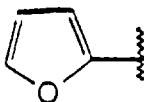
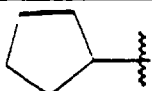
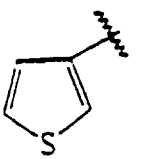
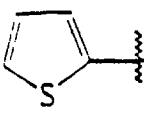
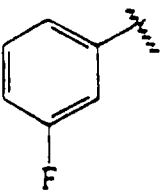
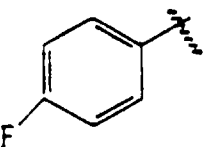
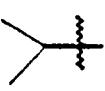
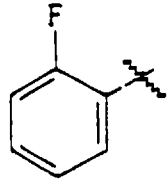




166166

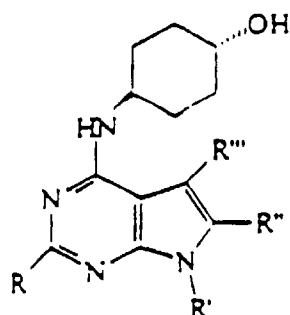
702		198.5	2782.5
703		443.6	>10000
704		61.1	297.0
705		30.1	194.7
706		19.9	
707		62.8	
708		214.5	
709		48.7	



G00002

TABLE 8

Effect of Pyrrole Ring Substituent



Compound	R	R'	R''	R'''	Al	
					Binding Ki (nM)	Yeast IC50 (nM)
800		Me	Me	Me	3311	>10000
801		H	Me	H	22.3	148.3
802		H	H	Me	8.9	
803			Me	Me	2210	>10000
804			Me	Me	863.1	
805			Me	Me	4512	

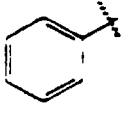
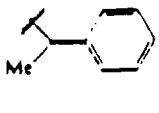
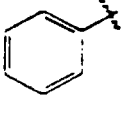
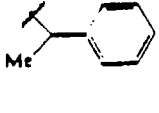
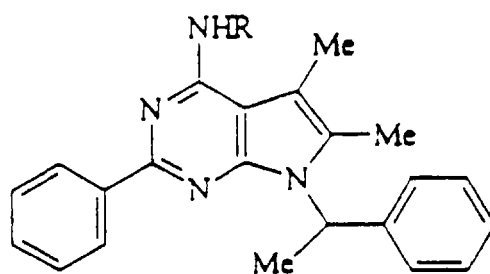
806			Me	Me	8451
807			Me	Me	35.3

TABLE 9



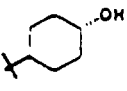
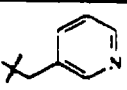
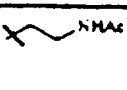
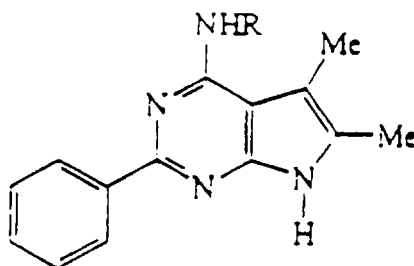
		A1	
Compound	R	Binding Ki (nM)	Yeast IC50 (nM)
900		863.1	
901		4512	
902		8451	
903		35.3	

TABLE 10

Effect of N₆-Substituent

Compound	R	A1	
		Binding K _i (nM)	Yeast IC ₅₀ (nM)
1000		1789	>10000
1001		54.4	1865
1002		9.8	82.8
1003		26.7	195.7
1004		32.8	545.8

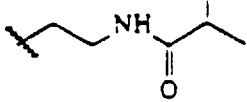
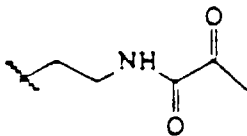
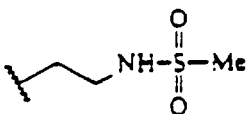
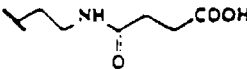
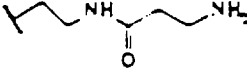
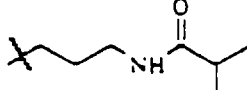
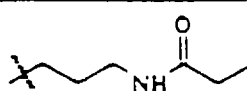
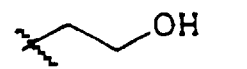
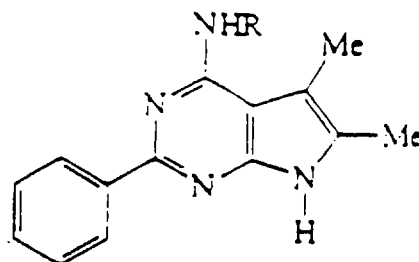
1005		147.5	3972
1006		151.7	2918
1007		692.5	>10000
1008		93.1	3217
1009		475.3	>10000
1010		674.9	9376.0
1011		121.9	2067.5
1012		233.9	3462
1013		270.1	3009.5
1014		384.9	2005
1015		179.3	3712
1016		176.1	5054

TABLE 11

Effect of N₆-Substituent:

Compound	R	A1	
		Binding K _i (nM)	Yeast IC ₅₀ (nM)
1100		9.8	115.4
1101		53.9	551.0
1102		10.3	101.3
1103		71.1	3217
1104		6.5	58.7
1105		105.4	472.1

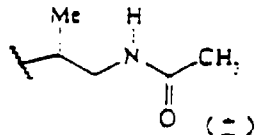
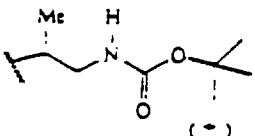
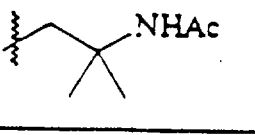
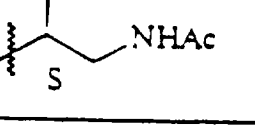
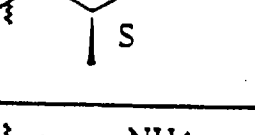
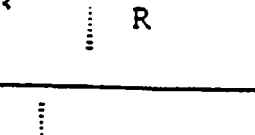
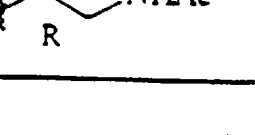
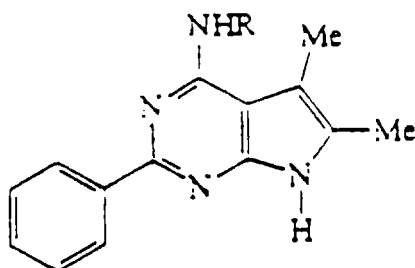
1106		27.8	162.4
1107		126.5	1297.0
1108		2.3	
1109		9.0	
1110		17.3	
1111		2.5	
1112		213	

TABLE 12
"Retro-Amide" Analogues



Compound	R	A1	
		Binding K _i (nM)	Yeast IC ₅₀ (nM)
1200		16.5	189.4
1201		7.4	45.7
1202		95.8	33-45.0
1203		529.1	4040.0
1204		1060.0	>10000

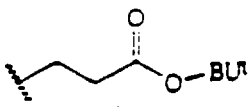
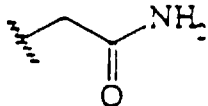
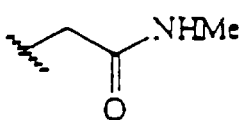
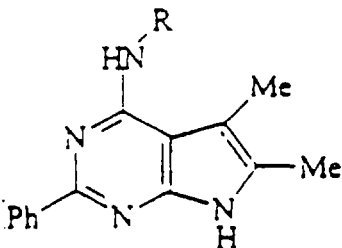
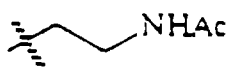
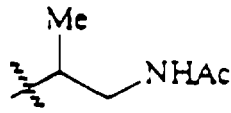
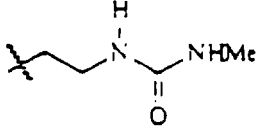
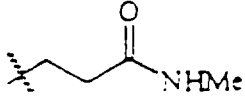
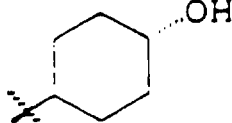
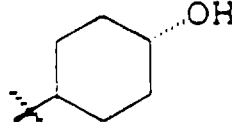
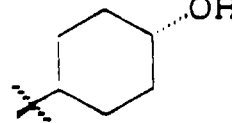
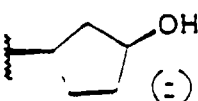
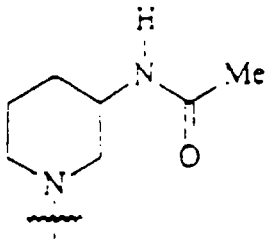
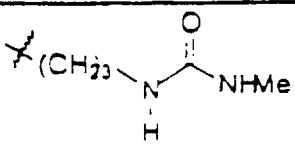
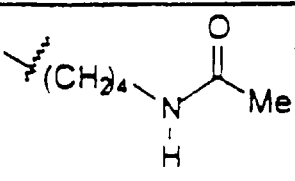
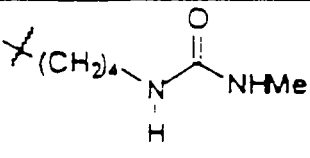
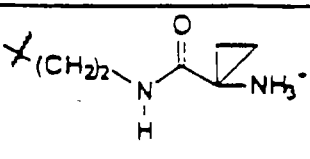
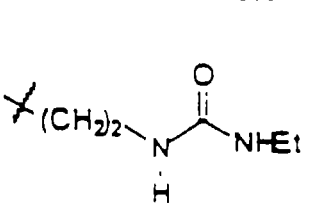
1205		1272	>10000
1206		50.8	4028
1207		48.5	701.5

TABLE 15

Profile of Selective Adenosine Antagonists

		Binding Ki (nM)			
Compound	R	A1	A2a	A2b	A3
1300		9.8- 25.1	18.0- 48.6	80.3	513.0
1301		27.8	50.7	84.6	429.8
1302		20.2	75.6	20.1	4.3

1303		17.4	111.5	120.6	4.6
1304		13.9- 30.9	933.7	138.0	21.5
1305		46.6	730.9	30%	9.9
1306		16.4	766.3	168.3	71.7
1307	 (dl)	29.1	190.6	1143.0	3.1
1308	 (-)	180	230	670	1.0

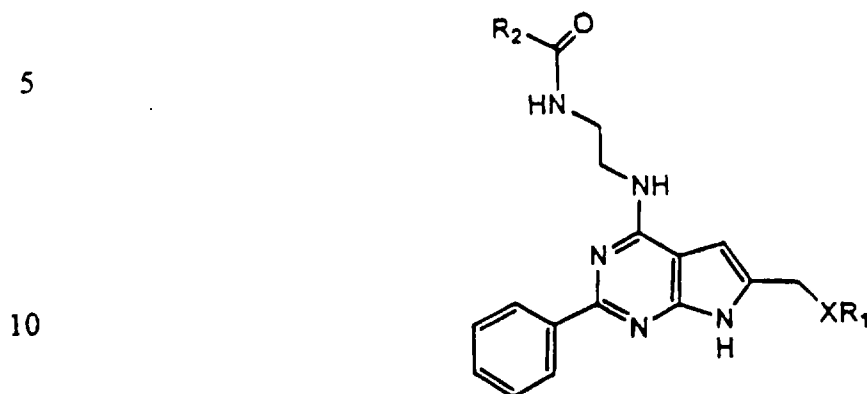
1309		40	109	109	0.3
1310		255	76%	275	≤2.6
1311		531	981	736	5.3
1312		443	2965	375	≤6.2
1313		30%	65%	515	24
1314		87	204	30	0.02

1315		75.000	720.000	3.400	507
1316		333	710.000	710.000	97
1317		710.000	710.000	720.000	369
1318 ⁴		3.7±0.5	630± 56.4	2307± 926	630±76
1319 ^{4,5}		1.8	206	802	270
1320 ^{4,6}		8.0	531	530	419
1321 ^{4,7}		8.0	131	1031	54% ⁸

¹ 2-thienyl-2-yl; ² C₅-H; ³ water soluble; ⁴ R₁ and R₂ are hydrogen; ⁵ R₁ is 3-fluorophenyl;

⁶ R₁ is 3-chlorophenyl; ⁷ R₁ is 4-pyridyl; ⁸ % activity @ 10 μM

Table 14:
Profile of Selective A_{2b} Antagonists

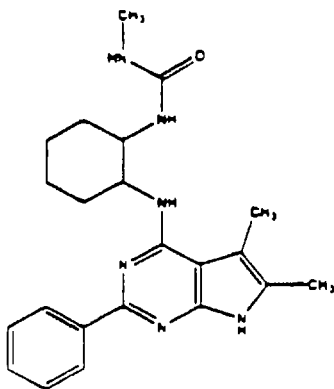
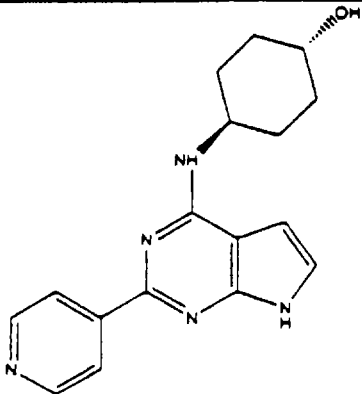
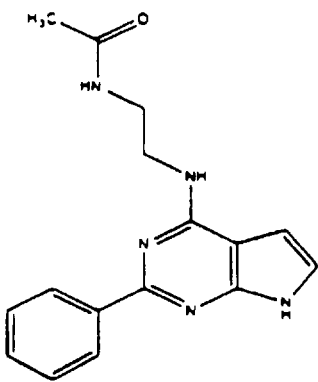
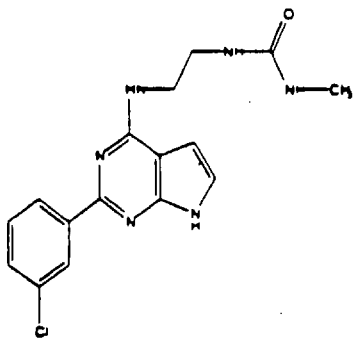


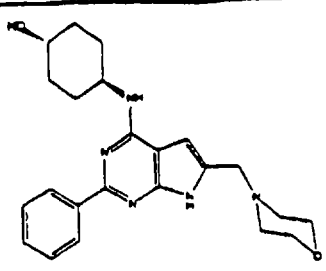
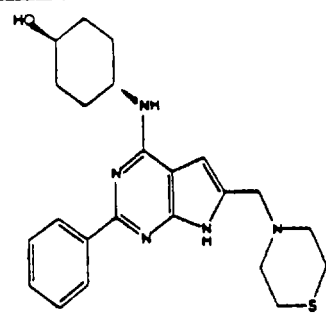
15	Compound	XR ₁	R ₂	Binding Data K _i (nM)			
				A ₁	A _{2a}	A _{2b}	A ₃
	1400	-O-Ph	Me	41.7	21	10.3	14.6
	1401	-O-Ph(p)F	Me	33	58	8.8	18
20	1402	-O-Ph(p)Cl	Me	825	591	22	60
	1403	-N-pyridin-2-one	Me	60	41	18	48
25	1404	-NH-Ph	Me	49	31	4.6	57

TABLE 15. Adenosine A₂ Receptor Selective Compounds

* at least 10 times more selective than other three subtypes.

Compound	Structure	Ki-A ₁	Relative Ki-A _{2a}	Relative Ki-A _{2b}	Relative Ki-A ₃
5 706		*			
10 1318		*			
15 1319		*			
20 1320		*			
25					

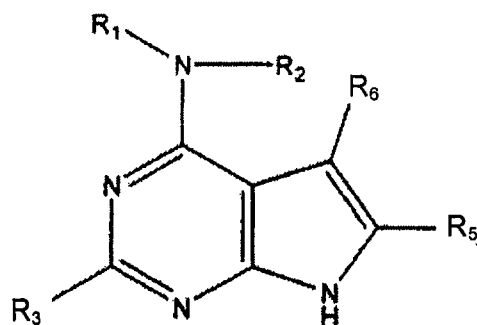
1500		*			
1321		*			
1501		*			
1502		*			

5	1503					
10	1504					
15						
20						
25						
30						

Pages 176-201 relate to compounds specific to the A_{2a} receptor
Summary of the Invention

The present invention is also based on compounds which
selectively bind to adenosine A_{2a} receptor, thereby treating a
disease associated with A_{2a} adenosine receptor in a subject by
administering to the subject a therapeutically effective amount
of such compounds. The disease to be treated are associated
with, for example, a central nervous system disorder, a
cardiovascular disorder, a renal disorder, an inflammatory
disorder, a gastrointestinal disorder, an eye disorder, an
allergic disorder or a respiratory disorder.

