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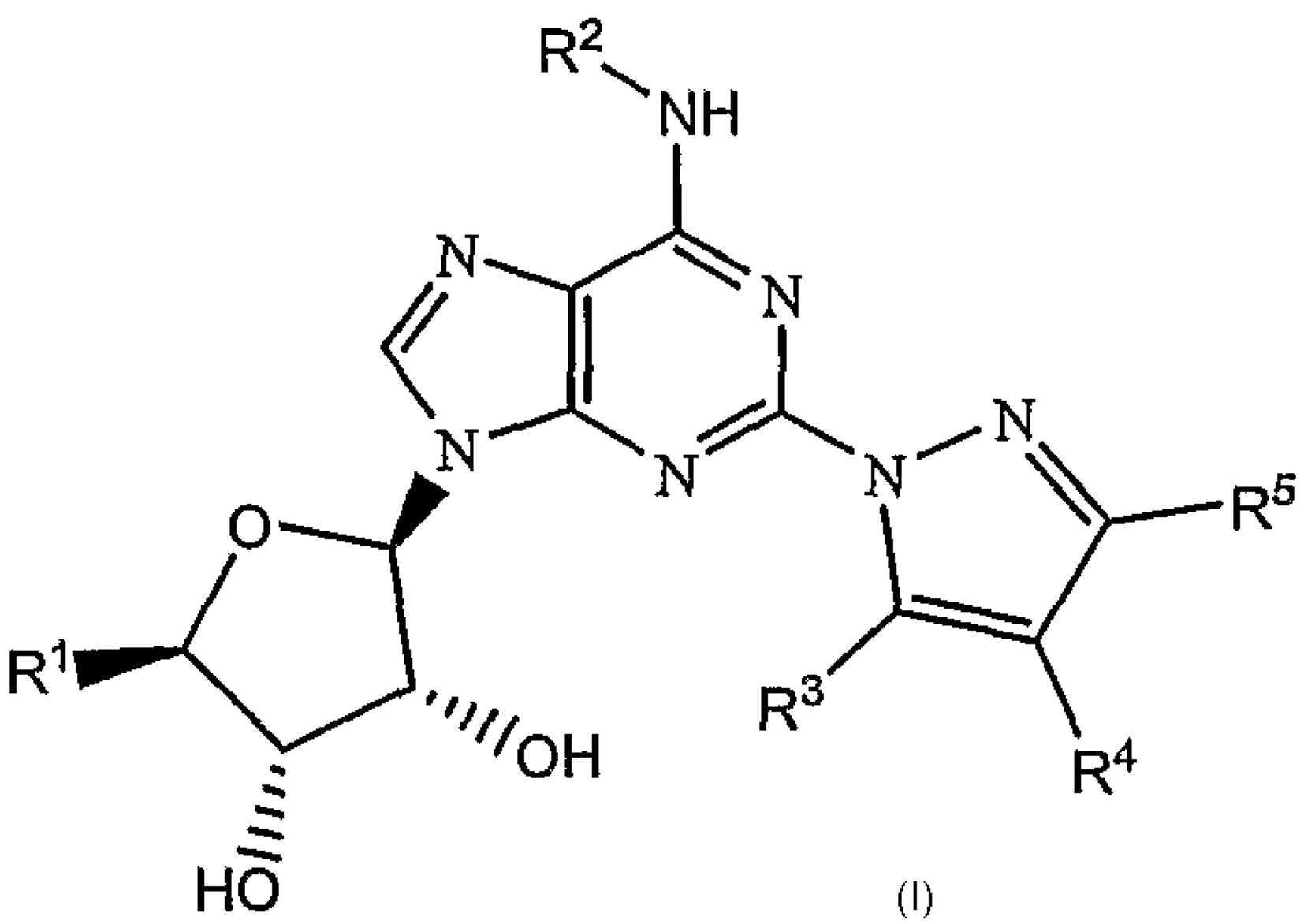
(54) Titre : AGONISTES DES RECEPTEURS DE L'ADENOSINE A_1

(54) Title: A_1 ADENOSINE RECEPTOR AGONISTS



(I)

(57) Abrégé/Abstract:
Disclosed are novel compounds that are partial and full A_1 adenosine receptor agonists having the structure of Formula (I): which are useful for treating various disease states, in particular tachycardia and atrial flutter, angina, and myocardial infarction.

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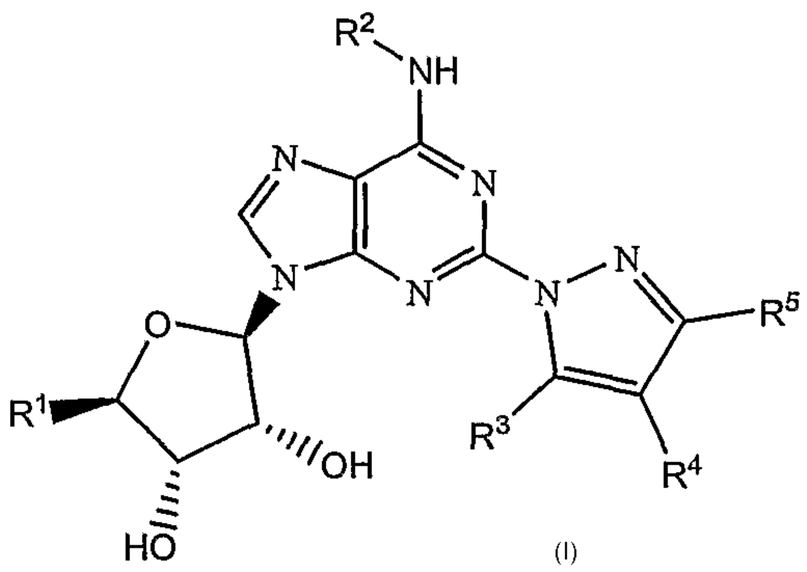
(54) Title: A_1 ADENOSINE RECEPTOR AGONISTS



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(57) Abstract: Disclosed are novel compounds that are partial and full A_1 adenosine receptor agonists having the structure of Formula (I): which are useful for treating various disease states, in particular tachycardia and atrial flutter, angina, and myocardial infarction.

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A_1 ADENOSINE RECEPTOR AGONISTS

Cross Reference to Related Applications

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 60/683,505, filed May 19, 2005, the complete disclosure of which is hereby incorporated by reference.

Field of the Invention

[0002] The present invention relates to novel compounds that are partial or full A_1 adenosine receptor agonists, and to their use in treating mammals for various disease states, including modifying cardiac activity, in particular treatment of arrhythmia. The compounds are also useful for treating CNS disorders, diabetic disorders, obesity, and modifying adipocyte function. The invention also relates to methods for their preparation, and to pharmaceutical compositions containing such compounds.

Background

[0003] Adenosine is a naturally occurring nucleoside, which exerts its biological effects by interacting with a family of adenosine receptors known as A_1, A_{2a}, A_{2b}, and A_3, all of which modulate important physiological processes. For example, activation of the A_{2A} adenosine receptors causes coronary vasodilation, A_{2B} receptors have been implicated in mast cell activation, asthma, vasodilation, regulation of cell growth, intestinal function, and modulation of neurosecretion (See Adenosine A_{2B} Receptors as Therapeutic Targets, *Drug Dev Res* 45:198; Feoktistov et al., *Trends Pharmacol Sci* 19:148-153), and A_3 adenosine receptors modulate cell proliferation processes.

[0004] The A_1 adenosine receptor is coupled to two distinct signaling pathways in heart cells. The first pathway is A_1 adenosine receptor to inhibitory G_{oc} protein to inhibition of adenylate cyclase activity to attenuation of the cardiostimulatory effects of catecholamines. The second signaling pathway is A_1 adenosine receptor to inhibitory

G protein $\beta\gamma$ subunits to activation of I_{kAdo} to slowing of both atrial SA nodal pacemaking and conduction of electrical impulses through the AV node. (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). Stimulation of the A_1 adenosine receptor shortens the duration and decreases the amplitude of the action potential of AV nodal cells, and hyperpolarizes and hence prolongs the refractory period of the AV nodal cell. Thus, stimulation of A_1 receptors provides a method of treating supraventricular tachycardias, including termination of nodal re-entrant tachycardias, and of controlling ventricular rate during atrial fibrillation and flutter.

[0005] Accordingly, A_1 adenosine receptor agonists are useful in the treatment of acute and chronic disorders of heart rhythm, especially those diseases characterized by rapid heart rate, in which 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.

[0006] A_1 adenosine receptor agonists, through their ability to inhibit the effects of catecholamines, decrease cellular cAMP, and thus have beneficial effects in the failing heart where increased sympathetic tone increases cellular cAMP levels. The latter condition has been shown to be associated with increased likelihood of ventricular arrhythmias and sudden death. See, for example, 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.

[0007] A_1 adenosine receptor agonists, as a result of their inhibitory action on cyclic AMP generation, have anti-lipolytic effects in adipocytes that lead to a decreased release of non-esterified 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). A glucose fatty acid cycle was proposed by P. J. Randle as early as 1963 (P. J. Randle et al (1963) *Lancet* 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).

[0008] The benefit of A_1 adenosine receptor agonists in central nervous disorders has been reviewed (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 A_1 adenosine receptor agonists (G. Zhang et al. *Eur. J. Pharmacol.* Vol. 255 (1994) p. 239-243). Furthermore, A_1 adenosine receptor agonists have been shown to have anticonvulsant activity in the DMCM model (L. J. S. Knutsen, Adenosine and Adenine 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 ischemia 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).

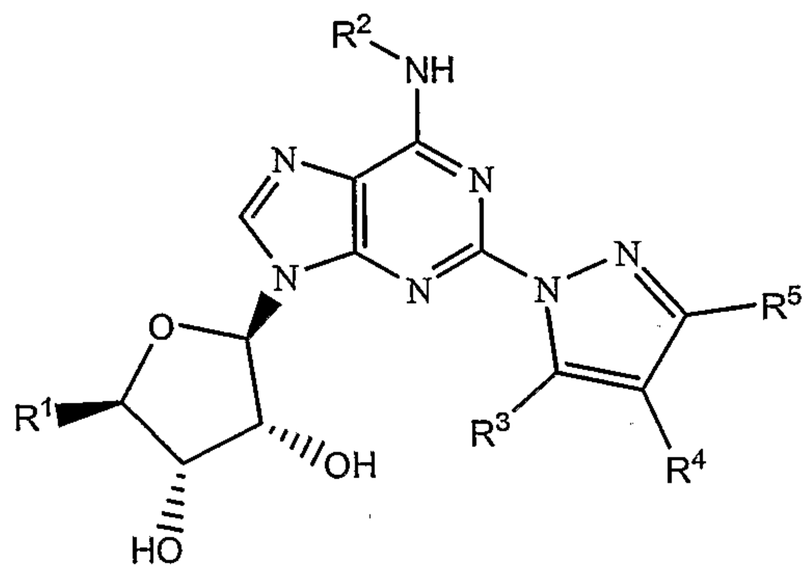
[0009] Adenosine itself has proven effective in treating disease states related to the A_1 adenosine receptor, for example in terminating paroxysmal supraventricular tachycardia. However, these effects are short-lived because adenosine's half-life is less than 10 sec. Additionally, as adenosine acts indiscriminately on the A_1, A_{2A}, A_{2B}, and the A_3 adenosine receptor subtypes, it also provides direct effects on sympathetic tone, coronary vasodilatation, systemic vasodilatation and mast cell degranulation.

[0010] Accordingly, it is an object of this invention to provide compounds that are

potent full A_1 adenosine receptor agonists or partial A_1 receptor agonists with a half life greater than that of adenosine, and that are selective for the A_1 adenosine receptor, which will ensure that undesired side effects related to stimulation or antagonism of the other adenosine receptors are avoided.

SUMMARY OF THE INVENTION

[0011] It is an object of this invention to provide compounds that are partial or full A_1 adenosine receptor agonists having the structure of Formula I:



wherein:

R^1 is hydroxymethyl, $-C(O)OR^6$, or $-C(O)NHR^6$, in which R^6 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aralkyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^2 is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, $-CO_2H$, $- SO_3H$, $-C(O)OR^6$, -

$CH(OH)R^6$, or $C(O)NR^6R^7$, wherein R^7 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aralkyl, optionally substituted aryl, or optionally substituted heteroaryl.

[0012] Another object of the invention is to provide methods for treating conditions that can be treated using the partial or full A_1 adenosine receptor agonists of the invention. Diseases that can be treated using the method of the invention include, but are not limited to, atrial fibrillation, atrial flutter, congestive heart failure, epilepsy, stroke, diabetes, obesity, ischemia, stable angina, unstable angina and myocardial infarction. The method of the invention is also useful in treating hyperlipidemic conditions, and is therefore useful for treating metabolic disorders, including type II diabetes, hypertriglyceridemia, and metabolic syndrome. The method of the invention also useful in protecting tissues being maintained for transplantation.

[0013] Preferred embodiments of the invention utilize compounds including, but not limited to:

[0014] (5-{6-[((3R)oxolan-3-yl)amino]-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide;

[0015] (5-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-quinolyl)pyrazolyl)purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide;

[0016] ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4- carboxylate;

[0017] (4S,3R,5R)-2-[2-(3,5-dimethylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

[0018] (4S,3R,5R)-2-[2-(3,5-dimethyl-4-propylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

[0019] (4S,3R,5R)-2-[2-(4-butyl-3,5-dimethylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

[0020] methyl 4-{[(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)carbonylamino]methyl}benzoate;

[0021] 4-{[(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)carbonylamino]methyl}benzoic acid;

[0022] 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylic acid;

[0023] 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxamide;

[0024] ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(bicyclo[2.2.1]hept-2-ylamino)purin-2-yl}pyrazole-4-carboxylate;

[0025] 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(bicyclo[2.2.1]hept-2-ylamino)purin-2-yl}pyrazole-4-carboxylic acid;

[0026] (1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide;

[0027] (4S,3R,5R)-2-[6-(bicyclo[2.2.1]hept-2-ylamino)-2-pyrazolylpurin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

[0028] 2-{6-[((3R)oxolan-3-yl)amino]-2-[4-(hydroxyphenylmethyl)pyrazolyl]purin-9-yl}(4S,2R,3R,5R)-5-(hydroxymethyl)oxolane-3,4-diol;

[0029] ethyl 1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylate;

[0030] 1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylic acid;

[0031] (1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide;

[0032] 2-{6-[((3R)oxolan-3-yl)amino]-2-(4-pyrazin-2-ylpyrazolyl)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol;

[0033] 2-{6-[((3R)oxolan-3-yl)amino]-2-(4-quinazolin-2-ylpyrazolyl)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol;

[0034] (1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide;

[0035] ethyl 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazole-4-carboxylate;

[0036] (1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-propylcarboxamide;

[0037] (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-propylcarboxamide;

[0038] (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide;

[0039] (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide;

[0040] 6-(1-{6-[((3R)oxolan-3-yl)amino]-9-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)pyridine-3-carboxylic acid;

[0041] (1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-[(4-chlorophenyl)methyl]carboxyamide;

[0042] (1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-[(4-fluorophenyl)methyl]carboxyamide;

[0043] (1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-benzylcarboxamide;

[0044] (1-{6-[((3R)oxolan-3-yl)amino]-9-[(3S,2R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-{[5-fluoro-3-(trifluoromethyl)phenyl]methyl}carboxyamide;

[0045] (5-{6-[((3R)oxolan-3-yl)amino]-2-(4-(4-pyridyl)pyrazolyl)purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide;

[0046] 5-{6-[((3R)oxolan-3-yl)amino]-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolane-2-carboxylic acid;

[0047] 5-(hydroxymethyl)-2-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}oxolane-3,4-diol;

[0048] 2-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-pyridyl)pyrazolyl)purin-9-yl}(4S,3R)-5-(hydroxymethyl)oxolane-3,4-diol;

[0049] 2-{6-[((3R)oxolan-3-yl)amino]-2-(4-(4-pyridyl)pyrazolyl)purin-9-yl}(4S,3R)-5-(hydroxymethyl)oxolane-3,4-diol;

[0050] 2-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-quinolyl)pyrazolyl)purin-9-yl}(4S,3R)-5-(hydroxymethyl)oxolane-3,4-diol;

[0051] (4S,3R,5R)-2-[6-(cyclopentylamino)-2-pyrazolylpurin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

[0052] 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}-5-methylpyrazole-3-carboxamide;

[0053] 2-(6-[((3R)oxolan-3-yl)amino]-2-{4-[4-(trifluoromethyl)phenyl]pyrazolyl}purin-9-yl)(4S,2R,3R,5R)-5-(hydroxymethyl)oxolane-3,4-diol;

[0054] (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}-5-methylpyrazol-3-yl)-N-methylcarboxamide;

[0055] 4-({9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-2-[4-(ethoxycarbonyl)pyrazolyl]purin-6-yl}amino)benzenesulfonic acid;

[0056] 1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carbonitrile;

[0057] ethyl (2E)-3-(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)prop-2-enoate;

[0058] ethyl 3-(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)propanoate;

[0059] ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazole-4-carboxylate;

[0060] (4S,3R,5R)-2-[6-(cyclohexylamino)-2-pyrazolylpurin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

[0061] 3-(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-methylpropanamide;

[0062] (1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide;

[0063] ethyl 1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylate;

[0064] (1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-(3,3,3-trimethyl-3-azabutyl)carboxamide;

[0065] 2-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-2-pyrazolylpurin-9-yl}(2R,5R)-5-(hydroxymethyl)oxolane-3,4-diol;

[0066] 1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylic acid;

[0067] (1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide;

[0068] 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazole-4-carboxamide;

[0069] 1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxamide;

[0070] 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazole-4-carboxylic acid;

[0071] (2R,5R)-2-{2-[4-(aminomethyl)pyrazolyl]-6-(cyclopentylamino)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol;

[0072] [(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)methyl][(4-fluorophenyl)sulfonyl]amine;

[0073] (1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(oxolan-3-ylamino)purin-2-yl}pyrazol-4-yl)-N-[(4-fluorophenyl)sulfonyl]carboxamide;

[0074] (1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-[(4-fluorophenyl)sulfonyl]carboxamide;

[0075] methyl 2-{[(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)carbonylamino]sulfonyl}benzoate;

[0076] (1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-(ethylsulfonyl)carboxamide;

[0077] (1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-[(2-chlorophenyl)sulfonyl]carboxamide;

[0078] N-(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)[(4-methylphenyl)sulfonyl]carboxamide;

[0079] N-(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)[benzylsulfonyl]carboxamide;

[0080] N-(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)(phenylsulfonyl)carboxamide;

[0081] N-(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl){[4-(trifluoromethyl)phenyl]sulfonyl}carboxamide; and

[0082] (1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-[(3-chlorophenyl)sulfonyl]carboxamide.

DEFINITIONS AND GENERAL PARAMETERS

[0083] The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-hexyl, n-decyl, tetradecyl, and the like.

[0084] The term "substituted alkyl" refers to:

1) an alkyl group as defined above, having from 1 to 5 substituents, for example 1 to 3 substituents, selected from the group consisting of alkenyl, alkynyl, alkoxy,

cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, heteroarylthio, heterocyclylthio, thiol, alkylthio, aryl, aryloxy, heteroaryl, aminosulfonyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclooxy, hydroxyamino, alkoxyamino, quaternary amino, nitro, -SO_3H, -SO-alkyl, -SO-aryl,-SO-heteroaryl, -SO_2-alkyl, SO_2-aryl and -SO_2-heteroaryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, quaternary amino, cyano, -SO_3H, and $-S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2; or

2) an alkyl group as defined above that is interrupted by 1-5 atoms or groups independently chosen from oxygen, sulfur and -$N(R_a)_v$-, where v is 1 or 2 and R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl and heterocyclyl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, quaternary amino, cyano, -SO_3H, and $-S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2; or

3) an alkyl group as defined above that has both from 1 to 5 substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

[0085] The term "lower alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms. Groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, t-butyl, n-hexyl, and the like exemplify this term.

[0086] The term "substituted lower alkyl" refers to lower alkyl as defined above having 1 to 5 substituents, for example 1 to 3 substituents, as defined for substituted alkyl, or a lower alkyl group as defined above that is interrupted by 1-5 atoms as defined for substituted alkyl, or a lower alkyl group as defined above that has both from 1 to 5 substituents as defined above and is also interrupted by 1-5 atoms as defined above.

[0087] The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, for example having from 1 to 20 carbon atoms, for example 1-10 carbon atoms, more for example 1-6 carbon atoms. This term is exemplified by groups such as methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), the propylene isomers (e.g., $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$) and the like.

[0088] The term "lower alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, for example having from 1 to 6 carbon atoms.

[0089] The term "substituted alkylene" refers to:

(1) an alkylene group as defined above having from 1 to 5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, heteroarylthio, heterocyclylthio, thiol, alkylthio, aryl, aryloxy, heteroaryl, aminosulfonyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclooxy, hydroxyamino, alkoxyamino, quaternary amino, nitro, $-SO_3H$, -SO-alkyl, -SO-aryl,-SO-heteroaryl, $-SO_2-$ alkyl, SO_2-aryl and $-SO_2$-heteroaryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, quaternary amino, cyano, $-SO_3H$, and $-S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2; or

(2) an alkylene group as defined above that is interrupted by 1-5 atoms or groups independently chosen from oxygen, sulfur and $-N(R_a)_v-$, where v is 1 or 2 and R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, heterocyclyl carbonyl, carboxyester, carboxyamide and sulfonyl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, quaternary amino, cyano, $-SO_3H$, and $-S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2; or

(3) an alkylene group as defined above that has both from 1 to 5 substituents as defined above and is also interrupted by 1-20 atoms as defined above. Examples of substituted alkylenes are chloromethylene (-CH(Cl)-), aminoethylene (-CH(NH_2)CH_2-), methylaminoethylene (-CH(NHMe)CH_2-), 2-carboxypropylene isomers(-CH_2CH(CO_2H)CH_2-), ethoxyethyl (-CH_2CH_2O-CH_2CH_2-), ethylmethylaminoethyl (-$CH_2CH_2N(CH_3)CH_2CH_2$-),1-ethoxy-2-(2-ethoxy-ethoxy)ethane (-CH_2CH_2O-CH_2CH_2-OCH_2CH_2-OCH_2CH_2-), and the like.

[0090] The term "aralkyl" refers to an aryl group covalently linked to an alkylene group, where aryl and alkylene are defined herein. "Optionally substituted aralkyl" refers to an optionally substituted aryl group covalently linked to an optionally substituted alkylene group. Such aralkyl groups are exemplified by benzyl, phenylethyl, 3-(4-methoxyphenyl)propyl, and the like.

[0091] The term "alkoxy" refers to the group R-O-, where R is optionally substituted alkyl or optionally substituted cycloalkyl, or R is a group -Y-Z, in which Y is optionally substituted alkylene and Z is optionally substituted alkenyl, optionally substituted alkynyl; or optionally substituted cycloalkenyl, where alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are as defined herein. Preferred alkoxy groups are optionally substituted alkyl-O- and include, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, trifluoromethoxy, and the like.

