^{20}SO_2R^{22}$ 的取代基任选地取代，并且其中每个任选的杂芳基、芳基和杂环基取代基可进一步任选地被卤素、NO_2、烷基、CF_3、氨基、单-或二-烷基氨基、CN 或 OR^{20} 取代；

R_5 选自 C_{1-15} 烷基、C_{2-15} 烯基、C_{2-15} 炔基、杂环基、芳基和杂芳基，这类烷基、烯基、炔基、芳基、杂环基和杂芳基可任选地被 1 至 3 个独立地选自卤素、烷基、杂环基、芳基、杂芳基、CF_3、CN、OR^{20}、SR^{20}、$N(R^{20})_2$、$S(O)R^{22}$、$S(O)_3R^{20}$、SO_2R^{22}、$SO_2N(R^{20})_2$、$NR^{20}CO_2R^{22}$、$NR^{20}CON(R^{20})_2$、COR^{20}、CO_2R^{20}、$CON(R^{20})_2$ 的取代基取代，并且每个任选的杂芳基和芳基取代基可任选地被卤素、烷基、CF_3、CO_2R^{20}、$CON(R^{20})_2$、$NR^{20}CON(R^{20})_2$、SR^{20}、$S(O)R^{22}$、SO_2R^{22}、$SO_2N(R^{20})_2$、CN 或 OR^{20} 取代；

R^{20} 选自 H、C_{1-15} 烷基、芳基和杂芳基，这类烷基、芳基和杂芳基每个任选地被 1 至 2 个独立地选自卤素、烷基、单-或二烷基氨基、CN、$O-C_{1-6}$ 烷基、CF_3 的取代基取代；和

R^{22} 选自 C_{1-15} 烷基、芳基和杂芳基，这类烷基、芳基和杂芳基每个任选地被 1 至 2 个独立地选自卤素、烷基、单-或二烷基氨基、烷基或 CN、$O-C_{1-6}$ 烷基和 CF_3 的取代基取代。

3. 如权利要求 1 所述的成分，其中 R_2 是氢；

R_3 和 R_4 各自独立地选自氢、-(CO)-R'和-(CO)-R''，其中 R'和 R''各自独立地选自 C_{1-10} 烷基、芳基和杂芳基，这类烷基、芳基和杂芳基各自可任选地被 1 至 2 个独立地选自卤素、NO_2、芳基、杂芳基、CF_3、CN、OR^{20}、$N(R^{20})_2$、$S(O)R^{22}$、SO_2R^{22}、$NR^{20}COR^{22}$、COR^{20}、CO_2R^{20}、$CON(R^{20})_2$、$NR^{20}SO_2R^{22}$

的取代基取代，并且其中每个任选的杂芳基、芳基和杂环基取代基可进一步任选地被卤素、NO_2、烷基、CF_3取代；

R_5选自 C_{1-15}烷基、C_{2-15}烯基、杂环基、芳基和杂芳基，这类烷基、烯基、芳基、杂环基和杂芳基可任选地被 1 至 3 个独立地选自卤素、烷基、芳基、杂芳基、CF_3、CN、OR^{20}、SR^{20}、$N(R^{20})_2$、$S(O)R^{22}$、SO_2R^{22}、$SO_2N(R^{20})_2$、$NR^{20}CO_2R^{22}$、$NR^{20}CON(R^{20})_2$、COR^{20}、CO_2R^{20}、$CON(R^{20})_2$的取代基取代，并且其中每个任选的杂芳基和芳基取代基可任选被卤素、烷基、CF_3、CO_2R^{20}、$CON(R^{20})_2$、$NR^{20}CON(R^{20})_2$、$S(O)R^{22}$、SO_2R^{22}、$SO_2N(R^{20})_2$、CN 或 OR^{20}进一步取代；

R^{20}选自 H、C_{1-6}烷基和芳基，这类烷基和芳基可任选地被 1 个选自卤素、烷基、单-或二烷基氨基、CN、O-C_{1-6}烷基、CF_3的取代基取代；和

R^{22}选自 C_{1-6}烷基和芳基，这类烷基和芳基可任选地被 1 个独立地选自卤素、烷基、单-或二烷基氨基、烷基或 CN、O-C_{1-6}烷基和 CF_3的取代基取代。

4. 如权利要求 1 所述的成分，其中 R_2是氢；

R_3和 R_4各自独立地选自氢、-(CO)-R'和-(CO)-R''，其中 R'和 R''各自独立地选自 C_{1-6}烷基和芳基，这类烷基和芳基由 1 至 2 个独立地选自卤素、NO_2、芳基、CF_3、CN、OR^{20}、$N(R^{20})_2$、$S(O)R^{22}$、SO_2R^{22}、$N(R^{20})_2$的取代基任选地取代，并且其中每个任选的芳基取代基可被卤素、NO_2、烷基、CF_3任选地取代；

R_5选自 C_{1-15}烷基、C_{2-15}烯基、芳基和杂芳基，这类烷基、烯基、芳基和杂芳基可任选地被 1 至 3 个独立地选自卤素、烷基、芳基、杂芳基、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}、$CON(R^{20})_2$的取代基任选地取代，并且每个任选的杂芳基和芳基取代基可任选地被卤素、烷基、CF_3、CO_2R^{20}、$CON(R^{20})_2$、$S(O)R^{22}$、SO_2R^{22}、

$SO_2N(R^{20})_2$、CN 或 OR^{20} 进一步取代；

R^{20} 选自 H、C_{1-6} 烷基和芳基，这类烷基和芳基可任选地被 1 个选自卤素、烷基、单-或二烷基氨基、CN、O-C_{1-6} 烷基、CF_3 的取代基取代；和

R^{22} 选自 C_{1-6} 烷基和芳基，这类烷基和芳基可任选地被 1 个选自卤素、烷基或 CN、O-C_{1-6} 烷基和 CF_3 的取代基取代。

5. 如权利要求 1 所述的成分，其中 R_2 是氢；

R_3 和 R_4 各自独立地选自氢、-(CO)-R'和-(CO)-R''，其中 R'和 R''各自独立地选自 C_{1-6} 烷基，这类烷基由 1 个选自芳基、CF_3、CN、OR^{20}、$N(R^{20})_2$ 的取代基任选地取代。并且其中每个任选的芳基取代基可进一步任选地被卤素、NO_2、烷基、CF_3 取代；

R_5 选自 C_{1-8} 烷基、C_{2-8} 烯基和芳基，这类烷基、烯基和芳基可任选地被 1 至 2 个独立地选自卤素、烷基、芳基、杂芳基、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}、$CON(R^{20})_2$ 的取代基取代，并且其中每个任选的杂芳基和芳基取代基可任选地被卤素、烷基、CF_3、CO_2R^{20}、CN 或 OR^{20} 进一步取代；

R^{20} 选自 H、C_{1-6} 烷基；和

R^{22} 选自 C_{1-6} 基团。

6. 如权利要求 1 所述的成分，其中 X'=S 或 SO_2；

R_2 是氢；

R_3 和 R_4 各自独立地选自氢、-(CO)-R'和-(CO)-R''，其中 R'和 R''每个独立地选自 C_{1-6} 烷基；

R_5 选自 C_{1-8} 烷基和芳基，其中烷基和芳基可任选地被 1 至 2 个独立地选自卤素、烷基、芳基、杂芳基、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}、$CON(R^{20})_2$ 的取代基取代，并且其中每个任选的杂芳基和芳基取代基可任选地被卤素、烷基、CF_3、CO_2R^{20}、CN 和 OR^{20} 进一步取

代；

R_{20}选自 H、C_{1-6}烷基；和

R_{22}选自 C_{1-6}基团。

7. 如权利要求 1 所述的成分，其中 X^1=S 或 SO_2；

R_2是氢；

R_3和 R_4是氢；

R_5选自 C_{1-8}烷基和芳基，其中烷基和芳基可任选地被 1 至 2 个独立地选自卤素、烷基、CF_3、CN、OR^{20}、CO_2R^{20}的取代基取代；和

R^{20}选自 H、C_{1-6}烷基。

8. 如权利要求 1 所述的成分，其中 X^1=S 或 SO_2；

R_2是氢；

R_3和 R_4是氢；

R_5选自 C_{1-8}烷基和芳基，其中烷基和芳基可任选地被 1 至 2 个独立地选自卤素、烷基、CF_3、OR^{20}的取代基取代；和

R^{20}选自 H、C_{1-6}烷基。

9. 如权利要求 1 所述的成分，其中 X^1=S 或 SO_2；

R_2是氢；

R_3和 R_4各自独立地选自氢原子，-(CO)-R'和-(CO)-R''，其中 R'和 R''各自独立地选自 C_{1-6}烷基，这类烷基可由 1 个选自芳基、CF_3、CN、OR^{20}、$N(R^{20})_2$的取代基任选地取代，并且其中每个任选的芳基取代基可进一步由卤素、NO_2、烷基、CF_3任选地取代；

R_5为 C_{1-8}烷基，其中烷基由 1 至 2 个独立地选自卤素、烷基、芳基、杂芳基、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}、$CON(R^{20})_2$的取代基任选地取代，其中每个任选的杂芳基和芳基取代基可由卤素、烷基、CF_3、CO_2R^{20}、CN 和 OR^{20}进一步任选地取代；

R^{20}选自 H、C_{1-6}烷基；

R^{22}选自 C_{1-6}基团。

10. 如权利要求 1 所述的成分，其中 X^1=S 或 SO_2；

R_2是氢；

R_3和 R_4各自独立地选自氢、-(CO)-R'和-(CO)-R''，其中 R'和 R''各自独立地选自 C_{1-6}烷基；

R_5选自 C_{1-8}烷基，它由 1 至 2 个独立地选自芳基、杂芳基、OR^{20}、$S(O)R^{22}$、CO_2R^{20}、$CON(R^{20})_2$的取代基任选地取代，并且其中每个任选的杂芳基和芳基取代基可由卤素、烷基、CF_3、CO_2R^{20}、CN 和 OR^{20}进一步任选地取代；

R^{20}选自 H、C_{1-3}烷基；和

R^{22}选自 C_{1-6}基团。

11. 如权利要求 1 所述的成分，其中 X^1=S 或 SO_2；

R_2是氢；

R_3和 R_4是氢；

R_5是 C_{1-8}烷基，它可任选地由 1 至 2 个独立地选自 CO_2R^{20}和 $CON(R^{20})_2$的取代基取代；

R^{20}选自 H 和甲基；

12. 如权利要求 11 所述的成分，其中 R_5是 C_{1-6}烷基。

13. 如权利要求 11 所述的成分，其中 R_5选自甲基和乙基和异丙基。

14. 如权利要求 1 所述的成分，其中 R_2是氢；

R_3和 R_4各自独立地选自氢，-(CO)-R'和-(CO)-R''，其中每个 R'和 R''独立地选自 C_{1-6}烷基和芳基，这类烷基和芳基可由 1 至 2 个独立地选自卤素、NO_2、芳基、CF_3、CN、OR^{20}、$N(R^{20})_2$、$S(O)R^{22}$、SO_2R^{22}、$N(R^{20})_2$的取代基任选地取代，并且其中每个任选的芳基的取代基可进一步由卤素、NO_2、烷基、CF_3任选地取代；

R_5选自芳基和杂芳基，其中芳基和杂芳基由1至3个独立地选自卤素、烷基、芳基、杂芳基、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}、$CON(R^{20})_2$的取代基任选地取代，并且其中每个任选的杂芳基和芳基取代基可由卤素、烷基、CF_3、CO_2R^{20}、$CON(R^{20})_2$、$S(O)R^{22}$、SO_2R^{22}、$SO_2N(R^{20})_2$、CN或OR^{20}进一步任选地取代；

R^{20}选自H、C_{1-6}烷基和芳基，这类烷基和芳基可由一个选自卤素、烷基、单-或二烷基氨基、CN、O-C_{1-6}烷基、CF_3的取代基任选地取代；和

R^{22}选自C_{1-6}烷基和芳基，这类烷基和芳基可由一个选自卤素、烷基或CN、O-C_{1-6}烷基和CF_3的取代基任选地取代。

15. 如权利要求1所述的成分，其中X^1=S；

R_2是氢；

R_3和R_4各自独立地选自氢，-(CO)-R'和-(CO)-R''，其中R'和R''各自独立地选自C_{1-6}烷基；

R_5选自芳基和杂芳基，其中芳基和杂芳基可任选地被1至3个独立地选自卤素、烷基、CF_3、CN、OR^{20}、SR^{20}、CO_2R^{20}、$CON(R^{20})_2$的取代基取代；和

R^{20}选自H、C_{1-3}烷基。

16. 如权利要求1所述的成分，其中X^1=S；

R_2是氢；

R_3和R_4是氢；

R_5是由1至2个独立地选自卤素、烷基、CF_3、OR^{20}、CO_2R^{20}、$CON(R^{20})_2$的取代基任选地取代的芳基；

R^{20}选自H、和甲基；和

R^{22}选自C_{1-6}烷基。

17. 如权利要求16所述的成分，其中R_5是由选自甲氧基、氯、氟、

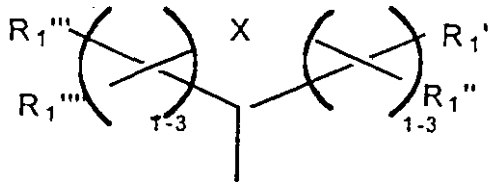
甲基和三氟甲基的取代基任选地取代的苯基。

18. 如权利要求 1 所述的成分，其中 R_1 被选自以下组的一种或多种化合物单或多取代：卤素、氧代、羟基、低级烷基、取代的低级烷基、烷氧基、芳基、酰基、芳氧基、羧基、取代的芳基、杂环、杂芳基、取代的杂芳基、环烷基、取代的环烷基、硝基、氰基和它们的混合物。

19. 如权利要求 1 所述的成分，其中 R^1 是含有 3 至 15 个碳原子的单环、双环或三环的环烷基，其中至少一个碳原子以选自 O 和 $S-(O)_{0-2}$ 的原子或分子取代。

20. 如权利要求 19 所述的成分，其中 R^1 被选自以下组的一种或多种化合物单或多取代：卤素、氧代、羟基、低级烷基、取代的低级烷基、烷氧基、芳基、酰基、芳氧基、羧基、取代的芳基、杂环、杂芳基、取代的杂芳基、环烷基、取代的环烷基、硝基、氰基和它们的混合物。