This invention also features a compound having the structure:



(VI)

wherein NR₁R₂ is a substituted or unsubstituted 4-8 membered
ring;

wherein R₃ is a substituted or unsubstituted four to six
membered ring;

wherein R₅ is H, alkyl, substituted alkyl, aryl, arylalkyl,
amino, substituted aryl, wherein said substituted alkyl is - C
(R₇) (R₈)XR₉, wherein X is O, S, or NR₁₀, wherein R₇ and R₈ are
each independently H or alkyl, wherein R₉ and R₁₀ are each

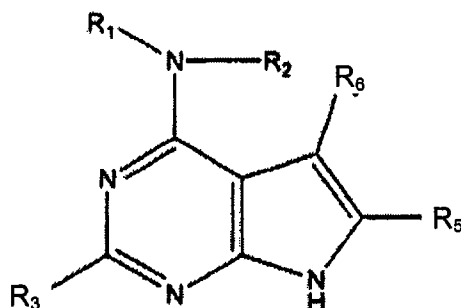
independently alkyl or cycloalkyl, or R_9 , R_{10} and the nitrogen together form a substituted or unsubstituted ring of between 4 and 7 members.

wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl ;

with the proviso that NR_1R_2 is not 3-acetamido piperidino, 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl, or pyrrolidino; wizih the proviso that NR_1R_2 is 3-hydroxymethyl piperadino only when R_3 is 4-pyridyl.

This invention also features a method for inhibiting the activity of an A_{2a} adenosine receptor in a cell, which comprises contacting said cell with the above-mentioned compounds.

This invention-also provides a compound having the structure:



(VI)

wherein NR_1R_2 is a substituted or unsubstituted 4-8 membered ring;

wherein R_3 is a substituted or unsubstituted four to six

membered ring;

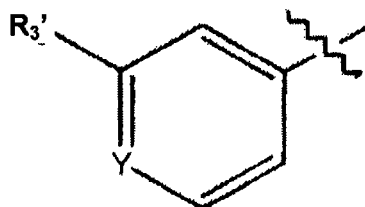
wherein R_5 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $-C(R_7)(R_8)XR_9$, wherein X is O, S, or NR_{10} , wherein R_7 and R_8 are each independently H or alkyl, wherein R_9 and R_{10} are each independently alkyl or cycloalkyl, or R_9 , R_{10} and the nitrogen together form a substituted or unsubstituted ring of between 4 and 7 members.

wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl

with the proviso that NR_1R_2 is not 3-acetamidopiperidino, 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl, or pyrrolidino; with the proviso that NR_1R_2 is 3-hydroxymethyl piperidino only when R_3 is 4-pyridyl.

In one embodiment of the compound, R_3 is a substituted or unsubstituted four to six membered ring, phenyl, pyrrole, thiophene, furan, thiazole, imidazole, pyrazole, 1,2,4-triazole, pyridine, 2 (1H)-pyridone, 4 (1H)-pyridone, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, tetrazole, naphthalene, tetralin, naphthyridine, benzofuran, benzothiophene, indole, 2,3-dihydroindole, 1H-indole, indoline, benzopyrazole, 1,3-benzodioxole, benzoxazole, purine, coumarin, chromone, quinoline, tetrahydroquinoline, isoquinoline, benzimidazole, quinazoline, pyrido[2,3-b]pyrazine, pyrido[3,4-b]pyrazine, pyrido[3,2-c]pyridazine, pyrido[3,4-b]pyridine, 1H-pyrazole[3,4-d]pyrimidine, pteridine, 2(1H)-quinolone, 1(2H)-isoquinolone, 1,4-benzisoxazine, benzothiazole,

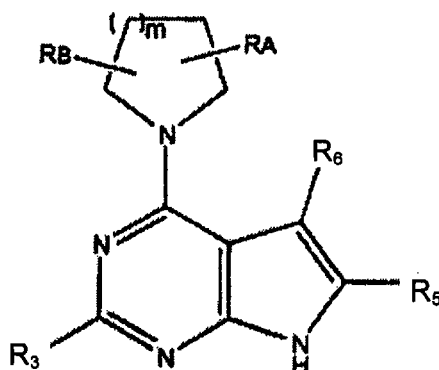
quinoxaline, quinoline-N-oxide, isoquinoline-N-oxide,
quinoxaline-N-oxide, quinazoline-N-oxide, benzoxazine,
phthalazine, cinnoline, or having a structure:



wherein Y is carbon or nitrogen;

wherein R_3' is H, substituted or unsubstituted alkyl,
substituted or unsubstituted aryl, halogen, methoxy, methyl
amino, methyl thio;

In another embodiment of the compound, the compound has the
structure:

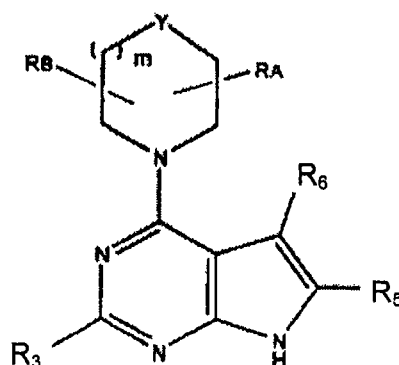


wherein m is 1 or 2; wherein R_A and R_B are each independently
be H, -OH, -CH₂OH, -CH₂CH₂OH, -C(=O)NH₂, a heteroatom, or - C
(=O) NR, $R_{11}R_{11}'$; wherein R_{11} is aryl, substituted aryl, or
heteroaryl; wherein R_{11}' is alkyl, or XR_{11}'' , wherein X is O, or
N and R_{11}'' is substituted alkyl or aryl.

In another embodiment of the compound, R_1R_2N is (D)-2-
aminocarbonyl pyrrolidino, (D)-2-hydroxymethyl pyrrolidino,

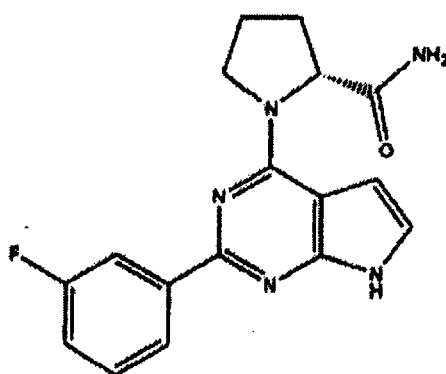
(D)-2-hydroxymethyl-trans-4-hydroxy pyrrolidino, piperazino, or 3-hydroxymethyl piperadino.

In another embodiment of the compound, the compound has the structure:



wherein m is 0, 1, 2, or 3; wherein Y is O, S, or NR, wherein R is R_A or R_B ; wherein R_A and R_B are each independently be H, -OH, -CH₂OH, -CH₂CH₂OH, -C(=O)NH₂, a heteroatom, or -C(=O)NR₁₁R₁₁'; wherein R_{11} is aryl, substituted aryl, or heteroaryl; wherein R_{11}' is alkyl, or XR₁₁", wherein X is O, or N and R_{11}'' is substituted alkyl or aryl.

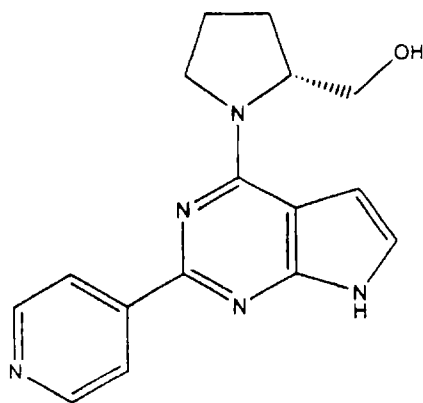
In another embodiment of the compound, the compound has the structure:



(Compound 1600)

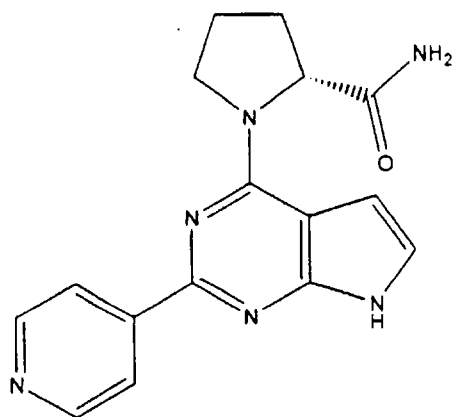
1 JUN 2005

In another embodiment of the compound, the compound has the structure:



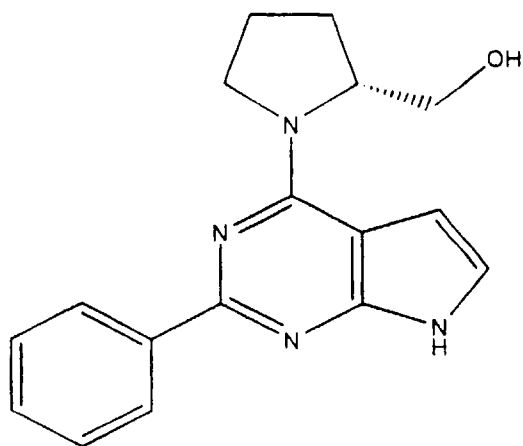
(Compound 1601)

In another embodiment of the compound, the compound has the structure:



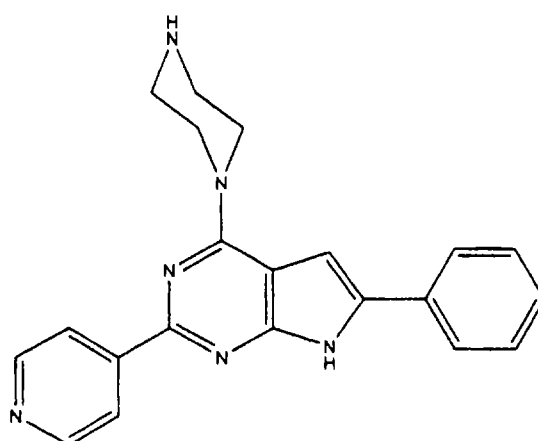
(Compound 1602)

In another embodiment of the compound, the compound has the structure:



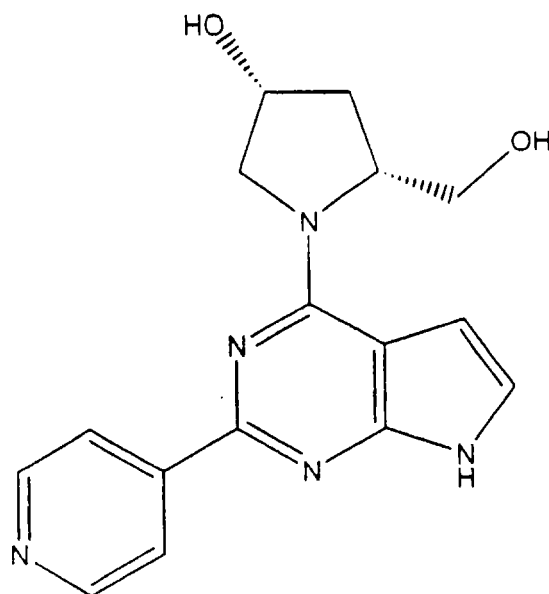
(Compound 1603)

20 In another embodiment of the compound, the compound has the structure:



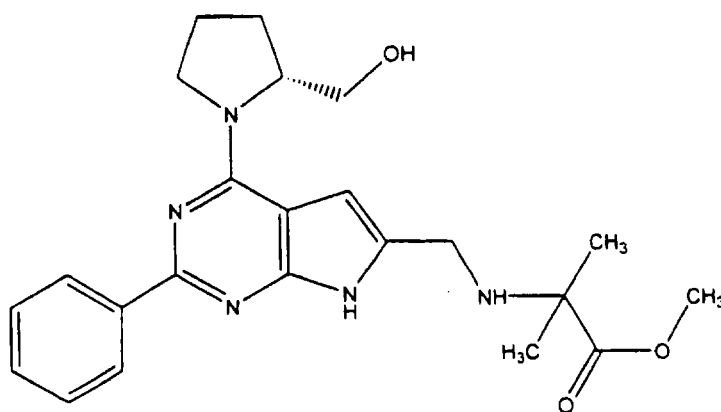
(Compound 1604)

In another embodiment of the compound, the compound has the structure:



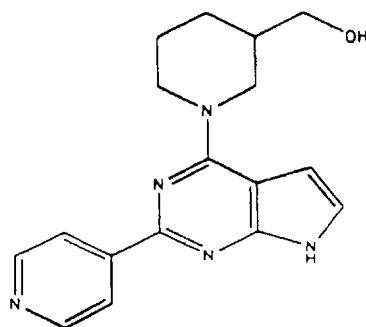
(Compound 1605)

In another embodiment of the compound, the compound has the structure:



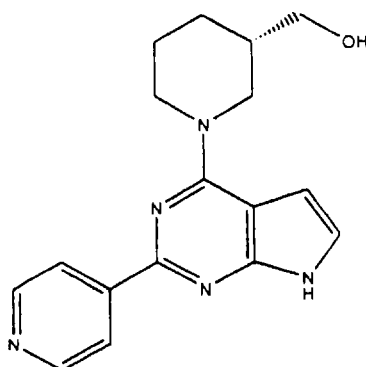
(Compound 1606)

In another embodiment of the compound, the compound has the structure:

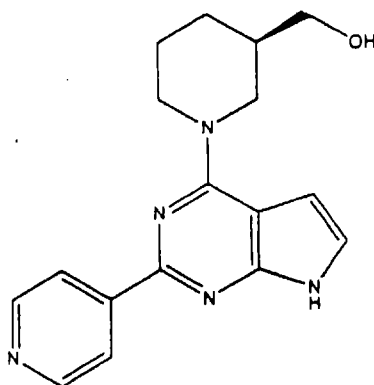


(Compound 1607)

In yet another embodiment of the compound, the compound has the structure:

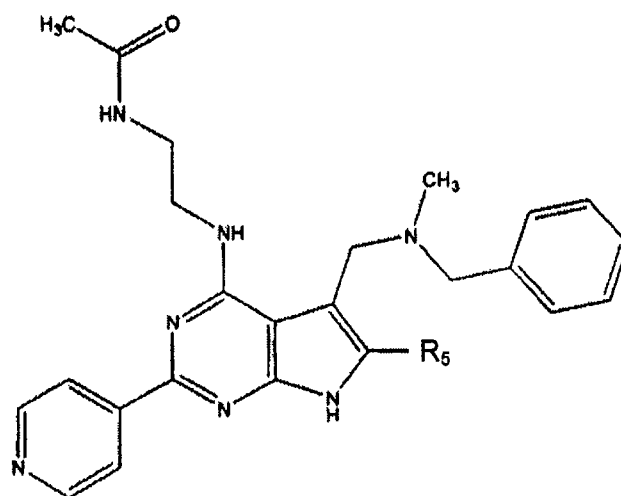


In a further embodiment of the compound, the compound has the structure:



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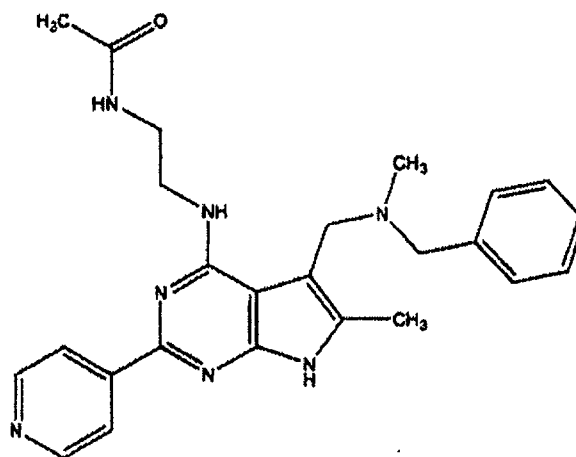
This invention further provides a compound having the structure (V):



(V)

Wherein R₅ is H, or methyl.

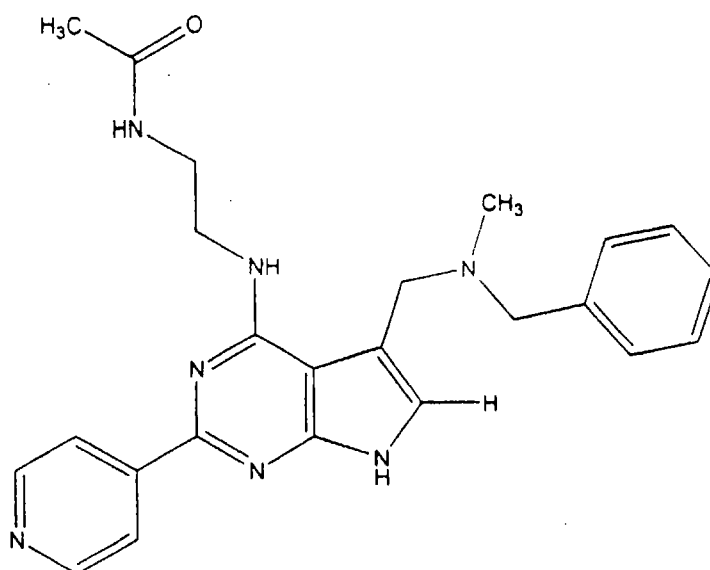
In one embodiment of the compound V, the compound has the structure:



(Compound 1608)

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In another embodiment of the compound V, the compound has the structure:



This invention also provides a method for treating a disease associated with A2a adenosine receptor in a subject, comprising administering to the subject a therapeutically effective amount of compounds IV, or V.

In one embodiment of the method, the compound treats said diseases by stimulating adenylate cyclase.