[0092] The term "alkylthio" refers to the group R-S-, where R is as defined for alkoxy.

[0093] The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group for example having from 2 to 20 carbon atoms, more for example 2 to 10 carbon atoms and even more for example 2 to 6 carbon atoms and having 1-6, for example 1, double bond (vinyl). Preferred alkenyl groups include ethenyl or vinyl (-CH=CH_2), 1-propylene or allyl (-CH_2CH=CH_2), isopropylene, (-C(CH_3)=CH_2), bicyclo[2.2.1]heptene, and the like. In the event that alkenyl is attached to nitrogen, the double bond cannot be alpha to the nitrogen.

[0094] The term "lower alkenyl" refers to alkenyl as defined above having from 2 to 6 carbon atoms.

[0095] The term "substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 5 substituents, and for example 1 to 3 substituents, selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, quaternary amino, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, heteroarylthio, heterocyclylthio, thiol, alkylthio, aryl, aryloxy, heteroaryl, aminosulfonyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, $-SO_3H$, -SO-alkyl, -SO-aryl,-SO-heteroaryl, $-SO_2$-alkyl, SO_2-aryl and $-SO_2$-heteroaryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, quaternary amino, $-SO_3H$, and $-S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

[0096] The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon, for example having from 2 to 20 carbon atoms, more for example 2 to 10 carbon atoms and even more for example 2 to 6 carbon atoms and having at least 1 and for example from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynyl groups include ethynyl, (-C≡CH), propargyl (or prop-1-yn-3-yl, $-CH_2C{\equiv}CH$), and the like. In the event that alkynyl is attached to nitrogen, the triple bond cannot be alpha to the nitrogen.

[0097] The term "substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 5 substituents, and for example 1 to 3 substituents, selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, quaternary amino, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, heteroarylthio, heterocyclylthio, thiol, alkylthio, aryl, aryloxy, heteroaryl, aminosulfonyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, $-SO_3H$, -SO-alkyl, -SO-aryl,-SO-heteroaryl, $-SO_2$-alkyl, SO_2-aryl and $-SO_2$-heteroaryl. Unless otherwise constrained by the definition, all

substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, quaternary amino, $-SO_3H$, and $-S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

[0098] The term "aminocarbonyl" refers to the group -C(O)NRR where each R is independently hydrogen, alkyl, aryl, heteroaryl, heterocyclyl or where both R groups are joined to form a heterocyclic group (e.g., morpholino). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, quaternary amino, $-SO_3H$, and $-S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

[0099] The term "acylamino" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, aryl, heteroaryl, or heterocyclyl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, quaternary amino, $-SO_3H$, and $-S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

[0100] The term "acyloxy" refers to the groups –O(O)C-alkyl, –O(O)C-cycloalkyl, –O(O)C-aryl, –O(O)C-heteroaryl, and –O(O)C-heterocyclyl. Unless otherwise constrained by the definition, all substituents may be optionally further substituted by alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, quaternary amino, $-SO_3H$, or $-S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

[0101] The term "aryl" refers to an aromatic carbocyclic group of 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple rings (e.g., biphenyl), or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like.

[0102] Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents, for example 1 to 3 substituents, selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy,

cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, quaternary amino, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, heteroarylthio, heterocyclylthio, thiol, alkylthio, aryl, aryloxy, heteroaryl, aminosulfonyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO_3H, -SO-alkyl, -SO-aryl,-SO-heteroaryl, -SO_2-alkyl, SO_2-aryl and -SO_2-heteroaryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1 to 3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, quaternary amino, -SO_3H, and –$S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

[0103] The term "aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above, and includes optionally substituted aryl groups as also defined above. The term "arylthio" refers to the group R-S-, where R is as defined for aryl.

[0104] The term "amino" refers to the group -NH_2.

[0105] The term "substituted amino" refers to the group -NRR where each R is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, carboxyalkyl (for example, benzyloxycarbonyl), aryl, heteroaryl and heterocyclyl provided that both R groups are not hydrogen, or a group -Y-Z, in which Y is optionally substituted alkylene and Z is alkenyl, cycloalkenyl, or alkynyl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, quaternary amino, -SO_3H, and –$S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

[0106] The term " quaternary amino" refers to the group –NRRR where each R is independently as defined for substituted amino. Any two of the R substituents may be joined to form a heterocyclic group as defined further herein.

[0107] The term "carboxyalkyl" refers to the groups -C(O)O-alkyl, -C(O)O-cycloalkyl, where alkyl and cycloalkyl, are as defined herein, and may be optionally further

substituted by alkyl, alkenyl, alkynyl, alkoxy, halogen, CF_3, amino, substituted amino, cyano, quaternary amino, $-SO_3H$, or $-S(O)_nR$, in which R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

[0108] The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, bicyclo[2.2.1]heptane, 1,3,3-trimethylbicyclo[2.2.1]hept-2-yl, (2,3,3-trimethylbicyclo[2.2.1]hept-2-yl), or cyclic alkyl groups to which is fused an aryl group, for example indane, and the like.

[0109] The term "substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 substituents, and for example 1 to 3 substituents, selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, heteroarylthio, heterocyclylthio, thiol, alkylthio, aryl, aryloxy, heteroaryl, aminosulfonyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, quaternary amino, $-SO_3H$, -SO-alkyl, -SO-aryl,-SO-heteroaryl, $-SO_2$-alkyl, SO_2-aryl and $-SO_2$-heteroaryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, quaternary amino, $-SO_3H$, and $-S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

[0110] The term "halogen" or "halo" refers to fluoro, bromo, chloro, and iodo.

[0111] The term "acyl" denotes a group -C(O)R, in which R is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl.

[0112] The term "heteroaryl" refers to an aromatic group (i.e., unsaturated) comprising 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring.

[0113] Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents, for example 1 to 3 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, heteroarylthio, heterocyclylthio, thiol, alkylthio, aryl, aryloxy, heteroaryl, aminosulfonyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, substituted amino, quaternary amino,-SO_3H, -SO-alkyl, -SO-aryl,-SO-heteroaryl, -SO_2-alkyl, SO_2-aryl and -SO_2-heteroaryl.

[0114] Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, quaternary amino, -SO_3H, and –$S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl, benzothiazolyl, or benzothienyl).

[0115] Examples of heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, and the like as well as N-alkoxy-nitrogen containing heteroaryl compounds.

[0116] The term "heteroaralkyl" refers to a heteroaryl group covalently linked to an alkylene group, where heteroaryl and alkylene are defined herein. "Optionally substituted heteroaralkyl" refers to an optionally substituted heteroaryl group covalently linked to an optionally substituted alkylene group. Such heteroaralkyl groups are exemplified by 3-pyridylmethyl, quinolin-8-ylethyl, 4-methoxythiazol-2-ylpropyl, and the like.

[0117] The term "heteroaryloxy" refers to the group heteroaryl-O-.

[0118] The term "heterocyclyl" refers to a monoradical saturated or partially unsaturated group having a single ring or multiple condensed rings, having from 1 to 40 carbon atoms and from 1 to 10 hetero atoms, for example 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring.

[0119] Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5, and for example 1 to 3 substituents, selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, heteroarylthio, heterocyclylthio, thiol, alkylthio, aryl, aryloxy, heteroaryl, aminosulfonyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, quaternary amino, $-SO_3H$, -SO-alkyl, -SO-aryl,-SO-heteroaryl, $-SO_2$-alkyl, SO_2-aryl and $-SO_2$-heteroaryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, quaternary amino, $-SO_3H$, and $-S(O)_nR$, where R is alkyl, aryl, or heteroaryl and n is 0, 1 or 2. Heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include tetrahydrofuranyl, morpholino, and piperidinyl.

[0120] The term "thiol" refers to the group -SH.

[0121] The term "substituted alkylthio" refers to the group –S-substituted alkyl.

[0122] The term "heteroarylthiol" refers to the group –S-heteroaryl wherein the heteroaryl group is as defined above including optionally substituted heteroaryl groups as also defined above.

[0123] The term "sulfoxide" refers to a group -S(O)R, in which R is alkyl, aryl, or heteroaryl. "Substituted sulfoxide" refers to a group -S(O)R, in which R is substituted alkyl, substituted aryl, or substituted heteroaryl, as defined herein.

[0124] The term "sulfone" refers to a group $-S(O)_2R$, in which R is alkyl, aryl, or heteroaryl. "Substituted sulfone" refers to a group $-S(O)_2R$, in which R is substituted alkyl, substituted aryl, or substituted heteroaryl, as defined herein.

[0125] The term "keto" refers to a group –C(O)-. The term "thiocarbonyl" refers to a group C(S)-. The term "carboxy" refers to a group –C(O)-OH.

[0126] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not.

[0127] The term "compound of Formula I" is intended to encompass the compounds of the invention as disclosed, and the pharmaceutically acceptable salts, pharmaceutically acceptable esters, and prodrugs of such compounds. Additionally, the compounds of the invention may possess one or more asymmetric centers, and can be produced as a racemic mixture or as individual enantiomers or diastereoisomers. The number of stereoisomers present in any given compound of Formula I depends upon the number of asymmetric centers present (there are 2^n stereoisomers possible where n is the number of asymmetric centers). The individual stereoisomers may be obtained by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis, or by resolution of the compound of Formula I by conventional means. The individual stereoisomers (including individual enantiomers and diastereoisomers) as well as racemic and non-racemic mixtures of stereoisomers are encompassed within the scope of the present invention, all of which are intended to be depicted by the structures of this specification unless otherwise specifically indicated.

[0128] "Isomers" are different compounds that have the same molecular formula.

[0129] "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space.

[0130] "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate.

[0131] "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0132] The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When the compound is a pure enantiomer, the stereochemistry at each

chiral carbon may be specified as either R or S. Resolved compounds whose absolute configuration is unknown are designated (+) or (-) depending on the direction (dextro- or laevorotary) in which they rotate the plane of polarized light at the wavelength of the sodium D line.

[0133] The term "therapeutically effective amount" refers to that amount of a compound of Formula I that is sufficient to effect treatment, as defined below, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

[0134] The term "treatment" or "treating" means any treatment of a disease in a mammal, including:

(i) preventing the disease, that is, causing the clinical symptoms of the disease not to develop;

(ii) inhibiting the disease, that is, arresting the development of clinical symptoms; and/or

(iii) relieving the disease, that is, causing the regression of clinical symptoms.

[0135] In many cases, the compounds of this invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of the compounds of Formula I, and which are not biologically or otherwise undesirable. Pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted

alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group.

[0136] Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0137] Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like.

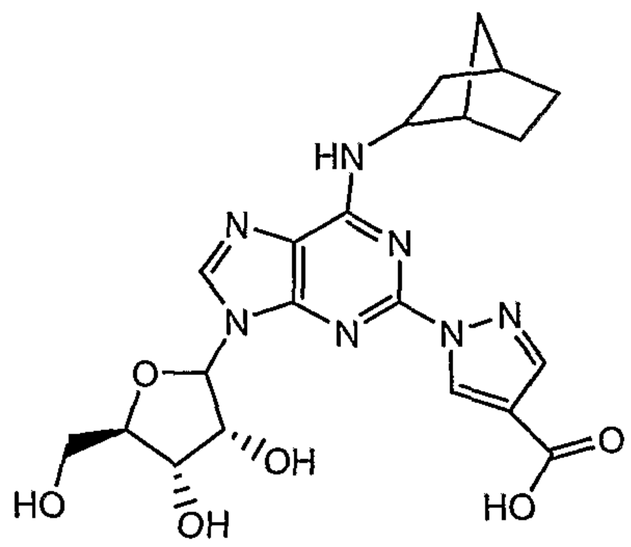
[0138] As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the

therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0139] A compound that is an agonist with high intrinsic efficacy evokes the maximal effect of which the biological system is capable. These compounds are known as "full agonists". They are able to elicit the maximum possible effect without occupying all the receptors, if the efficiency of coupling to the effector process is high. In contrast, "partial agonists" evoke a response but cannot evoke the maximal response of which the biological system is capable. They may have reasonable affinity but low intrinsic efficacy. Partial A_1 adenosine 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 less likely to cause side effects.

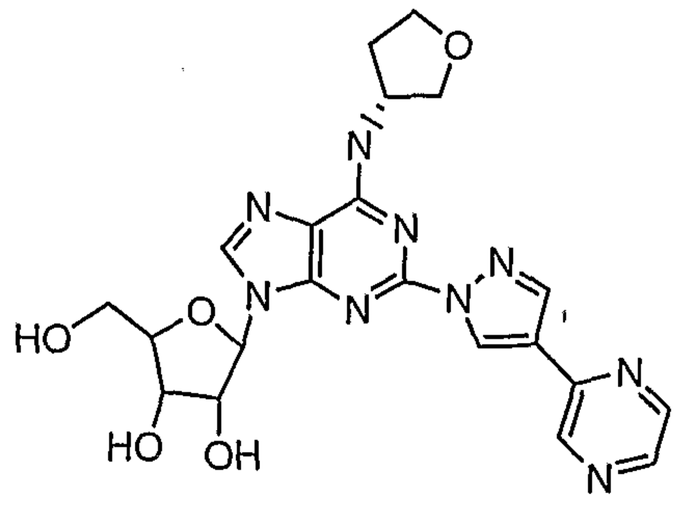
NOMENCLATURE

[0140] The naming and numbering of the compounds of the invention is illustrated with a representative compound of Formula I in which R^1 is hydroxymethyl 4, R^2 is bicyclo[2.2.1]hept-2-yl, R^4 is $-C(O)OR^6$, and R^3, R^5, and R^6 are hydrogen:



which is named 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(bicyclo[2.2.1]hept-2-ylamino)purin-2-yl}pyrazole-4-carboxylic acid.

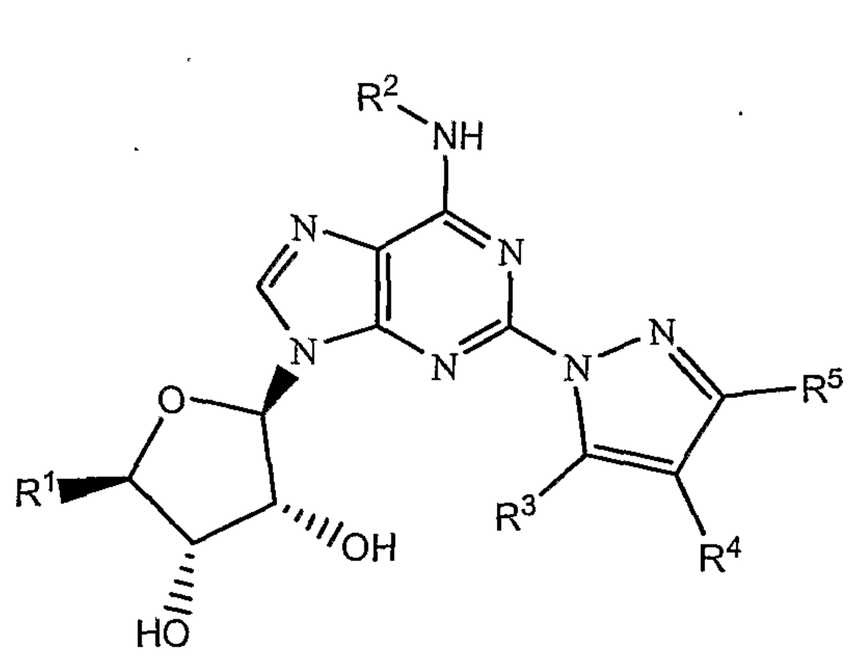
[0141] Similarly, a representative compound of Formula I in which R^1 is hydroxymethyl, R^2 is(3R)oxolan-3-yl, R^4 is pyrazin-2-yl, and R^3, R^5, and R^6 are hydrogen:



is named 2-{6-[((3R)oxolan-3-yl)amino]-2-(4-pyrazin-2-ylpyrazolyl)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol.

The Compounds of the Invention

[0142] As presented in the Summary of the Invention, the invention relates to compounds having the structure of Formula I:



wherein R^1, R^2, R^3, R^4, and R^5 are as defined above.

[0143] As stated previously, R^1 is hydroxymethyl, -C(O)OR^6, or -C(O)NHR^6, in which R^6 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aralkyl, optionally substituted aryl, or optionally substituted heteroaryl. Typically, R^1 is hydroxymethyl.

[0144] In the Formula I compounds, R^2 may be an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, or an optionally substituted heteroaryl moiety. In one embodiment, R^2 is an optionally substituted heterocyclic moiety. Preferred R^2 heterocycles are five membered heterocyclic rings having at least one nitrogen or oxygen atom. Particularly preferred R^2 heterocycles include, but are not limited to, optionally substituted pyrrolidine and oxolane rings.

[0145] In other embodiments, R^2 is an optionally substituted cycloalkyl moiety. Preferably, the cycloalkyl moiety is a five to eight membered ring structure. Examples of suitable cycloalkyl groups include, but are not limited to, cyclopentyl and bicyclo[2.2.1]hept-2-yl structures. In still other embodiments, R^2 is an optionally substituted aryl moiety, such as, but not limited to, optionally substituted phenyl and naphthyl rings. When R^2 is an optionally substituted alkyl group, it is commonly a C_{3-20} alkyl branched or linear alkyl moiety.

[0146] R^3, R^4, and R^5 may be hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, $-CO_2H$, $-SO_3H$, $-C(O)OR^6$, or $-C(O)NHR^6$. Preferred R^3 substituents include, but are not limited to, optionally substituted C_{1-6} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, benzyl, 4-methylcarboxybenzyl, 4-carboxybenzyl, and hydroxyphenylmethyl; optionally substituted aryl such as methylphenyl; optionally substituted heteroaryl such as pyrazol-4-yl, quinol-2-yl, pyrazin-2-yl, quinazolin-2-yl, pyrid-2-yl, and pyrid-4-yl.

[0147] When either R^1, R^3 R^4, or R^5 is $-C(O)OR^6$, $-CH(OH)R^6$, or $-C(O)NR^6R^7$, preferred R^6 and R^7 substituents include, but are not limited to, hydrogen, C_{1-4} alkyl, cyclopropyl, cyclobutyl, and optionally substituted benzyl groups such as 4-carboxybenzyl, 4-chlorobenzy, 4-fluorobenzyl, and 3-triflouromethyl-5-flourobenzyl. Substituted C_{1-4} alkyl groups having terminal quaternary amino of $-SO_3H$ groups are also suitable.

Synthetic Reaction Parameters

[0148] The terms "solvent", "inert organic solvent" or "inert solvent" means a solvent

inert under the conditions of the reaction being described in conjunction therewith [including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, pyridine and the like]. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert organic solvents.

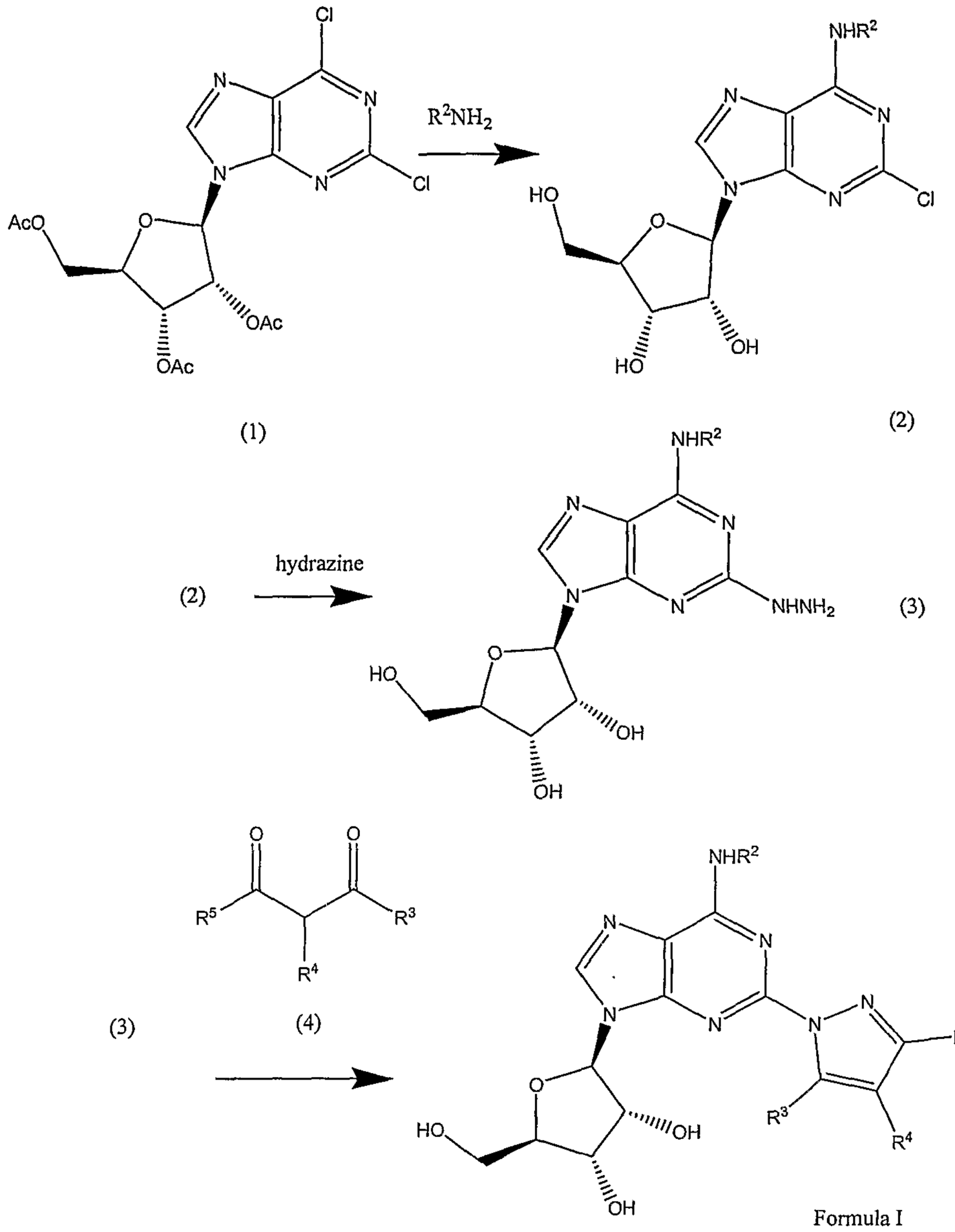
[0149] The term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

[0150] The compounds of the invention are generally synthesized by serial modification of a commercially available protected 2,6-dihalopurine riboside such as acyl-protected 2,6-dichloropurineriboside. The initial step involves addition of the R^2 moiety by reaction of the protected riboside with an amine of the desired R^2 substituent in the presence of base. Once the R^2 group has been added, formation of the pyrazole ring begins by addition of a hydrazine derivative to the 2 position of the purine residue. The pyrazole ring is then formed by reaction of the hydrazine modified purine with an optionally substituted 1,3-propanedione derivative or the like. As a final step, the protecting groups are removed.