21. 如权利要求 1 所述的成分，其中 R^1 为下式：



其中 R_1'、R_1''、R_1''' 和 R_1'''' 各自独立地选自卤素、羟基、低级烷基、取代的低级烷基、烷氧基、芳基、酰基、芳氧基、羧基、取代的芳基、杂环、杂芳基、取代的杂芳基、环烷基、取代的环烷基、硝基、氰基和其混合物，且 X 是 O 或 $S(-O)_{0-2}$。

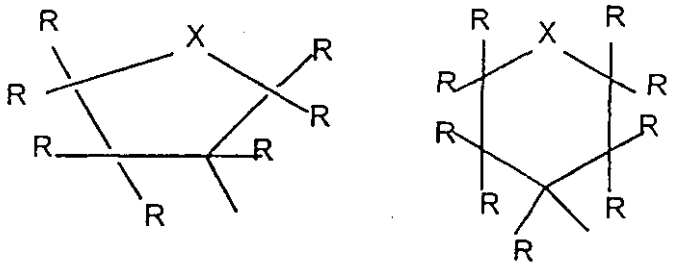
22. 如权利要求 21 所述的成分，其中 R_1''' 和 R_1'''' 可以在一起是单个的氧原子。

23. 如权利要求 21 所述的成分，其中 R_1'、R_1''、R_1''' 和 R_1'''' 各自独

立地选自 H、低级烷基、取代的低级烷基、烷氧基、芳基和取代的芳基。

24. 如权利要求 21 所述的成分，其中 R_1'、R_1''、R_1''' 和 R_1'''' 各自独立地选自 H、低级烷基和取代的低级烷基。

25. 如权利要求 1 所述的成分，其中 R^1 选自下式：



，或

其中每个 R 可独立地选自 H、低级烷基和取代的低级烷基，并且其中 X 是 O 或 $S(-O)_{0-2}$。

26. 如权利要求 1 或 2 或 3 或 4 或 5 或 6 或 7 或 8 或 9 或 10 或 11 或 12 或 13 或 14 或 15 或 16 所述的成分，其中 R_1 选自 3-四氢呋喃基、3-四氢噻吩基、4-吡喃基和 4-噻喃基。

27. 如权利要求 1 或 2 或 3 或 4 或 5 或 6 或 7 或 8 或 9 或 10 或 11 或 12 或 13 或 14 或 15 或 16 所述的成分，其中 R_1 是 3-四氢呋喃基。

28. 如权利要求 1 所述的成分，其中化合物选自以下化合物：

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(甲硫基甲基)氧杂环戊烷-3,4-二醇；

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(乙硫基)甲基]氧杂环戊烷-3,4-二醇；

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(甲基乙硫基)甲基]氧杂环戊烷-3,4-二醇；

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(苯硫基甲基)氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-甲氧基苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-氯苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-氟苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-甲基苯硫基)甲基]-氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-(三氟甲基)苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(2-甲氧基苯硫基)甲基]氧杂环戊烷-3,4-二醇;

(5-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(2S,3S,4R,5R)-3,4-二羟基氧杂环戊烷-2-基)(乙磺酰基)甲烷;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基嘌呤-9-基](4S,5S,2R,3R)-5-[(2,4-二氟苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(2,6-二氯苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(3-氟苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(2-氟苯硫基)甲基]氧杂环戊烷-3,4-二醇;

5-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9 基}(2S, 3R, 4R, 5R)-4-乙酰氧基-2-[(氟苯硫基)甲基]氧杂环戊烷-3-基乙酸酯;

2[(5-{6-[((3R)- 氧 杂 环 戊 烷 -3- 基) 氨 基] 嘌 呤 -9-基}(2S, 3S, 4R, 5R)-3, 4-二羟基氧杂环戊烷-2-基)甲硫基]苯甲酸甲酯;

{2[(5-{6-[((3R)- 氧 杂 环 戊 烷 -3- 基) 氨 基] 嘌 呤 -9 基}(2S, 3S, 4R, 5R)-3, 4-二羟基氧杂环戊烷-2-基)甲硫基]苯基}-N-甲基甲酰胺苯甲酸酯;

2-{6-[((3R)- 氧 杂 环 戊 烷 -3- 基) 氨 基] 嘌 呤 -9-基}(4S, 5S, 2R, 3R)-5-(苯并噁唑-2-基硫甲基)氧杂环戊烷-3, 4-二醇;

2-{6-[((3S)- 氧 杂 环 戊 烷 -3- 基) 氨 基] 嘌 呤 -9-基}(4S, 5S, 2R, 3R)-5-[(1-甲基咪唑-2-基-硫基)甲基]氧杂环戊烷-3, 4-二醇;

2-{6-[((3S)- 氧 杂 环 戊 烷 -3- 基) 氨 基] 嘌 呤 -9-基}(4S, 5S, 2R, 3R)-5-(嘧啶-2-基硫甲基)氧杂环戊烷-3, 4-二醇;

2-{6-[((3S)- 氧 杂 环 戊 烷 -3- 基) 氨 基] 嘌 呤 -9-基}(4S, 5S, 2R, 3R)-5-(2-吡啶基硫甲基)氧杂环戊烷-3, 4-二醇;

2-{6-[((3S)- 氧 杂 环 戊 烷 -3- 基) 氨 基] 嘌 呤 -9-基}(4S, 5S, 2R, 3R)-5-(4-吡啶基硫甲基)氧杂环戊烷-3, 4-二醇;和

(5-{6-[((3R) 氧 杂 环 戊 烷 -3- 基) 氨 基] 嘌 呤 -9-基}(2S, 3R, 4R, 5R)-4-乙酰氧基-2-[(4-氟苯硫基)甲基]氧杂环戊烷-3-基)乙酸酯。

29. 一种用于在患有可通过刺激 A_1 腺苷受体治疗的心电紊乱的哺乳动物中改善心脏活动的方法，其特征在于：包括给予哺乳动物治疗有效量的权利要求 1 的成分。

30. 一种用于通过刺激 A_1 腺苷受体改善哺乳动物脂肪细胞功能的方

法，其特征在于：包括给予哺乳动物治疗有效量的权利要求 1 的成分。

31. 一种在哺乳动物中通过刺激 A_1 腺苷受体恢复胰岛素敏感性和功效的方法，其特征在于：包括给予哺乳动物治疗有效量的权利要求 1 的成分。

32. 一种用于通过刺激 A_1 腺苷受体对哺乳动物提供中枢神经系统神经保护的方法，其特征在于：包括给予哺乳动物治疗有效量的权利要求 1 的成分。

33. 一种用于通过刺激 A_1 腺苷受体保护哺乳动物心肌细胞免于局部缺血的方法，其特征在于：包括给予哺乳动物治疗有效量的权利要求 1 的成分。

34. 如权利要求 29 或 30 或 31 或 32 或 33 所述的方法，其中治疗有效量的范围是约 0.01 至约 100mg/kg 哺乳动物体重。

35. 如权利要求 29 所述的方法，其中该成分给予患有选自室上性心动过速、心房纤维性颤动、心房扑动和 AV 结折返性心动过速的心电疾病的哺乳动物。

36. 如权利要求 30 或 31 所述的方法，其中该成分给予患有选自糖尿病和肥胖症的疾病的哺乳动物。

37. 如权利要求 32 所述的方法，其中该成分给予患有选自癫痫症和发作的中枢神经系统疾病的哺乳动物。

38. 如权利要求 33 所述的方法，其中该成分给予经受选自稳定的心绞痛、不稳定心绞痛、心移植和心肌梗塞的心脏局部缺血的哺乳动物。

39. 如权利要求 29 或 30 或 31 或 32 或 33 所述的方法，其中哺乳动物是人。

40. 一种药物组合物，包含权利要求 1 的成分和一种或多种药学赋形剂。

41. 如权利要求 40 所述的药物组合物，其中该药物组合物是以溶液形式存在。

42. 如权利要求 40 所述的药物组合物，其中该药物组合物是以片剂形式存在。

说　明　书

部分或完全 A_1 激动剂—N^6 杂环 5' 硫代腺苷衍生物

发明背景

(1) 发明领域

本发明包括是 N^6 杂环 5' 硫代改性腺苷衍生物的稳定和有效的药物和前体药物。本发明的组合物是选择性的 A_1 腺苷受体部分或完全激动剂，因而，可用于改善哺乳动物尤其是人类的心脏活动，改善脂肪细胞功能，治疗中枢神经系统疾病，以及治疗糖尿病和肥胖症。

(2) 现有技术描述

在心脏中至少有两种亚型的腺苷受体：A_1 和 A_{2A}。每个亚型影响不同的生理功能。A_1 腺苷受体介导两种不同的生理反应。儿茶酚胺心脏刺激作用的抑制通过抑制腺苷酸环化酶介导，而降低心率(HR)和延长 AV 节脉冲传播的直接作用很大程度归因于 I_{KAdo} 的活化。(B. Lerman 和 L. Belardinelli Circulation, Vol. 83 (1991), P 1499-1509 和 J. C. Shryock 和 L. Belardinelli, The Am. J. Cardiology, Vol. 79 (1997) p 2-10)。抗-β-肾上腺素能作用和对 SA 和 AV 结功能的直接抑制作用两者都由 A_1 受体介导；A_{2A} 受体在这种对腺苷的反应中不起作用。

A_{2A} 受体介导腺苷引起的冠状血管舒张。从而刺激 A_1 腺苷受体缩短了持续时间，降低了 AV 结细胞的动作电位的振幅，并因此而延长了 AV 结细胞的不应期。这些效应所带来的结果是限制了心房传导到心室的脉冲数。这就形成了临床采用 A_1 受体激动剂治疗室上性心动过速（包括折返性结性心动过速的末期）和在心房纤维性颤动和扑动期间控制心室速率的基础。

因此，A_1激动剂的临床应用是治疗急慢性心脏节律疾病，特别是以心率加快为特征、且该心率加快由窦房结、心房和 AV 结组织异常引起的疾病。这些疾病包括（但并不限于）心房纤维性颤动、室上性心动过速和心房扑动。使用 A_1 激动剂可降低心率，调整异常节律，从而改善心血管功能。

A_1 激动剂，通过其抑制儿茶酚胺效应的能力降低细胞 cAMP，从而对交感神经张力增高引起细胞 cAMP 升高的衰竭心脏应具有有益的作用。后者已经被显示与室性心律失常和突然死亡的可能性增加有关。在关于腺苷对心脏电生理学的作用的综述中讨论了以上各方面(参见 B. Lerman 和 L. Belardinelli Circulation, Vol. 83 (1991), P 1499-1509 和 J. C. Shryock 和 L. Belardinelli, Am. J. Cardiology, Vol. 79 (1997) p 2-10)。

A_1 腺苷激动作用领域争论之处是在局部缺血之前对心脏预先调节的益处可能归因于腺苷与 A_1 受体的结合。这种假设的证据来自家兔局部缺血模型，其中考虑到梗塞大小在局部缺血之前给予 2-氯-N6-环戊基腺苷(CCPA)和 R-PIA 提供保护(J. D. Thomton 等人. Circulation Vol. 85 (1992) 659-665)。

A_1激动剂，由于它们对环 AMP 产生的抑制作用而对脂肪细胞具有抗分解脂肪作用，这导致非酯化脂肪酸（NEFA）释放减少(E. A. van Schaick 等人，J. Pharmacokinetics 和 Biopharmaceutics, Vol. 25 (1997) p673-694 和 P. Strong Clinical Science Vol. 84 (1993) p. 663-669)。非胰岛素依赖性糖尿病(NIDDM)特征在于导致高血糖的胰岛素耐受性。引起观测到的高血糖的因素是正常葡萄糖摄取的缺乏和骨骼肌糖原合成酶(GS)的激活。已经证明 NEFA 水平的升高抑制胰岛素-刺激的葡萄糖摄取和糖原合成(D. Thiebaud 等人 Metab. Clin. Exp. Vol. 31 (1982) p

1128-1136 和 G. Boden 等人 J. Clin. Invest. Vol. 93 (1994) p 2438-2446)。P. J. Randle 早在 1963 年就提出了葡萄糖脂肪酸循环的假说(P. J. Randle 等人 Lancet (1963) p. 785-789)。该假说的原则是限制脂肪酸向外周组织的供应会促进碳水化合物的利用(P. Strong 等人 Clinical Science Vol. 84(1993) p. 663-669)。

A_1激动剂在中枢神经疾病中的益处已有综述，其内容一并纳入本文作为参考(L. J. S. Knutsen 和 T. F. Murray, Purinergic Approaches in Experimental Therapeutics, K. A. Jacobson 和 M. F. Jarvis 编著(1997) Wiley-Liss, N. Y., p-423-470)。简言之，基于癫痫实验模型，混合的 A_{2A}:A_1 激动剂腺苷地尔(metrifudil)已经显示是抗苯并二氮䓬反向激动剂 6,7-二甲氧基-4-乙基-β-咔啉-3-羧酸甲酯诱导的癫痫发作的一种有效的抗惊厥剂(DMCM, H. Klitgaard Eur. J. Pharmacol. (1993) Vol. 224 p. 221-228)。在其它的采用 CGS 21680（一种 A_{2A} 激动剂）的研究中，可以推断抗惊厥剂的活性归于 A_1 受体的激活(G. Zhang 等人 Eur. J. Pharmacol. Vol. 255 (1994) p. 239-243)。此外，在 DMCM 模型中显示 A_1 腺苷选择性激动剂具有抗惊厥活性(L. J. S. Knutsen, Adenosine and Adenne Nucleotides : From Molecular Biology to Integrative Physiology; L. Belardinelli 和 A. Pelleg, Kluwer 编: Boston, 1995, pp 479-487)。A_1 腺苷激动剂具有益处的第二方面是在前脑局部缺血动物模型中，如 Knutsen 等人介绍(J. Med. Chem. Vol. 42 (1999) p. 3463-3477)。据信神经保护的益处部分由于抑制兴奋性氨基酸的释放(同上)。

现有技术公开了存在大量的 A_1 完全激动剂。然而，所公开的激动剂通常在哺乳动物体是无效的形式。由于有 A_1 激动剂的有效形式并不总是稳定、可溶的，或者它们具有其它的使其难以加入到治疗剂型中的性能，