In another embodiment of the method, the subject is a mammal.

In another embodiment of the method, the mammal is a human.

In another embodiment of the method, said A2a adenosine receptor is associated with Parkinson's disease and diseases associated with locomotor activity, vasodilation, platelet inhibition, neutrophil superoxide generation, cognitive disorder, or senile dementia.

Diseases associated with adenosine A1, A2a, A2b and A3 receptors are disclosed in WO 99/06053 and WO-09822465, WO-09705138, WO-

09511681, WO-09733879, JP-09291089, PCT/US98/16053 and U.S. Patent No. 5,516,894, the entire content of which are fully incorporate herein by reference.

5 This invention also provides a water-soluble prodrug of compounds IV, or V; wherein said water-soluble prodrug that is metabolized *in vivo* to produce an active drug which selectively inhibit A2a adenosine receptor.

10 In one embodiment of the prodrug, said prodrug is metabolized *in vivo* by esterase catalyzed hydrolysis.

This invention also provides a pharmaceutical composition comprising the prodrug and a pharmaceutically acceptable carrier.
15

This invention also provides a method for inhibiting the activity of an A2a adenosine receptor in a cell, which comprises contacting said cell with compounds IV, or V.
20

In one embodiment of the method, the compound is an antagonist of said A2a adenosine receptor.

In another embodiment of the pharmaceutical composition, said
25 pharmaceutical composition is an ophthalmic formulation.

In another embodiment of the pharmaceutical composition, said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.
30

In another embodiment of the pharmaceutical composition, said pharmaceutical composition is a systemic formulation.

This invention also provides a method for treating a gastrointestinal disorder in an subject, comprising administering to the an effective amount of compounds IV, or V.

5 In one embodiment of the method, said disorder is diarrhea.

In another embodiment of the method, the subject is a human.

10 In another embodiment of the method, the compound is an antagonist of A2a adenosine receptors.

This invention further provides a method for treating respiratory disorder in a subject, comprising administering to the subject an effective amount of compounds IV, or V.

15

In one embodiment of the method, said disorder is asthma, chronic obstructive pulmonary disease, allergic rhinitis, or an upper respiratory disorder.

20 In another embodiment of the method, the subject is a human.

In another embodiment of the method, said compound is an antagonist of A2a adenosine receptors.

25 This invention also provides a method for treating damage to the eye of a subject which comprises administering to said subject an effective amount of compounds IV, or V.

30 In one embodiment of the method, said damage comprises retinal or optic nerve head damage.

In another embodiment of the method, said damage is acute or chronic.

In another embodiment of the method, said damage is the result of glaucoma, edema, ischemia, hypoxia or trauma.

In another embodiment of the method, the subject is a human.

5

In another embodiment of the method, the compound is an antagonist of A_{2a} adenosine receptors.

10

This invention also provide a pharmaceutical composition comprising a therapeutically effective amount of compounds IV, or V and a pharmaceutically acceptable carrier.

15

In one embodiment of the pharmaceutical composition, said therapeutically effective amount is effective to treat Parkinson's disease and diseases associated with locomotor activity, vasodilation, platelet inhibition, neutrophil superoxide generation, cognitive disorder, or senile dementia.

20

In another embodiment of the pharmaceutical composition, said pharmaceutical composition is an ophthalmic formulation.

25

In another embodiment of the pharmaceutical composition, said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.

30

In another embodiment of the pharmaceutical composition, said pharmaceutical composition is a systemic formulation.

In another embodiment of the pharmaceutical composition, said pharmaceutical composition is a surgical irrigating solution.

This invention also provides a combination therapy for Parkinson's disease comprising compounds IV and V, and any of

the dopamine enhancers.

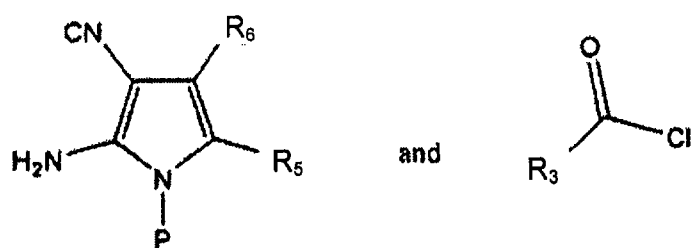
This invention further provides a combinational therapy for cancer comprising compounds IV and V, and any of the cytotoxic agents.

This invention further provides a combinational therapy for glaucoma, comprising compounds IV or V, and a prostaglandin agonist, a muscrinic agonist, or a β_2 antagonist.

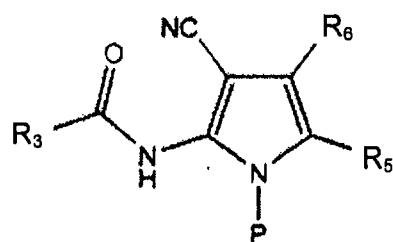
This invention also provides a packaged pharmaceutical composition for treating a disease associated with A_{2a} adenosine receptor in a subject, comprising: (a) a container holding a therapeutically effective amount of compounds IV, or V; and (b) instructions for using said compound for treating said disease in a subject.

This invention also provide a method of preparing compound IV, comprising the steps of

a) reacting

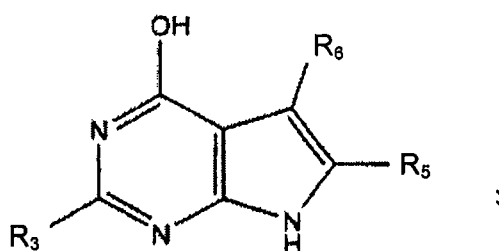


to provide

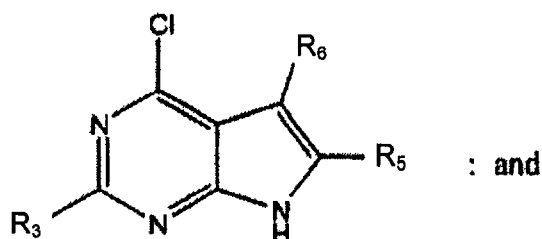


wherein P is a removable protecting group;

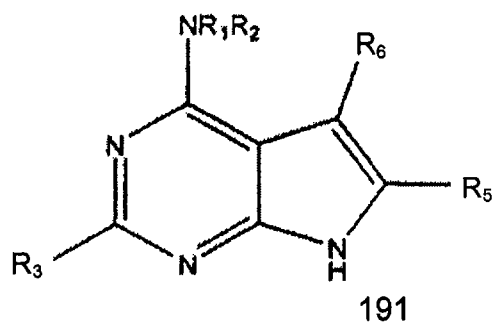
b) treating the product of step a) under cyclization conditions to provide



c) treating the product of step b) under suitable conditions to provide



d) treating the chlorinated product of step c) with NHR_1R_2 to provide



wherein NR_1R_2 is a substituted or unsubstituted 4-8 membered ring;

5 wherein R_3 is a substituted or unsubstituted four to six membered ring;

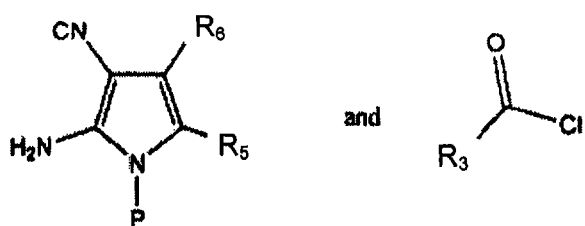
10 wherein R_5 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $-\text{C}(\text{R}_7)(\text{R}_8)\text{XR}_9$, wherein X is O, S, or NR_{10} , wherein R_7 and R_8 are each independently H or alkyl, wherein R_9 and R_{10} are each independently alkyl or cycloalkyl, or R_9 , R_{10} and the nitrogen together form a substituted or unsubstituted ring of between 4 and 7 members.

15 wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl

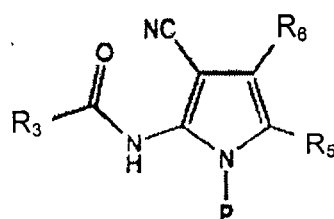
20 with the proviso that NR_1R_2 is not 3-acetamido piperidino, 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl, or pyrrolidino; with the proviso that NR_1R_2 is 3-hydroxymethyl piperadino only when R_3 is 4-pyridyl.

25 This invention further provides a method of preparing compound V, comprising the steps of

a) reacting

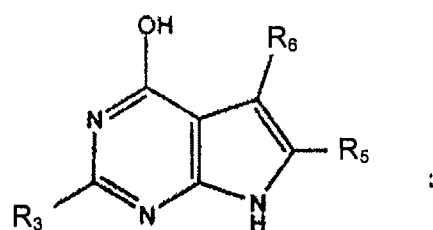


to provide

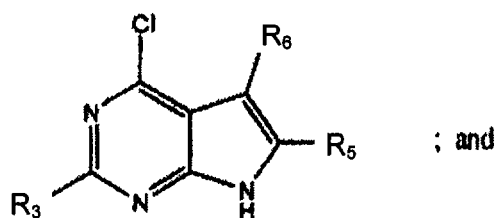


wherein P is a removable protecting group:

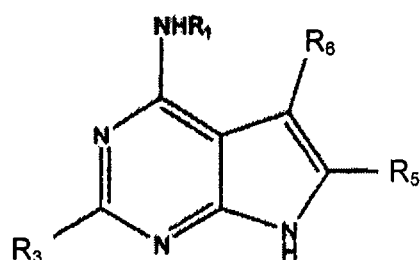
b) treating the product of step a) under cyclization conditions to provide



c) treating the product of step b) under suitable conditions to provide



d) treating the chlorinated product of step c) first with dimethylamine and formaldehyde, then with N-methyl benzylamine and finally with NH_2R_1 to provide



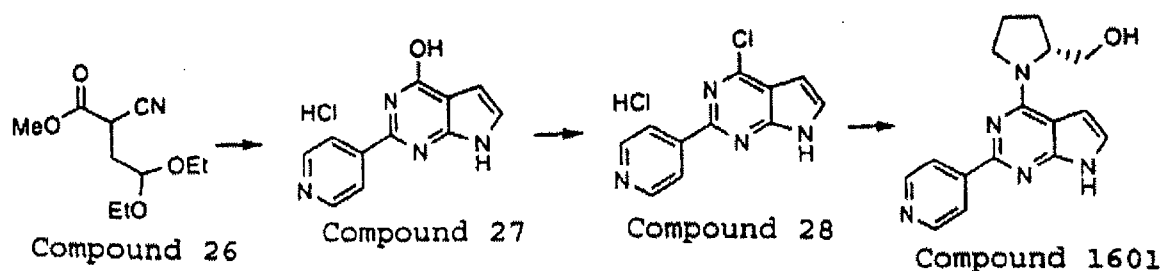
wherein R_1 is acetamido ethyl; wherein R_3 is 4-pyridyl;
 wherein R_5 is H, or methyl; wherein R_6 is N-methyl-N-benzyl aminomethyl.

As used herein, "A compound is A_{2a} selective." means that a compound has a binding constant to adenosine A_{2a} receptor of at least five time higher then that to adenosine A_1 , A_{2b} , or A_3 .

The invention is further illustrated by the following examples which in no way should be construed as being further limiting. The contents of all references, pending patent applications and published patent applications, cited throughout this application, including those referenced in the background section, are hereby incorporated by reference. It should be understood that the models used throughout the examples are accepted models and that the demonstration of efficacy in these models is predictive of efficacy in humans.

This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

Example 22: Synthesis of Adenosine A_{2a} Antagonists, compounds 1601, 1602, and 1603.



Compound 26 (10.93g, 50.76 mmol) was dissolved in DMF (67 mL). 4-Amidinopyridine hydrochloride (8.0g, 50.76 mmol) and DBU (15.4 g, 101.5 mmol) were added sequentially and the reaction was heated to 85°C. After 22 hours, the reaction was cooled to room temperature and the DMF was removed in vacuo. The dark oil was diluted with 2M HCl (80 mL). The reaction was allowed to stand. After 2 hours, the solution was cooled to 10°C and filtered. The solid was washed with cold water and dried to yield 7.40g of a yellow solid, compound 27 (69%). ¹H-NMR (200MHz, d₆-DMSO) δ 6.58 (s, 1H), 7.27 (s, 1H), 8.53 (d, 2H, J = 5.6), 9.00 (d, 2H, J = 5.2Hz), 12.35 (brs, 1H). MS (ES): 212.8 (M⁺+1).

Compound 27 (7.4 mmol, 29.8 mmol) was diluted with POCl₃ and heated to 105°C. After 18 hours, the reaction is cooled to room temperature and the POCl₃ is removed in vacuo. The thick dark oil is diluted with MeOH (75mL) followed by ether (120mL). The amorphous red solid is filtered and washed with ether to yield 3.82 g of a red solid. The crude solid, compound 28, is approximately 80% pure and used without further purification in the next reaction. ¹H-NMR (200MHz, d₆-DMSO) δ 6.58 (s, 1H), 7.27 (s, 1H), 8.53 (d, 2H, J = 5.6), 9.00 (d, 2H, J = 5.2Hz), 12.35 (brs, 1H). MS (ES): 212.8 (M⁺+1).

Compound 1601: DMSO (5 mL) and D-prolinol (500mg, 4.94 mmol) were added to compound 28 (500mg, 2.17 mmol) was added. The reaction was heated to 120°C. After 18 hours, The reaction was cooled to room temperature and diluted with EtOAc and H₂O. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with H₂O (2x), brine, dried over MgSO₄, filtered and concentrated to yield 200mg of a tan solid. The solid was recrystallized from

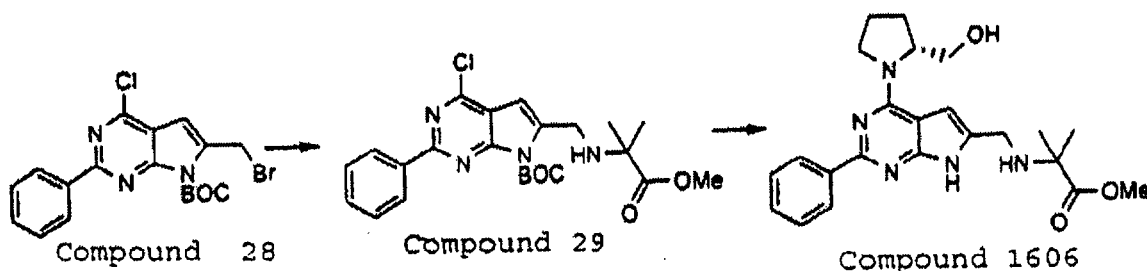
EtOAc to yield 82 mg of a tan solid (13%). ¹H-NMR (200 MHz, d₆-DMSO) δ 2.05 (m, 4H), 3.43 (m, 1H), 3.70 - 4.00 (m, 3H), 4.50 (brs, 1H), 4.92 (brs, 1H), 6.62 (m, 1H), 7.22 (m, 1H), 8.22 (d, 2H, J = 6.0 Hz), 6.64 (d, 2H, J = 6.2 Hz), MS (ES): 296.0 (M⁺+1), mp = 210 - 220°C (decomp.).

Compound 1602: Chromatography (silica, 9:1 CHCl₃/MeOH) yielded 10 mg of a tan solid (2%). ¹H-NMR (d₆-DMSO) δ 2.00 - 2.50 (m, 4H), 4.05 (m, 1H), 4.21 (m, 1H), 6.71 (d, 1H, J = 3.2 Hz), 7.18 (d, 1H, J = 3.2 Hz), 8.37 (d, 2H, J = 4.8 Hz), 8.56 (d, 2H, J = 5.0 Hz). MS (ES): 309.1 (M⁺+1).

Compound 1603. Chromatography (silica, 20:1 Hexanes /EtOAc) yielded 135 mg of a tan solid (53%). ¹H-NMR (d₆-DMSO) δ 2.00 (m, 4H), 3.43 (brs, 1H), 3.74 (brs, 2H), 3.87 (brs, 1H), 4.49 (brs, 1H), 4.93 (m, 1H), 6.56 (m, 1H), 7.12 (m, 1H), 7.40 (m, 3H), 8.34 (m, 2H), 11.62 (brs, 1H). MS (ES): 295.1 (M⁺+1).

Compound 1605. Into a 50mL RBF 60mg of 2-(4'-pyridyl)-4-Chloropyrimidinopyrrole HCl salt was dissolved in 2mL anhydrous DMSO. 3-(R)-Hydroxy-(D)-prolinol TFA salt (380mg) and 500mg sodium bicarbonate were added thereto. The mixture was then flashed with nitrogen gas for 5min and heated to 130°C. After 2 hours, the reaction was cooled to room temperature and the DMSO was removed in vacuo. The residue was partitioned between EtOAc (15mL) and saturated sodium bicarbonate aqueous solution (15mL). The organic layer was separated and washed with brine (15mL) and dried over Na₂SO₄. After removal of solvent, the crude product was purified by preparative TLC (CH₂Cl₂/MeOH = 95/5) to yield 35 mg (50%). ¹H-NMR (200MHz, CDCl₃) δ 2.3-2.5 (1H), 3.4-3.8 (3H), 4.4-4.6 (2H), 6.4 (1H); 7.1 (1H); 8.2 (d, 2H); 8.7 (d, 2H); 11.0 (1H). MS (ES): 312 (M⁺+1).