[0151] It will be appreciated by those of skill in the art that numerous variations of the above-described synthetic route may be derived. For example, the deprotection-step may be carried out prior to reaction with the optionally substituted 1,3-propanedione derivative. Additional modification of the pyrazole ring and/or modification the R^1 position may also be carried out either before or after deprotection of the sugar residue.

[0152] An example of a method for preparing the compounds of Formula I where R^1 is hydroxymethyl is shown in Reaction Scheme I.

REACTION SCHEME I



Formula I

where Ac is acetyl.

Step 1 - Preparation of Formula (2)

[0153] The compound of formula (2) is prepared by displacement of the 6-chloro of a compound of formula (1), which is prepared as described in J.F. Gorster and R.K. Robins, *J. Org. Chem.* 1966, Vol. 31, 3258-62. The compound of formula (1) is reacted with a compound of formula R^1NH_2 in the presence of a base. The reaction is carried out in an inert protic solvent, for example methanol, ethanol, n-butanol, and the

like, at a temperature of between room temperature and about reflux, for about 12-48 hours. When the reaction is substantially complete, the product of formula (2) is isolated by conventional means, for example by removal of the solvent under reduced pressure, followed by chromatography of the residue on silica gel. Alternatively, the compound of Formula (2) is used in the next step without purification.

Step 2 - Preparation of Formula (3)

[0154] The compound of formula (2) is converted to a compound of formula (3) by reaction with hydrazine hydrate. The reaction is carried out with no solvent, or optionally in a protic solvent, for example ethanol, at a temperature of between room temperature and about reflux, for about 12-48 hours. When the reaction is substantially complete, the product of formula (3) is isolated by conventional means, for example by removal of solvent under reduced pressure and triturating the product with ether. Alternatively, the compound of Formula (3) is used in the next step without purification.

Step 3 - Preparation of Formula I

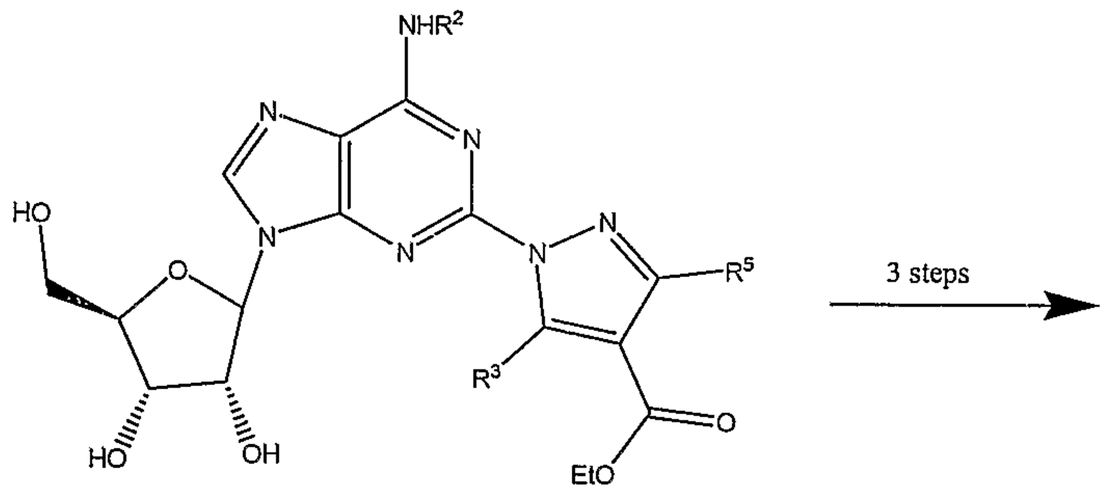
[0155] The compound of formula (3) is converted to a compound of Formula I by reaction with an optionally substituted 1,3-propanedione derivative of formula (4). The reaction is carried out by suspending the compound of formula (3) in a protic solvent, preferably ethanol, adding the compound of formula (4), and refluxing the mixture for about 2-16 hours. When the reaction is substantially complete, the product of Formula I is isolated by conventional means, for example filtering off the product.

[0156] For example, starting with a compound of formula (4) in which R^3 and R^5 are hydrogen and R^3 is 4-methoxyphenyl provides a compound of Formula I in which R^3 is similarly 4-methoxyphenyl.

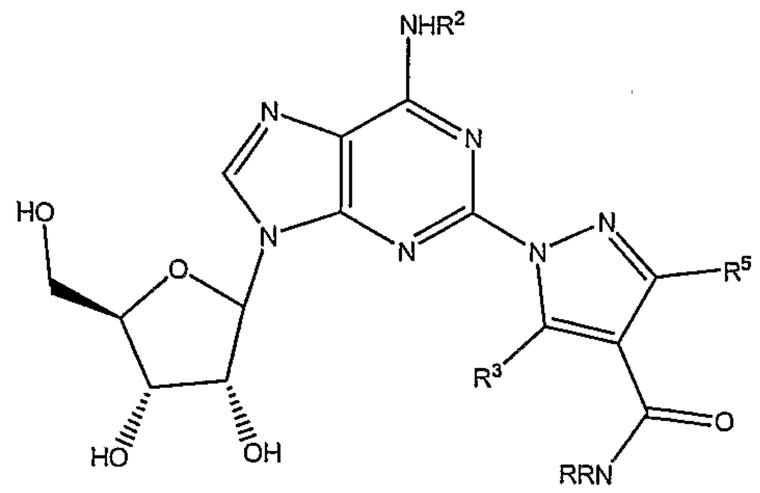
Modification of the R^3, R^4, or R^5 substituent

[0157] While desired R^3, R^4, and R^5 substituents can be added via reaction of the appropriately substituted propane-1,3-dione, additional modification at these positions can be conducted after the pyrazole ring has been formed. For example, starting with a compound of formula (4) in which R^3 and R^5 are hydrogen and R^4 is $-CO_2Et$ provides a compound of Formula I in which R^4 is 4-ethoxycarbonyl. This ester group can then be hydrolyzed under basic conditions to give the free acid, which in turn can be converted to acid derivatives such as optionally substituted amide by means well known to those skilled in the art, or by the method shown in Reaction Scheme II.

REACTION SCHEME II



Formula I where R^4 is ethoxycarbonyl



Formula I where R^4 is amido

Step 1 - Protection of the compound of Formula I where R^4 is Ethoxycarbonyl

[0158] The compound of Formula I in which R^4 is ethoxycarbonyl is dissolved in a polar solvent, preferably DMF, and imidazole and tertiary butyldimethylsilyl chloride added. The reaction is carried out at a temperature of 50-100°C, for about 12-48 hours. When the reaction is substantially complete, the product is isolated by conventional means, for example by removal of the solvent under reduced pressure, followed by flash chromatography of the residue on silica gel.

Step 2 - Hydrolysis of the Ethyl Ester to the Carboxylic Acid

[0159] The product from Step 1 is suspended in a mixture of water, an alcohol, and a strong base, preferably potassium hydroxide in methanol. The reaction is carried out at a temperature of 0-40°C, preferably about 25°C, for about 2-5 days, preferably about 3 days. When the reaction is substantially complete, the solvent is removed under reduced pressure, the residue acidified to a pH of about 5, and the product is isolated by conventional means, for example by filtration.

Step 3 - Preparation of an Amide

[0160] The product from Step 2 is dissolved in an inert solvent, preferably dichloromethane, to which is added HBTU, HOBt, N-methylmorpholine,a catalytic amount of DMAP, and an optionally substituted amine of formula HNRR, as defined above. The reaction is carried out at a temperature of 0-40°C, preferably about 25°C, for about 8-48 hours, preferably about 24 hours. When the reaction is substantially complete, the product is isolated by conventional means.

Step 4 - Deprotection

[0161] The product from Step 3 is treated with a solution of ammonium fluoride in methanol. The reaction is carried out at a temperature of about reflux, for about 8-48

hours, preferably about 24 hours. When the reaction is substantially complete, the solvent is removed under reduced pressure, the residue acidified to a pH of about 5, and the product is isolated by conventional means, for example by preparative TLC.

Alternative Modification of the R^3, R^4, or R^5 substituent

[0162] The free acid produced from the ester group can also be converted to an alcohol by reaction with a reducing agent in chilled tetrahydrofuran. This alcohol can then be modified to provide an aldehyde by reaction with an oxidizing agent such as pyridinium chlorochromate. Using this aldehyde, other modifications may be made such as the addition of optionally substituted alkyl, alkenyl, or aryl groups.

[0163] The ester group can also be directly converted to form a substituted amide by means well known to those skilled in the art, such as reaction with an appropriately substituted amine derivative in methanol. Alternatively, replacement of the ester group with an unsubstituted amide can be achieved by the reaction of the ester-substituted compound of Formula I in methanol with anhydrous NH_3 gas under cooled conditions. The resulting carboxamide group can then be further modified, e.g., by replacement with a cyano group via reaction triethylamine and chilled $POCl_3$ in dimethylformamide.

[0164] It will be readily appreciated by those of skill in the art that still further modification of the cyano group is also possible. In one example, the cyano group may first be converted to an amino methyl group via reaction with BH_3 in tetrahydrofuran and then secondarily modified by reaction in a protic solvent with halogenated substituents under basic conditions, e.g., in the presence of a tertiary amine such as triethylamine.

[0165] Any of the above-discussed modifications may be carried with or without the initial protection of the hydroxyl groups on the sugar moiety. Also, if protected, the sugar moiety may be deprotected prior to any secondary or tertiary modifications that may take place.

Modification of the R^1 substituent

[0166] It will be appreciated by those of skill in the art that modification of the R^1 substituent may be conducted after formation of the pyrazole ring. For example, using a compound of Formula I in which R^1 is hydroxymethyl, R^3 and R^5 are hydrogen and R^4 is 4-methylphenyl, one can selectively protect the 3 and 4 position hydroxy groups by reaction with 2,2-dimethoxypropane. The resulting 5' hydroxy compound can then be converted to a optionally substituted carbonyl group via reaction with catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) in combination with [bis(acetoxy)iodo]benzene (BAIB). This carboxylic acid can then be replaced with an optionally substituted carboxamide group and the protecting groups removed using conventional techniques.

Modification of the R^2 substituent

[0167] It will also be appreciated by those of skill in the art that modification of the R^2 substituent may be conducted after formation of the pyrazole ring. For example, using a compound of Formula I in which R^1 is hydroxymethyl, R^2, R^3, and R^5 are hydrogen, and R^4 is 4-methylphenyl, one can selectively protect the 3 and 4 position hydroxy groups by reaction with acetic anhydride. The R^2 position can then be modified by reaction with a halogen derivative of the desired R^2 moiety. After the R^2 group has been added, the compound is deprotected using conventional methods.

Utility, Testing and Administration

General Utility

[0168] The compounds of Formula I are effective in the treatment of conditions known to respond to administration of a partial or full agonist of an A_1 adenosine receptor. Such conditions include, but are not limited to, acute and chronic disorders of heart rhythm, especially those diseases characterized by rapid heart rate, in which the rate is driven by abnormalities in the sinoatrial, atria, and AV nodal tissues. Such disorders

include, but are not limited to, atrial fibrillation, and atrial flutter, congestive heart failure, non-insulin-dependent diabetes mellitus, hyperglycemia, epilepsy (anticonvulsant activity), and neuroprotection. A_1 adenosine receptor agonists also have antilipolytic effects in adipocytes, which leads to a decreased release of nonesterified fatty acids

Testing

[0169] Activity testing is conducted as described in those patents and literature citations referenced above, and in the Examples below, and by methods apparent to one skilled in the art.

Pharmaceutical Compositions

[0170] The compounds of Formula I are usually administered in the form of pharmaceutical compositions. This invention therefore provides pharmaceutical compositions that contain, as the active ingredient, one or more of the compounds of Formula I, or a pharmaceutically acceptable salt or ester thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. The compounds of Formula I may be administered alone or in combination with other therapeutic agents. Such compositions are prepared in a manner well known in the pharmaceutical art (see, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, PA 17th Ed. (1985) and "Modern Pharmaceutics", Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

Administration

[0171] The compounds of Formula I may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities,

for example as described in those patents and patent applications incorporated by reference, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

[0172] One mode for administration is parental, particularly by injection. The forms in which the novel compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles. Aqueous solutions in saline are also conventionally used for injection, but less preferred in the context of the present invention. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[0173] Sterile injectable solutions are prepared by incorporating the compound of Formula I in the required amount in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0174] Oral administration is another route for administration of the compounds of Formula I. Administration may be via capsule or enteric coated tablets, or the like. In making the pharmaceutical compositions that include at least one compound of

Formula I, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, in can be a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0175] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0176] The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770; 4,326,525; 4,902514; and 5,616,345. Another formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0177] The compositions are for example formulated in a unit dosage form. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for

human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient (e.g., a tablet, capsule, ampoule). The compounds of Formula I are effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. For example, for oral administration, each dosage unit contains from 10 mg to 2 g of a compound of Formula I, more for example from 10 to 700 mg, and for parenteral administration, for example from 10 to 700 mg of a compound of Formula I, more for example about 50-200 mg. It will be understood, however, that the amount of the compound of Formula I actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0178] For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0179] The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0180] Compositions for inhalation or insufflation include solutions and suspensions in

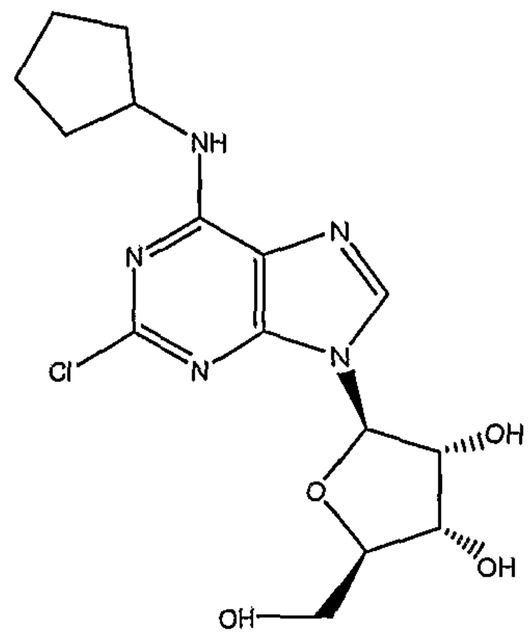
pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. For example the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in for example pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, for example orally or nasally, from devices that deliver the formulation in an appropriate manner.

[0181] The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques +disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

Preparation of a Compound of Formula (2)

A. Preparation of a Compound of Formula (2) where R^1 is Hydroxymethyl and R^2 is Cyclopentyl



(2)

[0182] [3,4-diacetoxy-5-(2,6-dichloropurin-9-yl)oxolan-2-yl]methyl acetate, the compound of formula (1) (2.2 mmol), was suspended in a mixture of 20 mL of ethanol. Triethylamine (20 mmol) and cyclopentyl amine (11.2 mmol) were then added. The solution was brought to reflux for 24 hours.

[0183] The solvent was removed under reduced pressure and the residue was dissolved in 100 mL of ethyl acetate and washed twice with 50 mL of water and twice with 10% citric acid. The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed, to afford (4S,2R,3R,5R) 5-[2-chloro-6-(cyclopentylamino)purin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol, a compound of formula (2).

B. Preparation of a Compound of Formula (2), varying R^2

[0184] Similarly, following the procedure of 1A above, but replacing cyclopentyl amine with tetrahydrofuran-3-amine, bicyclo[2.2.1]hept-2-ylamine, and benzylamine, the following compounds of formula (2) were prepared:

(4S,2R,3R,5R)-5-[2-chloro-6-(oxolan-3-ylamino)purin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[6-(bicyclo[2.2.1]hept-2-ylamino)-2-chloropurin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol; and

(4S,2R,3R,5R)-5-[6-(benzylamino)-2-chloropurin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol.

C. Preparation of a Compound of Formula (2), varying R^2

[0185] Similarly, following the procedure of 1A above, but replacing cyclopentyl amine by other compounds of formula R^2NH_2, the following compounds of formula (2) are prepared:

(4S,2R,3R,5R)-5-[6-(cyclopropylmethylamino)-2-chloropurin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[6-(cyclopropylamino)-2-chloropurin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[6-anilinopurin 2-chloropurin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[6-(4-chlorobenzylamino)-2-chloropurin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[6-(2-fluorobenzylamino)-2-chloropurin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[6-(pyrid-2-ylamino)-2-chloropurin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol; and

(4S,2R,3R,5R)-5-[6-(pyrrol-3-ylamino)-2-chloropurin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol.

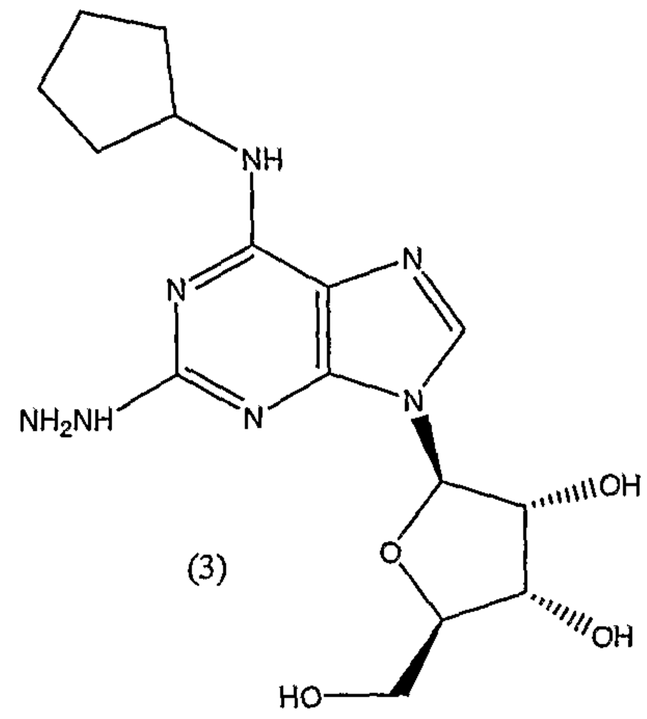
D. Preparation of a Compound of Formula (2), varying R^2

[0186] Similarly, following the procedure of 1A above, but replacing cylopentylamine by other compounds of formula R^2NH_2, other compounds of formula (2) are prepared.

EXAMPLE 2

Preparation of a Compound of Formula (3)

A. Preparation of a Compound of Formula (3) where R^1 is Hydroxymethyl and R^2 is Cyclopentyl



(3)

[0187] (4S,2R,3R,5R) 5-[2-chloro-6-(cyclopentylamino)purin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol, a compound of formula (2) as prepared in Example 1A, was suspended in hydrazine hydrate (5 mL), and the mixture was allowed to stir at room temperature for 24 hours. The hydrazine was removed by filtration and the residue triturated with ethanol and filtered, to afford (4S,2R,3R,5R)-2-[2-hydrazino-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol, a compound of formula (3), as a white solid.

B. Preparation of a Compound of Formula (3), varying R^2

[0188] Similarly, following the procedure of 2A above, but replacing 2-(2-chloro-6-methylaminopurin-9-yl)-5-hydroxymethyltetrahydrofuran-3,4-diol with the tetrahydrofuran-3-amine, bicyclo[2.2.1]hept-2-ylamine, and benzylamine analogs of formula (2), the following compounds of formula (3) were prepared:

(4S,2R,3R,5R)-5-[2-hydrazino-6-(oxolan-3-ylamino)purin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[6-(bicyclo[2.2.1]hept-2-ylamino)-2-hydrazino purin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol; and

(4S,2R,3R,5R)-5-[6-(benzylamino)-2-hydrazinopurin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol.

C. Preparation of a Compound of Formula (3), varying R^2

[0189] Similarly, following the procedure of 2A above, but replacing 2-(2-chloro-6-methylaminopurin-9-yl)-5-hydroxymethyltetrahydrofuran-3,4-diol by other compounds of formula (2), the following compounds of formula (3) are prepared:

(4S,2R,3R,5R)-5-[2-hydrazino-6-(cyclopropylmethylamino)purin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[2-hydrazino-6-(cyclopropylamino)purin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[2-hydrazino-6-anilinopurin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[2-hydrazino-6-(4-chlorobenzylamino)purin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[2-hydrazino-6-(2-fluorobenzylamino)purin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol;

(4S,2R,3R,5R)-5-[2-hydrazino-6-(pyrid-2-ylamino)purin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol; and

(4S,2R,3R,5R)-5-[2-hydrazino-6-(pyrrol-3-ylamino)purin-9-yl]-2-(hydroxymethyl)oxolane-3,4-diol.

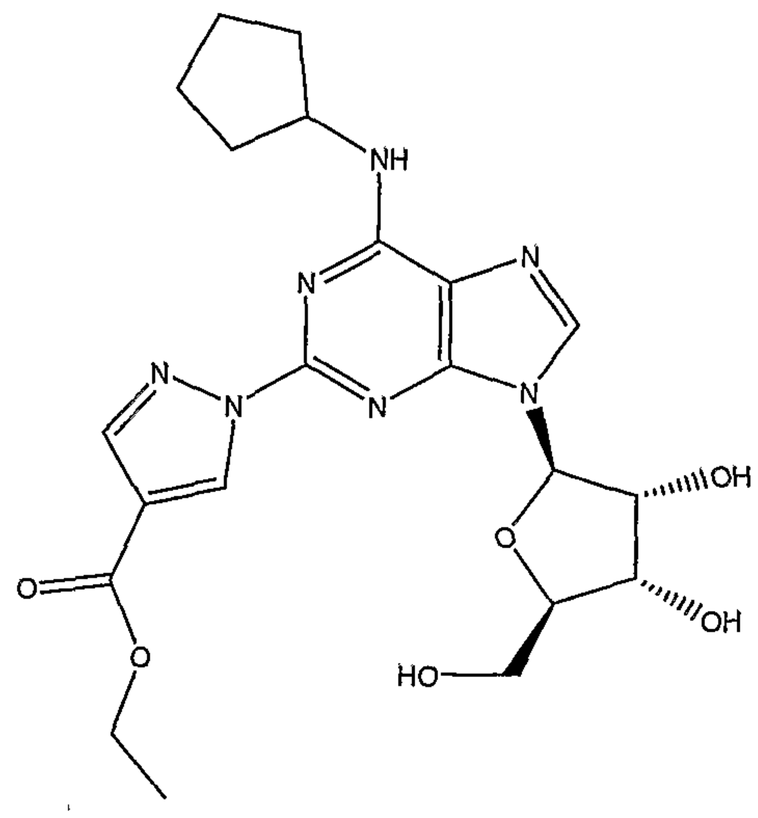
D. Preparation of a Compound of Formula (3), varying R^2

[0190] Similarly, following the procedure of 2A above, but replacing 2-(2-chloro-6-cyclopentylaminopurin-9-yl)-5-hydroxymethyltetrahydrofuran-3,4-diol by other compounds of formula (2), other compounds of formula (3) are prepared.