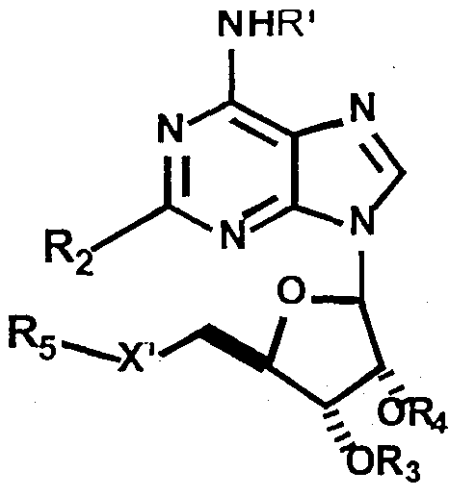
识别更容易加入到治疗剂型的化合物以便提供所需的治疗作用通常是必需的。同样，由于这些激动剂对一切生物学上可得到的组织中的 A_1 腺苷受体的非选择性刺激所引起的副作用以及妨碍其作为慢性剂用途的所需反应的脱敏作用，因此不能用作有用的治疗剂。因此，对特异的和选择性的 A_1 激动剂、在体内转化成有效治疗组合物的前体和/或前体药物仍有需求。

发明概述

一方面，本发明包括有用的腺苷 A_1 受体部分或完全激动剂杂环 5'-硫代改性腺苷衍生物。

另一方面，本发明包括含一种或多种耐受性好、副作用少的杂环 5'-硫代改性腺苷衍生物组分的药物组合物。

在另一个实施方案中，本发明包括杂环 5'-硫代改性腺苷衍生物，它具有以下结构式：

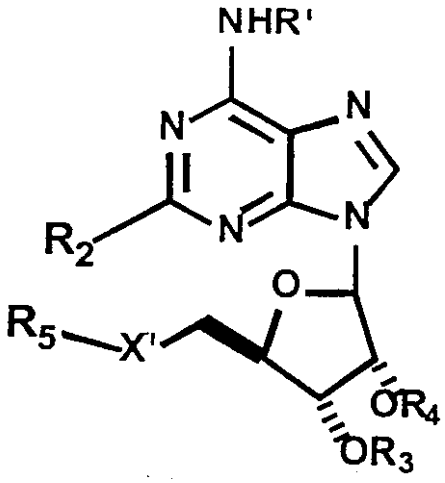


在又一个实施方法中，本发明包括对哺乳动物尤其是人给予本发明的组合物以激发冠状活性、改善脂肪细胞功能、治疗中枢神经系统疾病及治疗糖尿病的方法。

在进一步的实施方案中，本发明是含有至少一种本发明的组分和一种或多种药用赋形剂的药物组合物。

当前实施方案的描述

本发明包括一类杂环 5'-硫代改性腺苷衍生物，其具有如下结构式：



其中 X^1=S、S(O)、$S(O_2)$；

其中 R^1 是含有 3 至 15 个碳原子的单环或多环杂环基，其中至少一个碳原子被选自 N、O、P 和 $S-(O)_{0-2}$ 的原子或分子取代，且 R^1 不含有环氧基，R_2 选自氢、卤素、CF3 和氰基；其中 R_3 和 R_4 独立地选自氢、-(CO)-R'和-(CO)-R''，其中 R'和 R''独立地选自 C_{1-15} 烷基、C_{2-15} 烯基、C_{2-15} 炔基、杂环基、芳基和杂芳基，这类烷基、烯基、炔基、芳基、杂环基和杂芳基可任选地被 1 至 3 个独立地选自卤素、NO_2、杂环基、芳基、杂芳基、CF_3、CN、OR^{20}、SR^{20}、$S(O)R^{22}$、SO_2R^{22}、$SO_2N(R^{20})_2$、$SO_2NR^{20}COR^{22}$、$SO_2NR^{20}CO_2R^{22}$、$SO_2NR^{20}CON(R^{20})_2$、$N(R^{20})_2$、$NR^{20}COR^{22}$、$NR^{20}CO_2R^{22}$、$NR^{20}CON(R^{20})_2$、$NR^{20}C(NR^{20})NHR^{23}$、$COR^{20}$、$CO_2R^{20}$、$CON(R^{20})_2$、$CONR^{20}SO_2R^{22}$、$NR^{20}SO_2R^{22}$、$SO_2NR^{20}CO_2R^{22}$、$OCONR^{20}SO_2R^{22}$、$OC(O)R^{20}$、$C(O)OCH_2OC(O)R^{20}$ 和 $OCON(R^{20})_2$ 的

取代基取代，并且每个任选的杂芳基、芳基和杂环基取代基可任选地被卤素、NO_2、烷基、CF_3、氨基、单-或二-烷基氨基、烷基或芳基或杂芳基酰胺、$NR^{20}COR^{22}$、$NR^{20}SO_2R^{22}$、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 或 OR^{20}取代；

其中 R_5选自 C_{1-15}烷基、C_{2-15}烯基、C_{2-15}炔基、杂环基、芳基和杂芳基，这类烷基、烯基、炔基、芳基、杂环基和杂芳基可任选地被 1 至 3 个分别选自卤素、烷基、NO_2、杂环基、芳基、杂芳基、CF_3、CN、OR^{20}、SR^{20}、$S(O)_3R^{20}$、$S(O)R^{22}$、SO_2R^{22}、$SO_2N(R^{20})_2$、$SO_2NR^{20}COR^{22}$、$SO_2NR^{20}CO_2R^{22}$、$SO_2NR^{20}CON(R^{20})_2$、$P(O)(OR^{20})_2$、$N(R^{20})_2$、$NR^{20}COR^{22}$、$NR^{20}CO_2R^{22}$、$NR^{20}CON(R^{20})_2$、$NR^{20}C(NR^{20})NHR^{23}$、$COR^{20}$、$CO_2R^{20}$、$CON(R^{20})_2$、$CONR^{20}SO_2R^{22}$、$NR^{20}SO_2R^{22}$、$SO_2NR^{20}CO_2R^{22}$、$OCONR^{20}SO_2R^{22}$、$OC(O)R^{20}$、$C(O)OCH_2OC(O)R^{20}$和 $OCON(R^{20})_2$的取代基取代，并且每个任选的杂芳基、芳基和杂环基取代基可任选地被卤素、NO_2、烷基、CF_3、氨基、单-或二-烷基氨基、烷基或芳基或杂芳基酰胺、$NR^{20}COR^{22}$、$NR^{20}SO_2R^{22}$、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 或 OR^{20}取代；

其中 R^{20}选自 H、C_{1-15}烷基、C_{2-15}烯基、C_{2-15}炔基、杂环基、芳基和杂芳基，这类烷基、烯基、炔基、杂环基、芳基和杂芳基可任选地由 1 至 3 个分别选自卤素、烷基、单-或二烷基氨基、烷基或芳基或杂芳基酰胺、CN、O-C_{1-6}烷基、CF_3、芳基和杂芳基的取代基取代；和

R^{22}选自 C_{1-15}烷基、C_{2-15}烯基、C_{2-15}炔基、杂环基、芳基和杂芳基，这类烷基、烯基、炔基、杂环基、芳基和杂芳基可任选地被 1 至 3 个分别选自卤素、烷基、单-或二烷基氨基、烷基或芳基或杂芳基酰胺、CN、O-C_{1-6}烷基、CF_3和杂芳基的取代基取代。

在优选的成分中，X^1=S 或 SO_2；R_2是氢；R_3和 R_4各自独立地选自氢、-(CO)-R'和-(CO)-R''，其中 R'和 R''各自独立地选自 C_{1-6}烷基，并且更

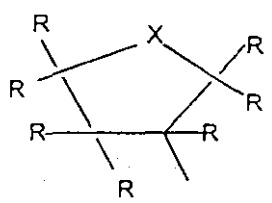
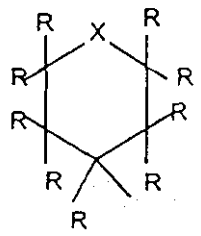
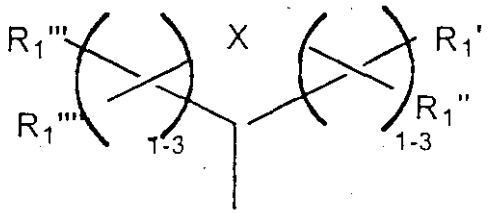
优选地，R_3和R_4各为氢；R_5选自C_{1-8}烷基和芳基，其中烷基和芳基可任选地被1至2个分别选自以下基团的取代基取代：卤素、烷基、芳基、杂芳基、CF_3、CN、OR^{20}、$S(O)R^{22}$、SO_2R^{22}、$SO_2N(R^{20})_2$、$NR^{20}CON(R^{20})_2$、CO_2R^{20}、$CON(R^{20})_2$，并且其中每个任选的杂芳基和芳基取代基可任选地被卤素、烷基、CF_3、CO_2R^{20}、CN和OR^{20}进一步取代；R_{20}选自H、C_{1-6}烷基；R_{22}选自C_{1-6}基团。在上述成分中，R_5更优选地选自C_{1-8}烷基和芳基，其中烷基和芳基可任选地被1至2个分别选自卤素、烷基、CF_3和OR^{20}的取代基取代。

在更优选的成分中，X^1=S 或 SO_2；R_2是氢；R_3和 R_4独立地选自氢、-(CO)-R'和-(CO)-R''，其中R'和R''各自独立地选自可被1个选自芳基、CF_3、CN、OR^{20}、$N(R^{20})_2$的取代基任选地取代的C_{1-6}烷基，并且其中每个任选的芳基取代基可任选地进一步被卤素、NO_2、烷基、CF_3取代；R_5是C_{1-8}烷基，其中烷基由可任选地被1至2个分别选自卤素、烷基、芳基、杂芳基、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}、$CON(R^{20})_2$的取代基取代，其中每个任选的杂芳基和芳基取代基可进一步任选地被卤素、烷基、CF_3、CO_2R^{20}、CN和OR^{20}取代；R^{20}选自H、C_{1-6}烷基；和R_{22}选自C_{1-6}基团。在上述成分中，R_5更优选为被1至2个分别选自芳基、杂芳基、OR^{20}、$S(O)R^{22}$、CO_2R^{20}、$CON(R^{20})_2$的取代基任选地取代的C_{1-8}烷基，并且其中每个任选的杂芳基和芳基取代基可进一步任选地被卤素、烷基、CF_3、CO_2R^{20}、CN和OR^{20}取代，并且R_5甚至更优选地为可被选自CO_2R^{20}和$CON(R^{20})_2$的一个取代基任选地取代的C_{1-8}烷基，R_5还更优选地为C_{1-6}烷基，最优选地为甲基或乙基或异丙基。同样在以上的成分中，R_3和 R_4每个更优选地为氢，并且R_{20}更优选地选自H和甲基。

在另一类优选成分中，R_2是氢；R_3和R_4各自独立地选自氢、-(CO)-R'和-(CO)-R''，其中R'和R''分别选自C_{1-6}烷基和芳基，这类烷基和芳基可任选地被1至2个分别选自以下基团的取代基取代：卤素、NO_2、芳基、

CF_3、CN、OR^{20}、$N(R^{20})_2$、$S(O)R^{22}$、SO_2R^{22}，并且其中每个任选的芳基取代基可进一步任选地被卤素、NO_2、烷基、CF_3取代；R_5选自芳基和杂芳基，其中芳基和杂芳基可任选地被1至3个分别选自以下基团的取代基取代：卤素、烷基、芳基、杂芳基、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}、$CON(R^{20})_2$，并且其中每个任选的杂芳基和芳基取代基可进一步任选地被卤素、烷基、CF_3、CO_2R^{20}、$CON(R^{20})_2$、$S(O)R^{22}$、SO_2R^{22}、$SO_2N(R^{20})_2$、CN或OR^{20}取代；R^{20}选自H、C_{1-6}烷基和芳基，这类烷基和芳基可任选地被一个选自卤素、烷基、单-或二-烷基氨基、CN、O-C_{1-6}烷基、CF_3的取代基取代；R^{22}选自C_{1-6}烷基和芳基，这类烷基和芳基可任选地被一个选自卤素、烷基或CN、O-C_{1-6}烷基和CF_3的取代基取代。在以上成分中，X^1优选S；R_3和R_4更优选氢；R_5更优选地选自芳基和杂芳基，其中芳基和杂芳基可任选地被1至3个分别选自以下基团的取代基取代：卤素、烷基、CF_3、CN、OR^{20}、SR^{20}、CO_2R^{20}、$CON(R^{20})_2$。甚至更优选R_5是可任选地被1至2个分别选自卤素、烷基、CF_3、OR^{20}、CO_2R^{20}、$CON(R^{20})_2$的取代基取代的芳基。最优选地，R_5是可任选地被选自甲氧基、氯、氟、甲基和三氟甲基的取代基取代的苯基。在上述化合物中，R^{20}优选选自H、C_{1-3}烷基，最优选为H或甲基，同时R_{22}优选C_{1-6}烷基。

在本发明的成分中，R_1较佳为被选自以下组的一种或多种化合物单取代或多取代：卤素、氧代、羟基、低级烷基、取代的低级烷基、烷氧基、芳基、酰基、芳氧基、羧基、取代的芳基、杂环、杂芳基、取代的杂芳基、环烷基、取代的环烷基、硝基、氰基和它们的混合物。更优选地，R_1是含有3至15个碳原子的单环、双环或三环环烷基，其中至少一个碳原子被选自O和S-$(O)_{0-2}$的原子或分子取代。优选的R_1基团的一些例子包括：

或　　或

其中 R_1'、R_1''、R_1''' 和 R_1'''' 可各自独立地选自卤素、羟基、低级烷基、取代的低级烷基、烷氧基、芳基、酰基、芳氧基、羧基、取代的芳基、杂环、杂芳基、取代的杂芳基、环烷基、取代的环烷基、硝基和氰基，且 X 是 O 或 $S(-O)_{0-2}$，或者，R_1''' 和 R_1'''' 可以是单个氧原子。更优选地，R_1'、R_1''、R_1''' 和 R_1'''' 各自独立地选自氢、低级烷基和取代的低级烷基。在以上成分中，每个 R 独立地选自 H、低级烷基和取代的低级烷基，并且其中 X 是 O 或 $S(-O)_{0-2}$。