Example 23: Synthesis of Adenosine A₂ Antagonist, compound 1606.



10 Compound 28 (200mg) was treated with DMF (30mL), (-2,2-dimethylglycine methyl ester (73mg HCl salt in 2mL water) and 500mg sodium bicarbonate. After 18 hours, the DMF was removed in vacuo. The residue was partitioned between EtOAc (30mL) and saturated sodium bicarbonate aqueous solution (15mL). The organic layer was washed with brine (15mL), dried over sodium sulfate, filtered and concentrated. Chromatography (silica, 10:4 hexanes/EtOAc) yielded 150mg of pure product, compound 29 (69%). ²H-NMR (200MHz, CDCl₃), (1.4 (s, 6H), 3.8 (s, 3H); 3.9 (s, 2H) ; 6.4 (s, 1H); 7.4-7.5 (m, 3H); 8.4 (m, 2H); 9.8 (s, 1H).

15

20

Compound 1606 :

Procedure is the same as Compound 1605 (72%). ²H-NMR (200MHz, CDCl₃), (1.3 (s, 6H), 1.7-1.9 (m, 2H); 2.05-2.30 (m, 2H); 3.6-4.1 (m, 11H) ; 4.80-4.95 (m, 1H) ; 6.4 (s, 1H) ; 7.4-7.6 (m, 3H); 8.3-8.4 (d, J = 8.5 Hz, 2H), 10 (s, 1H). MS (ES): 424.0 (M'+1).

25

30 The following compounds can be synthesized in the same manner.

Compound 1600: (51%). MS (ES): 326.0 (M'+1).

Compound 1607: $^1\text{H-NMR}$ (200MHz, CDCl_3), (1.40 - 1.80 (m, 5H), 2.80 - 3.50 (m, 3H), 4.60 - 4.80 (m, 3H), 6.66 (d, 1H, $J = 6.2\text{Hz}$), 7.26 (m, 1H), 8.21 (d, 2H, $J = 6.3\text{Hz}$), 8.65 (d, 2H, $J = 5.8\text{Hz}$), 11.90 (s, 1H). MS (ES): 310.1 ($\text{M}^+ + 1$).

5

Compound 1608: (64%). $^1\text{H-NMR}$ (200MHz, d_6 -DMSO), (1.75 (s, 3H), 2.11 (s, 3H), 2.29 (s, 3H), 3.56 (m, 6H), 7.23 - 7.41 (m, 5H), 8.00 (brs, 1H), 8.23 (d, 2H, $J = 6.0\text{Hz}$), 8.63 (d, 2H, $J = 5.4\text{Hz}$), 8.82 (brs, 1H), 11.56 (brs, 1H). MS (ES): 444.0 ($\text{M}^+ + 1$).

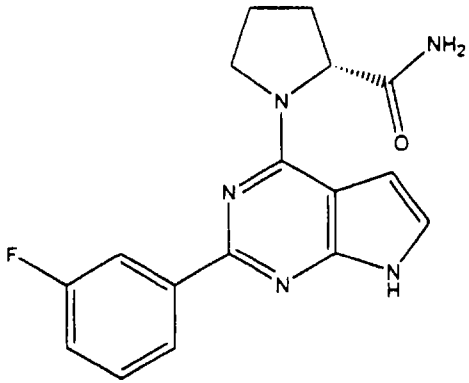
10

Compound 1604: $^1\text{H-NMR}$ (200MHz, CD_3OD) (3.40 (m, 4H), 4.29 (m, 4H), 6.99 (s, 1H), 7.5 - 7.2 (m, 3H), 7.90 (d, 2H), 8.39 (d, 2H), 8.61 (d, 2H). MS (ES): 357.0 ($\text{M}^+ + 1$).

15

TABLE 16. Adenosine A_{2a} Receptor Selective Compounds

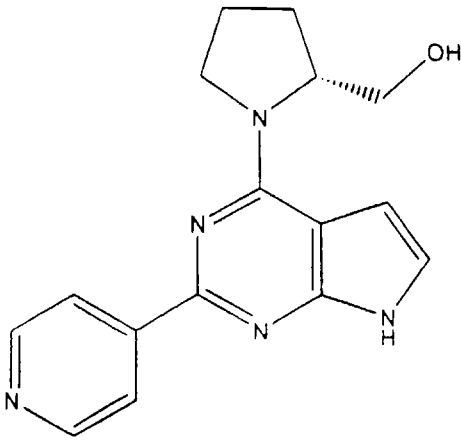
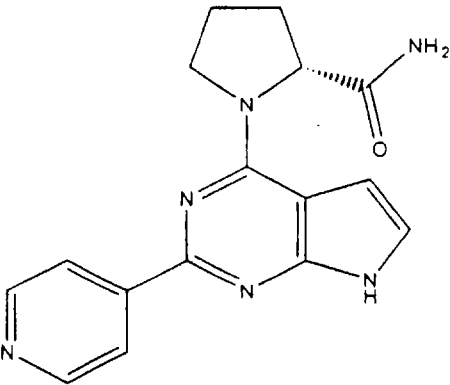
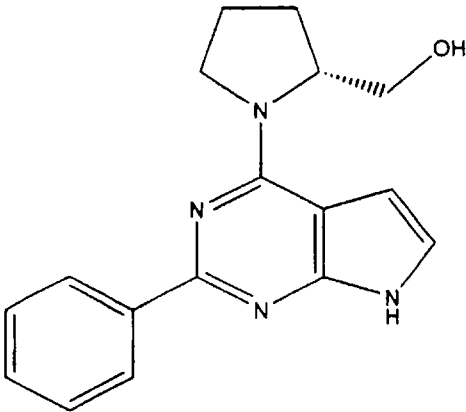
* at least 5 times more selective than other three subtypes.

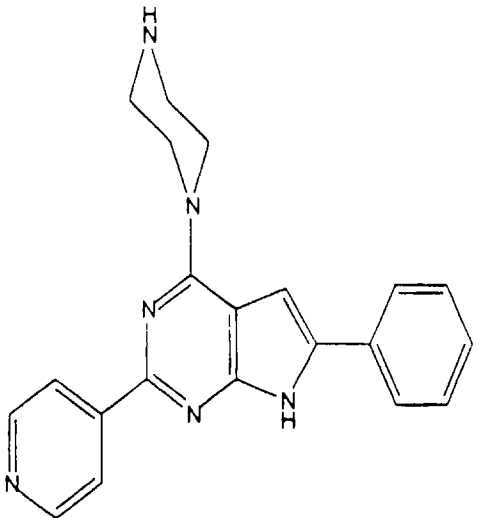
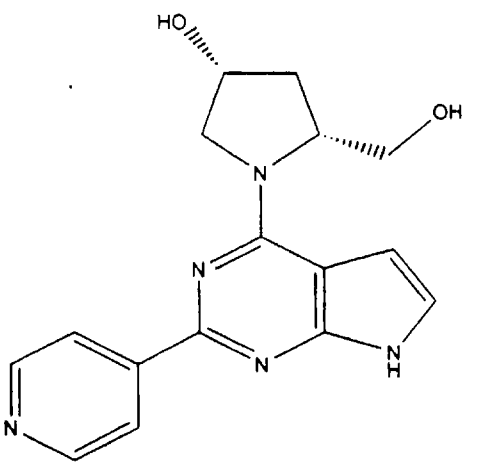
Compound	Structure	Relative Ki-A1	Relative Ki-A2a	Relative Ki-A2b	Relative Ki-A3
1600			*		

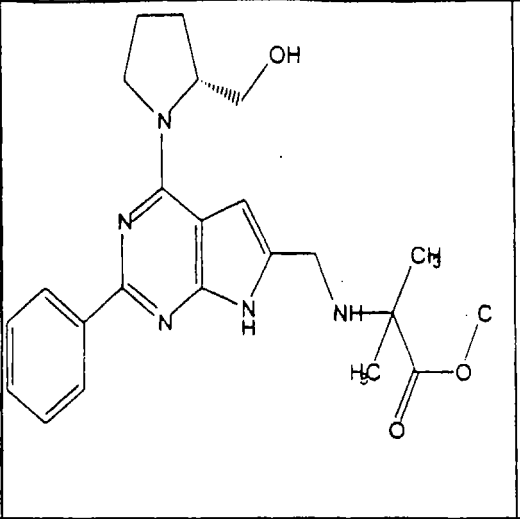
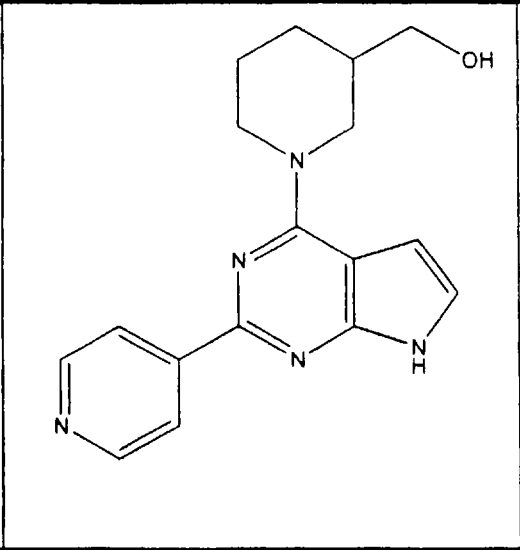
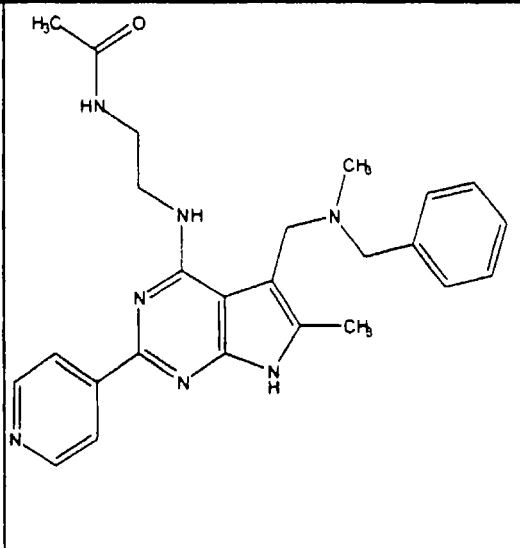
20

25

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1601			*		
1602			*		
1603			*		

1604			*		
1605			*		

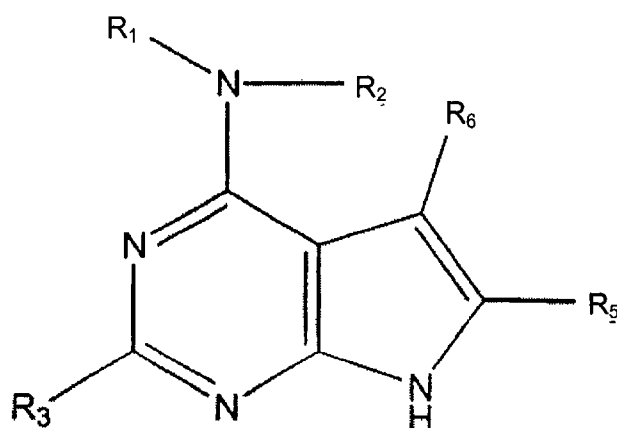
1606			*		
1607			*		
1608			*		

Pages 202-256 relate to compounds specific to the A3 receptor

Summary of the Invention

The present invention is also based on compounds which selectively bind to adenosine A₃ receptor, thereby treating a disease associated with A₃ adenosine receptor in a subject by administering to the subject a therapeutically effective amount of such compounds. The disease to be treated are associated with, for example, asthma, hypersensitivity, rhinitis, hay fever, serum sickness, allergic vasculitis, atopic dermatitis, dermatitis, psoriasis, eczema, idiopathic pulmonary fibrosis, eosinophilic chloreycystitis, chronic airway inflammation, hypereosinophilic syndromes, eosinophilic gastroenteritis, edema, urticaria, eosinophilic myocardial disease, episodic angioedema with eosinophilia, inflammatory bowel disease, ulcerative colitis, allergic granulomatosis, carcinomatosis, eosinophilic granuloma, familial histiocytosis, hypertension, mast cell degranulation, tumor, carciac hypoxia, cerebral ischemia, diuresis, renal failure, neurological disorder, mental disorder, cognitive disorder, myocardial ischemia, bronchoconstriction, arthritis, autoimmune disease, Crohn's disease, Grave's disease, diabetes, multiple sclerosis, anaemia, psoriasis, fertility disorders, lupus erthyematosus, reperfusion injury, brain arteriole diameter, the release of allergic mediators, scleroderma, stroke, global ischemia, central nervous system disorder, cardiovascular disorder, renal disorder, inflammatory disorder, gastrointestinal disorder, eye disorder, allergic disorder, respiratory disorder, or immunological disorder.

This invention also features a compound having the structure:



wherein R1 is H and R2 is cyclopropyl methylamino carbonylethyl, cis-3-hydroxy cyclopentyl, acetamido butyl, methylamino carbonylamino butyl, ethylamino carbonylamino propyl, methylamino carbonylamino propyl, 2-acetyl amino-3-methyl butyl, N, N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1- (R)-phenyl-2-hydroxyethyl, N-methylaminocarbonyl pyridyl-2-methyl, or R1, R2 and the nitrogen together are 3-acetamido piperadino, 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino, or 3-hydroxymethyl piperadino.

wherein R3 is a substituted or unsubstituted four to six membered ring, pyrrole, thiophene, furan, thiazole, imidazole, pyrazole, 1,2,4-triazole, pyridine, 2 (1H)-pyridone, 4 (1H)-pyridone, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, tetrazole, naphthalene, tetralin, naphthyridine, benzofuran,

benzothiophene, indole, 2,3-dihydroindole, 1H-indole,
indoline, benzopyrazole, 1,3-benzodioxole, benzoxazole,
purine, coumarin, chronone, quinoline,
tetrahydroquinoline, isoquinoline, benzimidazole,
5 quinazoline, pyrido[2,3-b]pyrazine, pyrido[3,4-b]pyrazine,
pyrido[3,2-c]pyridazine, pyrido[3,4-b]-pyridine, 1H-
pyrazole [3,4-d] pyrimidine, pteridine, 2 (1H)-quinolone,
1 (2H)-isoquinolone, 1,4-benzisoxazine, benzothiazole,
quinoxaline, quinoline-N-oxide, isoquinoline-N-oxide,
10 quinoxaline-N-oxide, quinazoline-N-oxide, benzoxazine,
phthalazine, or cinnoline.

wherein R_5 is H, alkyl, substituted alkyl, aryl, or
15 substituted aryl.

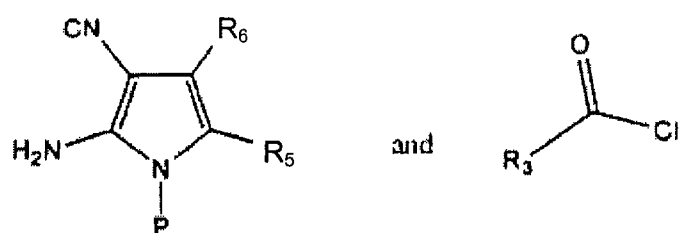
wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl ;

This invention also features a method for inhibiting the
20 activity of an A_3 adenosine receptor in a cell, which comprises
contacting said cell with the above-mentioned compounds.

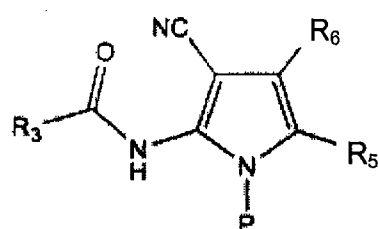
Typical synthetic schemes for the preparation of deazapurine
intermediates of the invention are outlined below in Scheme I.

25 This invention also provides a method of preparing compound IV,
comprising the steps of

a) reacting

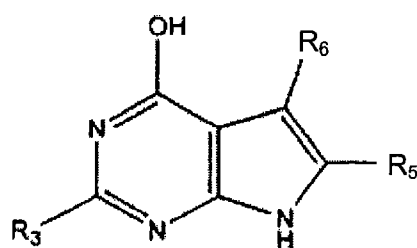


to provide

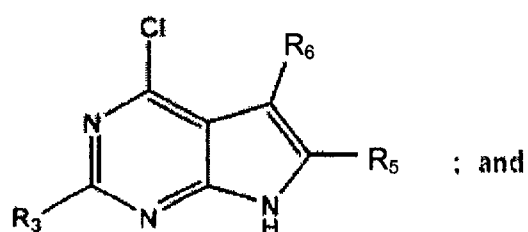


wherein P is a removable protecting group:

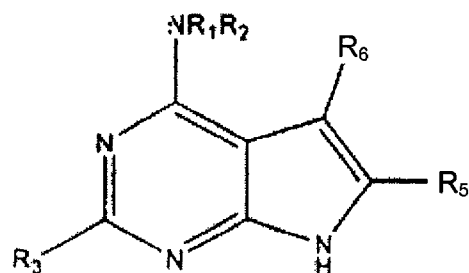
b) treating the product of step a) under cyclization conditions to provide



c) treating the product of step b) under suitable conditions to provide



d) treating the chlorinated product of step c) with NHR₁R₂ to provide



wherein R₁ is H and R₂ is cyclopropyl methylamino carbonylethyl, cis-3-hydroxy cyclopentyl, acetamido butyl, methylamino carbonylamino butyl, ethylamino carbonylamino propyl, methylamino carbonylamino propyl, 2-acetyl amino-3-methyl butyl, N,N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1-(R)-phenyl-2-hydroxyethyl, N-methylaminocarbonyl pyridyl-2-methyl, or R₁, R₂ and the nitrogen together are 3-acetamido piperadino, 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino, or 3-hydroxymethyl piperadino.