EXAMPLE 3

Preparation of a Compound of Formula I

A. Preparation of a Compound of Formula I where R^1 is Hydroxymethyl, R^2 is Cyclopentyl, R^4 is Carboxyethyl, and R^3 and R^5 are Hydrogen



Formula I

[0191] (4S,2R,3R,5R)-2-[2-hydrazino-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol (0.2 mmol) and ethyl 2,2-diformylacetate (0.28 mmol) were suspended in 3 mL of ethanol and to the suspension was added 5 mmol of diisopropylethylamine. The mixture was heated at reflux for 3 hours. Upon cooling to room temperature, the precipitate thus formed was collected by filtration, and washed with ethanol and ether to afford ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4- carboxylate, a compound of Formula I.

B. Preparation of a Compound of Formula I, varying R^2, R^3, R^4, and R^5

[0192] Similarly, following the procedure of 3A above, but optionally replacing (4S,2R,3R,5R)-2-[2-hydrazino-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol with other compounds of formula (3), and optionally

replacing 2 ethyl 2,2-diformylacetate with other compounds of formula (4), the following compounds of Formula I were prepared:

(4S,3R,5R)-2-[2-(3,5-dimethylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

(4S,3R,5R)-2-[2-(3,5-dimethyl-4-propylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

(4S,3R,5R)-2-[2-(4-butyl-3,5-dimethylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(bicyclo[2.2.1]hept-2-ylamino)purin-2-yl}pyrazole-4-carboxylate;

(4S,3R,5R)-2-[6-(bicyclo[2.2.1]hept-2-ylamino)-2-pyrazolylpurin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

ethyl 1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylate;

2-{6-[((3R)oxolan-3-yl)amino]-2-(4-pyrazin-2-ylpyrazolyl)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol;

2-{6-[((3R)oxolan-3-yl)amino]-2-(4-quinazolin-2-ylpyrazolyl)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol;

ethyl 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazole-4-carboxylate;

6-(1-{6-[((3R)oxolan-3-yl)amino]-9-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)pyridine-3-carboxylic acid;

5-(hydroxymethyl)-2-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}oxolane-3,4-diol;

2-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-pyridyl)pyrazolyl)purin-9-yl}(4S,3R)-5-(hydroxymethyl)oxolane-3,4-diol;

2-{6-[((3R)oxolan-3-yl)amino]-2-(4-(4-pyridyl)pyrazolyl)purin-9-yl}(4S,3R)-5-(hydroxymethyl)oxolane-3,4-diol;

2-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-quinolyl)pyrazolyl)purin-9-yl}(4S,3R)-5-(hydroxymethyl)oxolane-3,4-diol;

(4S,3R,5R)-2-[6-(cyclopentylamino)-2-pyrazolylpurin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}-5-methylpyrazole-3-carboxamide;

2-(6-[((3R)oxolan-3-yl)amino]-2-{4-[4-(trifluoromethyl)phenyl]pyrazolyl}purin-9-yl)(4S,2R,3R,5R)-5-(hydroxymethyl)oxolane-3,4-diol;

ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazole-4-carboxylate;

(4S,3R,5R)-2-[6-(cyclohexylamino)-2-pyrazolylpurin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

ethyl 1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylate; and

2-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-2-pyrazolylpurin-9-yl}(2R,5R)-5-(hydroxymethyl)oxolane-3,4-diol.

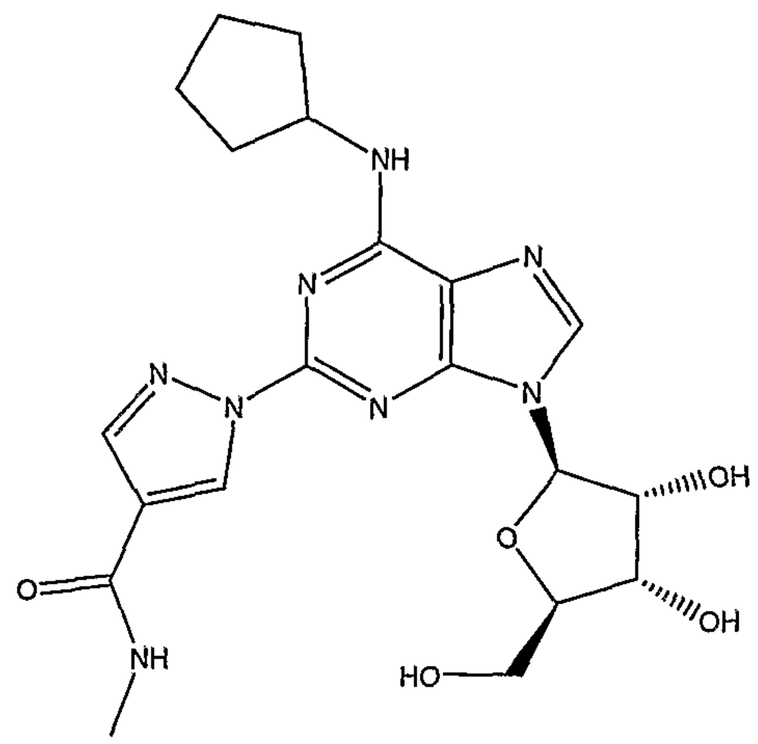
C. Preparation of a Compound of Formula I, varying R^2, R^3, R^4, and R^5

Similarly, following the procedure of 3A above, but optionally replacing (4S,2R,3R,5R)-2-[2-hydrazino-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol with other compounds of formula (3), and optionally replacing 2 ethyl 2,2-diformylacetate with other compounds of formula (4), other compounds of Formula I are prepared:

EXAMPLE 4

Preparation of a Compound of Formula I

A. Preparation of a Compound of Formula I where R^1 is Hydroxymethyl, R^2 is Cyclopentyl, R^4 is N-Methylcarboxamide, and R^3 and R^5 are Hydrogen



Formula I

[0193] 70 mg of the ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate prepared in Example 3 was dissolved in 5 mL of 2M methylamine in methanol in a sealed tube. The mixture was stirred at 50°C for 24 hours. The solvent was then removed and the residue purified using TLC with a 15:1 dichloromethane:methanol solution to yield (1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide.

B. Preparation of a Compound of Formula I, varying R^4

[0194] Similarly, following the procedure of 3A above, but optionally replacing ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate with other R^4 carboxylate compounds of Formula I, and optionally replacing methylamine with other amines, the following compounds of Formula I were prepared:

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide;

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide;

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-propylcarboxamide;

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-propylcarboxamide;

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide; and

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide.

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}-5-methylpyrazol-3-yl)-N-methylcarboxamide;

(1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide;

(1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide; and

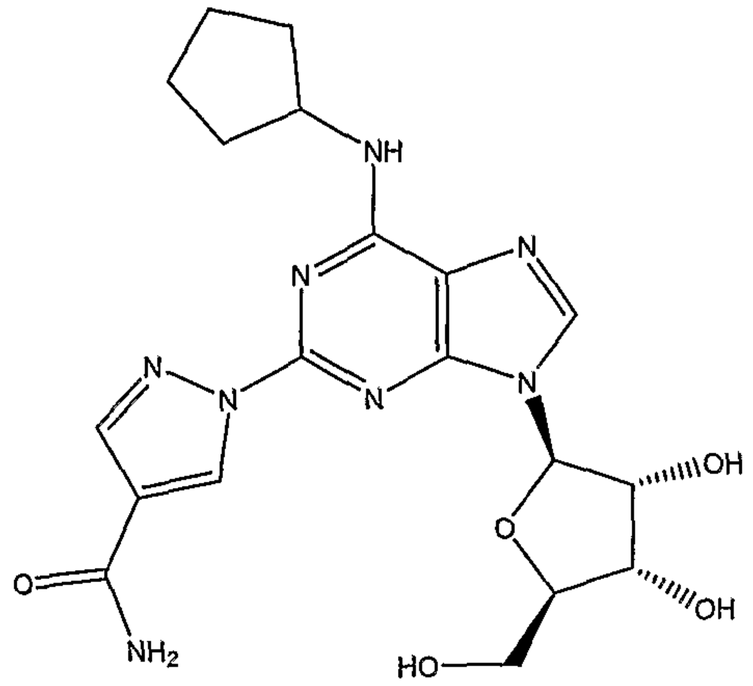
(1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-(3,3,3-trimethyl-3-azabutyl)carboxamide.

C. Preparation of a Compound of Formula I, varying R^4

[0195] Similarly, following the procedure of 3A above, but optionally replacing ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate with other R^4 carboxylate compounds of Formula I, and optionally replacing methylamine with other amines, other compounds of Formula I are prepared:

EXAMPLE 5

Preparation of a Compound of Formula I where R^1 is Hydroxymethyl, R^2 is Cyclopentyl, R^4 is Carboxamide, and R^3 and R^5 are Hydrogen



Formula I

[0196] 30 mg of the ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate prepared in Example 3 was dissolved in 3 mL of methanol in a tube. The tube was cooled to 0°C and anhydrous NH_3 gas was bubbled into the solution for one minute. The tube was then sealed and the mixture was stirred at 50°C for 72 hours. The solvent was then removed and the residue purified using TLC with a 15:1 dichloromethane:methanol solution to yield 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxamide;.

B. Preparation of a Compound of Formula I, varying R^2

[0197] Similarly, following the procedure of 5A above, but replacing ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate by other R^4 carboxylate compounds of Formula, the following compounds of Formula I were prepared:

1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazole-4-carboxamide; and

1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxamide.

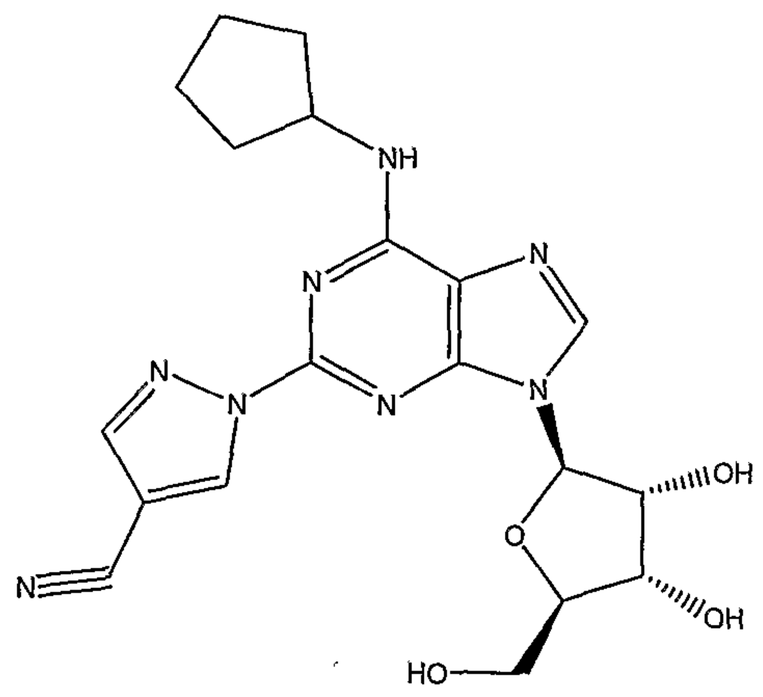
C. Preparation of a Compound of Formula I, varying R^2

[0198] Similarly, following the procedure of 5A above, but optionally replacing ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate with other R^4 carboxylate compounds of Formula I, other compounds of Formula I are prepared.

EXAMPLE 6

Preparation of a Compound of Formula I

A. Preparation of a Compound of Formula I where R^1 is Hydroxymethyl, R^2 is Cyclopentyl, R^4 is Cyano, and R^3 and R^5 are Hydrogen



Formula I

[0199] 429 mg of the 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxamide prepared in Example 5A was dissolved in 5 mL of dimethylformamide(DMF). To this solution was added 0.68 mL

of triethylamine followed by chilled (0°C) $POCl_3$ (0.44 mL). The mixture was stirred and allowed to warm to room temperature. Stirring at room temperature continued 4 hours. The solvent was removed and the residue purified using TLC with a 10:1 dichloromethane:methanol solution to yield 1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carbonitrile.

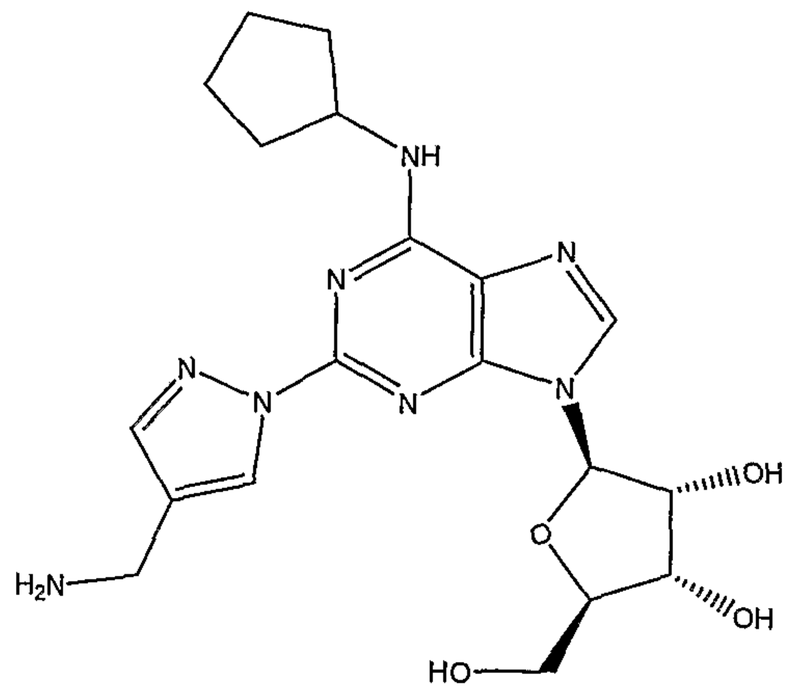
B. Preparation of a Compound of Formula I, varying R^2

[0200] Similarly, following the procedure of 6A above, but optionally replacing 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazole-4-carboxamide with other R^4 carboxamide of Formula I, other R^4 carbonitrile compounds of Formula I are prepared:

EXAMPLE 7

Preparation of a Compound of Formula I

A. Preparation of a Compound of Formula I where R^1 is Hydroxymethyl, R^2 is Cyclopentyl, R^4 is Aminomethyl, and R^3 and R^5 are Hydrogen



Formula I

[0201] 380 mg of the 1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carbonitrile prepared in Example 6A was

dissolved in 5 mL of tetrahydrofuran (THF). To this solution was added 40 ml of a 1.5M BH_3 in THF solution. The mixture was stirred at to room temperature overnight. In the morning the reaction mixture was slowly poured into 80 mL of ice cooled MeOH. The solvent was removed and the residue purified using HPLC to yield (2R,5R)-2-{2-[4-(aminomethyl)pyrazolyl]-6-(cyclopentylamino)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol.

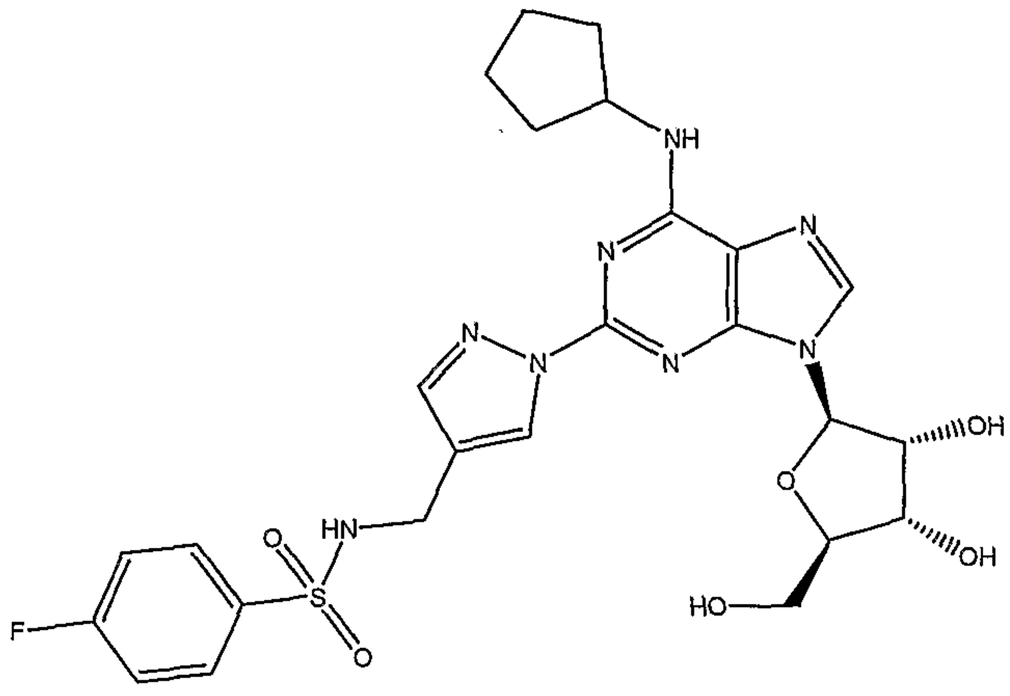
B. Preparation of a Compound of Formula I, varying R^2

[0202] Similarly, following the procedure of 6A above, but optionally replacing 1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carbonitrile with other R^4 carbonitrile compounds of Formula I, other R^4 aminomethyl compounds of Formula I are prepared.

EXAMPLE 8

Preparation of a Compound of Formula I

A. Preparation of a Compound of Formula I where R^1 is Hydroxymethyl, R^2 is Cyclopentyl, R^4 is [(4-Fluorophenyl)sulfonyl]aminomethyl, and R^3 and R^5 are Hydrogen



Formula I

[0203] 60 mg of the (2R,5R)-2-{2-[4-(aminomethyl)pyrazolyl]-6-(cyclopentylamino)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol prepared in Example 7A was dissolved in 10 mL of DMF. To this solution was added 0.04 mL of triethylamine followed by 54 mg of (4-fluorophenyl)sulfonylchloride. The mixture was stirred at to room temperature overnight. In the morning, the solvent was removed and the residue purified using Prep-TLC followed by HPLC to yield [(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)methyl][(4-fluorophenyl)sulfonyl]amine.

B. Preparation of a Compound of Formula I, varying R^2 and/or R^4

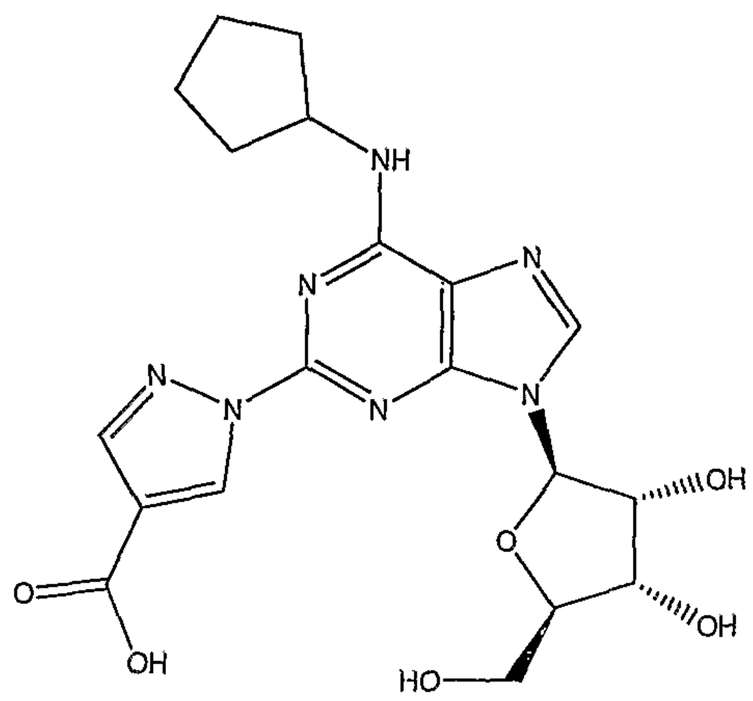
[0204] Similarly, following the procedure of 7A above, but optionally replacing (2R,5R)-2-{2-[4-(aminomethyl)pyrazolyl]-6-(cyclopentylamino)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol with other R^4 aminomethyl compounds of Formula I

and/or replacing (4-fluorophenyl)sulfonylchloride with other substituted sulfonlychlorides, other R^4 sulfonylaminomethyl compounds of Formula I are prepared.

EXAMPLE 9

Preparation of a Compound of Formula I

A. Preparation of a Compound of Formula I where R^1 is Hydroxymethyl, R^2 is Cyclopentyl, R^4 is Carboxyl, and R^3 and R^5 are Hydrogen



[0205] 40 mg of the ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate prepared in Example 3 was dissolved in 2 mL of 1 N KOH in methanol. 200 mL of water was then added and the mixture stirred at at 50°C for 24 hours. The solvent was then removed and the residue dissolved in 3 mL water and brought to a pH of 3-4 by addition of 37% HCl. The resulting solid was collected by filtration and washed with water and ether then air dried to provide the product, 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylic acid.

B. Preparation of a Compound of Formula I, varying R^2

[0206] Similarly, following the procedure of 9A above, but optionally replacing ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-

(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate with other R^4 carboxylate compounds of Formula I, the following compounds of Formula I were prepared:

1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(bicyclo[2.2.1]hept-2-ylamino)purin-2-yl}pyrazole-4-carboxylic acid; and

1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylic acid;

1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylic acid; and

1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazole-4-carboxylic acid.

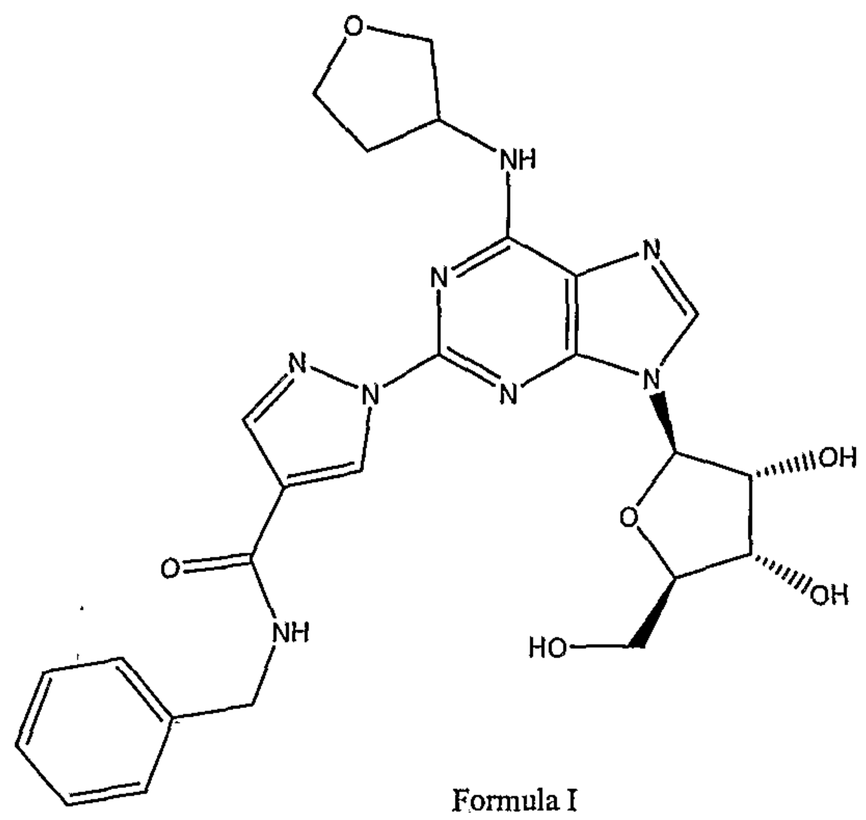
C. Preparation of a Compound of Formula I, varying R^2

[0207] Similarly, following the procedure of 9A above, but optionally replacing ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate with other R^4 carboxylate compounds of Formula I, other compounds of Formula I are prepared.