本发明最优选的化合物包括下述化合物：

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(甲硫基甲基)氧杂环戊烷(oxolane)-3,4-二醇；

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(乙硫基)甲基]氧杂环戊烷-3,4-二醇；

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(甲基乙硫基)甲基]氧杂环戊烷-3,4-二醇；

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(苯硫基甲基)氧杂环戊烷-3,4-二醇；

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-

基}(4S,5S,2R,3R)-5-[(4-甲氧基苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-氯苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-氟苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-甲基苯硫基)甲基]-氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-(三氟甲基)苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(2-甲氧基苯硫基)甲基]氧杂环戊烷-3,4-二醇;

(5-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(2S,3S,4R,5R)-3,4-二羟基氧杂环戊烷-2-基)(乙磺酰基)甲烷;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基嘌呤-9-基](4S,5S,2R,3R)-5-[(2,4-二氟苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(2,6-二氯苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(3-氟苯硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(2-氟苯硫基)甲基]氧杂环戊烷-3,4-二醇;

5-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9 基}(2S,3R,4R,5R)-4-乙酰氧基-2-[(氟苯硫基)甲基]氧杂环戊烷-3-基乙酸酯;

2[(5-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-

基}(2S,3S,4R,5R)-3,4-二羟基氧杂环戊烷-2-基)甲硫基]苯甲酸甲酯;

{2[(5-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9基}(2S,3S,4R,5R)-3,4-二羟基氧杂环戊烷-2-基)甲硫基]苯基}-N-甲基甲酰胺苯甲酸酯;

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(苯并噁唑-2-基硫甲基)氧杂环戊烷-3,4-二醇;

2-{6-[((3S)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(1-甲基咪唑-2-基-硫基)甲基]氧杂环戊烷-3,4-二醇;

2-{6-[((3S)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(嘧啶-2-基硫甲基)氧杂环戊烷-3,4-二醇;

2-{6-[((3S)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(2-吡啶基硫甲基)氧杂环戊烷-3,4-二醇;

2-{6-[((3S)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(4-吡啶基硫甲基)氧杂环戊烷-3,4-二醇;和

(5-{6-[((3R)氧杂环戊烷-3-基)氨基]嘌呤-9-基}(2S,3R,4R,5R)-4-乙酰氧基-2-[(4-氟苯硫基)甲基]氧杂环戊烷-3-基]乙酸酯。

下列定义适用于本文采用的术语。

"卤"或"卤素"-单独或组合地意指所有卤素，即，氯(Cl)、氟(F)、溴(Br)、碘(I)。

"羟基"指基团-OH。

"硫醇"或"巯基"指基团-SH。

"烷基"-单独或组合地意指含有1至20、优选1至15个碳原子的烷烃衍生的基团(除非具体限定)。它是直链烷基、支链烷基或环烷基。直

链或支链烷基含有 1-15 个碳原子为宜，较佳为 1 至 8、更佳为 1-6、还要更佳为 1-4、最佳为 1-2 个碳原子，例如甲基、乙基、丙基、异丙基、丁基、叔丁基等等。本文使用的术语"低级烷基"是以上刚描述的直链烷基。优选地，环烷基是单环、双环或三环体系，每个环优选 3-8 元，更优选 3-6 元环，例如环丙基、环戊基、环己基、金刚烷基(adamantyl)等等。烷基也包括含有或由环烷基部分中断的直链或支链烷基。这种直链或支链烷基连接在任何可利用的位置以产生稳定的化合物。其例子包括（但不限于）4-(异丙基)-环己基乙基或 2-甲基环丙基戊基。取代的烷基是前述定义的直链烷基、支链烷基或环烷基，其独立地以 1 至 3 个基团或取代基取代，所述基团或取代基选自卤素，羟基，烷氧基，烷硫基，烷基亚磺酰基，烷基磺酰基，酰氧基，芳氧基，杂芳氧基，以烷基、芳基或杂芳基任选地单-或二取代的氨基，脒基，以烷基、芳基、杂芳基或杂环基任选取代的脲，以烷基、芳基或杂芳基任选地 N-单-或 N,N-二取代的氨基磺酰基，烷基磺酰氨基，芳基磺酰氨基，杂芳基磺酰氨基，烷基羰基氨基，芳基羰基氨基，杂芳基羰基氨基，等等。

"烯基"-单独或组合地意指直链、支链或环烃，其含有 2-20、优选 2-17、更优选 2-10、还要优选 2-8、最优选 2-4 个碳原子，并且至少一个、优选 1-3、更优选 1-2、最优选一个碳碳双键。在环烷基的情形下，多于一个碳碳双键的共轭未达到给予环芳香性的程度。碳碳双键可以是或者被包含在除了环丙基之外的环烷基部分之内，或者在直链或支链部分之内。烯基的例子包括乙烯基、丙烯基、异丙烯基、丁烯基、环己烯基、环己烯基烷基等等。取代的烯基是前述定义的直链烯基、支链烯基或环烯基，其独立地被 1 至 3 个连接在任何可利用位置以产生稳定化合物的基团或取代基取代，所述基团或取代基为卤素，羟基，烷氧基，烷硫基，烷基亚磺酰基，烷基磺酰基，酰氧基，芳氧基，杂芳氧基，以烷基、芳基或杂芳基

任选地单-或二取代的氨基，脒基，以烷基、芳基、杂芳基或杂环基任选地取代的脲，以烷基、芳基或杂芳基任选地 N-单-或 N,N-二取代的氨基磺酰基，烷基磺酰氨基，芳基磺酰氨基，杂芳基磺酰氨基，烷基羰基氨基，芳基羰基氨基，杂芳基羰基氨基，羧基，烷氧基羰基，芳氧基羰基，杂芳氧基羰基等等。

"炔基"-单独或组合地意指直链或支链烃，其含有 2-20、优选 2-17、更优选 2-10、还要优选 2-8、最优选 2-4 个碳原子，含有至少一个、优选一个碳碳三键。炔基的例子包括乙炔基、丙炔基、丁炔基等等。取代的炔基指前述定义的直链或支链炔基，其独立地以 1 至 3 个连接在任何可利用位置以产生稳定化合物的基团或取代基取代，所述基团或取代基为卤素，羟基，烷氧基，烷硫基，烷基亚磺酰基，烷基磺酰基，酰氧基，芳氧基，杂芳氧基，以烷基、芳基或杂芳基任选地单-或二-取代的氨基，脒基，以烷基、芳基、杂芳基或杂环基任选地取代的脲，以烷基、芳基或杂芳基任选地 N-单-或 N,N-二取代的氨基磺酰基，烷基磺酰氨基，芳基磺酰氨基，杂芳基磺酰氨基，烷基羰基氨基，芳基羰基氨基，杂芳基羰基氨基等等。

"烷基烯基"指基团-R-CR'=CR"'R'"'，这里 R 是低级烷基或取代的低级烷基，R'，R"'，R'"'可分别是氢、卤素、低级烷基、取代的低级烷基、酰基、芳基、取代的芳基、杂芳基或如下定义的取代的杂芳基。

"烷基炔基"指基团-RC≡CR'，这里 R 是低级烷基或取代的低级烷基，R'是氢、低级烷基、取代的低级烷基、酰基、芳基、取代的芳基、杂芳基或如下定义的取代的杂芳基。

"烷氧基"表示基团-OR，这里 R 是如定义的低级烷基、取代的低级烷基、酰基、芳基、取代的芳基、芳烷基、取代的芳烷基、杂烷基、杂芳基烷基、环烷基、取代的环烷基、环杂烷基或取代的环杂烷基。

"烷硫基"表示基团-SR、$-S(O)_{n=1-2}-R$，这里 R 是如本文定义的低级烷基、取代的低级烷基、芳基、取代的芳基、芳烷基或取代的芳烷基。

"酰基"表示基团-C(O)R，这里 R 是氢、如本文定义的低级烷基、取代的低级烷基、芳基、取代的芳基等等。

"芳氧基"表示基团-OAr，这里 Ar 是如本文定义的芳基、取代的芳基、杂芳基或取代的杂芳基。

"氨基"表示基团 NRR'，这里 R 和 R'可分别为氢、如本文定义的低级烷基、取代的低级烷基、芳基、取代的芳基、杂芳基或取代的杂芳基或酰基。

"酰氨基"表示基团-C(O)NRR'，这里 R 和 R'可分别为氢、如本文定义的低级烷基、取代的低级烷基、芳基、取代的芳基、杂芳基、取代的杂芳基。

"羧基"表示基团-C(O)OR，这里 R 是氢、如本文定义的低级烷基、取代的低级烷基、芳基、取代的芳基、杂芳基和取代的杂芳基。

"芳基"-单独或组合地意指苯基或萘基，它们任选地与优选 5-7、更优选 5-6 元环烷基的碳环稠合，和/或任选地被 1 至 3 个基团或取代基取代，所述基团或取代基为卤素，羟基，烷氧基，烷硫基，烷基亚磺酰基，烷基磺酰基，酰氧基，芳氧基，杂芳氧基，以烷基、芳基或杂芳基任选地单-或二-取代的氨基，脒基，以烷基、芳基、杂芳基或杂环基任选地取代的脲，以烷基、芳基或杂芳基任选地 N-单-或 N,N-二-取代的氨基磺酰基，烷基磺酰氨基，芳基磺酰氨基，杂芳基磺酰氨基，烷基羰基氨基，芳基羰基氨基，杂芳基羰基氨基，等等。

"取代的芳基"指以一个或多个官能基团任选地取代的芳基，所述官能基团为例如卤原子、低级烷基、低级烷氧基、烷硫基、乙炔、氨基、酰氨基、羧基、羟基、芳基、芳氧基、杂环、杂芳基、取代的杂芳基、硝基、

氰基、硫醇、磺酰胺基等等。

"杂环"指饱和、不饱和或芳香碳环基团，其具有单环(例如吗啉代、吡啶基或呋喃基)或多稠合环(例如，萘吡啶基、喹喔啉基、喹啉基、吲嗪基或苯并[b]噻吩基)，环内具有至少一个杂原子，例如 N、O 或 S，它可任选地未取代或取代，例如以卤素、低级烷基、低级烷氧基、烷硫基、乙炔、氨基、酰氨基、羧基、羟基、芳基、芳氧基、杂环、杂芳基、取代的杂芳基、硝基、氰基、硫醇、磺酰胺基等等取代。

"杂芳基"-单独或组合地意指含有 5 至 6 个环原子的单环芳环结构，或者含有 8 至 10 个原子的双环芳香基团，其含有一个或多个，优选 1-4、更优选 1-3、还优选 1-2 个分别选自 O、S 和 N 的杂原子，并且可任选地以 1 至 3 个基团或取代基取代，所述基团或取代基为卤素，羟基，烷氧基，烷硫基，烷基亚磺酰基，烷基磺酰基，酰氧基，芳氧基，杂芳氧基，以烷基、芳基或杂芳基任选地单-或二-取代的氨基，脒基，以烷基、芳基、杂芳基或杂环基任选地取代的脲，以烷基、芳基或杂芳基任选地 N-单-或 N,N-二取代的氨基磺酰基，烷基磺酰氨基，芳基磺酰氨基，杂芳基磺酰氨基，烷基羰基氨基，芳基羰基氨基，杂芳基羰基氨基，等等。杂芳基也包括氧化的 S 或 N，例如亚磺酰基、磺酰基和叔环氮的 N-氧化物。碳或氮原子位于杂芳环结构的连接点，这样保持稳定的芳环。杂芳基基团的例子是吡啶基、哒嗪基、吡嗪基、喹唑啉基、噌吟基、吲哚基、喹啉基、嘧啶基、吡咯基、噁唑基、噻唑基、噻吩基、异噁唑基、噁噻二唑基、异噻唑基、四唑基、咪唑基、三嗪基、呋喃基、苯并呋喃基、吲哚基等等。取代的杂芳环含有连接在可利用的碳原子或硝基上的取代基，以产生稳定的化合物。

"杂环基"-单独或组合地意指具有 5 至 10 个原子的非芳香环烷基基团，其中环上 1 至 3 个碳原子由杂原子 O、S 或 N 取代，并且被任选地苯

并稠合或 5-6 元环杂芳基稠合和/或在环烷基情形下被任选地取代。杂环基也包括氧化的 S 或 N，例如亚磺酰基、磺酰基和叔环氮的 N-氧化物。连接点在碳或氮原子上。杂环基的例子是四氢呋喃基、二氢吡啶基、哌啶基、吡咯烷基、哌嗪基、二氢苯并呋喃基、二氢吲哚基等等。取代的杂环含有连接在可利用的碳或氮上的取代基氮以产生稳定的化合物。

"取代的杂芳基"指以一种或多种官能基团任选地单或多取代的杂环，这些官能基团为例如卤素、低级烷基、低级烷氧基、烷硫基、乙炔、氨基、酰氨基、羧基、羟基、芳基、芳氧基、杂环、取代的杂环、杂芳基、取代的杂芳基、硝基、氰基、硫醇、磺酰胺基等等。

"芳烷基"指基团-R-Ar，这里 Ar 是芳基基团，R 是低级烷基或取代的低级烷基基团。芳基基团可任选地为未取代或以如卤素、低级烷基、烷氧基、烷硫基、乙炔、氨基、酰氨基、羧基、羟基、芳基、芳氧基、杂环、取代的杂环、杂芳基、取代的杂芳基、硝基、氰基、硫醇、磺酰氨基等等取代。

"杂烷基"指基团-R-Het，这里 Het 是杂环基团，R 是低级烷基基团。杂烷基基团可任选地是未取代或以如卤素、低级烷基、低级烷氧基、烷硫基、乙炔、氨基、酰氨基、羧基、芳基、芳氧基、杂环、取代的杂环、杂芳基、取代的杂芳基、硝基、氰基、硫醇、磺酰氨基等等取代。

"杂芳基烷基"指基团-R-HetAr，这里 HetAr 是杂芳基，R 是低级烷基或取代的低级烷基。杂芳基烷基基团可任选地是未取代或以例如卤素、低级烷基、取代的低级烷基、烷氧基、烷硫基、乙炔、芳基、芳氧基、杂环、取代的杂环、杂芳基、取代的杂芳基、硝基、氰基、硫醇、磺酰氨基等等取代。