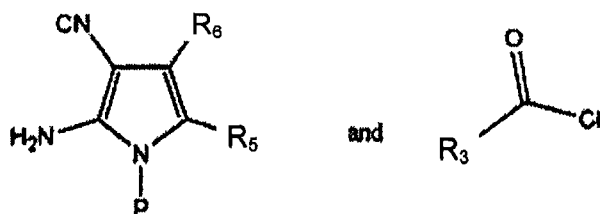
wherein R₃ is a substituted or unsubstituted four to six membered ring;

wherein R₄ is H, alkyl, substituted alkyl, or cycloalkyl;

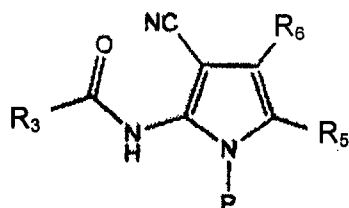
wherein R₅ is H, alkyl, substituted alkyl, aryl, or substituted aryl.

This invention also provides a method of preparing compound of V, comprising the steps of

a) reacting

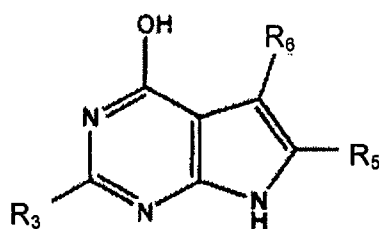


to provide

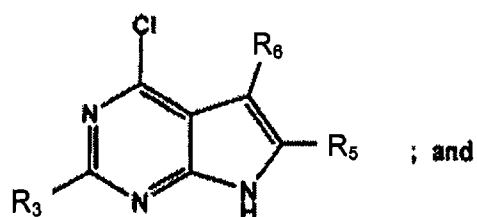


wherein P is a removable protecting group;

b) treating the product of step a) under cyclization conditions to provide

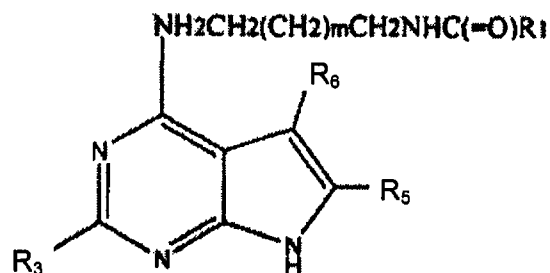


c) treating the product of step b) under suitable conditions to provide



; and

d) treating the chlorinated product of step c) with $\text{NH}_2\text{CH}_2(\text{CH}_2)_m\text{CH}_2\text{NHC}(=\text{O})\text{R}_1$ to provide



wherein m is 0, 1, or 2;

wherein R₁ is cyclopropyl methyl, methyl, methylamino, or aminomethyl;

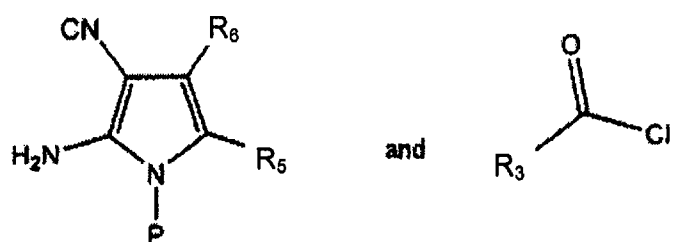
wherein R₃ is aryl, substituted aryl, heteroaryl;

wherein R₆ is H, alkyl, substituted alkyl, or cycloalkyl ;

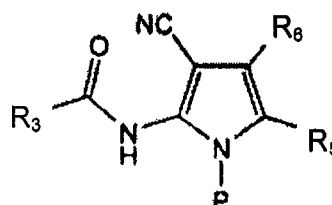
wherein R₅ is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is -C(R₇)(R₈)NR₉R₁₀, wherein R₇ and R₈ are each H or alkyl, wherein R₉ and R₁₀ are each alkyl or cycloalkyl, or R₉, R₁₀ and the nitrogen together form a ring system of between 4 and 7 members.

This invention further provided a method of preparing compound VI, comprising

a) reacting

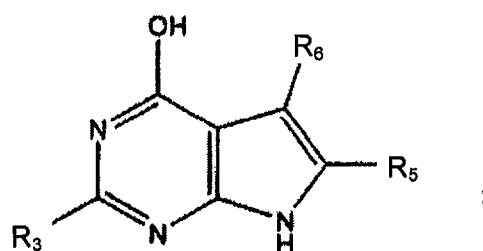


to provide

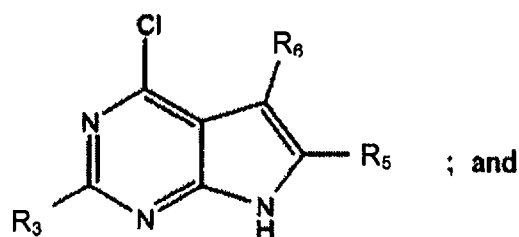


wherein P is a removable protecting group:

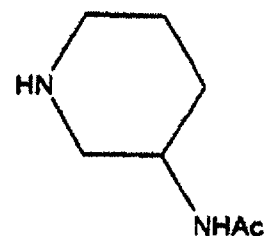
b) treating the product of step a) under cyclization conditions to provide



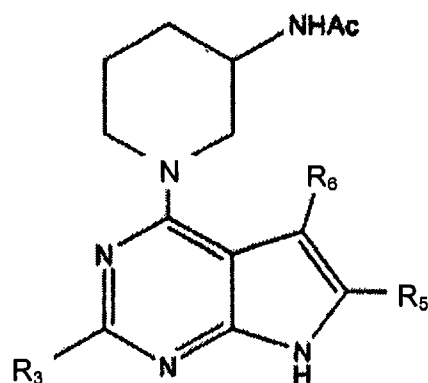
c) treating the product of step b) under suitable conditions to provide



d) treating the chlorinated product of step c) with



to provide

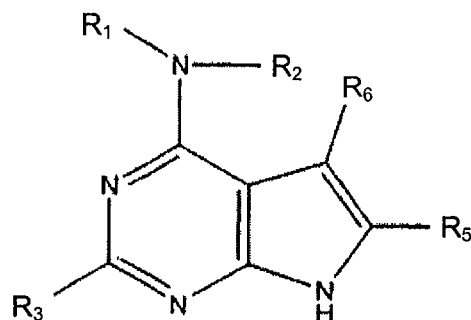


wherein R_3 is unsubstituted aryl.

wherein R_5 H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is
 5 $-C(R_7)(R_8)NR_9R_{10}$, wherein R_7 and R_8 are each H or alkyl, wherein R_9 and R_{10} are each alkyl or cycloalkyl, or R_9 , R_{10} and the nitrogen together form a ring system of between 4 and 7 members.

10 wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl ;

(This invention also provides a compound having the structure:



20 IV

wherein R_1 is H and R_2 is cyclopropyl methylamino carbonyl ethyl, cis-3-hydroxy cyclopentyl, acetamido butyl, methylamino carbonylamino butyl, ethylamino carbonylamino propyl, methylamino carbonylamino propyl, 2-acetyl amino-3-methyl butyl, N, N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1- (R)-phenyl-2-hydroxyethyl, N-methylaminocarbonyl pyridyl-2-methyl,

or R_1 , R_2 and the nitrogen together are 3-acetamido piperadino, 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino, or 3-hydroxymethyl piperadino.

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wherein R_3 is a substituted or unsubstituted benzene, pyrrole, thiophene, furan, thiazole, imidazole, pyrazole, 1,2,4-triazole, pyridine, 2 (1H)-pyridone, 4(1H)-pyridone, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, tetrazole, naphthalene, tetralin, naphthyridine, benzofuran, benzothiophene, indole, 2,3-dihydroindole, 1H-indole, indoline, benzopyrazole, 1,3-benzodioxole, benzoxazole, purine, coumarin, chromone, quinoline, tetrahydroquinoline, isoquinoline, benzimidazole, quinazoline, pyrido[2,3-b]pyrazine, pyrido[3,4-b] pyrazine, pyrido [3,2-c] pyridazine, pyrido [3,4-b]-pyridine, 1H-pyrazole[3,4-d] pyrimidine, pteridine, 2(1H)-quinolone, 1(2H)-isoquinolone, 1,4-benzisoxazine, benzothiazole, quinoxaline, quinoline-N-oxide, isoquinoline-N-oxide, quinoxaline-N-oxide, quinazoline-N-oxide, benzoxazine, phthalazine, or cinnoline.

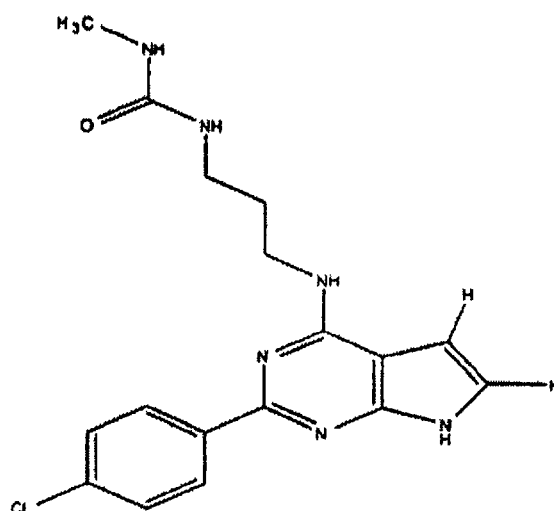
(-)

25

wherein R_5 is H, alkyl, substituted alkyl, aryl, or substituted aryl.

wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl ;

In one embodiment of the compound, the compound has the structure:

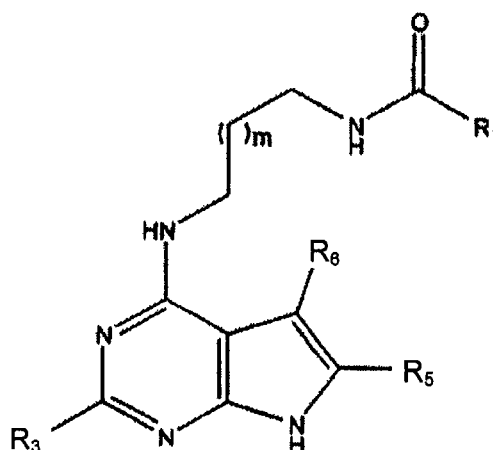


In another embodiment of the compound, R_3 is phenyl.

In another embodiment of the compound, R_6 is hydrogen or methyl.

In another embodiment of the compound, R_5 is hydrogen, methyl, phenyl, 3-chlorophenyl, or trans-2-phenylamino methyl pyrrolidino methyl.

This invention further provides a compound having the structure:



wherein m is 0, 1, or 2;

wherein R₁ is cyclopropyl methyl, methyl, methylamino, or aminomethyl;

5

wherein R₃ is aryl, substituted aryl, or heteroaryl;

10

wherein R₅ is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is -C(R₇)(R₈)NR₉R₁₀, wherein R₇ and R₈ are each H or alkyl, wherein R₉ and R₁₀ are each alkyl or cycloalkyl, or R₉, R₁₀ and the nitrogen together form a ring system of between 4 and 7 members.

15

wherein R₆ is H, alkyl, substituted alkyl, or cycloalkyl ;

In one embodiment of compound V, m is 0 and R₃ is phenyl.

20

In another embodiment of compound V, m is 1 and R₃ is phenyl.

In another embodiment of compound V, m is 2 and R₃ is phenyl.

G

In another embodiment of compound V, R₅ and R₆ are methyl.

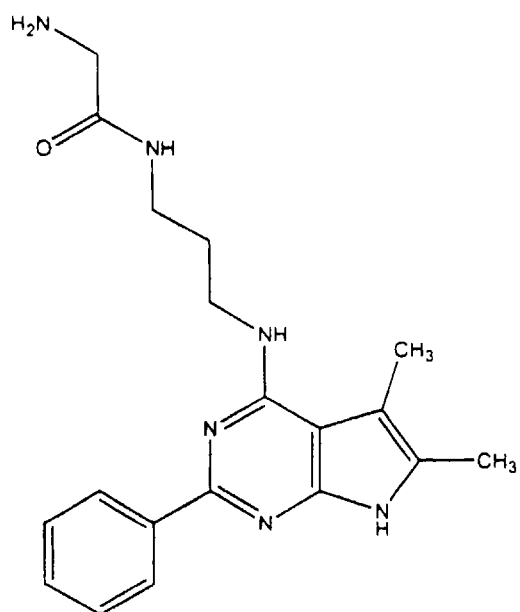
25

In another embodiment of compound V, R₅ and R₆ are methyl.

In another embodiment of compound V, R₅ and R₆ are methyl.

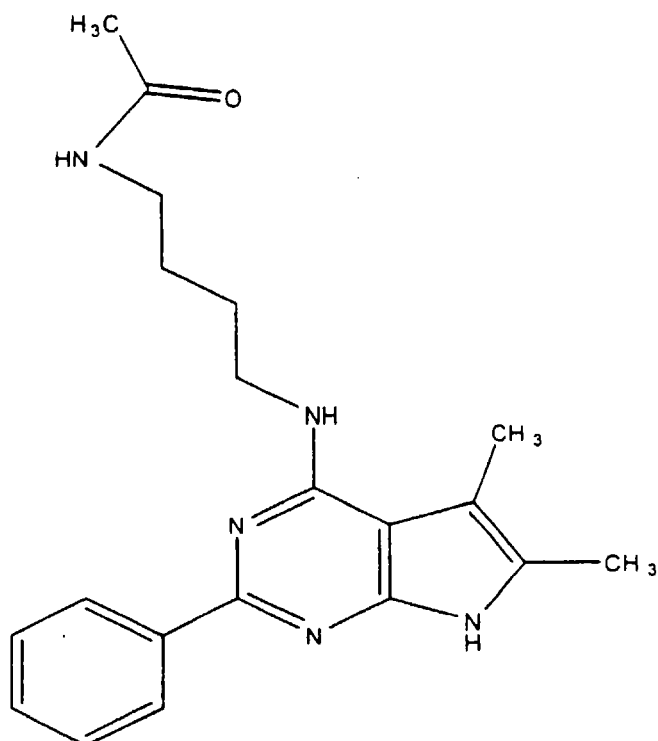
30

In another embodiment of compound V, the compound has the structure:



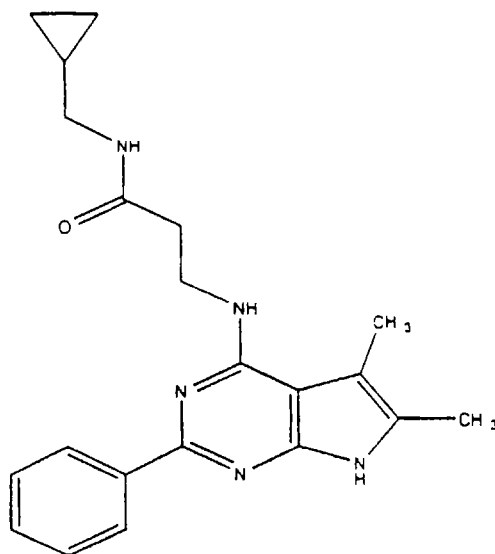
(Compound 1316)

In another embodiment of compound V, the compound has the structure:



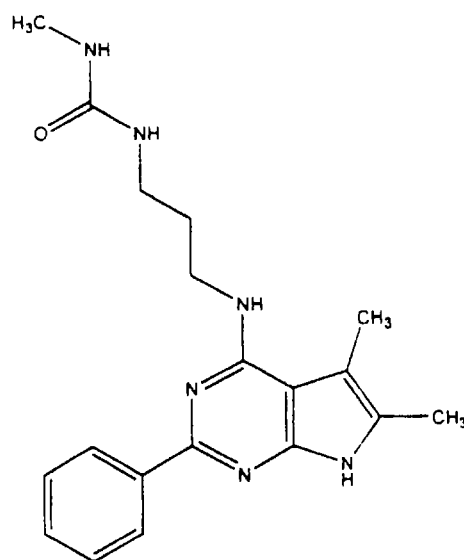
(Compound 1311)

In another embodiment of compound V, the compound has the structure:



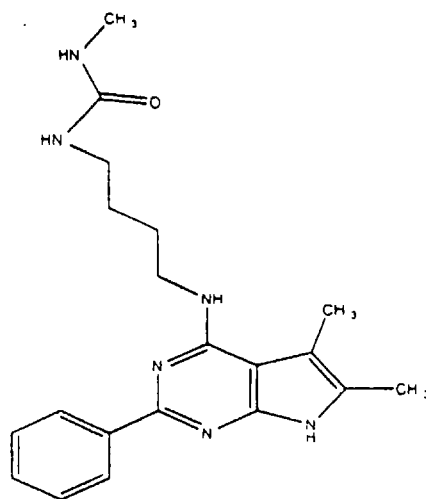
(Compound 1202)

In another embodiment of compound V, the compound has the structure:



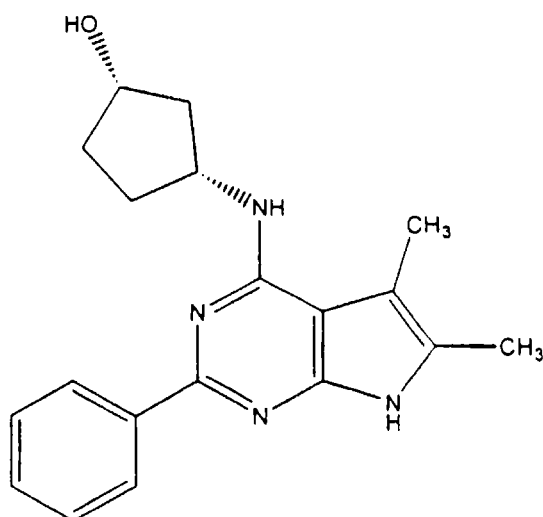
(Compound 1310)

In another embodiment of compound V, the compound has the structure:



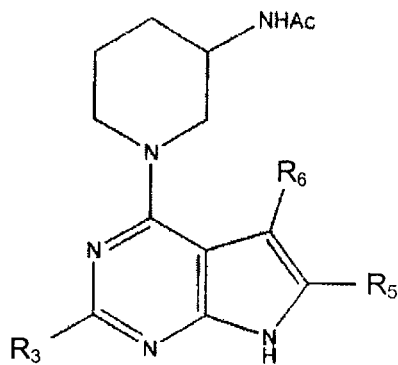
(Compound 1312)

This invention further provides a compound having the structure:



(Compound 609)

This invention also provides a compound having the structure:



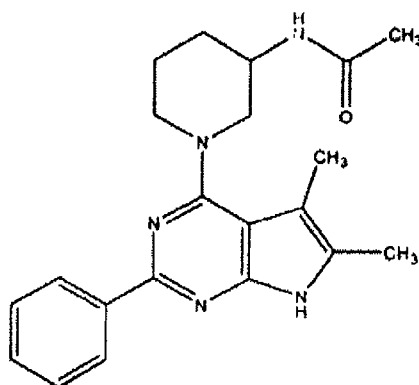
VI

wherein R_3 is unsubstituted aryl.

wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl ;

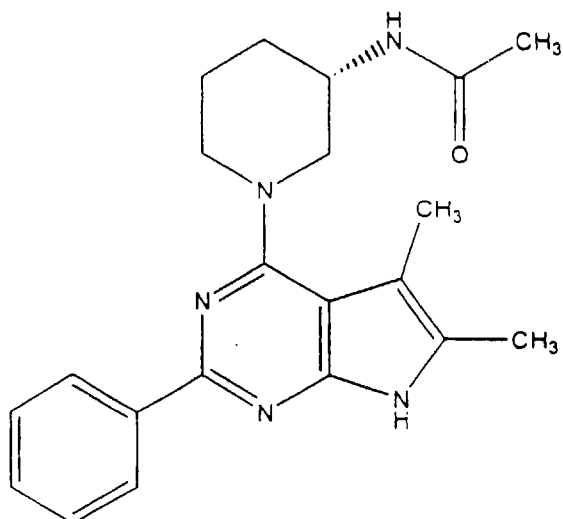
wherein R_5 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $-C(R_7)(R_8)NR_9R_{10}$, wherein R_7 and R_8 are each H or alkyl, wherein R_9 and R_{10} are each alkyl or cycloalkyl, or R_9 , R_{10} and the nitrogen together form a ring system of between 4 and 7 members.

In one embodiment of compound VI, the compound has the structure:

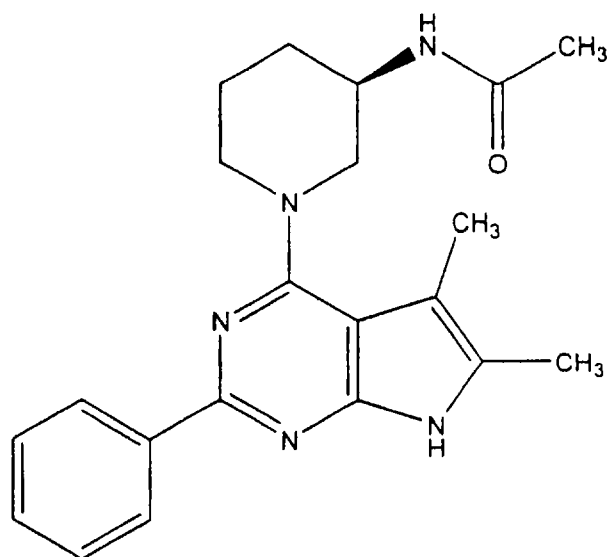


(Compound 1309)

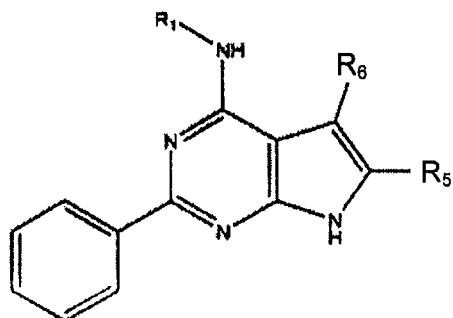
In one embodiment of compound 1309, the compound has the structure:



In another embodiment of compound 1309, the compound has the structure:



This invention also provides a compound having the structure:

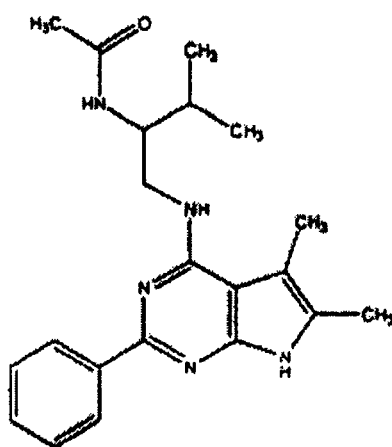


VII

wherein R₁ is 3-hydroxy cyclopentyl ethylamino carbonylamino propyl, N,N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1-(R)-phenyl-2-hydroxyethyl, or N-methylaminocarbonyl pyridyl-2-methyl;

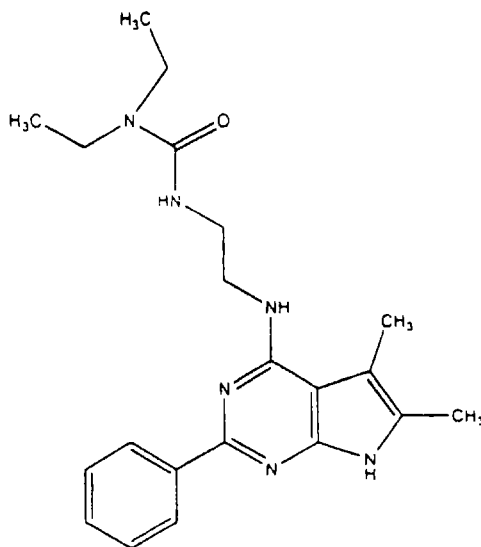
wherein R₅ and R₆ are independently H, substituted or unsubstituted alkyl, or aryl.

In one embodiment of the compound, the compound has the structure:



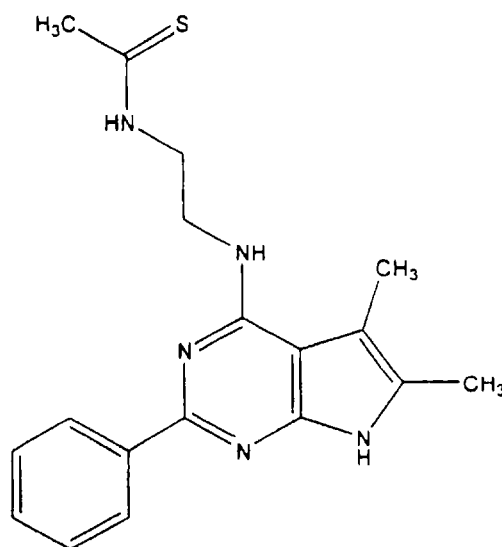
(Compound 1700)

In another embodiment of the compound, the compound has the structure:



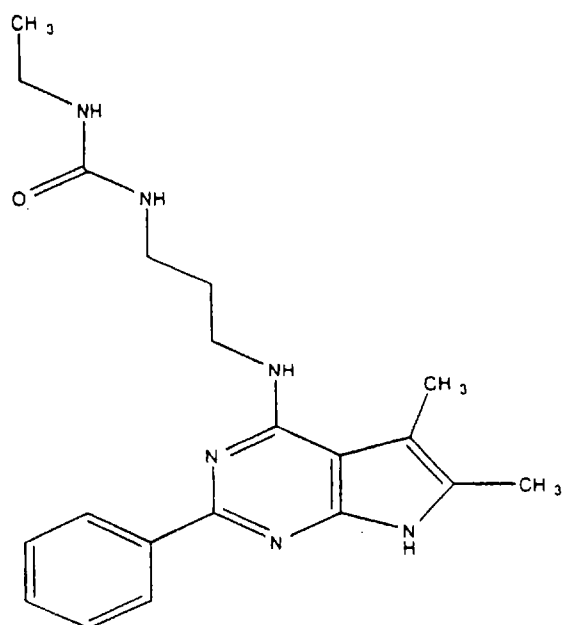
(Compound 1701)

In another embodiment of the compound, the compound has the structure:



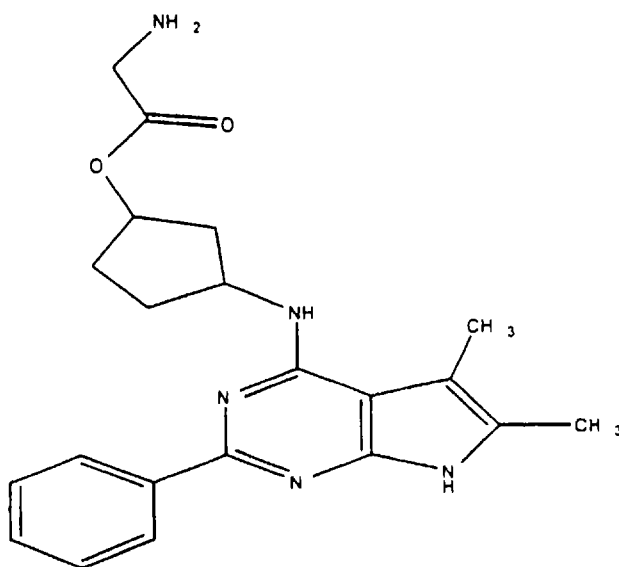
(Compound 1702)

In another embodiment of the compound, the compound has the structure:



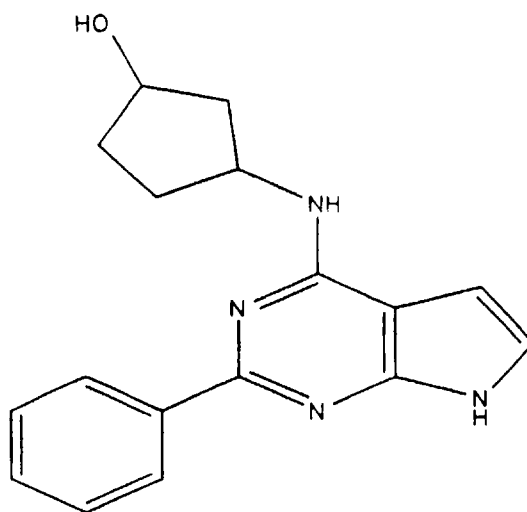
(Compound 1704)

In another embodiment of the compound, the compound has the structure:



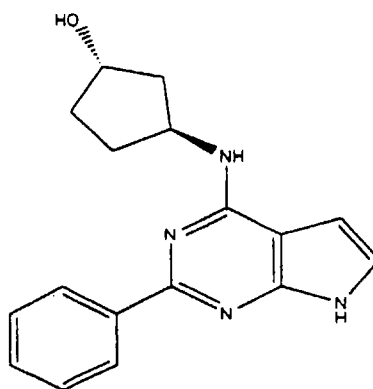
(Compound 1705)

In another embodiment of the compound, the compound has the structure:

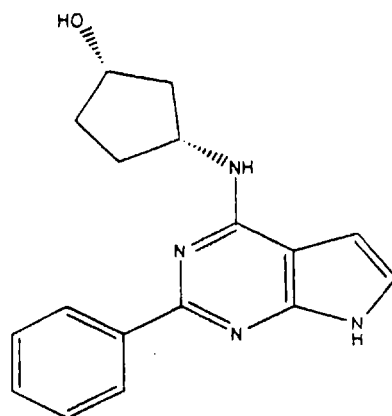


(Compound 1706)

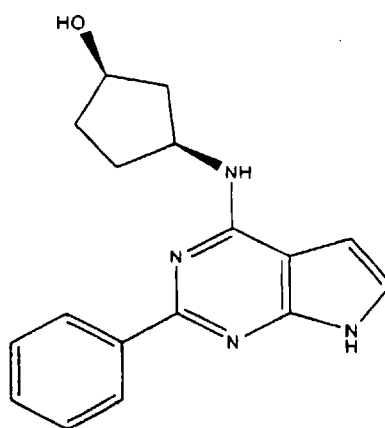
In another embodiment of the compound, the compound has the structure:



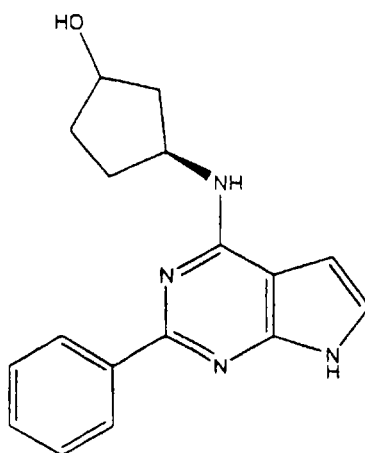
In another embodiment of the compound, the compound has the structure:



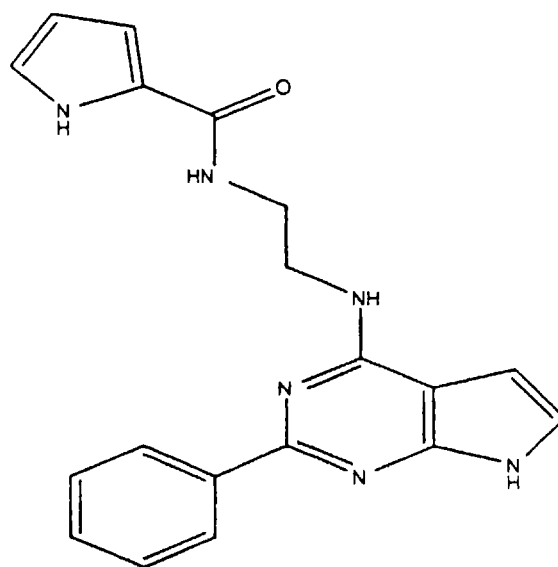
In another embodiment of the compound, the compound has the structure:



In another embodiment of the compound, the compound has the structure:

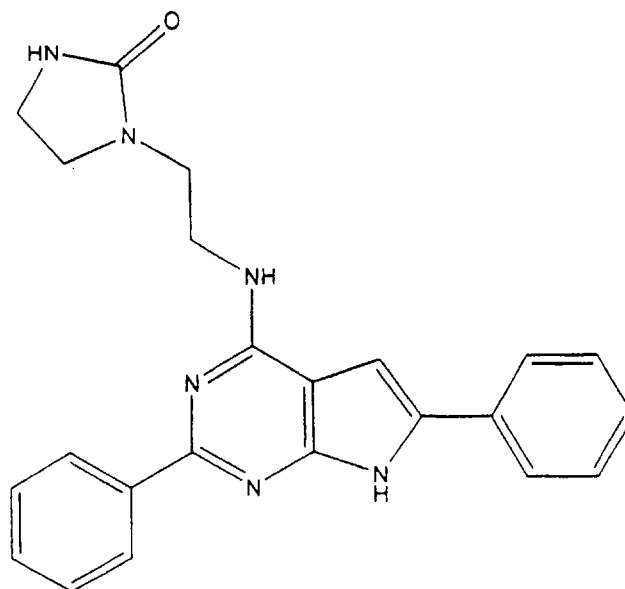


In another embodiment of the compound, the compound has the structure:



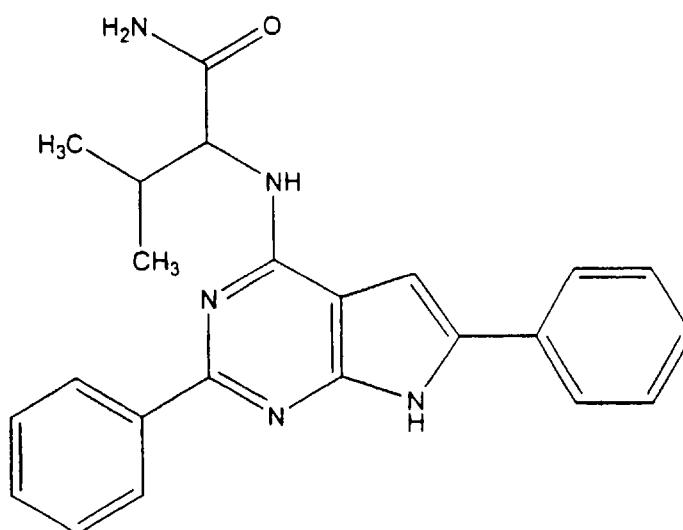
(Compound 1707)

In another embodiment of the compound, the compound has the structure:



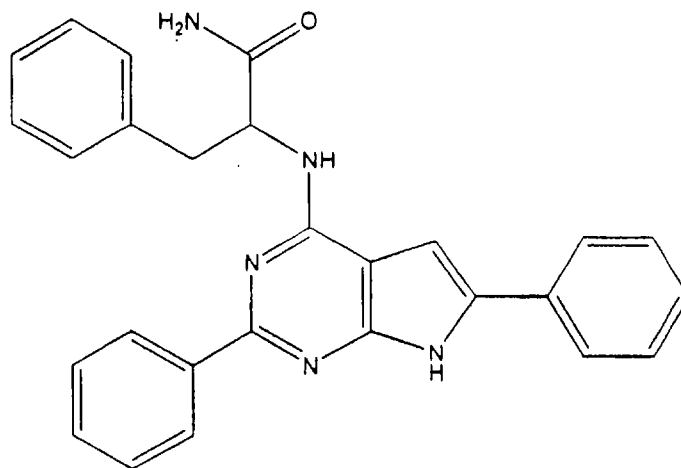
(Compound 1708)

In another embodiment of the compound, the compound has the structure:



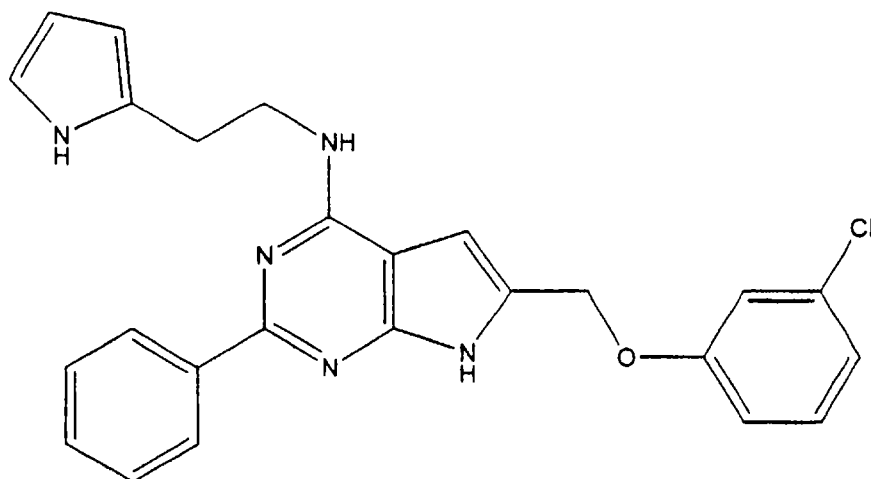
(Compound 1709)

In another embodiment of the compound, the compound has the structure:



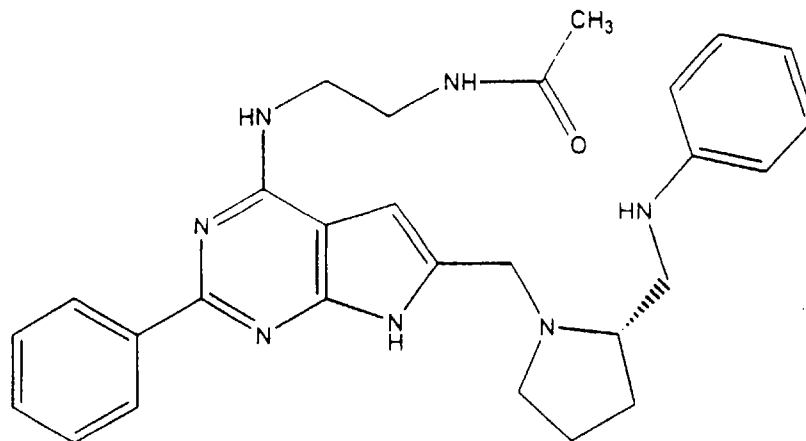
(Compound 1710)

In another embodiment of the compound, the compound has the structure:



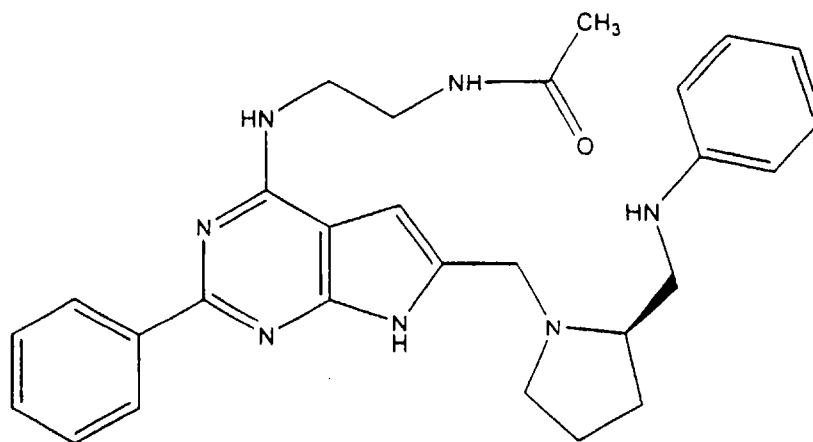
(Compound 1712)

In another embodiment of the compound, the compound has the structure:

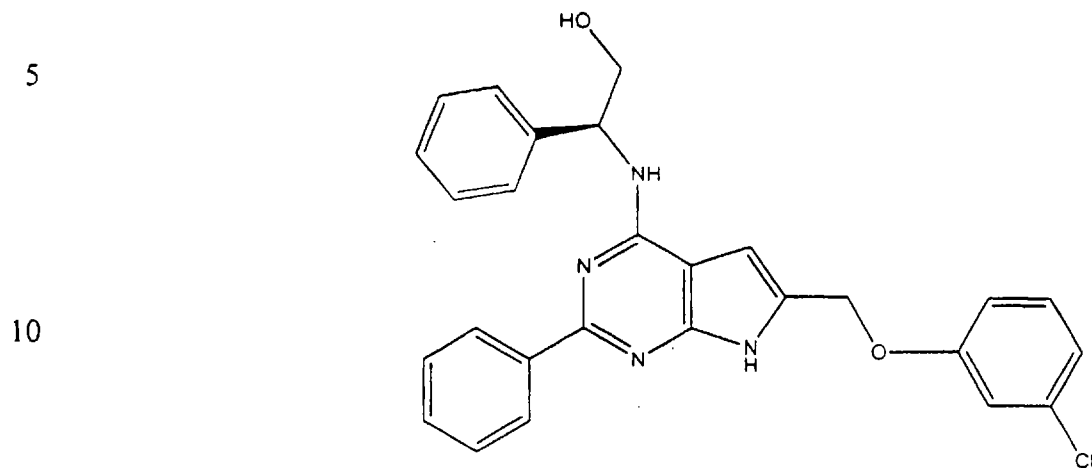


(Compound 1713)

In another embodiment of the compound, the compound has the structure:

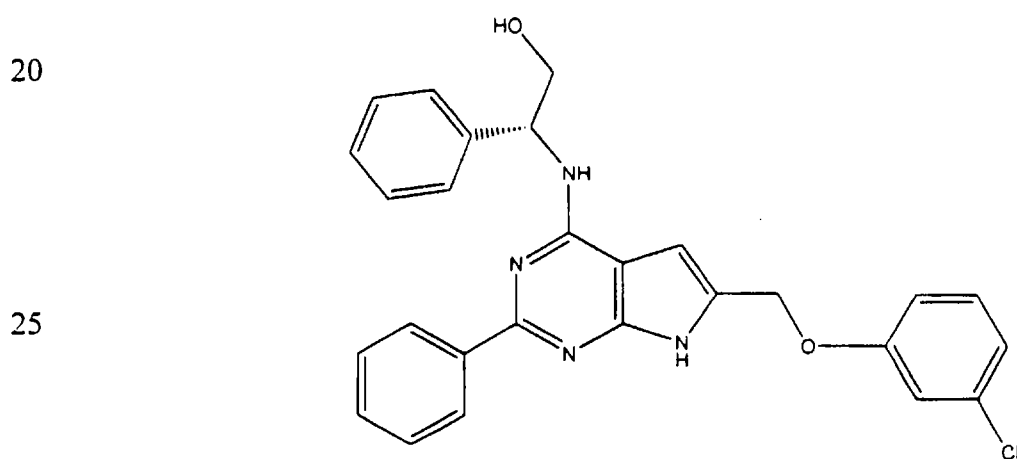


In another embodiment of the compound, the compound has the structure:



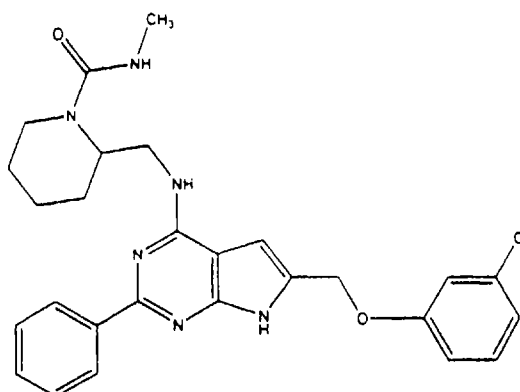
(Compound 1714)

In another embodiment of the compound, the compound has the structure:



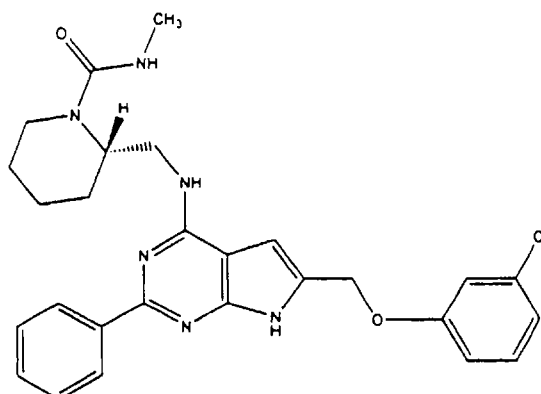
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In another embodiment of the compound, the compound has the structure:

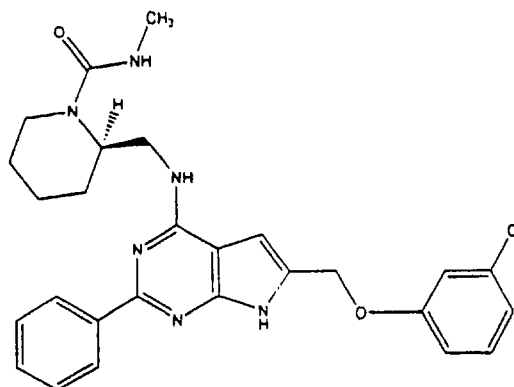


(Compound 1715)

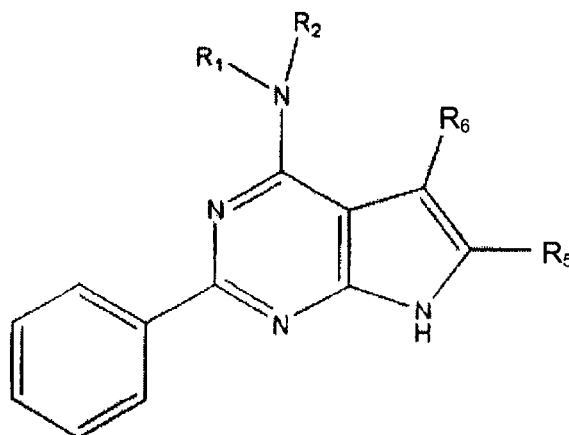
In another embodiment of the compound, the compound has the structure:



In another embodiment of the compound, the compound has the structure:



This invention also provides a compound having the structure:

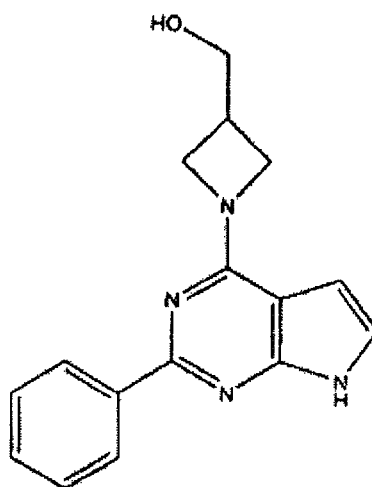


VIII

wherein R_1 , R_2 and the nitrogen together are 3-hydroxy pyrrolidino, 3-methoxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino, or 3-hydroxymethyl piperadino;

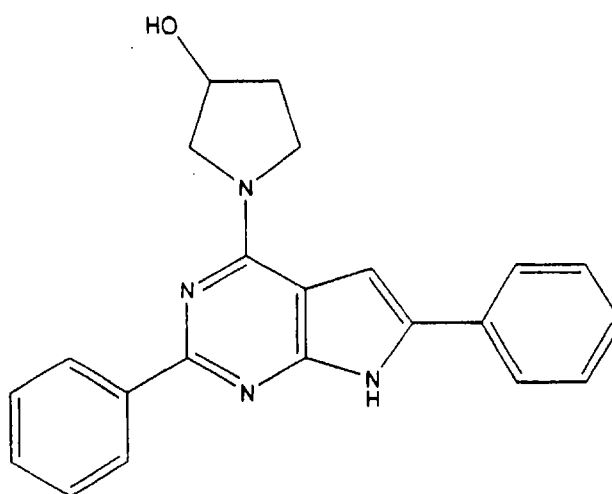
wherein R_5 and R_6 are independently H, substituted or unsubstituted alkyl, or aryl.