EXAMPLE 10

Preparation of a Compound of Formula I

A. Preparation of a Compound of Formula I where R^1 is Hydroxymethyl, R^2 is (3R)Oxolan-3-yl, R^4 is N-Benzylcarboxamide, and R^3 and R^5 are Hydrogen



Formula I

[0208] 150 mg of the 1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylic acid prepared in Example 9B was dissolved in 5 mL of dimethylformamide(DMF) and mixed with the following:

254 mg of 2-(1H-benzotriazo 1-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate (HBTU),
90.5 mg of 1-hydroxybenzotriazole (HOBt),
440 mL of benzylamine; and
a catalytic amount of dimethylaminopyridine (DMAP).

The mixture was stirred overnight at room temperature. The solvent was removed and the residue purified using TLC with a 15:1 dichloromethane:methanol solution to yield (1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide.

B. Preparation of a Compound of Formula I, varying R^2

Similarly, following the procedure of 10A above, but optionally replacing 1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylic acid with other R^4 carboxylic acids of Formula I or replacing benzylamine with other desired benzylamine residues, the following compounds of Formula I were prepared:

methyl 4-{[(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)carbonylamino]methyl}benzoate;

4-{[(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)carbonylamino]methyl}benzoic acid;

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-[(4-chlorophenyl)methyl]carboxamide;

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-[(4-fluorophenyl)methyl]carboxamide;

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-benzylcarboxamide; and

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(3S,2R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-{[5-fluoro-3-(trifluoromethyl)phenyl]methyl}carboxamide.

C. Preparation of a Compound of Formula I, varying R^2

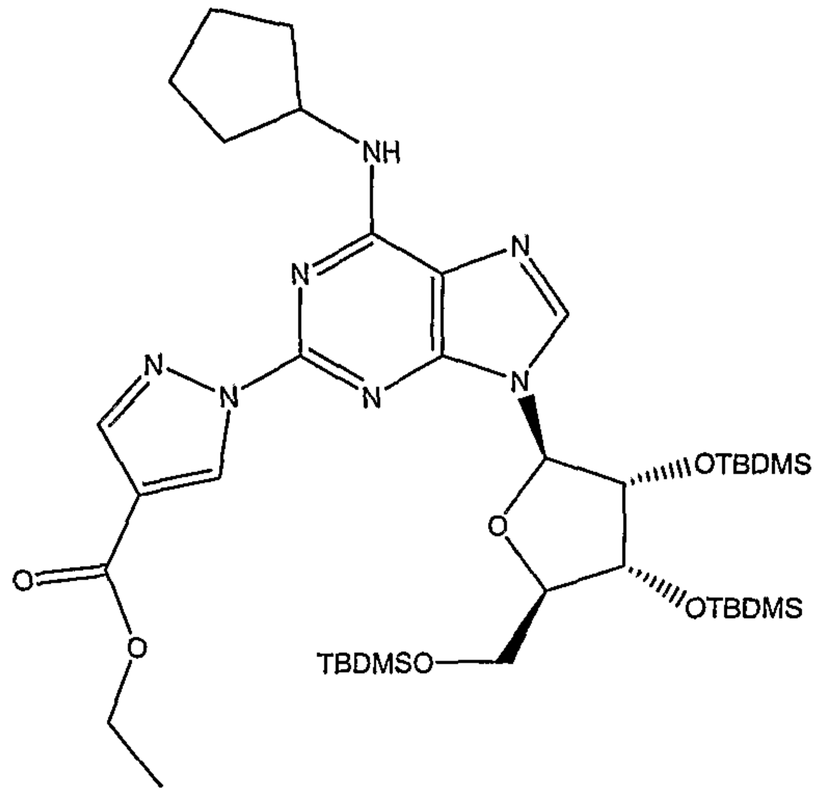
Similarly, following the procedure of 10A above, but optionally replacing 1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylic acid with other R^4 carboxylic acids of Formula I or replacing benzylamine with other desired benzylamine residues, other compounds of Formula I are prepared:

EXAMPLE 11

Preparation of a Compound of Formula I:

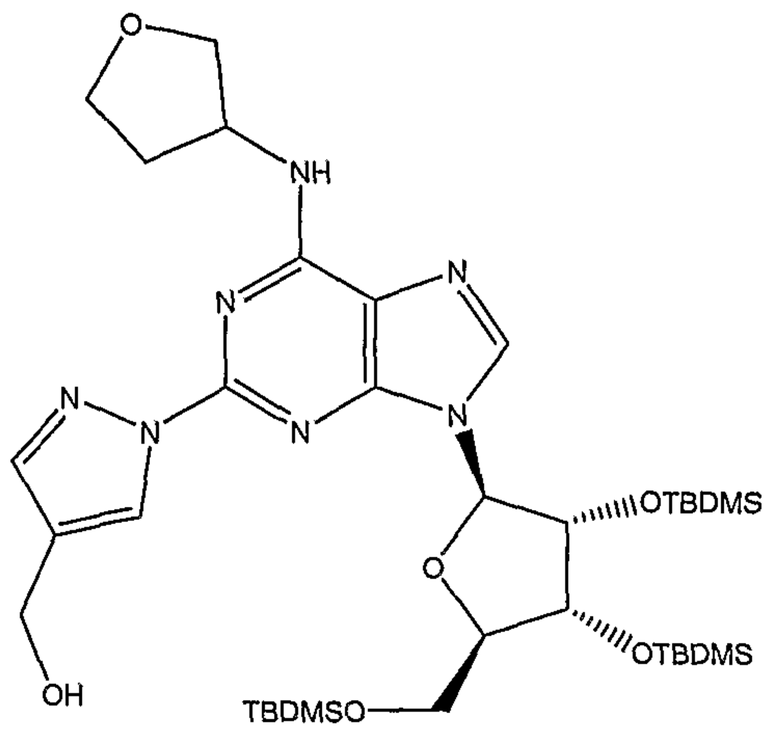
Protection and Secondary Modification of the R^4 Substituent

A. Protection of the Sugar Residue



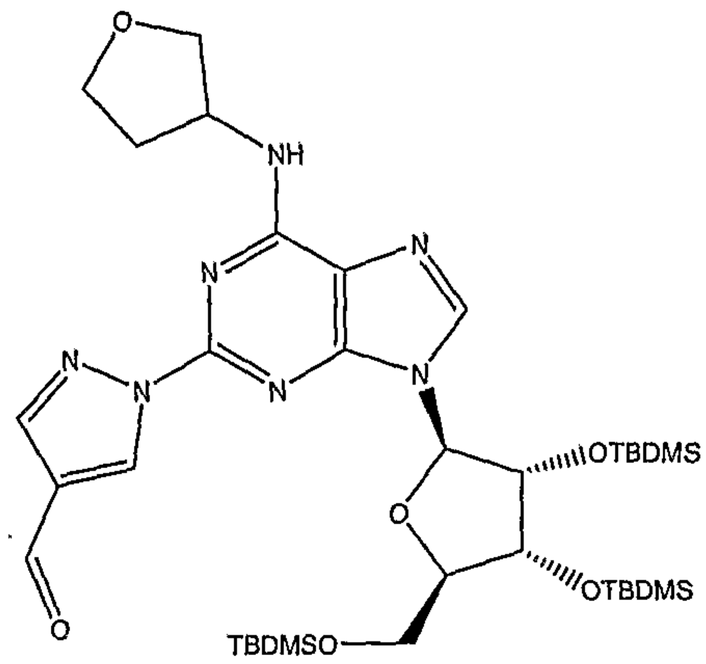
[0209] 3.3 g of the ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate prepared in Example 3 was dissolved in 120 mL of DMF. To this was added 5.76 g of *t*-butyldimethylchlorosilane and 2.6 g of imidazole. The mixture was stirred at 70°C overnight. The solvent was then evaporated off and the residue purified using TLC with a 20% ethylacetate/hexane solution to yield ethyl 1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(cyclopentylamino)purin-2-yl)pyrazole-4-carboxylate.

B. Formation of the Alcohol Intermediate



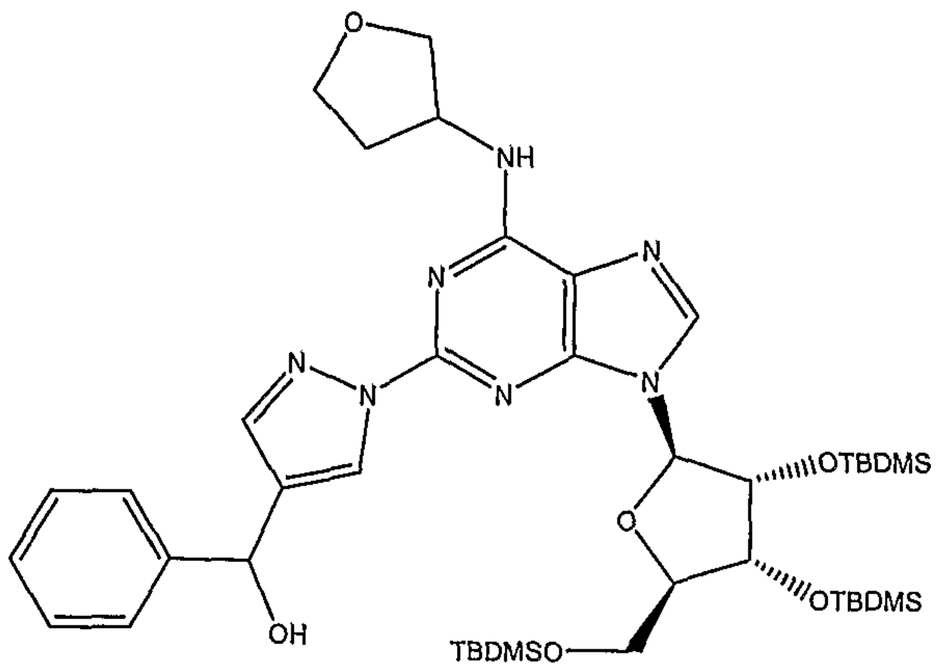
[0210] 1.3 g of ethyl 1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(oxolan-3-ylamino)purin-2-yl)pyrazole-4-carboxylate prepared according to the method described in Example 11A was dissolved in 7 mL of THF and chilled in a 0°C bath. 1.91 ml of $LiAlH_4$ was dropwise added to this solution. The mixture was then allowed to warm to room temperature over a course of several hours. A saturated solution of NH_4CL was added dropwise to the room temperature solution until no bubbles were observed. The resulting precipitate was filtered off and the filtrate concentrated down to remove all of the remaining solvent. The remaining aqueous solution was extracted with dichloromethane and the organic layer dried of $MgSO_4$, filtered, and concentrated down to form a brown oil. The product, [1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(oxolan-3-ylamino)purin-2-yl)pyrazol-4-yl]methan-1-ol, was purified by chromatography in a 5% methanol/dichloromethane solution.

C. Formation of the Aldehyde Intermediate



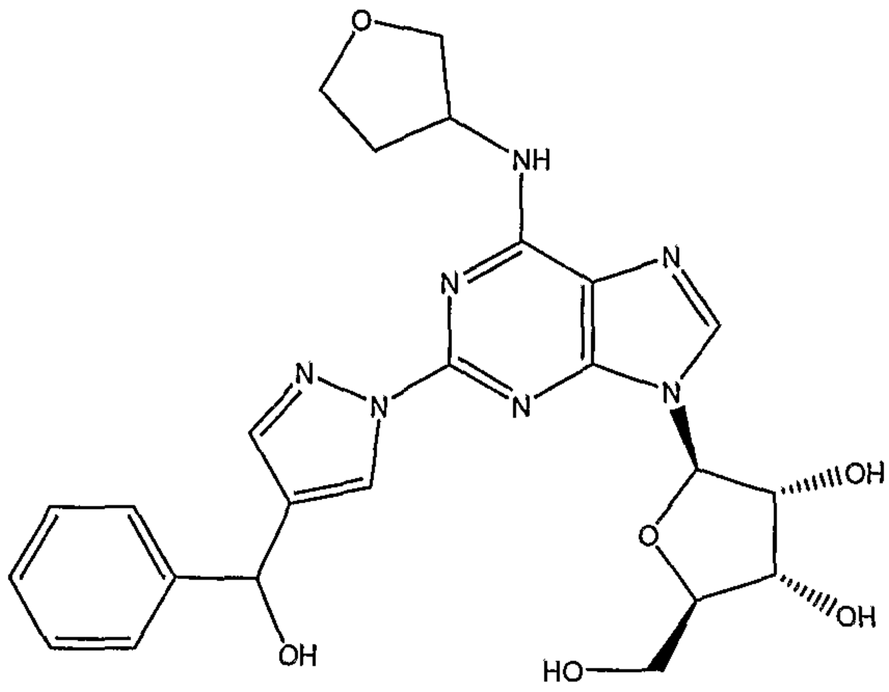
[0211] 324 mg of pyridinium chlorochromate (PCC) was stirred in 10 mL of dry dichloromethane. In to this suspension, was added 780 mg of the [1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(oxolan-3-ylamino)purin-2-yl)pyrazol-4-yl]methan-1-ol prepared in Example 11B. The mixture was stirred at room temperature for 24 hours and filtered. The resulting filtrate was condensed to remove the solvent. The product, 1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(oxolan-3-ylamino)purin-2-yl)pyrazole-4-carbaldehyde, was purified by chromatography.

D. Addition of the R^4 Substituent



[0212] A solution of 500 mg of 1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(oxolan-3-ylamino)purin-2-yl)pyrazole-4-carbaldehyde, prepared as disclosed in part C above, in 3 mL of THF was chilled in a dry ice/acetone bath. To the chilled solution was added 1.3 mL of a 1 M phenylmagnesium bromide/THF solution in a dropwise fashion. The reaction mixture was then warmed to room temperature over the course of 24 hours. The solvent was then removed and the residue concentrated. The residue was then mixed with water and a saturated solution of NH_4Cl was added. The product, [1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(oxolan-3-ylamino)purin-2-yl)pyrazol-4-yl]phenylmethan-1-ol, was extracted with ethyl acetate and purified by chromatography.

E. Deprotection of the Sugar Residue



[0213] 180 mg of the protected product of part D was placed in 3 mL of methanol. To this solution was added 3 mL of .5 M NH_4F in methanol. The reaction mixture was held at reflux for 8 hours and the solvent was then removed. The residue was purified by chromatography in a 10% methanol/dichloromethane solution to give the final product, (3S,2R,4R,5R)-2-(hydroxymethyl)-5-{2-[4-(hydroxyphenylmethyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}oxolane-3,4-diol.

F. Preparation of a Compound of Formula I, varying R^1, R^2, R^3, R^4, and R^5

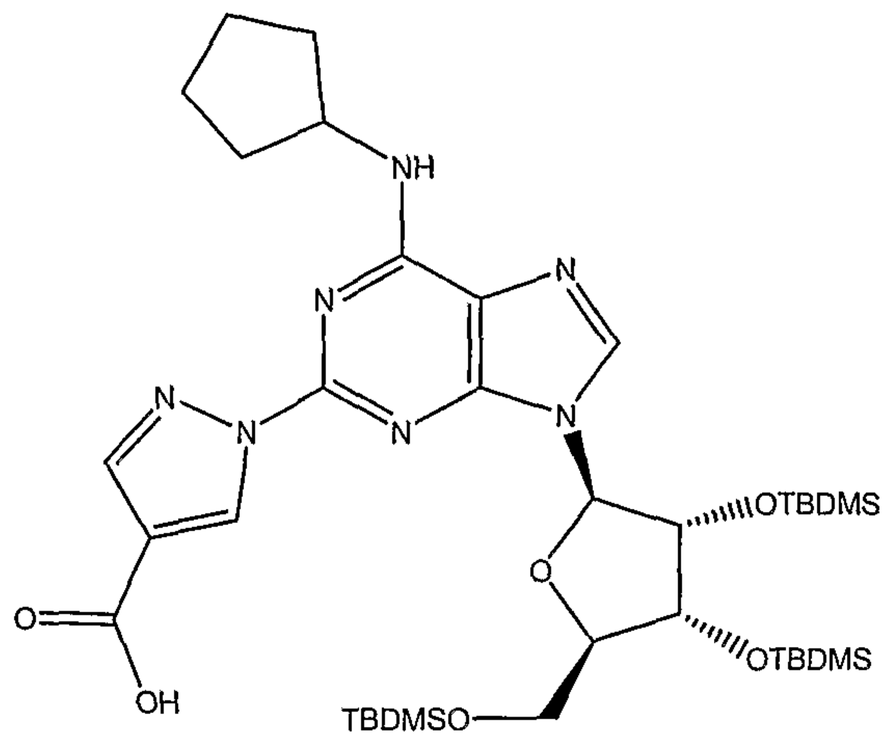
[0214] Similarly, following the procedure of 11A-E above, but optionally replacing ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate with other R^4 carboxylates of Formula I or replacing phenylmagnesium bromide with differently-modified magnesium bromide residues, other compounds of Formula I are prepared.

EXAMPLE 12

Preparation of a Compound of Formula I

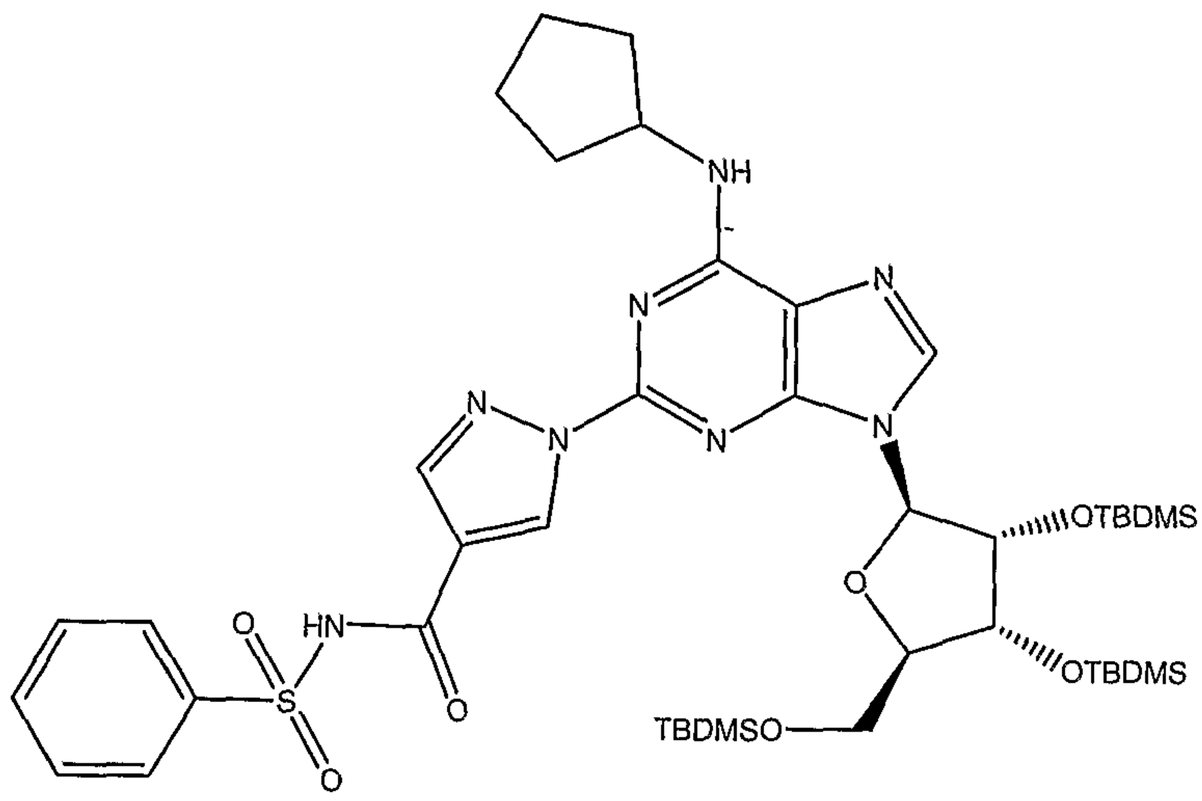
Protection and Secondary Modification of the R^4 Substituent

A. Formation of the Acid Intermediate



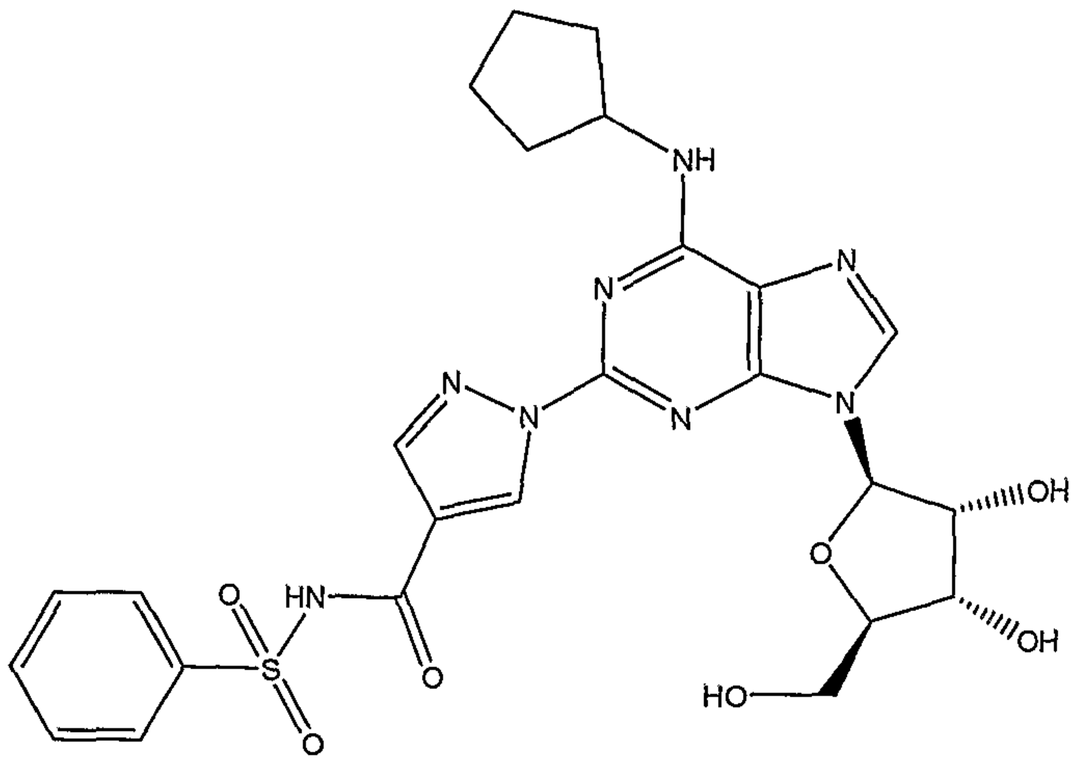
[0215] 2.75 g of ethyl 1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(cyclopentylamino)purin-2-yl)pyrazole-4-carboxylate prepared as described in Example 11A and 0.5 g KOH were stirred in 50 mL of ethanol at room temperature overnight. In the morning the mixture was refluxed for 1.5 hours. After reflux, the product was concentrated and the residue dissolved in 30 mL of water and acidified to a pH of 2.0 using a 2N aqueous HCl solution. The product was then extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4. The solvent was removed by evaporation and the product purified using a graduated, 2:3 to 3:2 ethyl acetate/hexane column to provide 1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(cyclopentylamino)purin-2-yl)pyrazole-4-carboxylic acid.