"环烷基"指含有 3 至 15 个碳原子的二价环或多环烷基基团。

"取代的环烷基"指包括一个或多个取代基的环烷基，所述取代基是例

如卤素、低级烷基、取代的低级烷基、烷氧基、烷硫基、乙炔、芳基、芳氧基、杂环、取代的杂环、杂芳基、取代的杂芳基、硝基、氰基、硫醇、磺酰氨基等等。

"环杂烷基"指环烷基基团，其中一个或多个环碳原子以杂原子(例如，N、O、S 或 P)取代。

"取代的环杂烷基"指如本文定义的环杂烷基基团，它含有一个或多个的取代基，例如卤素、低级烷基、低级烷氧基、烷硫基、乙炔、氨基、酰氨基、羧基、羟基、芳基、芳氧基、杂环、取代的杂环、杂芳基、取代的杂芳基、硝基、氰基、硫醇、磺酰氨基等等。

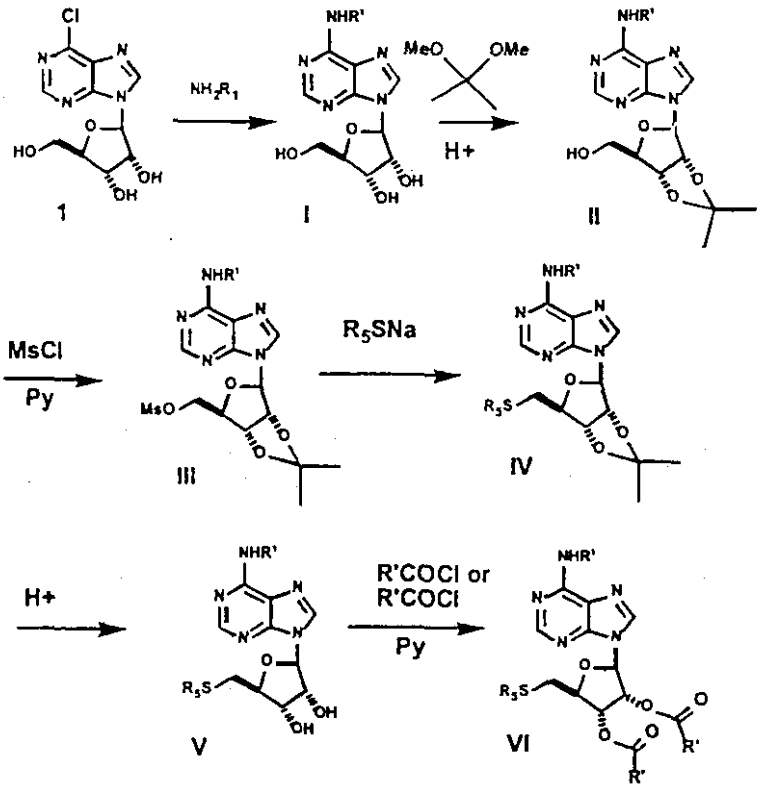
"烷基环烷基"表示基团-R-环烷基，这里环烷基是环烷基基团，且 R 是低级烷基或取代的低级烷基。环烷基基团可任意地是未取代的或以例如卤素、低级烷基、低级烷氧基、烷硫基、乙炔、氨基、酰氨基、羧基、羟基、芳基、芳氧基、杂环、取代的杂环、杂芳基、取代的杂芳基、硝基、氰基、硫醇、磺酰氨基等等取代。

"烷基环杂烷基"表示基团-R-环杂烷基，这里 R 是低级烷基或取代的低级烷基。环杂烷基基团可任选地是未取代或以例如卤素、低级烷基、低级烷氧基、烷硫基、氨基、酰氨基、羧基、乙炔、羟基、芳基、芳氧基、杂环、取代的杂环、杂芳基、取代的杂芳基、硝基、氰基、硫醇、磺酰氨基等等取代。

本发明的化合物可以如以下流程 1-5 所略述的制备。制备 V 和 VI 的一般概要如流程 1 所示。按照早期报道的方法，通过 6-氯嘌呤核苷 1 与伯胺 R^1NH_2 反应，可制备化合物 I(美国专利 No. 5,789,416,其说明书引入本文作为参考)。通过 I 与 2, 2'-二甲氧基丙烷在催化量的 TsOH[Evans, Parrish 和 Long Carbohydrat. Res., 3, 453 (1967)]存在下反应来保护 2',3'羟基为丙酮化合物，以产生 II。在吡啶中 II 的 5'-羟基以 MsCl

活化，可以产生 5'-甲磺酸酯 III。以 R^5SNa 置换 5'-甲磺酸酯可以产生具有通式 IV 结构的硫化物。以酸处理 IV 可释放出 2',3' 羟基以产生具有通式 V 的硫化物衍生物。V 的酯化可产生具有通式 VI 的 2',3' 二酯。

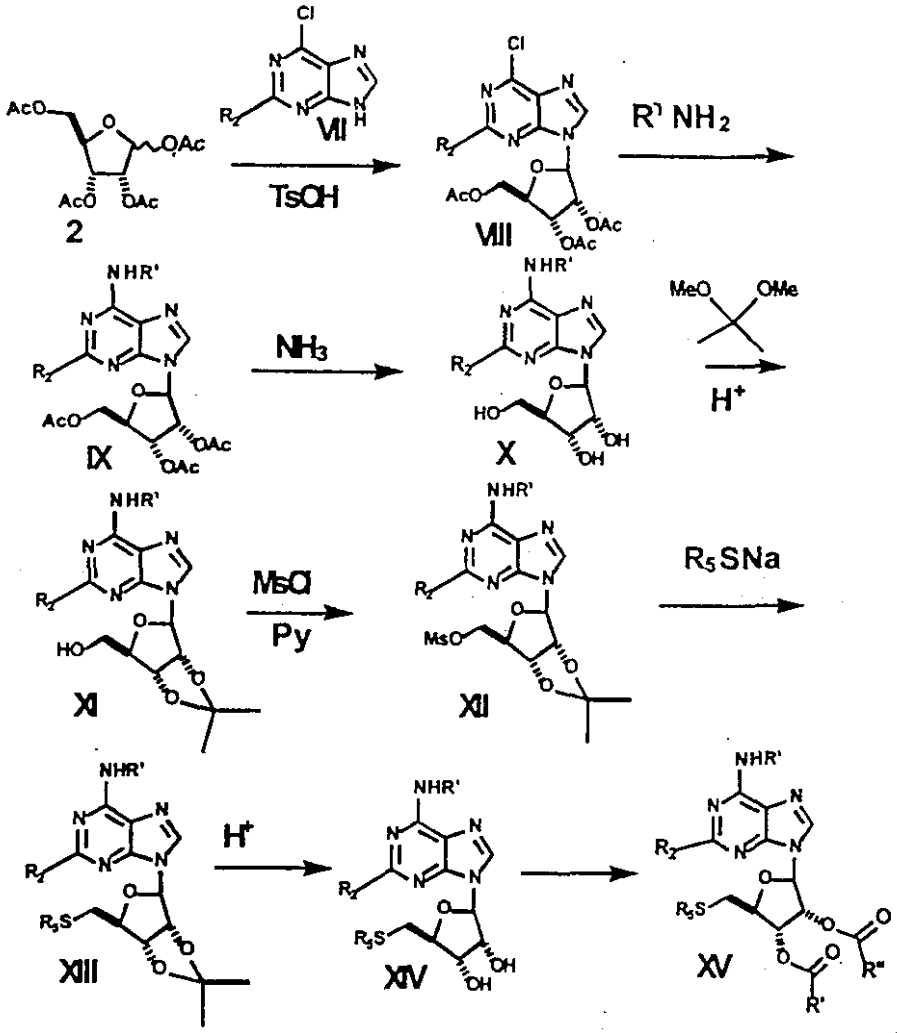
流程 1



具有通式 XV 的 2-取代的衍生物可以如流程 2 所示制备。1,2,3,5-四乙酰呋喃核苷(ribofuranaside)2 与 2-取代-6 氯嘌呤 VII 的缩合可以产生 2-取代-6-氯嘌呤核苷三乙酸酯 VIII，它与伯胺 R'NH 反应，可产生 2-取代-6-烷基氨基衍生物 IX。接着 2',3' 羟基保护为丙酮化合物的乙酸酯水解可产生 XI。在吡啶中 XI 的 5'-羟基以 MsCl 激活可以产生 5'-甲磺酸酯 XII。以 R^5SNa 置换 5'-甲磺酸酯可以产生具有通式 XIII 结构的硫化物，

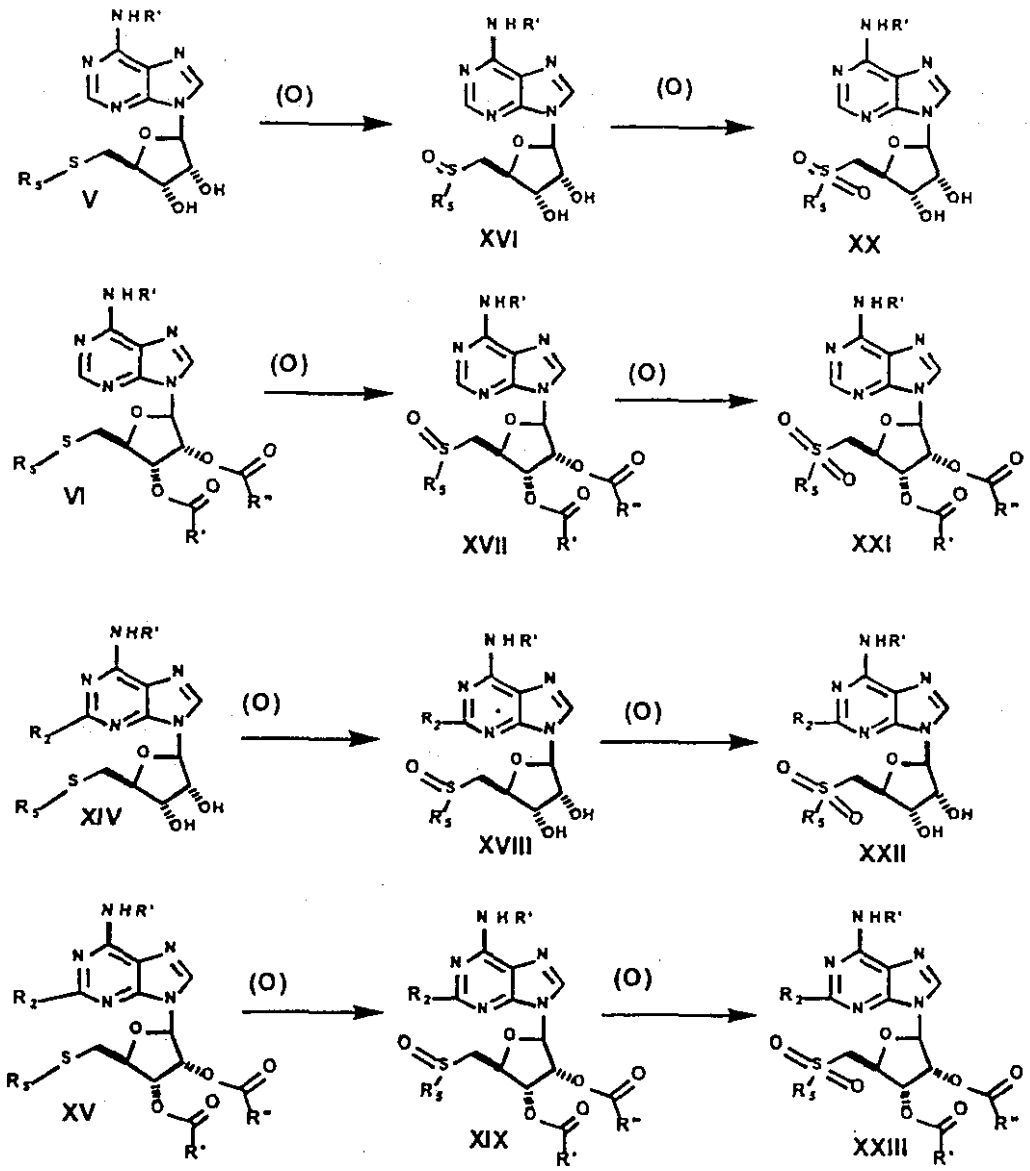
它可脱去保护产生具有通式 XIV 的硫化物。2',3'位置的酯化可产生具有通式 XV 结构的 2',3'二酯。

流程 2



以氧化剂氧化通式 V, VI, XIV, XV 的硫化物(流程 3) (Drabowicz, 等人, The chemistry of sulfones and sulfoxides, Wiley, New York, 1988, 233-378)可产生相应的具有通式 XVI、XVII、XVIII、XIX 的亚砜。这些亚砜进一步氧化后可产生具有通式 XX、XXI、XMI、XXIII 的砜。

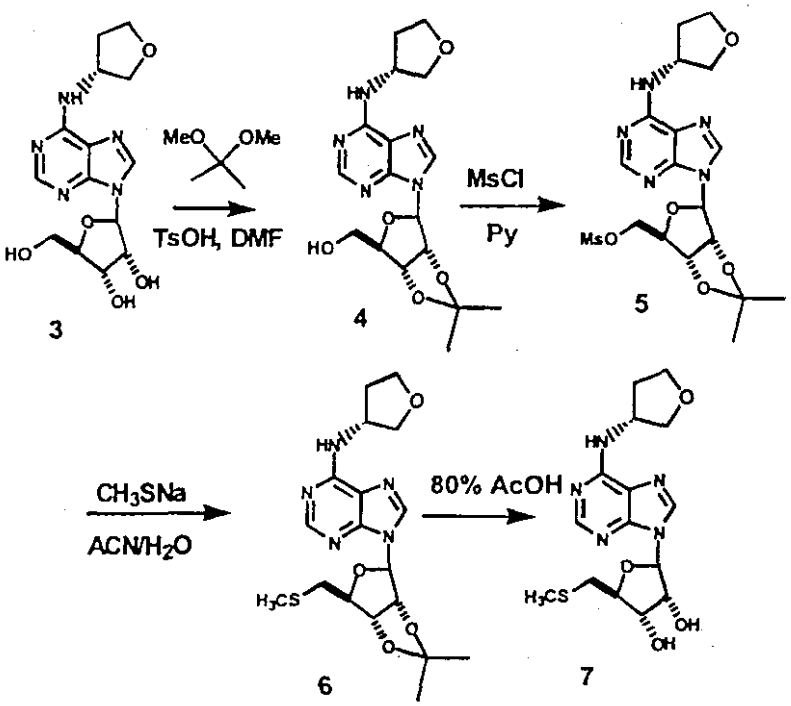
流程 3



本发明的一种化合物的具体合成例如流程 4 所示。始于化合物 3 的化合物 7 的制备如流程 3 所示。化合物 3 可以由 6-氯嘌呤核苷 1 和 3-(R)-氨基四氢呋喃，按照前述报道的方法制备(参见美国专利 No. 5,789,164)。在 TsOH(cat.)存在下 2' 和 3' 羟基以二甲氧基丙烷来保护产生丙酮化合物 4。在吡啶中 4 与 MsCl 于 0℃反应产生甲磺酸酯 5，它用甲硫醇钠(sodium