B. Addition of the R^4 Substituent



[0216] 79 mg of 1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(cyclopentylamino)purin-2-yl)pyrazole-4-carboxylic acid, prepared as disclosed in part A above, was placed in 5 mL of dichloromethane. To this solution was added 17 mg of benzenesulfonamide, 14 mg of 4-dimethylaminopyridine (DMAP), and 21 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCl). The reaction mixture was stirred at room temperature over the weekend. The solvent was then removed and the residue concentrated. The produce, [1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(cyclopentylamino)purin-2-yl)pyrazol-4-yl]-N-(phenylsulfonyl)carboxamide, was purified using prep-TLC with a 5% MeOH/CH_2Cl_2 solution.

C. Deprotection of the Sugar Residue



[0217] 180 mg of the protected product of part B was placed in 3 mL of methanol. To this solution was added 3 mL of .5 M NH_4F in methanol. The reaction mixture was held at reflux for 8 hours and the solvent was then removed. The residue was purified by chromatography in a 10% methanol/dichloromethane solution to give the final product, (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-(phenylsulfonyl)carboxamide.

D. Preparation of a Compound of Formula I, varying R^2, R^3, R^4, and/or R^5

[0218] Similarly, following the procedure of 12A-C above, but replacing benzenesulfonamide with differently-substituted sulfonamides or 1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(cyclopentylamino)purin-2-yl)pyrazole-4-carboxylic acid with other protected carboxylic acid compounds, the following compounds of Formula I were prepared:

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(oxolan-3-ylamino)purin-2-yl}pyrazol-4-yl)-N-[(4-fluorophenyl)sulfonyl]carboxamide;

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-[(4-fluorophenyl)sulfonyl]carboxamide;

methyl 2-{[(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)carbonylamino]sulfonyl}benzoate;

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-(ethylsulfonyl)carboxamide;

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-[(2-chlorophenyl)sulfonyl]carboxamide;

N-(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)[(4-methylphenyl)sulfonyl]carboxamide;

N-(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)[benzylsulfonyl]carboxamide;

N-(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)(phenylsulfonyl)carboxamide;

N-(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl){[4-(trifluoromethyl)phenyl]sulfonyl}carboxamide; and

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-[(3-chlorophenyl)sulfonyl]carboxamide.

E. Preparation of a Compound of Formula I, varying R^1, R^2, R^3, R^4, and R^5

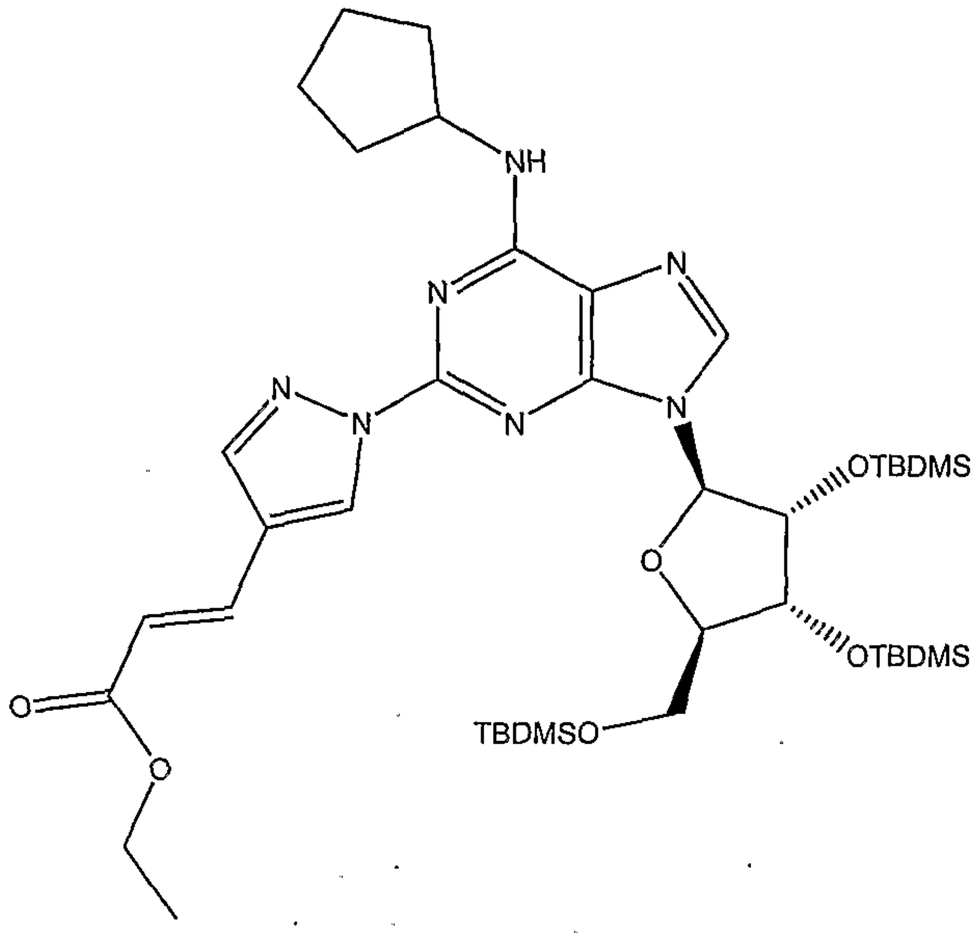
Similarly, following the procedure of 12A-C above, but optionally replacing benzenesulfonamide with differently-substituted sulfonamides and/or replacing 1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(cyclopentylamino)purin-2-yl)pyrazole-4-carboxylic acid with other protected carboxylic acid compounds, other compounds of Formula I are prepared.

EXAMPLE 13

Preparation of a Compound of Formula I

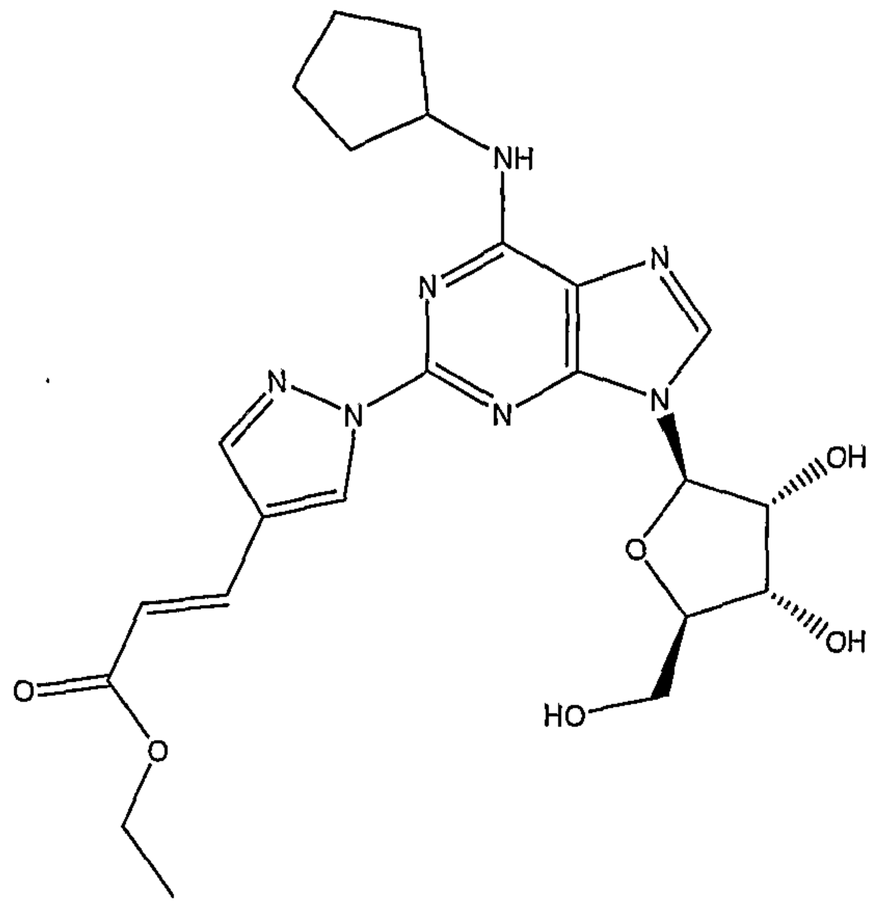
Protection and Secondary Modification of the R^4 Substituent

A. Addition of the R^4 Substituent



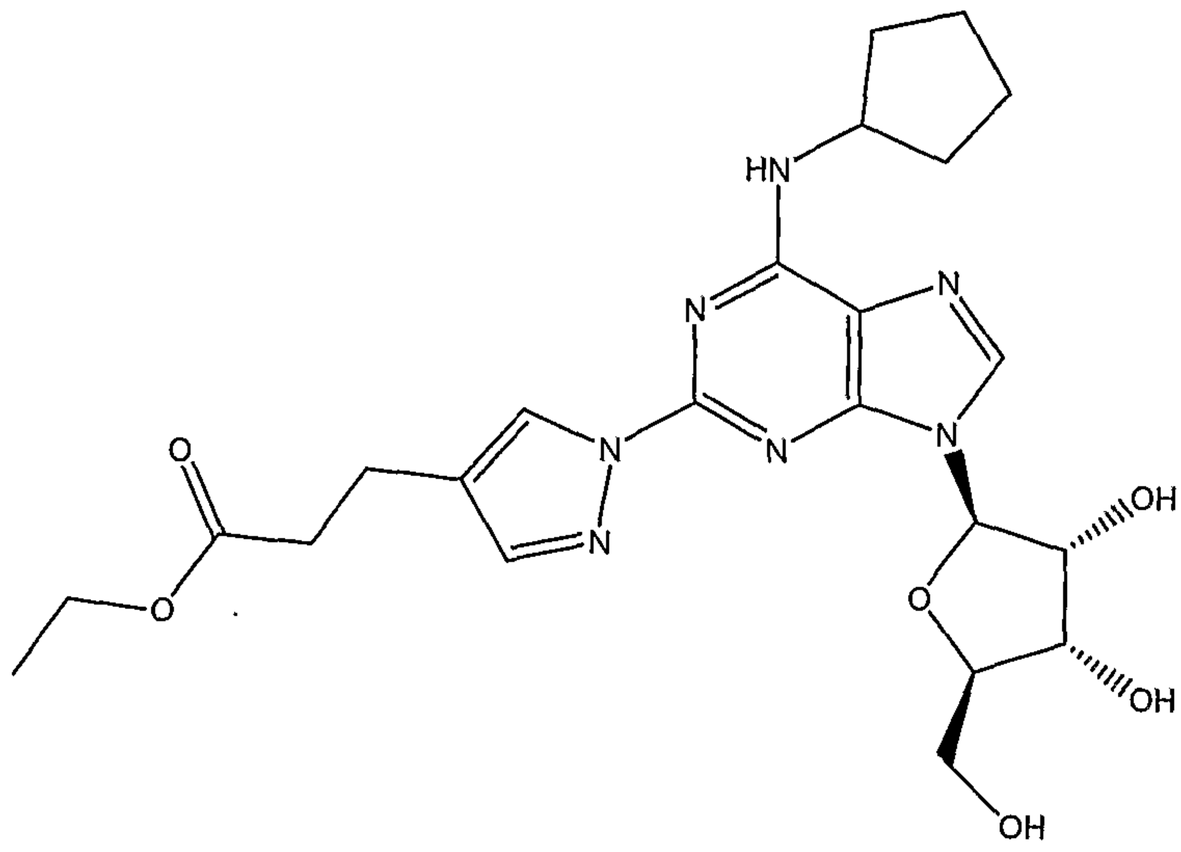
[0219] A solution of (ethoxycarbonylmethyl)triphenylphosphonium bromide (79 mg) in 1 mL of 5% aqueous NaOH was prepared. To the NaOH solution was added a solution of 1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(cyclopentylamino)purin-2-yl)pyrazole-4-carbaldehyde (71 mg), prepared according the method described in Example 11A-C above, in 3 mL of dichloromethane. The reaction mixture was stirred at room temperature overnight and the product, ethyl (2E)-3-[1-(9-{(3S,4S,5S,2R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(cyclopentylamino)purin-2-yl)pyrazol-4-yl]prop-2-enoate, purified using prep TLC (10% MeOH:CH_2Cl_2).

B. Deprotection of the Sugar Residue



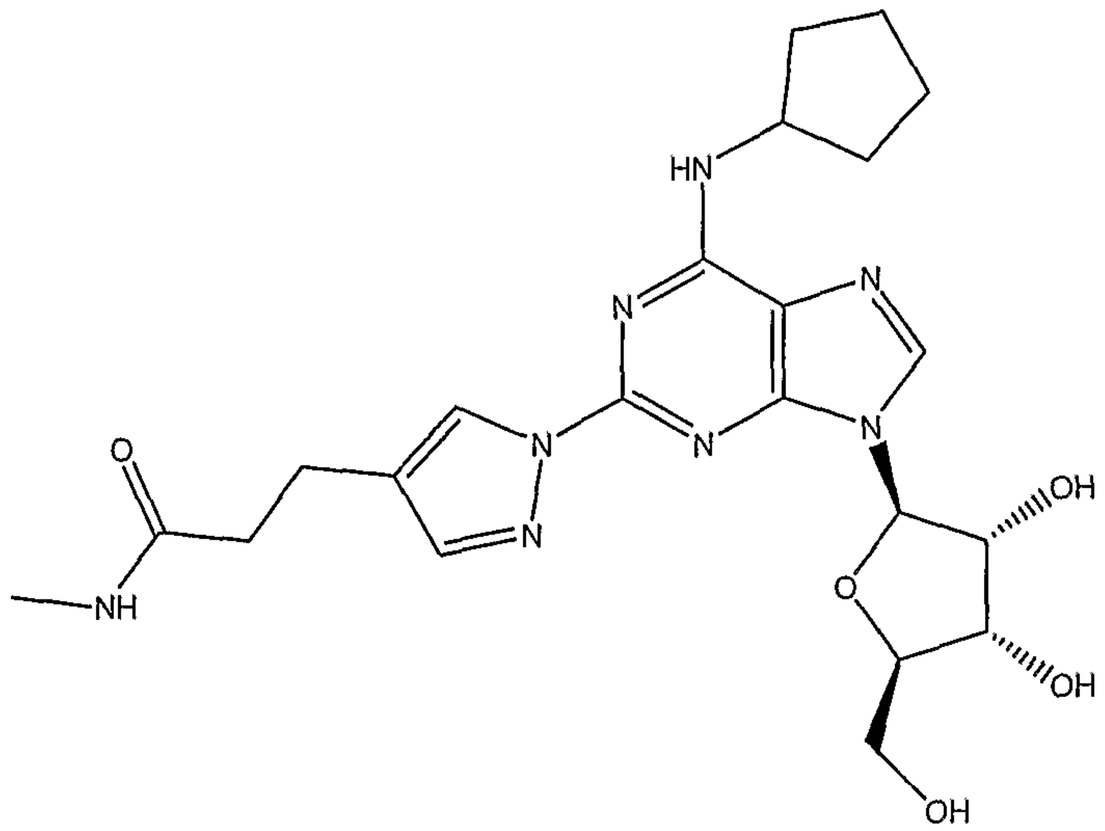
[0220] 81 mg of the protected product of part A was placed in 3 mL of methanol. To this solution was added 3 mL of .5 M NH_4F in methanol. The reaction mixture was held at reflux overnight and the solvent then removed. The residue was purified by chromatorgraphy in a 10% methanol/dichloromethane solution to give the final product, ethyl (2E)-3-(1-{9-[(3S,5S,2R,4R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)prop-2-enoate.

C. Optional Hydrogenation of the Double Bond



[0221] 10 mg of the ethyl (2E)-3-(1-{9-[(3S,5S,2R,4R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)prop-2-enoate prepared in the preceding step was combined in a par bottle with 3 mL of MeOH and approximately 5 mg of 10%Pd/C (Aldrich) and the solution hydrogenated at 25-30 psi at room temperature. The Pd/c was filtered off and the filtrate condensed to provide ethyl 3-(1-{9-[(3S,5S,2R,4R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)propanoate.

D. Optional Additional Modification of the R^4 Substituent



[0222] 15 mg of the ethyl 3-(1-{9-[(3S,5S,2R,4R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)propanoate prepared in the preceding step was combined with 2 mL of 40% $MeNH_2$ in H_2O and 2 mL of MeOH. The reaction mixture was heated to 55°C overnight. In the morning, the reaction mixture was concentrated and the product, 3-(1-{9-[(3S,5S,2R,4R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-methylpropanamide, purified using Prep TLC.

E. Preparation of a Compound of Formula I, varying R^1, R^2, R^3, R^4, and R^5

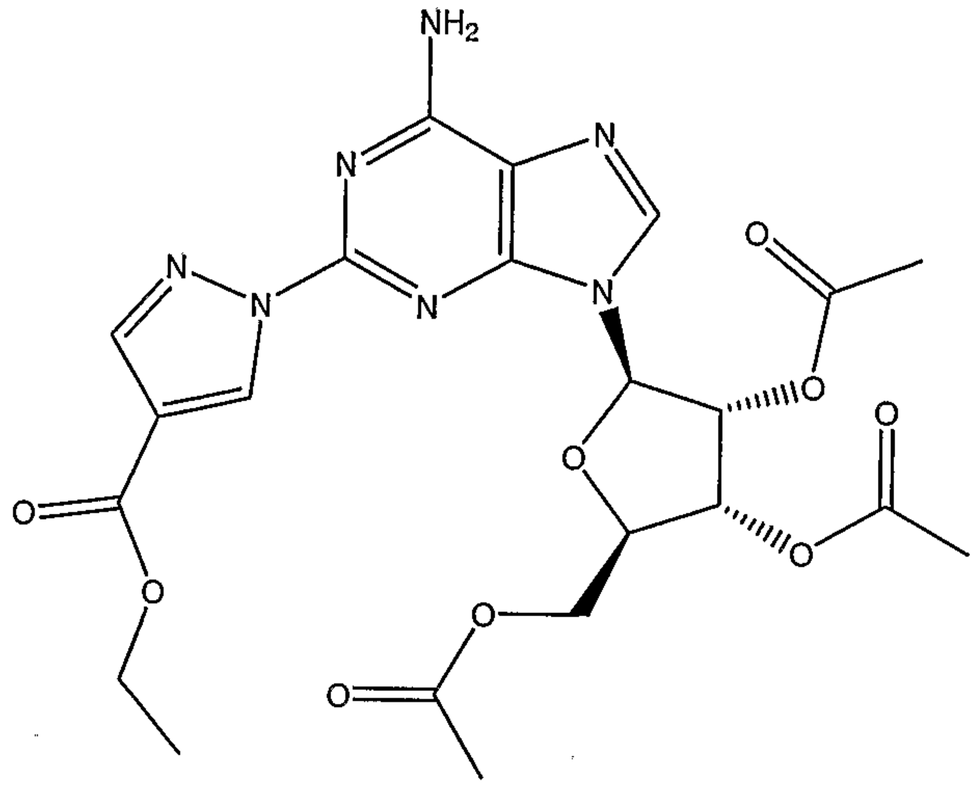
[0223] Similarly, following the procedure of 13A and B, 13A-C, or 13A-D, above, but optionally replacing 1-(9-{(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-6-(cyclopentylamino)purin-2-yl)pyrazole-4-carbaldehyde with other R^4 carbaldehydes of Formula I or replacing (ethoxycarbonylmethyl)triphenylphosphonium bromide with differently-modified triphenylphosphonium bromides, or replacing $MeNH_2$ with other amines, other compounds of Formula I are prepared.

EXAMPLE 14

Preparation of a Compound of Formula I

Protection and Secondary Modification of the R^2 Substituent

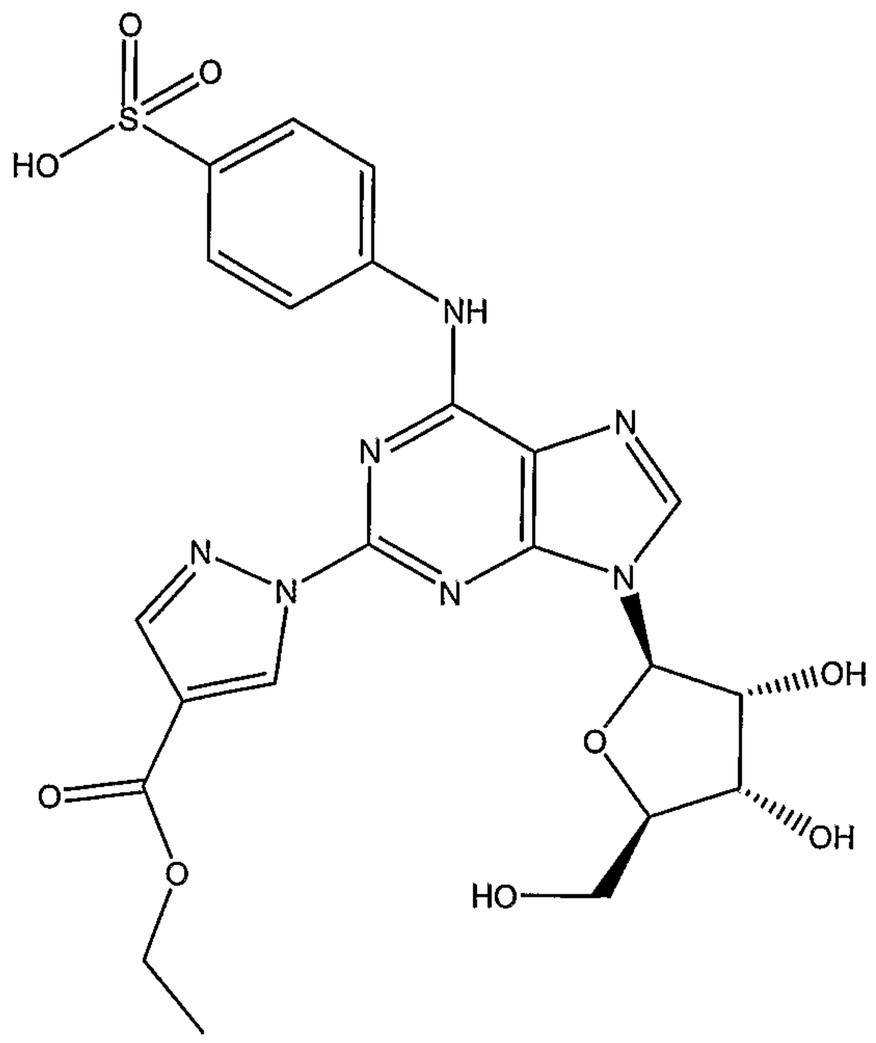
A. Protection of the Sugar Residue



[0224] 2.03g of ethyl 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylate, as prepared in Example 3, was placed in 40 mL of DMF. To this was added 5 g of the ion-exchange resin, Amberlyst 15 (Rohm &Haas). 10 mL of acetic anhydride was then slowly added at room temperature. The reaction was allowed to continue overnight at room temperature under constant stirring.