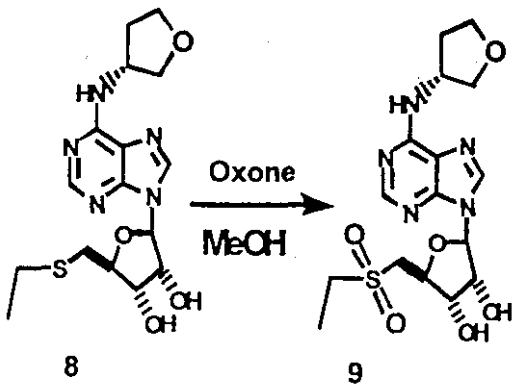
methanethiolate)在乙腈/水混合物中置换产生硫化物 6。以 80%乙酸/水使 6 脱保护产生目的化合物 7。

流程 4



乙硫醚 8 以过硫酸氢钾制剂(oxone)在 MeOH 中进行氧化(Trost, B.M.; Curran, D.P. Tetrahedron Letters 1981, 22, 1287)产生砜 9(流程 5)。

流程 5



本发明也包括本发明的 A_1 激动剂成分的前体药物。前体药物是一种经化学修饰并且在其作用部位无生物活性的药物，但是通过一种或多种酶促或体内过程，它会降解或修饰或生物活性形式。本发明的前体药物应该具有不同于母体的药动学特征，能够改善经粘膜上皮吸收，有较好的盐制剂和/或溶解度以及系统稳定性改善。本发明的化合物优选在一个或多个羟基基团上被修饰，以形成前体药物。这种修饰可以是(1)例如，可通过酯酶或脂肪酶裂解的酯或氨基甲酸酯衍生物；(2)可被特异性或非特异性蛋白酶识别的肽；或者(3)经过膜选择可蓄积在作用部位的衍生物或者前体药物形式或者经修饰的前体药物形式，或者以上(1)至(3)的任何组合。

如果本发明的化合物含有碱基，可以制成相应的酸加成盐。用标准方法，在适当的溶剂中，从母体化合物和过量的酸，例如盐酸、氢溴酸、硫酸、磷酸、乙酸、马来酸、琥珀酸或甲磺酸，制备该化合物的酸加成盐。盐酸盐形式是尤其有用的。如果本发明的化合物含有酸性基团，则可以制备相应的阳离子盐。一般地，将母体化合物以过量的含有适当阳离子的碱性试剂，例如氢氧化物、碳酸盐或醇盐处理。阳离子，例如 Na^+，K^+，Ca^{+2} 和 NH_4^+，是药学上可接受的盐中存在的阳离子的例子。某些化合物形成惰性盐或两性离子，它们亦是可接受的。

本发明的成分可用于治疗 A_1 腺苷受体介导的哺乳动物尤其是人的各种疾病。例如，本发明的成分可在患有可通过刺激 A_1 腺苷受体治疗的冠脉电紊乱(coronary electrical disorder)的哺乳动物中用于改善心脏活性。通过本发明的成分治疗的冠脉电紊乱的例子包括室上心动过速，包括心房纤维性颤动、心房扑动和 AV 结折返性心动过速。此外，在治疗室上心律失常中显示良好的安全性的本发明的口服活性 A_1 激动剂也可用作心肌缺血高危人群的预防剂。

本发明的成分也适用于通过刺激引起 NEFA 释放减少和瘦素释放增加

的 A_1 腺苷受体来改善脂肪细胞功能。与可用本发明的成分改善的脂肪细胞功能有关的疾病包括糖尿病和肥胖症。

在骨骼肌细胞，A_1AdoR 激动剂介导胰岛素的葡萄糖摄取和转移的协同刺激 (Vergauwen, L. 等人, J. Clin. Invest. 1994, 93, 974-81 ; Challiss, R. A. 等人, Eur. J. Pharacol., 1992, 226, 121-8)。本发明成分的另一治疗应用是在受糖尿病折磨的患者中更有效地调节葡萄糖和减少循环的胰岛素。

A_1 受体激动剂 R-PIA$_1$ 已经显示增加瘦素从白色脂肪细胞的释放和增加胰岛素-刺激的瘦素的产生 (M. Ozeck Master's Thesis Univ. of Florida 1999 with L. Belardinelli)。证据表明，儿茶酚胺类通过激活β-肾上腺素能受体抑制脂肪细胞产生瘦素。脂肪细胞上 A_1 激动剂的抗肾上腺素能作用确信在增加瘦素的释放中起作用。瘦素的功能作用是多方面的，包括降低食欲、刺激能量利用和增加生育力。

本发明的成分通过刺激 A_1 腺苷受体，亦可用于提供中枢神经系统神经保护。可以采用本发明的成分治疗的中枢神经系统疾病包括癫痫和发作。

在肾脏，有证据表明，刺激 A_1AdoR 促进钠潴留，促进尿中的钠钾交换，及因排钠增加而减少肾小球滤过率 (Gellai, M. 等人, JPET, 1998, 286, 1191-6 ;Wilcox, C. S. 等人, J. Am. Soc. Nephrol., 1999, 10, 714-720)。据信，通过腺苷的慢性局部产生可以引发这些反应。换言之，在肾脏存在腺苷刺激 A_1AdoR 的激励效应。因此，本发明成分的另一临床应用，是肾脏 A_1AdoR 的选择性拮抗作用以抑制钠潴留，抑制钠钾交换，并且当排钠增加时保持肾小球滤过率，以产生保护肾功能的保钾利尿作用 (potassium sparring diuretic)。

本发明的成分进一步适用于通过刺激 A_1 腺苷受体对心肌细胞提供免

受缺血影响的保护。用本发明的成分能治疗的局部缺血包括稳定性心绞痛、不稳定性心绞痛、心脏移植和心肌梗塞。

本发明化合物的一个重要方面是每个化合物具有与其相关的内在活性(参见 T. P. Kenakin: 刺激反应机制, Pharmacological Analysis of Drug-Receptor Interaction, Kenakin, T. P.编著 New York : Raven Press, p 39-68)。这种内在活性并非由其对受体的亲和性限定，而是限定为该化合物在一定的细胞类型中激活一定的效应器系统(例如 cAMP 产生)的定量效应。细胞类型与细胞类型之间和/或效应器系统与效应器系统之间给定化合物的内在活性可以不同。当化合物具有低于完全激动剂的内在活性（即次最大）时，这种激动剂称为部分激动剂。从而，部分激动剂是与受体结合引起小于完全激动剂的反应（次最大）、并且竞争性地拮抗完全激动剂引起的反应的分子。腺苷对于肾功能的激励作用是部分 A_1 激动剂可望充当拮抗剂的最好例证。据信，本发明的化合物具有治疗学上有用的对腺苷 A_1 受体的亲和性，并且它们具有从完全激动剂至部分激动剂的内在活性。换言之，一些化合物在某些细胞类型中可能不具有对特定效应器系统的作用，但是在另一种细胞类型和/或效应器系统中却是完全激动剂。这种可变性药理学性质的原因涉及在任何给定细胞类型(例如 AV 结细胞对脂肪细胞)中对于 A_1 腺苷受体和给定反应的受体储备量。受体储备(空闲受体容量)是受体总数减去用完全激动剂引起最大反应所需的受体部分(L. E. Limbird, Cell Surface Receptors : A Short Course on Theory and Methods, Kluwer Acad. Pub. 1996, Boston, Mass.)。因此，激动剂可以是引起反应的完全激动剂，和在其它组织或细胞引起另一反应的部分激动剂，以及还是对另一组织或细胞中的第三种反应的拮抗剂或对其无活性。因此，针对选定目标的部分激动剂与完全激动剂相比可能引起较少的副作用。作为必然的结果，完全激动剂引起由各自受体介导的

所有反应，而部分激动剂则未必如此。本发明化合物基于其对 A_1 受体的亲和性及其引起 A_1 受体介导的反应的强度和选择性，在多种以上介绍的疾病中具有治疗干预潜力。

部分 A_1 激动剂还有益于长期治疗，由于它们很少诱发 A_1 受体脱敏(R. B. Clark, B. J. Knoll, R. Barber TiPS, Vol. 20 (1999) p. 279-286)和产生副作用。完全激动剂 R-N6-苯基异丙基腺苷(R-PIA)的 7 天慢性给药，通过豚鼠的变导性反应导致 A_1 受体脱敏(注意:观察到受体数量的减少-D. M. Dennis, J. C. Shryock, L. Belardinelli JPET, Vol. 272 (1995) p. 1024-1035)。A_1 激动剂引起脂肪细胞腺苷酸环化酶生成 cAMP 作用的抑制，已被证明在以 A_1 激动剂长期治疗时产生脱敏(W. J. Parsons 和 G. L. Stiles J. Biol. Chem. Vol. 262 (1987) p. 841-847)。

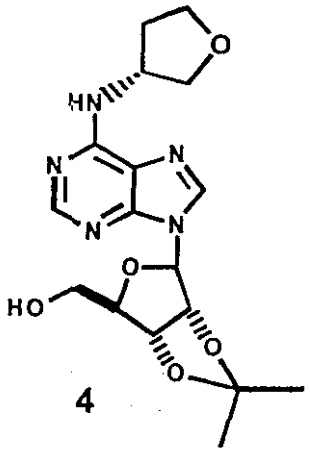
本发明的成分可以口服、静脉内、经皮、经鼻、吸入或者通过本领域已知的给予治疗剂的任何其它方式给药。这种治疗方法包括有效量的选定化合物的给药，优选分散在药用载体中。活性成分的剂量单位通常选自 0.01 至 100 mg/kg 的范围，但是本领域熟练技术人员根据给药途径、患者年龄和病情可以容易地确定。

包括本发明化合物的药物组合物，和/或其衍生物，可配制成溶液或冻干粉用于非胃肠道给药。粉末可在使用之前加入适当的稀释剂或其它药学上可接受的载体重建。如果以液体形式使用，本发明的组合物优选掺入缓冲过的、等渗的水溶液。适当的稀释剂的例子是等渗生理盐水，5%标准葡萄糖水溶液和乙酸钠或乙酸铵缓冲溶液。这类液体制剂适于非胃肠道给药，但也可用于口服给药。较理想的是，向包括本发明化合物的药物组合物中加入赋形剂，例如聚乙烯吡咯烷酮、明胶、羟基纤维素、阿拉伯胶、聚乙二醇、甘露醇、氯化钠、枸橼酸钠或任何其它本领域熟练人员已知的赋形剂。或者，该药物化合物可以装胶囊、压片或制成乳剂或糖浆剂用于

口服。可以加入药学上可接受的固体或液体载体以增强或稳定组合物，或者促进组合物的制备。液体载体包括糖浆、花生油、橄榄油、甘油、盐水、醇类和水。固体载体包括淀粉、乳糖、硫酸钙、二水合物、teffa alba、硬脂酸镁或硬脂酸、滑石粉、果胶、阿拉伯胶、琼脂或明胶。载体亦可包括持续释放的材料，例如甘油一硬脂酸酯或甘油二硬脂酸酯，单独或与蜡合用。固体载体的用量可变化，但优选每剂量单位约 20 mg 至约 1 克之间。需要时，采用常规的技术，例如研磨、混合、制粒、压片制备片剂；或者研磨、混合和充填制备硬明胶胶囊。当使用液体载体时，制剂为糖浆剂、酏剂、乳剂或者水性或非水悬浮液。这样的液体制剂可以直接给药，或者填充入软明胶胶囊。

以下的实施例有助于说明本发明。这些实施例决不意味对本发明范围的限制，而仅用来显示如何制备和使用本发明的化合物。

实施例 1

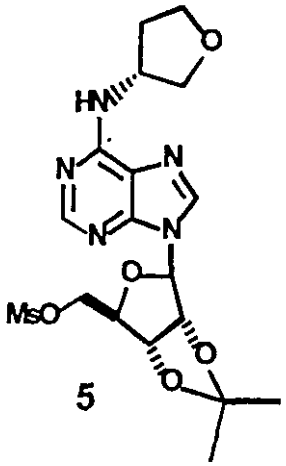


4

中间体 (4-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(1R,2R,5R)-7,7-二甲基-3,6,8-三噁二环[3.3.0]辛-2-基)甲-1-醇 (4)

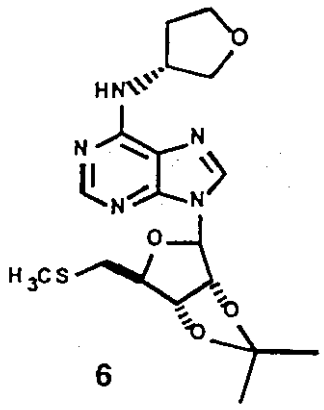
向化合物 3(2.0g, 6.0mmol)和 2,2-二甲氧基丙烷(1.2g, 11.8mmol)

的二甲基甲酰胺（20mL）溶液中于 70℃加入 p-甲苯磺酸(50mg, 0.26mmol)。70℃48 小时之后，将反应物真空浓缩，产生一固体。将该固体溶解于甲醇(3mL)，接着以乙醚(50mL)研碎。通过真空过滤收集产物晶体，得到中间体 4。