[0225] After 12 hours, the reaction mixture was filtered, rinsed/washed with CH_2Cl_2 (3 x 40 mL). The combined organic phase was concentrated in vacuo to give an orange, gel-like, slurry. The slurry was taken up in chloroform (50 mL), partitioned/washed with 50 mL of $NH_4Cl_{(aq)}$, H_2O (50mL), and 50 mL of brine, and then dried over Na_2SO_4 The reaction mixture was concentrated to a slurry. The product, (2R,3R,4R,5R)-4-acetyloxy-5-(acetyloxymethyl)-2-{6-amino-2-[4-(ethoxycarbonyl)pyrazolyl]purin-9-yl}oxolan-3-yl acetate, was then purified using Prep-TLC over silica gel with a 5% MeOH/CH_2Cl_2 solution.

B. Addition of the R^2 Substituent and Deprotection



[0226] The following were placed into a 5 ml tube with a stir bar:

115 mg of (2R,3R,4R,5R)-4-acetyloxy-5-(acetyloxymethyl)-2-{6-amino-2-[4-(ethoxycarbonyl)pyrazolyl]purin-9-yl}oxolan-3-yl acetate, prepared above;
51 mg 4-bromobenzenesulfonic acid;
2 mg $Pd(OAc)_2$;
56 mg potassium tert-butoxide;
1.5 mL *t*-BuOH; and
0.5 mL toluene.

The reaction mixture was stirred for 2 hours under nitrogen gas and then 8 mg of dicyclohexyl{2-[2,4,6-tris(methylethyl)phenyl]phenyl}phosphine was added at once. The tube was then sealed and placed in the Personal Chemistry Microwave System™ for irradiation at 180°C for 15 minutes.

[0227] After irradiation, the mixture was cooled, filtered through a layer of celite, and washed with methanol (4 x 10 mL). The combined organic phases were concentrated in vacuo and the resulting liquid taken up with ethyl acetate (3 x 25 mL). This solution was then washed with 0.5% HCl (25 mL), NH_4Cl (25 mL), and brine (150). After washing, the solution was dried over $MgSO_4$, concentrated to form a slurry, dissolved in MeOH, and subjected to prep-TLC with a 10% MeOH/CH_2Cl_2, to provide the final, deprotected product, 4-({9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-

yl]-2-[4-(ethoxycarbonyl)pyrazolyl]purin-6-yl}amino)benzenesulfonic acid.

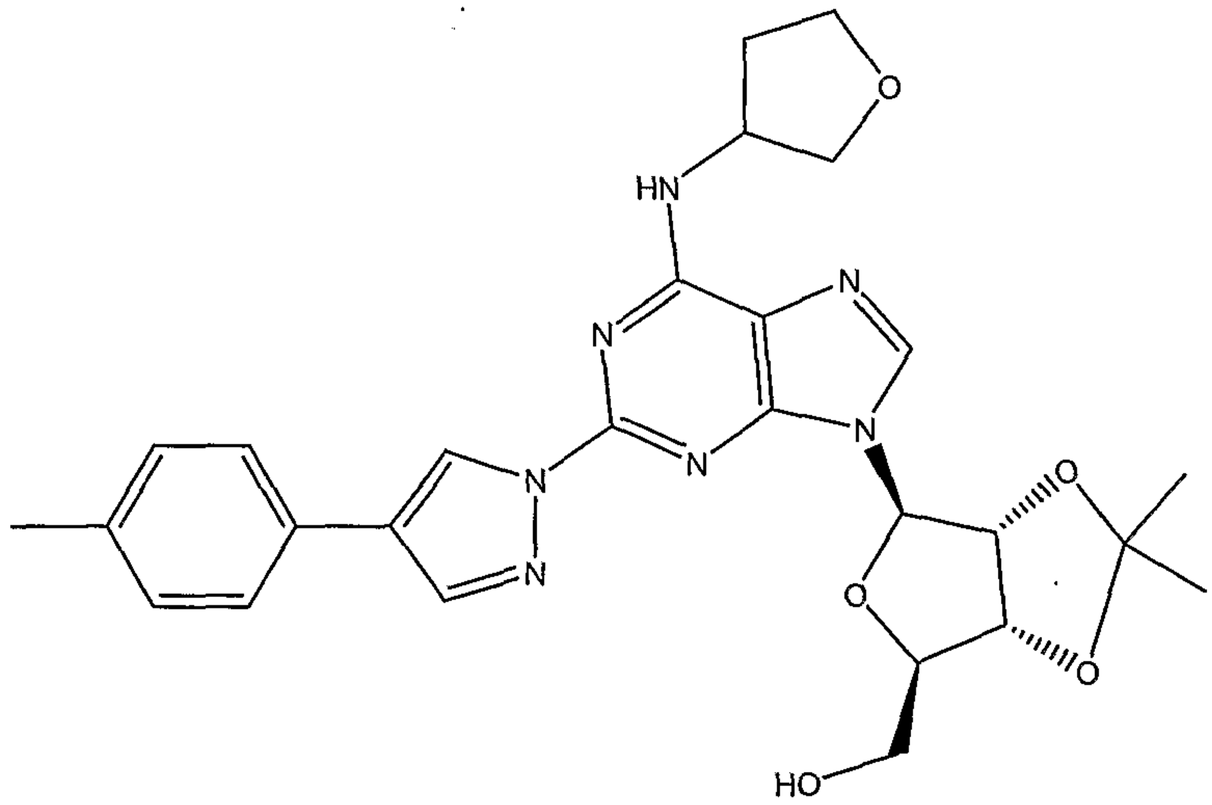
C. Preparation of a Compound of Formula I, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedure of 14A and B above, but optionally replacing ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylate with other R^4 carboxylates of Formula I or replacing 4-bromobenzenesulfonic acid with differently-modified bromide residues, other compounds of Formula I are prepared.

EXAMPLE 15

Preparation of a Compound of Formula I
Protection and Secondary Modification of the R^1 Substituent

A. Protection of the 3' and 4' Hydroxyl Moieties on the Sugar Residue

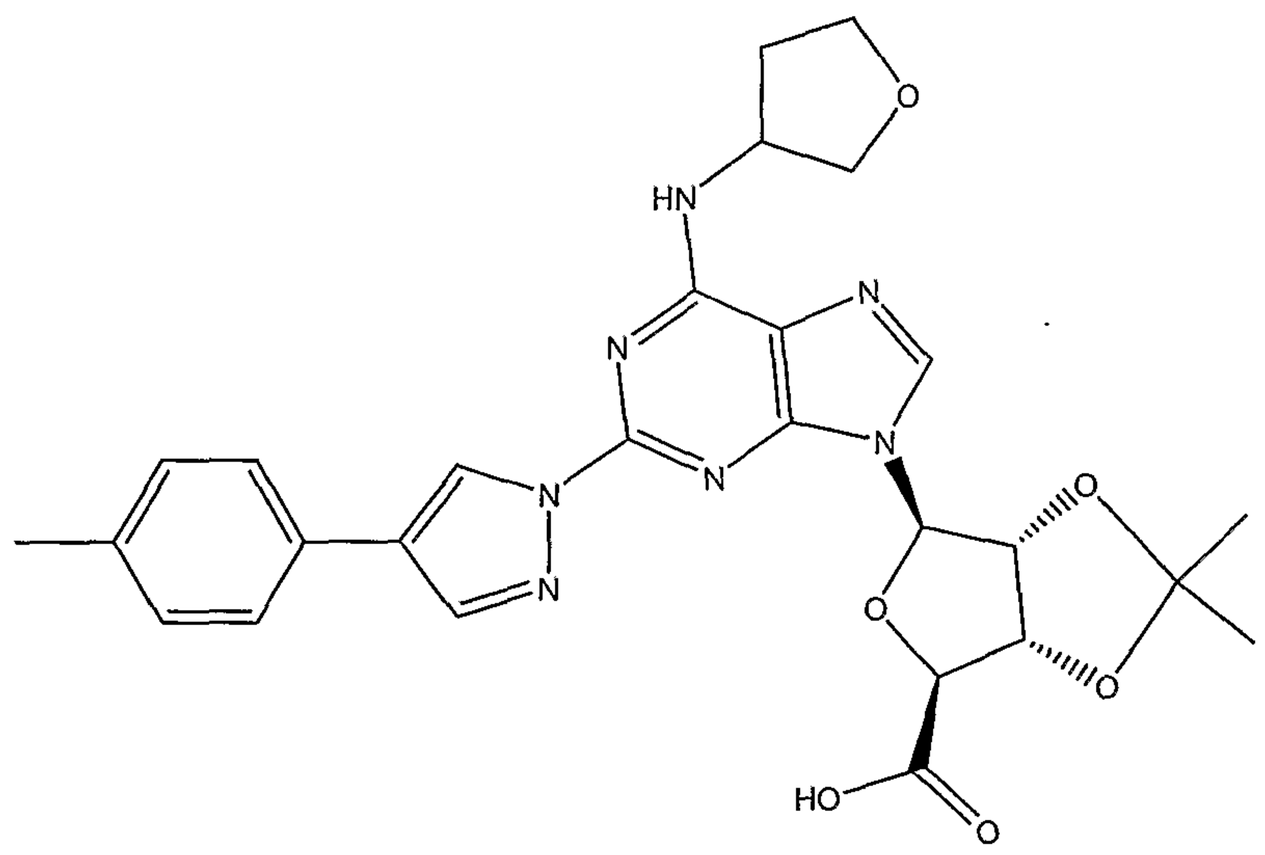


[0228] 0.513 g of (3S,2R,4R,5R)-2-(hydroxymethyl)-5-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}oxolane-3,4-diol, prepared according to the method described in Example 3, 1.3 mL of 2,2-dimethoxypropane, and

1 mL of a (0.190 g pTSOH/10mL DMF) solution were mixed in 10 mL of DMF. The solution was heated to 80°C overnight in a pressure tube.

[0229] The following morning, the volatile materials were removed and the acid catalyst quenched by the addition of 10 drops of concentrated NH_4OH solution. The product, ((1R,2R,4R,5R)-7,7-dimethyl-4-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}-3,6,8-trioxabicyclo[3.3.0]oct-2-yl)methan-1-ol, was purified by Biotage™ chromatography (405 cartridge) using stepped 200 mL aliquots of 0%, 5%, 10%, 15%, and 20 % methanol in dichloromethane solvent. The product eluted in the 5-15% solvent strength fractions. The material was carried onto the next step without further manipulation.

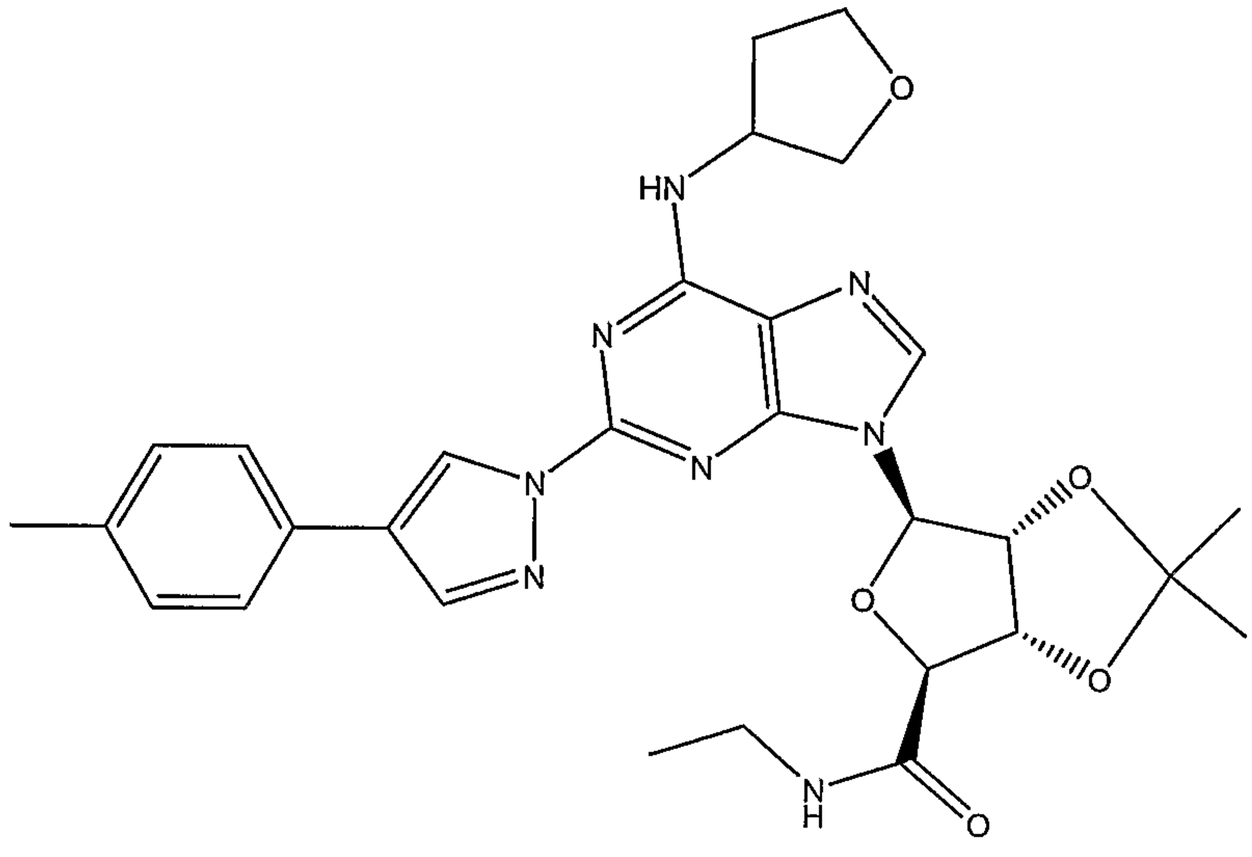
B. Preparation of the 5' Carboxylic Acid



[0230] 0.514 g of ((1R,2R,4R,5R)-7,7-dimethyl-4-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}-3,6,8-trioxabicyclo[3.3.0]oct-2-yl)methan-1-ol as prepared in Part A above, 30.1 mg of TEMPO, and 0.683 g of BAIB wer combined n a flask, CH_3CN (1.5 mL) and H_2O (1.5 mL) were added and the resulting solution stirred at ambient temperature for 3 hours. The product, (2S,1R,4R,5R)-7,7-dimethyl-4-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}-3,6,8-

trioxabicyclo[3.3.0]octane-2-carboxylic acid, precipitated from solution and was collected by filtration and triturated with diethylether.

C. Conversion of the 5' Carboxylic Acid to a 5' Carboxamide



[0231] 0.0821 g of (2S,1R,4R,5R)-7,7-dimethyl-4-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}-3,6,8-trioxabicyclo[3.3.0]octane-2-carboxylic acid, as prepared in Part C above was taken up in 4 mL of dichloromethane. To this solution was added the following:

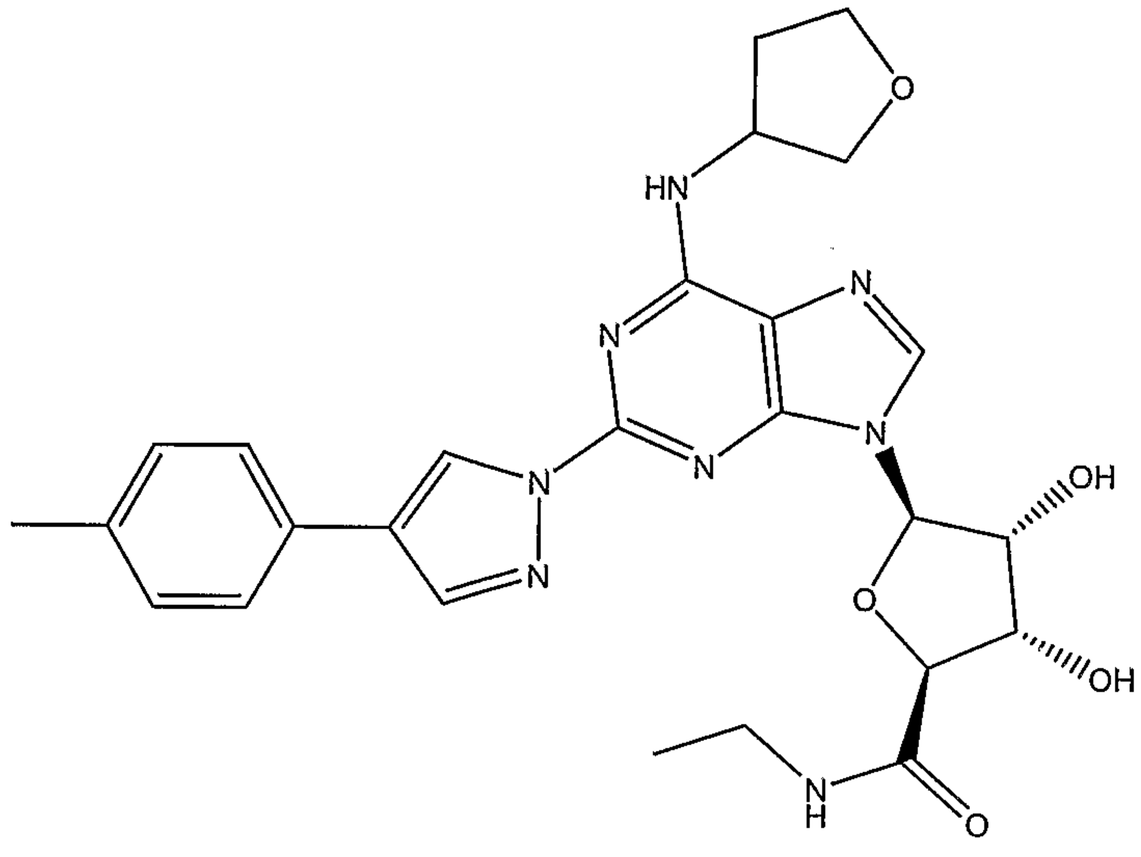
0.114 g of 2-(1H-benzotriazo 1-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate (HBTU),
0.041 g of 1-hydroxybenzotriazole (HOBt),
a catalytic amount of dimethylaminopyridine (DMAP); and
0.12 mL of triethylamine.

The mixture was stirred at ambient temperature for 20 minutes and then 0.049 g of ethylamine hydrochloride was added. This mixture was stirred overnight at room temperature.

[0232] The following morning the reaction mixture was diluted with 50 mL of dichloromethane and wished with 10 mL of a 10% citric acid solution, 10 mL of $NaHCO_{3(aq)}$, and 10 mL of brine. The organic solution was dried over $MgSO_4$. The solvent was then removed on a rotovap and the product purified by prep TLC using

10% methanol in dichloromethane to yield ((2S,1R,4R,5R)-7,7-dimethyl-4-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}-3,6,8-trioxabicyclo[3.3.0]oct-2-yl)-N-ethylcarboxamide.

D. Deprotection of the 3' and 4' Hydroxyl Moieties on the Sugar Residue



[0233] 72 mg of the 3',4' protected carboxamide prepared in Part C above, ((2S,1R,4R,5R)-7,7-dimethyl-4-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}-3,6,8-trioxabicyclo[3.3.0]oct-2-yl)-N-ethylcarboxamide, was taken up in acetic acid (4 mL) and H_2O (1 mL). The resulting solution was heated at 80°C overnight. The following morning, the reaction mixture was cooled to room temperature.

[0234] The solvents were removed on a rotovap and the resulting solid taken up in methanol. Some white solid remained insoluble and this was collected via filtration. The mother liquor was used to spot a prep TLC plate that was eluted using 10% methanol in dichloromethane as the eluent. The lower fluorescent spot was collected. After desorption and solvent removal, an additional amount of product was recovered. This product and the initial insoluble product were confirmed by GC/MS to be ((2S,3S,4R,5R)-3,4-dihydroxy-5-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}oxolan-2-yl)-N-ethylcarboxamide.

E. Preparation of Other Compounds of Formula I, varying R^1, R^2, and R^4

[0235] Similarly, following the procedure of 9A-C or 9A-D above, but optionally replacing (3S,2R,4R,5R)-2-(hydroxymethyl)-5-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}oxolane-3,4-diol with other R^1 hydroxymethyl compounds of Formula I and optionally replacing the ethylamine hydrochloride with other amine salts, the following other compounds were prepared:

5-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-quinolyl)pyrazolyl)purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolane-2-carboxylic acid;

5-{6-[((3R)oxolan-3-yl)amino]-2-(4-(4-pyridyl)pyrazolyl)purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolane-2-carboxylic acid

(5-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-quinolyl)pyrazolyl)purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide; and

(5-{6-[((3R)oxolan-3-yl)amino]-2-(4-(4-pyridyl)pyrazolyl)purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide.

D. Preparation of Other Compounds of Formula I, varying R^1, R^2, R^3, R^4, and R^5

[0236] Similarly, following the procedure of 9A-C or 9A-D above, but optionally replacing (3S,2R,4R,5R)-2-(hydroxymethyl)-5-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}oxolane-3,4-diol with other R^1 hydroxymethyl compounds of Formula I and optionally replacing the ethylamine hydrochloride with other amine salts, other compound of Formula I are prepared.

EXAMPLE 16

[0237] Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules.

EXAMPLE 17

[0238] A tablet formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets.

EXAMPLE 18

[0239] Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules.

EXAMPLE 19

[0240] A tablet formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets.

EXAMPLE 20

[0241] A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Active Ingredient	5
Lactose	95

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

EXAMPLE 21

[0242] Tablets, each containing 30 mg of active ingredient, are prepared as follows:

Ingredient	Quantity (mg/tablet)
Active Ingredient	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in sterile water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50 °C to 60 °C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

EXAMPLE 22

[0243] Suppositories, each containing 25 mg of active ingredient are made as follows:

Ingredient	Amount
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

EXAMPLE 23

[0244] Suspensions, each containing 50 mg of active ingredient per 5.0 mL dose are made as follows:

Ingredient	Amount
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%)	
Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 mL

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

EXAMPLE 24

[0245] A subcutaneous formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	5.0 mg
Corn Oil	1.0 mL

EXAMPLE 25

[0246] An injectable preparation is prepared having the following composition:

Ingredients	Amount
Active ingredient	2.0 mg/mL
Mannitol, USP	50 mg/mL
Gluconic acid, USP	q.s. (pH 5-6)
water (distilled, sterile)	q.s. to 1.0 mL
Nitrogen Gas, NF	q.s.

EXAMPLE 26

[0247] A topical preparation is prepared having the following composition:

Ingredients	grams
Active ingredient	0.2-10
Span 60	2.0
Tween 60	2.0
Mineral oil	5.0
Petrolatum	0.10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. to100

All of the above ingredients, except water, are combined and heated to 60° C with stirring. A sufficient quantity of water at 60° C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. 100 g.

EXAMPLE 27

Sustained Release Composition

Ingredient	Weight Range (%)	Preferred Range (%)	Most Preferred
Active ingredient	50-95	70-90	75
Microcrystalline cellulose (filler)	1-35	5-15	10.6
Methacrylic acid copolymer	1-35	5-12.5	10.0
Sodium hydroxide	0.1-1.0	0.2-0.6	0.4
Hydroxypropyl methylcellulose	0.5-5.0	1-3	2.0
Magnesium stearate	0.5-5.0	1-3	2.0

[0248] The sustained release formulations of this invention are prepared as follows: compound and pH-dependent binder and any optional excipients are intimately mixed(dry-blended). The dry-blended mixture is then granulated in the presence of an aqueous solution of a strong base that is sprayed into the blended powder. The granulate is dried, screened, mixed with optional lubricants (such as talc or magnesium stearate), and compressed into tablets. Preferred aqueous solutions of strong bases are solutions of alkali metal hydroxides, such as sodium or potassium hydroxide, for example sodium hydroxide, in water (optionally containing up to 25% of water-miscible solvents such as lower alcohols).

[0249] The resulting tablets may be coated with an optional film-forming agent, for identification, taste-masking purposes and to improve ease of swallowing. The film forming agent will typically be present in an amount ranging from between 2% and 4% of the tablet weight. Suitable film-forming agents are well known to the art and include hydroxypropyl. methylcellulose, cationic methacrylate copolymers (dimethylaminoethyl methacrylate/ methyl-butyl methacrylate copolymers - Eudragit® E - Röhm. Pharma), and the like. These film-forming agents may optionally contain colorants, plasticizers, and other supplemental ingredients.

[0250] The compressed tablets for example have a hardness sufficient to withstand 8 Kp compression. The tablet size will depend primarily upon the amount of compound in the tablet. The tablets will include from 300 to 1100 mg of compound free base. For example, the tablets will include amounts of compound free base ranging from 400-600 mg, 650-850 mg, and 900-1100 mg.

[0251] In order to influence the dissolution rate, the time during which the compound containing powder is wet mixed is controlled. For example the total powder mix time, i.e. the time during which the powder is exposed to sodium hydroxide solution, will range from 1 to 10 minutes and for example from 2 to 5 minutes. Following granulation, the particles are removed from the granulator and placed in a fluid bed dryer for drying at about 60°C.

EXAMPLE 28

Binding Assays – DDT_1 Cells

Cell Culture

[0252] 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 μg 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 1.2×10^5 cells per plate and experiments were performed 4 days later at approximately one day preconfluence.

Membrane Preparations

[0253] 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 was 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 again 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 adenosine receptor 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

and stored at –80°C. Aliquots of the membrane suspension were later thawed and used for assays. The protein content was determined with a Bradford™ Assay Kit using bovine serum albumin as standard.

Competitive Binding Assay

[0254] Compounds of Formula I were assayed by use of competitive radioligand binding methods to determine their affinity for the A_1 adenosine receptor sites on the membranes of DDT cells. Briefly, 50-70 ug of membrane protein were incubated in a mixture containing 2U/ml adenosine deaminase and 10 μM GTP-γS in 50 mM Tris-HCl buffer, pH 7.4, with 1 mM EDTA in glass tubes. Stock solutions of the compounds of the invention were serially diluted (10^{-10}M to 10^{-4}M) in Tris buffer and added to the incubation mixture. Finally, tritiated 8-cyclopentyl-1,1-dipropylxanthine (^{3}H-CPA) was added to a final concentration of 1.5 nM. After incubation at 23°C 90 minutes, the reaction was stopped by filtration on a Brandel MR24 cell harvester and washing with ice-cold Tris-EDTA buffer (three times, approximate volume 10 ml/wash) over Whatman GF/B filters (presoaked for 1 h in 0.3% polyethylenimine to reduce non-specific binding). Filters were transferred to scintillation vials and 5 ml of **Scintisafe (VWR, Brisbane, CA)** was added. The amount of radioactivity retained on the filters was determined by liquid scintillation spectrometry. Protein determinations were by the method of Bradford (1976. *Anal. Biochem.* 72:248) using bovine serum albumin as the standard.

[0255] The compounds of Formula I were shown to be of high, medium, or low affinity for the A_1 adenosine receptor in this assay. The K_i values for several of the compounds of the invention are presented in Table 1 below.

TABLE 1. A_1 BINDING AFFINITY

NUMBER	NAME	K_i nM
I.	(5-{6-[((3R)oxolan-3-yl)amino]-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide	2000

NUMBER	NAME	K_i nM
II.	(5-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-quinolyl)pyrazolyl)purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide	74
III.	ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4- carboxylate	36
IV.	(4S,3R,5R)-2-[2-(3,5-dimethylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol	134
V.	(4S,3R,5R)-2-[2-(3,5-dimethyl-4-propylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol	39
VI.	(5-{6-[((3R)oxolan-3-yl)amino]-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide	2
VII.	(5-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-quinolyl)pyrazolyl)purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide	24
VIII.	ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4- carboxylate	23
IX.	(4S,3R,5R)-2-[2-(3,5-dimethylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol	20
X.	(4S,3R,5R)-2-[2-(3,5-dimethyl-4-propylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol	160
XI.	(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide	10
XII.	ethyl 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazole-4-carboxylate	1720
XIII.	(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-propylcarboxamide	10
XIV.	(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-propylcarboxamide	1090
XV.	(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide	1530
XVI.	(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide	1790
XVII.	6-(1-{6-[((3R)oxolan-3-yl)amino]-9-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)pyridine-3-carboxylic acid	64
XVIII.	(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-[(4-chlorophenyl)methyl]carboxamide	27

NUMBER	NAME	K_i nM
XIX.	(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-[(4-fluorophenyl)methyl]carboxamide	43
XX.	(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-benzylcarboxamide	1
XXI.	(1-{6-[((3R)oxolan-3-yl)amino]-9-[(3S,2R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-{[5-fluoro-3-(trifluoromethyl)phenyl]methyl}carboxamide	56
XXII.	(5-{6-[((3R)oxolan-3-yl)amino]-2-(4-(4-pyridyl)pyrazolyl)purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide	1060
XXIII.	5-{6-[((3R)oxolan-3-yl)amino]-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolane-2-carboxylic acid	121
XXIV.	(5-{6-[((3R)oxolan-3-yl)amino]-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide	89
XXV.	ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4- carboxylate	0.9
XXVI.	(4S,3R,5R)-2-[2-(3,5-dimethylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol	94
XXVII.	(4S,3R,5R)-2-[2-(3,5-dimethyl-4-propylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol	395
XXVIII.	(4S,3R,5R)-2-[2-(4-butyl-3,5-dimethylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol	188
XXIX.	methyl 4-{[(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)carbonylamino]methyl}benzoate	6
XXX.	4-{[(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)carbonylamino]methyl}benzoic acid	8
XXXI.	1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylic acid	8
XXXII.	1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxamide	0.59
XXXIII.	ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(bicyclo[2.2.1]hept-2-ylamino)purin-2-yl}pyrazole-4-carboxylate	2
XXXIV.	1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(bicyclo[2.2.1]hept-2-ylamino)purin-2-yl}pyrazole-4-carboxylic acid	1
XXXV.	(1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide	1

NUMBER	NAME	K_i nM
XXXVI.	(4S,3R,5R)-2-[6-(bicyclo[2.2.1]hept-2-ylamino)-2-pyrazolylpurin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol	0.4

EXAMPLE 29

[^{35}S]GTPγS Binding Assays

[0256] A_1 adenosine receptor agonist stimulated [^{35}S] GTPγS binding was determined by a modification of the method described by Giersckik 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.

[0257] The compounds of Formula I were shown to be partial or full agonists of the A_1 adenosine receptor in this assay.

EXAMPLE 30

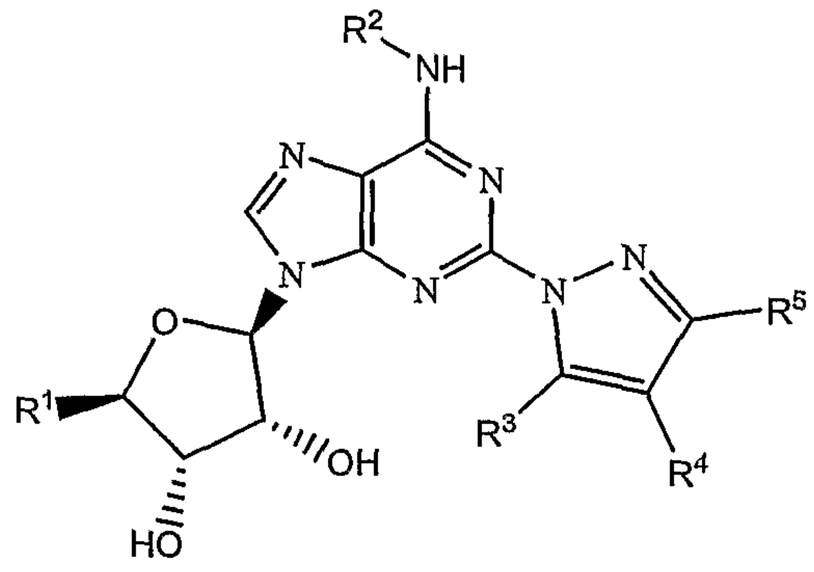
cAMP Assay

[0258] A scintillation proximity assay (SPA) using rabbit antibodies directed at cAMP and 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 with 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.

[0259] The compounds of Formula I were shown to be functionally active as A_1 agonists with a partial or full decrease in cAMP in this assay.

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula I:



wherein:

R^1 is hydroxymethyl, -C(O)OR^6, or -C(O)NHR^6, in which R^6 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aralkyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^2 is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, -CO_2H, - SO_3H, -C(O)OR^6, -CH(OH)R^6, or C(O)NR^6R^7, wherein R^7 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aralkyl, optionally substituted aryl, or optionally substituted heteroaryl,

or a salt, hydrate, or pharmaceutically acceptable ester thereof.

2. The compound of claim 1, wherein R^2 is an optionally substituted heterocyclic moiety.

3. The compound of claim 2, wherein R^2 is an optionally substituted five membered heterocyclic ring having at least one nitrogen or oxygen atom.

4. The compound of claim 3, wherein R^3 and R^5 are hydrogen or optionally substituted lower alkyl.

5. The compound of claim 4, wherein R^4 is optionally substituted aryl.

6. The compound of claim 5, selected from the group consisting of:

2-(6-[((3R)oxolan-3-yl)amino]-2-{4-[4-(trifluoromethyl)phenyl]pyrazolyl}purin-9-yl)(4S,2R,3R,5R)-5-(hydroxymethyl)oxolane-3,4-diol;

5-{6-[((3R)oxolan-3-yl)amino]-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolane-2-carboxylic acid;

(5-{6-[((3R)oxolan-3-yl)amino]-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide; and

5-(hydroxymethyl)-2-{2-[4-(4-methylphenyl)pyrazolyl]-6-(oxolan-3-ylamino)purin-9-yl}oxolane-3,4-diol.

7. The compound of claim 4, wherein R^4 is optionally substituted heteroaryl.

8. The compound of claim 7, selected from the group consisting of:

(5-{6-[((3R)oxolan-3-yl)amino]-2-(4-(4-pyridyl)pyrazolyl)purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide;

(5-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-quinolyl)pyrazolyl)purin-9-yl}(2S,4S,3R,5R)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide;

6-(1-{6-[((3R)oxolan-3-yl)amino]-9-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)pyridine-3-carboxylic acid;

2-{6-[((3R)oxolan-3-yl)amino]-2-(4-pyrazin-2-ylpyrazolyl)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol;

2-{6-[((3R)oxolan-3-yl)amino]-2-(4-quinazolin-2-ylpyrazolyl)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol;

2-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-pyridyl)pyrazolyl)purin-9-yl}(4S,3R)-5-(hydroxymethyl)oxolane-3,4-diol;

2-{6-[((3R)oxolan-3-yl)amino]-2-(4-(4-pyridyl)pyrazolyl)purin-9-yl}(4S,3R)-5-(hydroxymethyl)oxolane-3,4-diol; and

2-{6-[((3R)oxolan-3-yl)amino]-2-(4-(2-quinolyl)pyrazolyl)purin-9-yl}(4S,3R)-5-(hydroxymethyl)oxolane-3,4-diol.

9. The compound of claim 4, wherein R^4 is $-CO_2H$, $-SO_3H$, $-C(O)OR^6$, $-CH(OH)R^6$, or $C(O)NR^6R^7$.

10. The compound of claim 9, selected from the group consisting of:

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(oxolan-3-ylamino)purin-2-yl}pyrazol-4-yl)-N-[(4-fluorophenyl)sulfonyl]carboxamide;

methyl 4-{[(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)carbonylamino]methyl}benzoate;

4-{[(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)carbonylamino]methyl}benzoic acid;

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-[(4-chlorophenyl)methyl]carboxamide;

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-[(4-fluorophenyl)methyl]carboxamide;

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-benzylcarboxamide;

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(3S,2R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-{[5-fluoro-3-(trifluoromethyl)phenyl]methyl}carboxamide;

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-propylcarboxamide;

ethyl 1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylate;

1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylic acid;

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide; and

(1-{6-[((3R)oxolan-3-yl)amino]-9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide.

11. The compound of claim 4, wherein R^4 is hydrogen or optionally substituted alkyl.

12. The compound of claim 11, namely 2-{6-[((3R)oxolan-3-yl)amino]-2-[4-(hydroxyphenylmethyl)pyrazolyl]purin-9-yl}(4S,2R,3R,5R)-5-(hydroxymethyl)oxolane-3,4-diol.

13. The compound of claim 1, wherein R^2 is an optionally substituted cycloalkyl moiety.

14. The compound of claim 13, wherein R^3 and R^5 are hydrogen or optionally substituted lower alkyl.

15. The compound of claim 14, wherein R^4 is $-CO_2H$, $-SO_3H$, $-C(O)OR^6$, $-CH(OH)R^6$, or $C(O)NR^6R^7$.

16. The compound of claim 15, selected from the group consisting of:

ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4- carboxylate;

1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxylic acid;

1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carboxamide;

ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(bicyclo[2.2.1]hept-2-ylamino)purin-2-yl}pyrazole-4-carboxylate;

1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(bicyclo[2.2.1]hept-2-ylamino)purin-2-yl}pyrazole-4-carboxylic acid;

(1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide;

1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}-5-methylpyrazole-3-carboxamide;

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}-5-methylpyrazol-3-yl)-N-methylcarboxamide;

ethyl 1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazole-4-carboxylate;

(1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide;

ethyl 1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylate;

1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxylic acid;

(1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide;

1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazole-4-carboxamide;

1-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]purin-2-yl}pyrazole-4-carboxamide;

1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclohexylamino)purin-2-yl}pyrazole-4-carboxylic acid;

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-[(4-fluorophenyl)sulfonyl]carboxamide;

methyl 2-{[(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)carbonylamino]sulfonyl}benzoate;;

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-(ethylsulfonyl)carboxamide;

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-[(2-chlorophenyl)sulfonyl]carboxamide;

(1-{9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-(3,3,3-trimethyl-3-azabutyl)carboxamide;

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-[(4-methylphenyl)sulfonyl]carboxamide;

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-[benzylsulfonyl]carboxamide;

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-(phenylsulfonyl)carboxamide;

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-{[4-(trifluoromethyl)phenyl]sulfonyl}carboxamide; and

(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-[(3-chlorophenyl)sulfonyl]carboxamide.

17. The compound of claim 14, wherein R^4 is hydrogen or optionally substituted alkyl, alkenyl, or alkynyl.

18. The compound of claim 17, selected from the group consisting of:

(4S,3R,5R)-2-[2-(3,5-dimethylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

(4S,3R,5R)-2-[2-(3,5-dimethyl-4-propylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

(4S,3R,5R)-2-[2-(4-butyl-3,5-dimethylpyrazolyl)-6-(cyclopentylamino)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

(4S,3R,5R)-2-[6-(bicyclo[2.2.1]hept-2-ylamino)-2-pyrazolylpurin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

(4S,3R,5R)-2-[6-(cyclopentylamino)-2-pyrazolylpurin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazole-4-carbonitrile;

ethyl (2E)-3-(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)prop-2-enoate;

ethyl 3-(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)propanoate;

(4S,3R,5R)-2-[6-(cyclohexylamino)-2-pyrazolylpurin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol;

3-(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)-N-methylpropanamide;

2-{6-[((1R,2R)-2-hydroxycyclopentyl)amino]-2-pyrazolylpurin-9-yl}(2R,5R)-5-(hydroxymethyl)oxolane-3,4-diol;

(2R,5R)-2-{2-[4-(aminomethyl)pyrazolyl]-6-(cyclopentylamino)purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol; and

[(1-{9-[(2R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(cyclopentylamino)purin-2-yl}pyrazol-4-yl)methyl][(4-fluorophenyl)sulfonyl]amine.

19. The compound of claim 1, wherein R^2 is an optionally substituted aryl or benzyl.

20. The compound of claim 19, wherein R^3 and R^5 are hydrogen or optionally substituted lower alkyl.

21. The compound of claim 20, wherein R^4 is $-CO_2H$, $-SO_3H$, $-C(O)OR^6$, $-CH(OH)R^6$, or $C(O)NR^6R^7$.

22. The compound of claim 21, selected from the group consisting of:

ethyl 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazole-4-carboxylate;

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-propylcarboxamide;

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide;

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-[benzylamino]purin-2-yl}pyrazol-4-yl)-N-methylcarboxamide; and

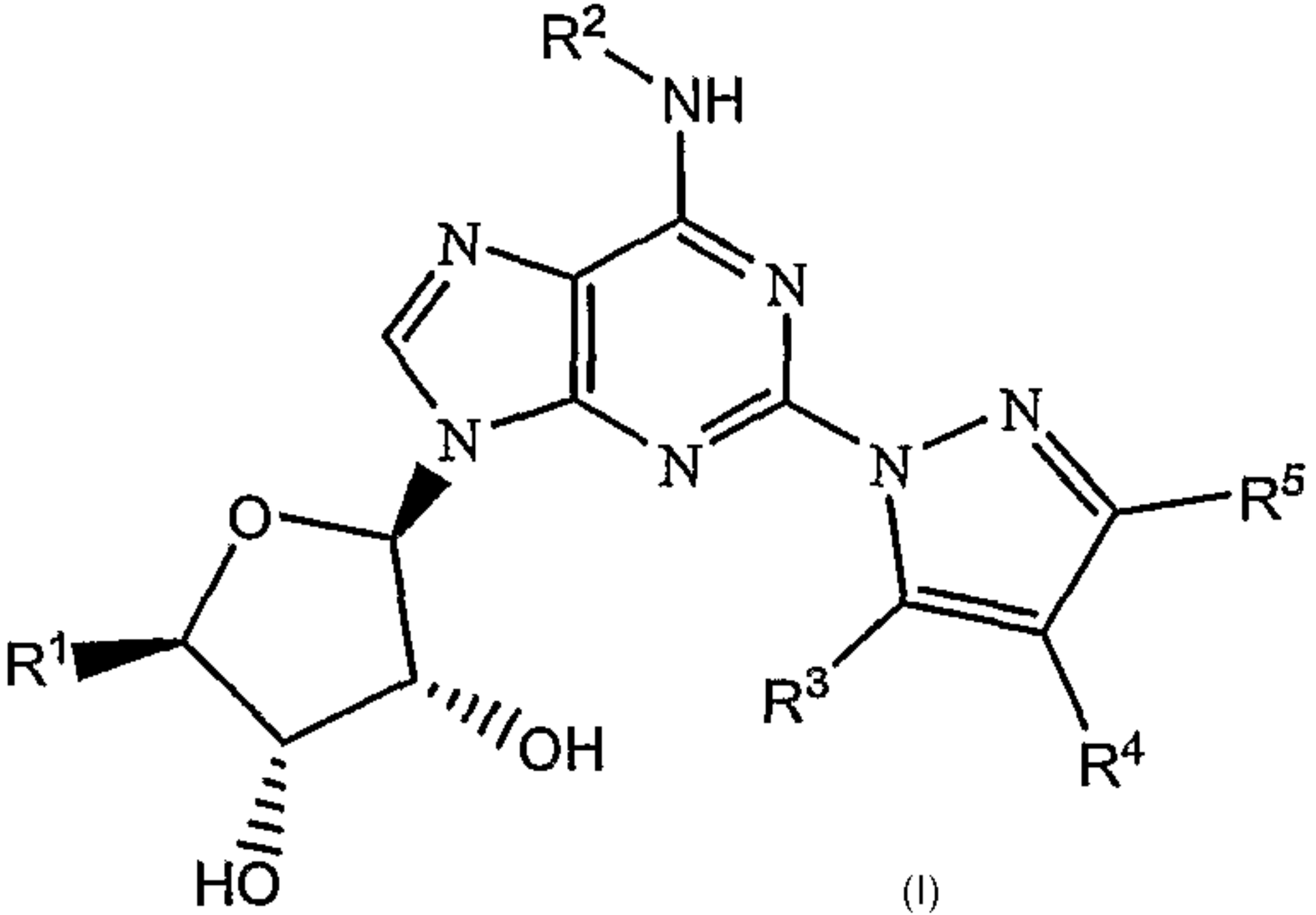
4-({9-[(4S,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-2-[4-(ethoxycarbonyl)pyrazolyl]purin-6-yl}amino)benzenesulfonic acid.

23. A method for treating a disease or condition that can be treated with partial or full A_1 adenosine receptor agonists comprising the administration to a mammal in need thereof of an amount of a compound of claim 1 therapeutically effective to fully or partially agonize an adenosine A_1 receptor.

24. The method of claim 23, wherein the disease state is chosen from atrial fibrillation, atrial flutter, congestive heart failure, epilepsy, stroke, diabetes, obesity, ischemia, stable angina, unstable angina, myocardial infarction, cardiac transplant, hyperlipidemia, hypertriglyceridemia, and metabolic syndrome.

25. The method of claim 23, wherein the mammal is human.

26. A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of claim 1.



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