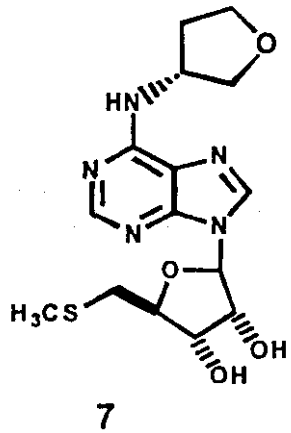
5

向 4(190mg, 0.5mmol)的无水吡啶(5mL)溶液中于 0℃加入 MsCl(80mL, 1mmol)。反应混合物在同样温度下搅拌 2 小时。减压除去吡啶，残余物溶于二氯甲烷(50mL)，以水洗涤(3x20mL)并干燥(Na_2SO_4)。溶剂蒸发，得到白色泡沫状产品 5: ^1H NMR(CDCl3) δ1.4(s, 3H), 1.6(s, 3H), 2.0-2.2(m, IH), 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

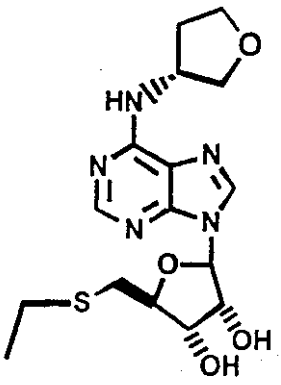
将甲磺酸酯 5(150mg)和甲硫醇盐(methanethiolate)(150mg)在乙腈(2mL)和水(1mL)中的混合物于 70℃加热 24 小时。减压蒸发溶剂，通过制备性 TLC 纯化残余物[甲醇-二氯甲烷(1:19)]以产生产物 6: ^{1}H NMR(CDC13) δ1.35(s,3H),1.60(s,3H),1.90-2.05(m,1H),2.05(s,3H),2.30-2.40(m,1H),2.70(AB 四重峰的双峰,2H),3.75-3.90(m,2H),3.95-4.00(m,2H),4.3-4.4(m,1H),4.8-4.95(m,1H),5.00-5.05(m,IH),5.45-5.50(d,1H),6.00-6.10(m,2H),7.85(s,1H),8.3(s,1H)。



7

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(甲硫基甲基)氧杂环戊烷-3,4-二醇(7)

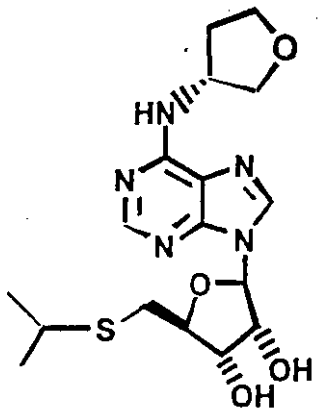
将化合物 6(50mg)溶于乙酸(8mL)和水(2mL)的混合物中，并在 90℃加热 16 小时。减压除去溶剂，通过制备性 TLC 纯化残余物[甲醇-二氯甲烷 (1:19)]以产生化合物 7：^{1}H NMR($CDCl_3$) δ1.90-2.05(m,1H), 2.15(s,3H), 2.30-2.40(m,1H), 2.75-2.85(m,2H), 3.80-3.90(m,2H), 3.90-4.00(m,2H), 4.30-4.45(m,2H), 4.50-4.55(m,1H), 4.75-4.95(m,1H), 5.90-5.95(m,1H), 6.30-6.60(m,1H), 7.95(s,1H), 8.25(s,1H)。



8

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(乙硫基)甲基]氧杂环戊烷-3,4-二醇(8)

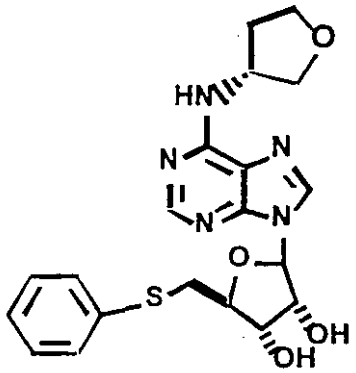
用与 7 相同的方法，以乙硫醇盐代替甲硫醇盐制备化合物 8。(M+1)=382.30



10

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5[(甲基乙硫基)甲基]氧杂环戊烷-3,4-二醇(10)

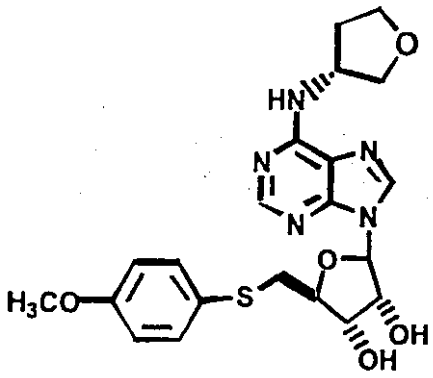
用与 7 相同的方法，以异丙硫醇盐代替甲硫醇盐制备化合物 10。^{1}H NMR(CDCl3)δ1.25(d,6H),1.90-2.05(m,1H),2.15(s,3H),2.30-2.40(m,1H),2.85-2.87(d,2H),2.95(七重峰,1H),3.80-3.90(m,2H), 3.95-4.05(m,2H),4.35-4.40(m,2H),4.50-4.55(m,1H),4.75-4.85(m,1H),5.90-5.95(d,1H),6.85-6.95(m,1H),7.95(s,1H),8.25(s,1H)。



11

2-{6-[((3R)-氧杂环戊烷-3-yl)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(苯硫基甲基)氧杂环戊烷-3,4-二醇(11)

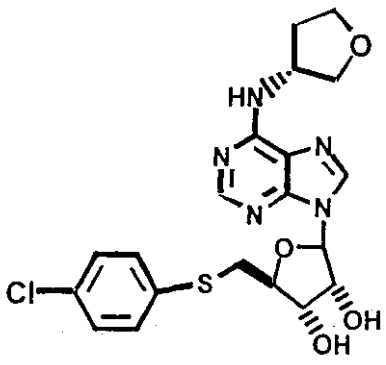
用与 7 相同的方法，以苯硫醇盐代替甲硫醇盐，制备化合物 11。^{1}H NMR($CDCl_3$)1.95-2.05(m,1H), 2.30-2.40(m,1H), 3.2(d,2H), 3.80-3.90(m,2H), 3.95-4.10(m,2H), 4.35-4.40(d,1H), 4.45(t,1H), 4.50-4.55(m,1H), 4.80-4.90(m,1H), 5.85(d,1H), 6.70-6.80(m,1H), 7.15-7.30(m,3H),7.35(d,2H),7.75(s,1H),8.25(s,1H)。



12

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-甲氧基苯硫基)甲基]氧杂环戊烷-3,4-二醇(12)

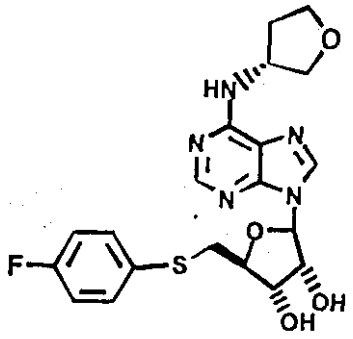
用与 7 相同的方法，以 4-甲氧基苯硫醇盐代替甲硫醇盐制备此化合物。(M+1)=460.4



13

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-氯苯硫基)甲基]氧杂环戊烷-3,4-二醇(13)

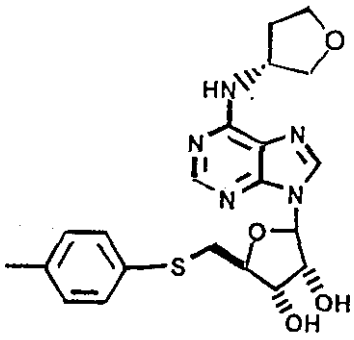
用与 7 相同的方法，以 4-氯苯硫醇盐代替甲硫醇盐制备该化合物。(M+1)=464.3



14

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-氟苯硫基)甲基]氧杂环戊烷-3,4-二醇(14)

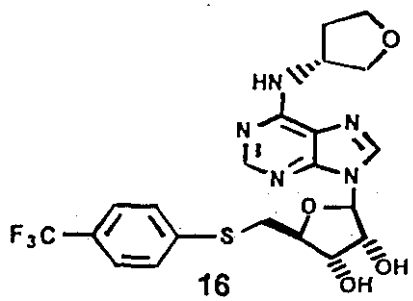
用与7相同的方法，以4-氟苯硫醇盐代替甲硫醇盐制备这种化合物。(M+1)=448.3



15

2-{6[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4-甲基苯硫基)甲基]氧杂环戊烷-3,4-二醇(15)

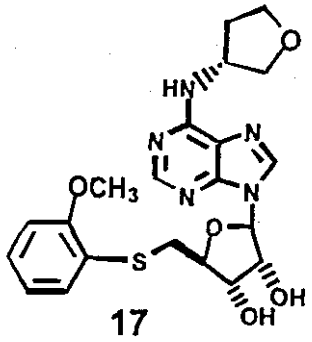
用与7相同的方法，以4-甲基苯硫醇盐代替甲硫醇盐制备这种化合物。(M+1)=444.38



16

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(4(三氟甲基)苯硫基)甲基]氧杂环戊烷-3,4-二醇(16)

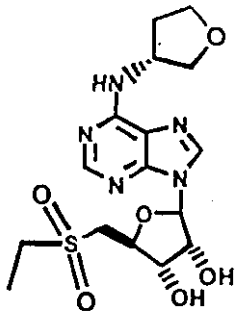
用与 7 相同的方法，以 4-三氟甲基苯硫醇盐代替甲硫醇盐制备这种化合物。(M+1)=488.36



17

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(2-甲氧基苯硫基)甲基]氧杂环戊烷-3,4-二醇(17)

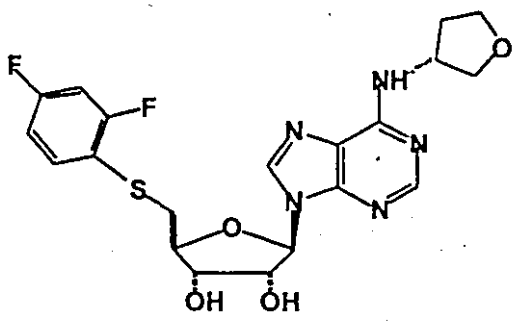
用与 7 相同的方法，以 2-甲氧基苯硫醇盐代替甲硫醇盐制备这种化合物。(M+1)=460.4



9

(5-{6-[((3R)氧杂环戊烷-3-基)氨基]嘌呤-9-基}(2S,3S,4R,5R)-3,4-二羟基氧杂环戊烷-2-基)(乙磺酰基)甲烷(9)

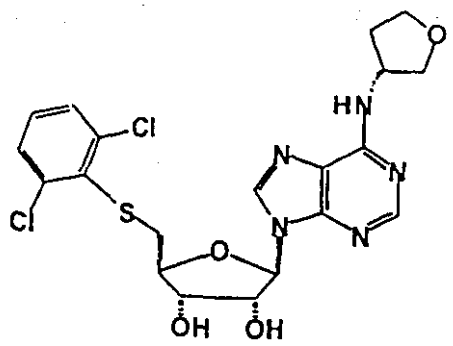
在0℃氮气下向冷却的硫化物8甲醇溶液中加入3当量的过硫酸氢钾制剂(Potassium peroxy monosulfate)，反应混合物在同样温度下搅拌1小时。在原料消耗(用TLC检测)之后,浓缩反应混合物并经硅胶小塞过滤。通过制备性 TLC[甲醇-二氯甲烷(1:19)]产生黄白色吸湿性固体 9。(M+1)=414.28



18

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(2,4-二氟苯硫基)甲基]氧杂环戊烷-3,4-二醇(18)

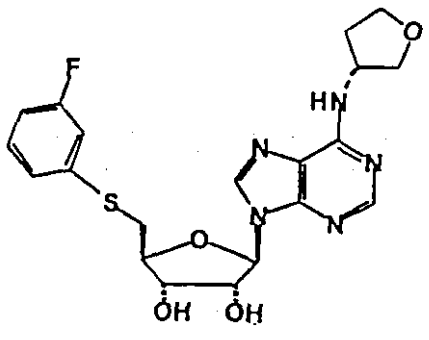
用与 7 相同的方法，以 2,4-二氟苯硫醇盐代替甲硫醇盐制备这种化合物。(M+1)=466.23



19

2-{6-[((3R)- 氧 杂 环 戊 烷 -3- 基) 氨 基] 嘌 呤 -9-基}(4S,5S,2R,3R)-5-[(2,6-二氟苯硫基)甲基]氧杂环戊烷-3,4-二醇(19)

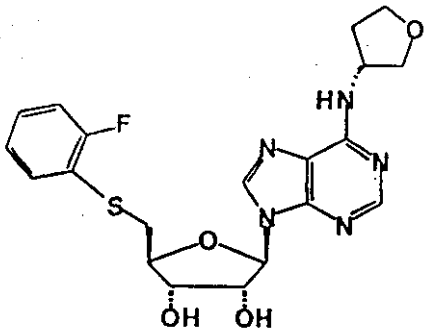
以与 7 相同的方法，以 2,6-二氯苯硫醇盐代替甲硫醇盐，制备这种化合物。(M+1)=498.18。



20

2-{6-[((3R)- 氧 杂 环 戊 烷 -3- 基) 氨 基] 嘌 呤 -9-基}(4S,5S,2R,3R)-5-[(3-二氟苯硫基)甲基]氧杂环戊烷-3,4-二醇(20)

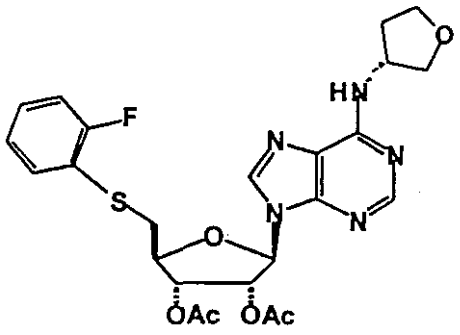
用与 7 相同的方法，以 3-氟苯硫醇盐代替甲硫醇盐，制备这种化合物。(M+1)=448.26。



21

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-[(2-氟苯硫基)甲基]氧杂环戊烷-3,4-二醇(21)

用与 7 相同的方法，以 2-氟苯硫醇盐代替甲硫醇盐，制备这种化合物。(M+1)=448.24。

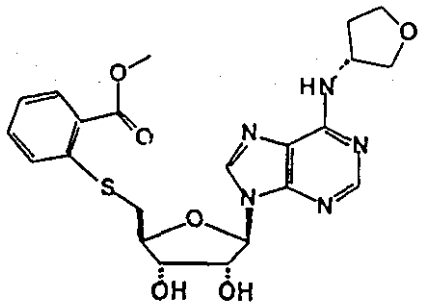


22

(5-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(2S,3S,4R,5R)-4-乙酰氧基-2-[(氟代苯硫基)甲基]氧杂环戊烷-3-基乙酸酯(22)

在 23℃，向化合物 21(139mg)的吡啶(2mL)溶液中加入醋酸酐(0.1mL)。23℃3 小时之后，将反应物真空浓缩。残余物溶于二氯甲烷

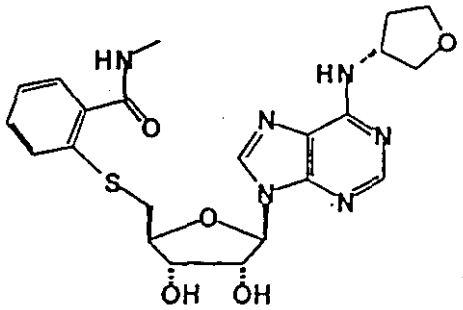
(50mL)，以水洗涤(3x10mL)，并干燥(Na_2SO_4)。真空浓缩之后，残余物经快速色谱法(二氯甲烷:甲醇 20:1，之后 9:1)纯化产生化合物 22(170mg)：



23

2[(5-{6-[((3R)氧杂环戊烷-3-基)氨基]嘌呤-9-基}(2S,3S,4R,5R)-3,4-二羟基氧杂环戊烷-2-基)甲硫基]苯甲酸甲酯(23)

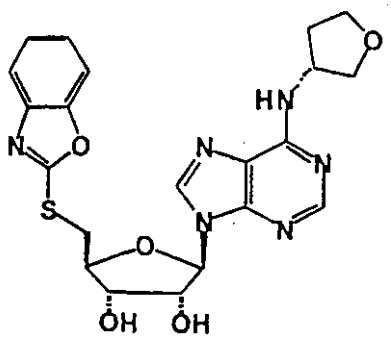
向化合物 4(0.377g,1mmol)的 5mL THF 溶液中，加入三苯基膦(0.524g,2mmol)、DEAD(0.40mL,2mmoles)，在加入 2-甲酯基苯硫酚(0.5mL)之前搅拌 5 分钟。使反应液回流搅拌。回流 72 小时之后，将反应液真空浓缩，残余物通过快速柱色谱法(20%EtOAc/己烷)纯化产生澄明的粘油。它被置入乙酸(8mL)和水(2mL)的混合物中并在 80℃加热 16 小时。真空除去溶剂，残余物通过制备性 TLC[甲醇-二氯甲烷(1:9)]纯化，得到化合物 23。(M+1)=488.5。



24

{2[(5-{6-[((3R)[氧杂环戊烷-3-基)氨基]嘌呤-9-基}(2S,3S,4R,5R)-3,4-二羟基氧杂环戊烷-2-基)甲硫基]苯基}-N-甲基酰胺苯甲酸酯(24)

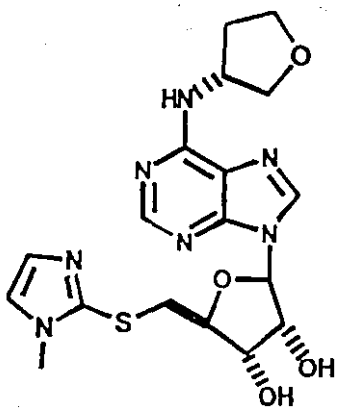
将化合物 23 置于甲胺(2mL)和 1-丙醇(2mL)的 40%水溶液中，70℃加热 16 小时。真空除去溶剂，残余物通过制备性 TLC[甲醇-二氯甲烷(1:9)]纯化以得到化合物 24。(M+1)=487.5



25

2-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(苯并噁唑-2-基硫代甲基)氧杂环戊烷-3,4-二醇(25)

用与 23 相同的方法，以 2-巯基苯并噁唑代替 2-甲酯基(carbmethoxy)苯硫酚制备这种化合物。(M+1)=471.4。

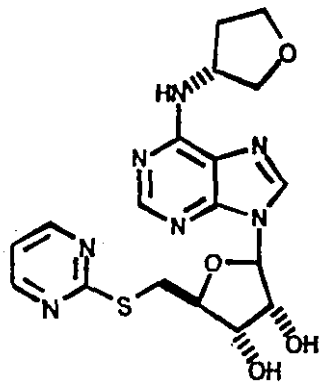


26

2-{6-[((3S)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(1-甲基咪唑-2-基-硫代)甲基]氧杂环戊烷-3,4-二醇(26)

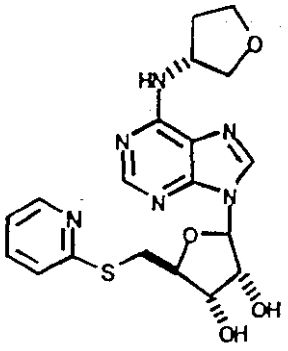
用制备化合物23的方法，以2-巯基-1-甲基-咪唑代替2-甲酯基苯硫酚制备化合物26[MS 434.4(M+1)]。

2-{6-[((3S)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(嘧啶-2-基硫代甲基)氧杂环戊烷-3,4-二醇(27)



27

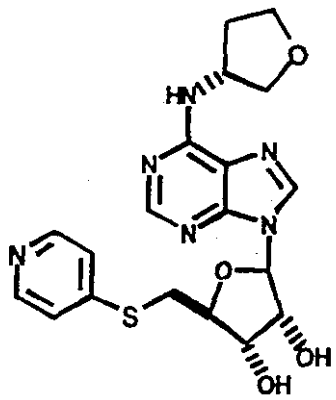
用制备化合物23的方法，以2-巯基嘧啶代替2-甲酯基苯硫酚制备化合物27[MS432.4(M+1)]。



28

2-{6-[((3S)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(2-吡啶基硫代甲基)氧杂环戊烷-3,4-二醇(28)

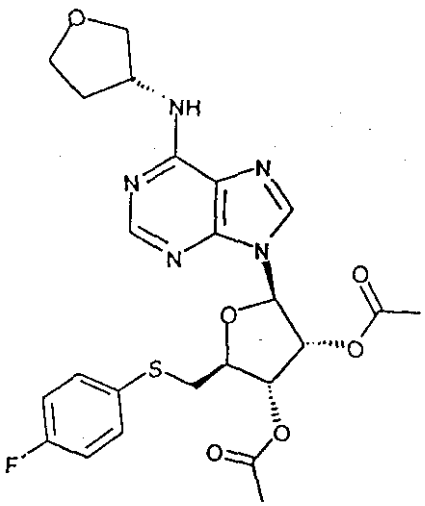
用制备化合物23的方法，以2-巯基吡啶代替2-甲酯基苯硫酚制备化合物28[MS431.4(M+1)]。



29

2-{6-[((3S)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(4S,5S,2R,3R)-5-(4-吡啶基硫代甲基)氧杂环戊烷-3,4-二醇(29)

用制备化合物23的方法，以4-巯基吡啶代替2-甲酯基苯硫酚制备化合物29[MS431.4(M+1)]。



5-{6-[((3R)-氧杂环戊烷-3-基)氨基]嘌呤-9-基}(2S,3R,4R,5R)-4-乙酰氧基-2-[(4-氟苯硫基)甲基]氧杂环戊烷-3-基]乙酸酯(30)(M+1)=532.17。

实施例 2

结合试验-DDT_1细胞

细胞培养

DDT 细胞(仓鼠输精管平滑肌细胞系)在北特利平皿中采用含有 2.5g ml^{-1}两性霉素 B、100U ml^{-1}青霉素 G、0.1mg ml^{-1}硫酸链霉素和 5%牛胎血清的 Dulbecco 改进的 Eagle 培养基(DMEM),在 95%空气和 5%CO_2的潮湿空气中以单分子层生长。每周两次将细胞分散到不含二价阳离子和含有 1mM EDTA 的 Hank's 平衡盐溶液(HBSS)中进行次代培养。然后将这些细胞以每板 $1.2x10^5$个细胞的密度种入生长培养基,在约一天的预汇合后 4 天进行实验。

膜制备

贴壁细胞以 HBSS 洗涤两次(2×10ml),在 4℃借助于橡胶淀帚从板上刮离到 50mM Tris-HCl 缓冲液(pH 7.4,4℃)5ml 中,将悬浮液匀化 10 秒。然后将悬浮液于 27,000×g 离心 10 分钟。通过涡旋将沉淀再悬浮于匀浆化缓冲液中,再如上所述进行离心。最后的沉淀再悬浮于 1 体积含 5mM $MgCl_2$的 50mM Tris-HCl 缓冲液(pH7.4),用于 A_1 Ado R 试验。对于[^{35}S]GTPγS 结合试验,最终沉淀在含有 5mM $MgCl_2$、100mM NaCl 和 1mM 二硫苏糖醇的 50 mM Tris-HCl(pH7.4)中再悬浮。这种膜悬浮液置于液氮内 10 分钟,融化,用于试验。采用 Bradford™试验试剂盒以牛血清白蛋白作标准,测定蛋白含量。

竞争性结合试验

在 50mM Tris 缓冲液中匀浆化制备猪纹状体(5x 体积的组织物质，pH=7.4)。于 4℃、19,000 rpm 离心 25 分钟之后，弃去上清液，该步骤重复两次。试验本发明的成分以测定它们对猪纹状体膜制备或 DDT_1 膜制备 A_1 受体的亲和力。简言之，以腺苷脱氨基酶和 50mM Tris 缓冲液处理 0.2mg 猪纹状体膜或 DDT_1 细胞膜，然后混合。向这种猪膜加入浓度为 100μM 至 10nM 的本发明化合物的连续稀释 DMSO 储液 2μl。对照组仅接受 2 微升 DMSO，然后加入拮抗剂[^{3}H]8-环戊基黄嘌呤(CPX)（猪纹状体）或者激动剂[^{3}H]2-氯-6-环戊基腺苷(CCPA)（DDT_1 膜）的 Tris 缓冲溶液(50mM, pH 7.4)，以获得终浓度 2nM。23℃培养 2 小时之后，将该溶液用膜收集器过滤，多次洗涤膜(3x)。滤板在闪烁混合物中计数，给出氚标记 CPX 的置换量，或者通过竞争性结合本发明成分的置换量。采用多于 5 点的曲线以产生 Ki 值，如下表 1 的标记的栏内表明实验编号：

表 1

化合物#	Ki-DDT_1 细胞膜	Ki-猪纹状体
7	--	222nM
10	--	188nM
11	--	44nM
12	820nM	--
14	363nM	--
15	922nM	--
16	7701nM	--
17	947nM	--

实施例 3

[^{35}S]GTPγS 结合试验

A_1-激动剂刺激[^{35}S]GTPγS 结合可用 Gierscikik 等人(1991)和 Lorenzen 等人(1993)所述方法的改进法进行测量。在含有 50mM Tris-HCl 缓冲液（pH7.4）、5mM $MgCl_2$、100mM NaCl、1mM 二硫苏糖醇、0.2 单位 ml^{-1} 腺苷脱氨基酶、0.5% BSA、1mM EDTA、10mM GDP、0.3nM[^{35}S]GTPγS 以及含或不含各种浓度 CPA 的 0.1ml 体积溶液中，将膜蛋白（30-50μg）于 30℃培养 90 分钟。加入 10μM GTPγS，测量非特异性结合。测定激动剂刺激的结合，为CPA存在下的总结合和无CPA时测得的本底结合之间的差。早先的报道已经显示激动剂刺激的[^{35}S]GTPγS 结合取决于 GDP 的存在 (Gierschik 等人，1991; Lorenzen 等人，1993; Traynor & Nahorski, 1995)。在初步的实验中，发现 10μM GDP 产生 CPA 依赖性[^{35}S]GTPγS 结合的最佳刺激，这种浓度因此用于所有研究中。在饱和实验中，以 0.5-1000nM GTPγS 温孵 0.5nM [^{35}S]GTPγS。温孵结束时，过滤各悬浮液并且如上介绍测量保留的放射性。结果以完全激动剂 N-6-环戊基腺苷（CPA）为标准表示。

表 2

化合物#	GTPγS
CPA	100%
8	104%
12	52%
13	69%
14	61%
15	48%
16	31%
17	52%

实施例 4

cAMP 试验

采用家兔抗 cAMP 抗体，添加示踪剂腺苷 3'，5'-环磷酸 2'-O-琥珀酰-3-[^{125}I]碘酪氨酸甲酯和含抗家兔特异性抗体的荧光微球体，如 Amersham Pharmacia Biotech(Biotrak cellular assays)所描述的进行闪烁亲近测定（SPA）。简言之，在具有不透明孔、底部清晰的 96 孔微量滴定板中，以每孔 10^4~10^5个细胞的浓度（在 40μl HBSS 中）于 37℃（5%CO_2和 95%湿度）培养 DDT_1细胞。将本发明的部分或完全 A_1激动剂(5μl)以各种浓度与 DDT_1细胞在咯利普兰(rolipram)(50μM)和 5μM 弗司扣林(forskolin)存在下于 37℃培养 10 分钟。用 5μl 10%十二烷基三甲基铵溴化物处理后采用微板震荡器震荡微量板，使这些细胞立即溶解。培养 5 分钟之后，将免疫试剂溶液(150μl，含有等体积示踪剂、抗血清和 SPA 荧光球)加入每个孔，然后密封板。23℃下培养 15-20 小时之后，在微滴定板闪烁计数器中计数 2 分钟，测量与荧光微球结合的 [^{125}I]cAMP 量。计数与采用同样方案产生的 cAMP 标准曲线比较，得出细胞溶解后的 cAMP 含量。显示的结果以完全激动剂 N-6-环戊基腺苷（CPA）为标准表示。因此，完全激动剂 CPA 将弗司扣林诱导的 cAMP 生成减少至基础水平。

表 3

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