In one embodiment of the compound, the compound has the structure:



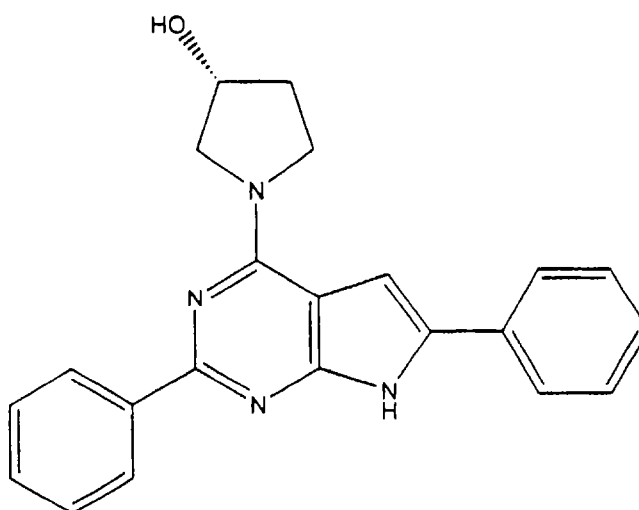
(Compound 1711)

In another embodiment of the compound, the compound has the structure:

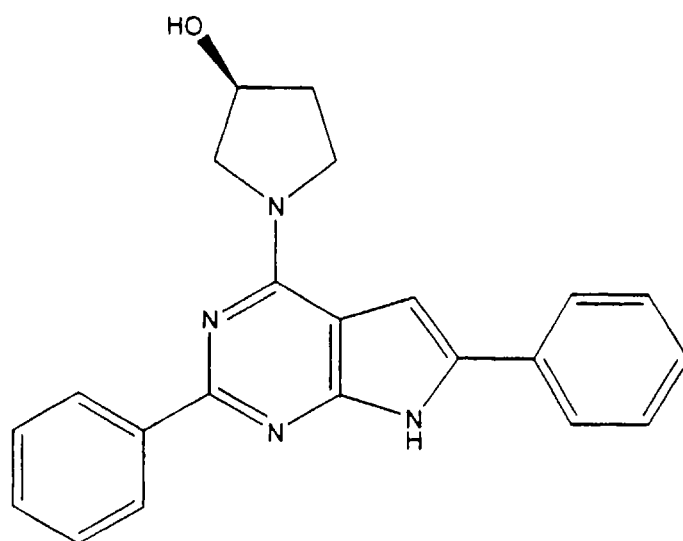


(Compound 1703)

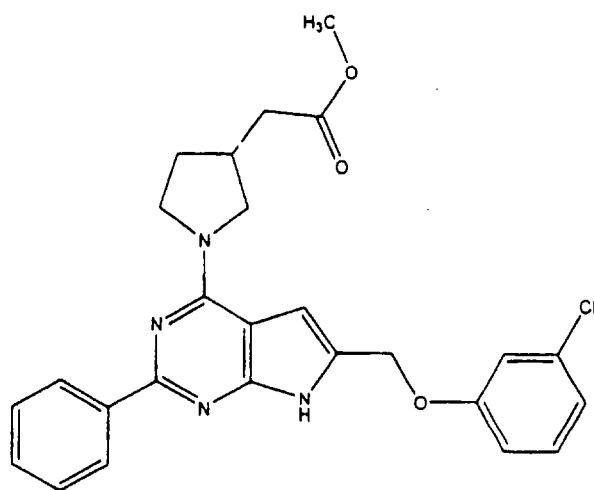
In another embodiment of the compound, the compound has the structure:



In another embodiment of the compound, the compound has the structure:

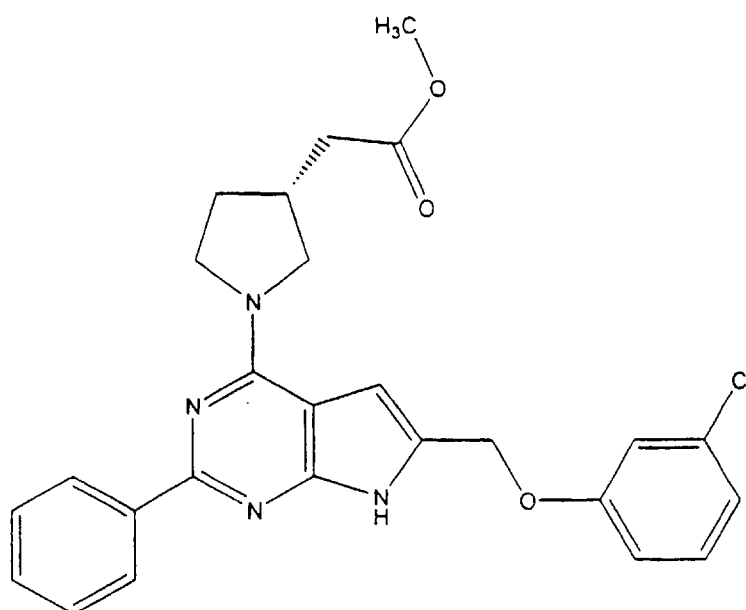


15 In another embodiment of the compound, the compound has the structure:

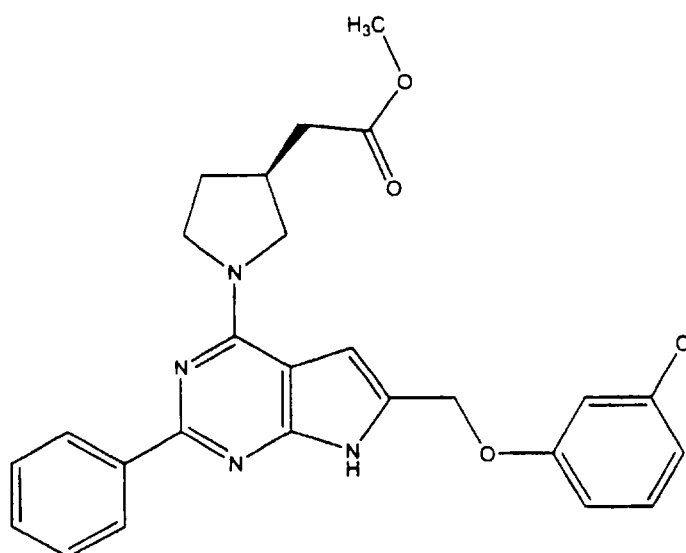


30 (Compound 1716)

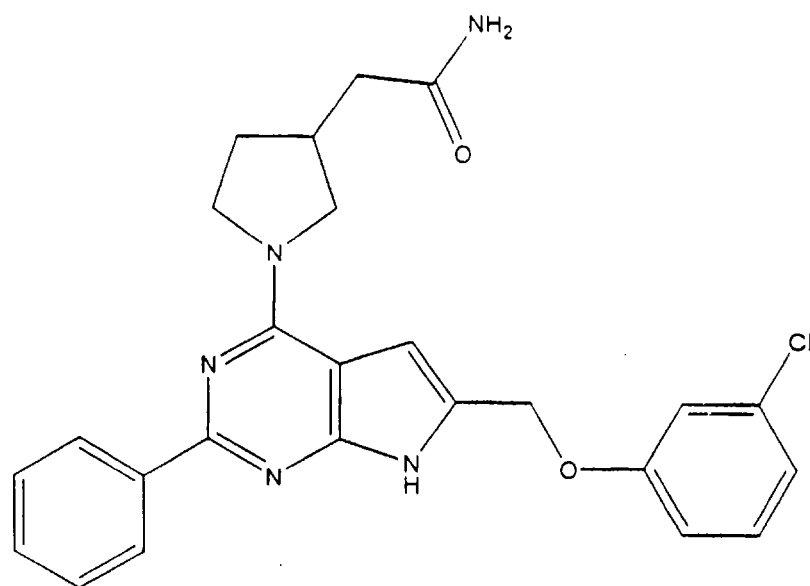
In another embodiment of the compound, the compound has the structure:



In another embodiment of the compound, the compound has the structure:

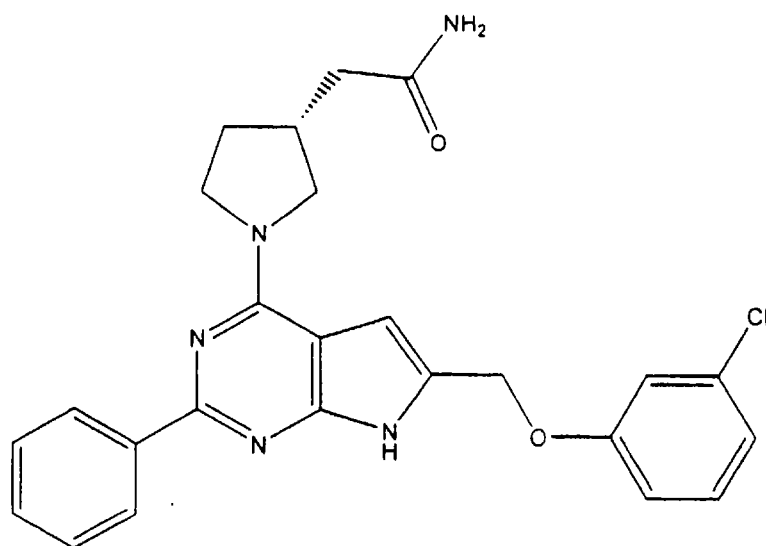


In another embodiment of the compound, the compound has the structure:

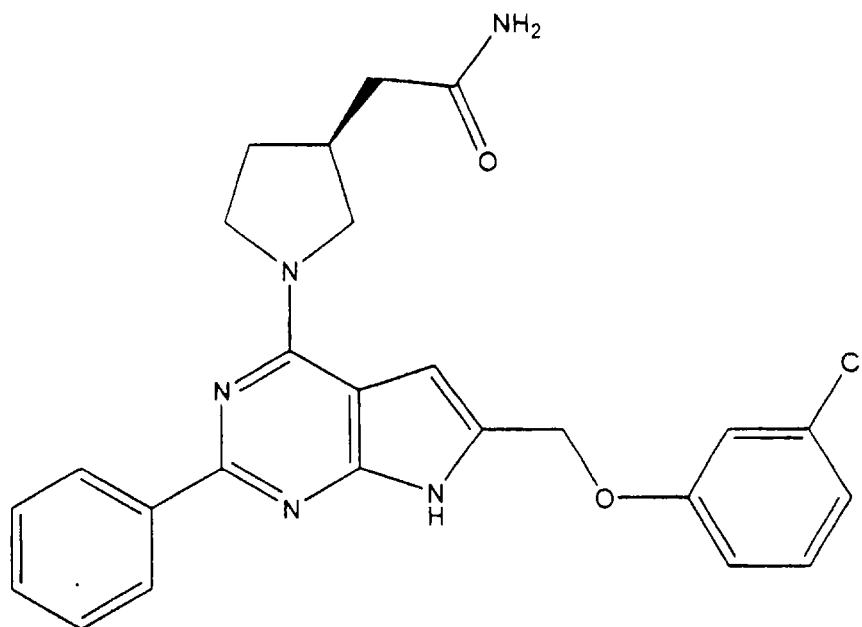


(Compound 1717)

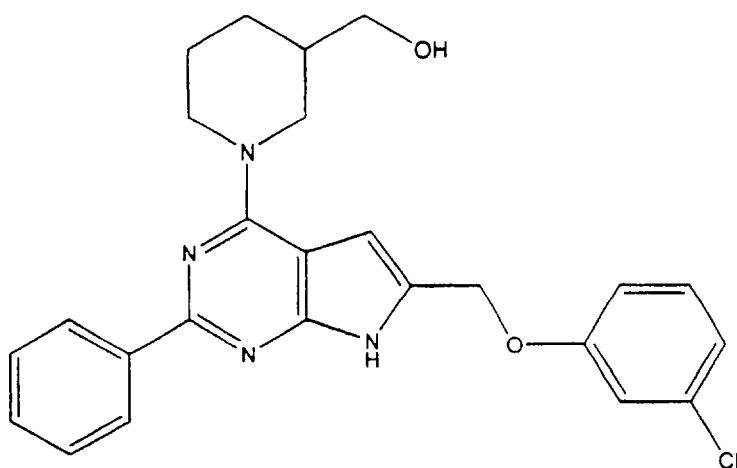
In another embodiment of the compound, the compound has the structure:



In another embodiment of the compound, the compound has the structure:

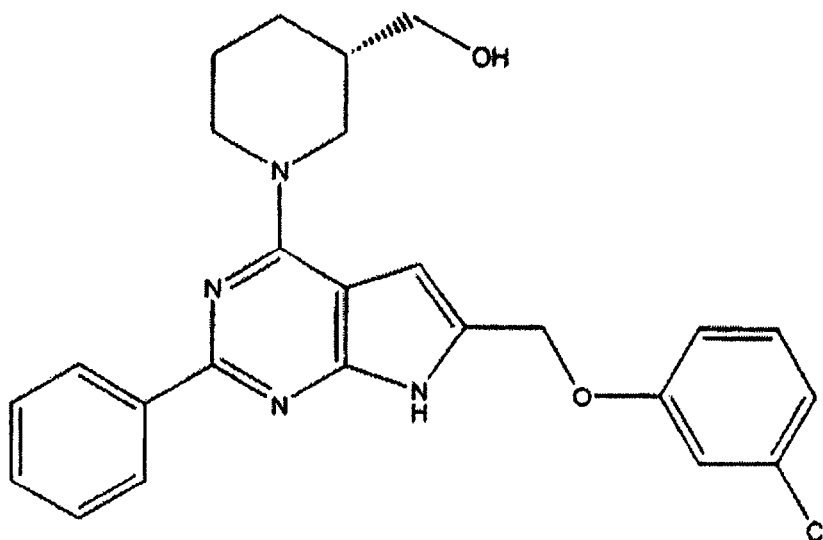


In another embodiment of the compound, the compound has the structure:

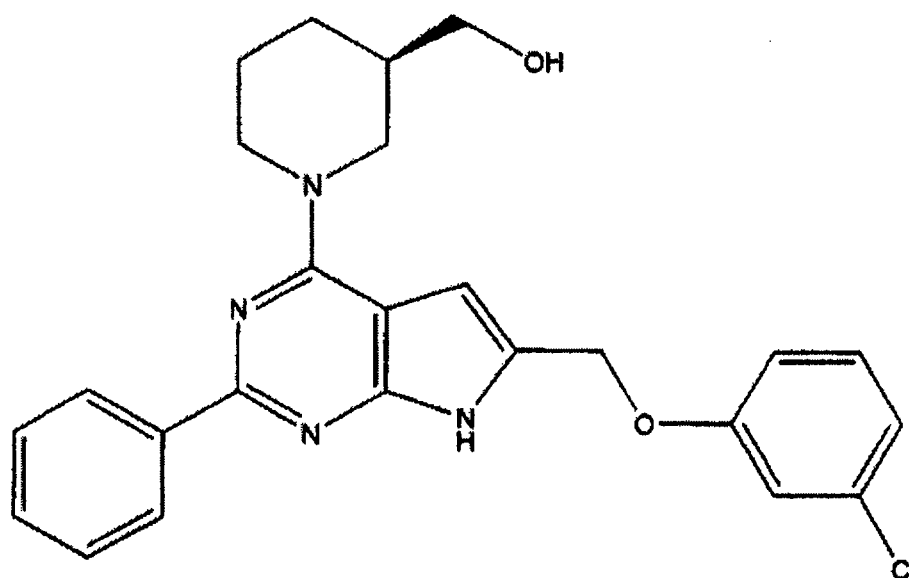


(Compound 1718)

In another embodiment of the compound, the compound has the structure:



In another embodiment of the compound, the compound has the structure:



This invention also provides a method for treating a disease associated with A₃ adenosine receptor in a subject, comprising administering to the subject a therapeutically effective amount of any of the compounds IV, V, VI, VII, or VIII.

In one embodiment of the method, the subject is a mammal.

In another embodiment of the method, the mammal is a human.

5 In another embodiment of the method, said A₃ adenosine receptor is associated with a central nervous system disorder, a cardiovascular disorder, asthma, hypersensitivity, rhinitis, hay fever, serum sickness, allergic vasculitis, atopic dermatitis, dermatitis, psoriasis, eczema, idiopathic pulmonary
10 fibrosis, eosinophilic cholecystitis, chronic airway inflammation, hypereosinophilic syndromes, eosinophilic gastroenteritis, edema, urticaria, eosinophilic myocardial disease, episodic angioedema with eosinophilia, inflammatory bowel disease, ulcerative colitis, allergic granulomatosis, carcinomatosis, eosinophilic granuloma, familial histiocytosis,
15 hypertension, mast cell degranulation, tumor, cardiac hypoxia, cerebral ischemia, diuresis, renal failure, neurological disorder, mental disorder, cognitive disorder, myocardial ischemia, bronchoconstriction, arthritis, autoimmune disease, Crohn's disease, Grave's disease, diabetes, multiple sclerosis,
20 anaemia, psoriasis, fertility disorders, lupus erythematosus, reperfusion injury, brain arteriole diameter, the release of allergic mediators, scleroderma, stroke, global ischemia, central nervous system disorder, cardiovascular disorder, renal disorder, inflammatory disorder, gastrointestinal disorder, eye disorder, allergic disorder, respiratory disorder, or immunological disorder.

30 Diseases associated with adenosine A₁, A_{2a}, A_{2b} and A₃ receptors are disclosed in WO 99/06053 and WO-09822465, WO-09705138, WO-09511681, WO-09733879, JP-09291089, PCT/US98/16053 and U.S. Patent No. 5,516,894, the entire content of which are fully

incorporate herein by reference.

5 This invention also provides a water-soluble prodrug of any of the compounds IV, V, VI, VII, or VIII; wherein said water-soluble prodrug that is metabolized *in vivo* to an active drug which selectively inhibit A3 adenosine receptor.

10 In one embodiment of the prodrug, said prodrug is metabolized *in vivo* by esterase catalyzed hydrolysis.

This invention also provides a pharmaceutical composition comprising the prodrug and a pharmaceutically acceptable carrier.

15 This invention also provides a method for inhibiting the activity of an A3 adenosine receptor in a cell, which comprises contacting said cell with any of the compounds IV, V, VI, VII, or VIII.

20 In one embodiment of the method, the compound is an antagonist of said A3 adenosine receptor.

In another embodiment of the pharmaceutical composition, said pharmaceutical composition is an ophthalmic formulation.

25 In another embodiment of the pharmaceutical composition, said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.

30 In another embodiment of the pharmaceutical composition, said pharmaceutical composition is a systemic formulation.

This invention also provides a method for treating a gastrointestinal disorder in an subject, comprising administering to the an effective amount of any of the compounds IV, V, VI, VII, or VIII.

5

In one embodiment of the method, said disorder is diarrhea.

In another embodiment of the method, the subject is a human.

10

In another embodiment of the method, the compound is an antagonist of A3 adenosine receptors.

15

This invention further provides a method for treating respiratory disorder in a subject, comprising administering to the subject an effective amount of any of the compounds IV, V, VI, VII, or VIII.

20

In one embodiment of the method, said disorder is asthma, chronic obstructive pulmonary disease, allergic rhinitis, or an upper respiratory disorder.

In another embodiment of the method, the subject is a human.

25

In another embodiment of the method, said compound is an antagonist of A3 adenosine receptors.

30

This invention also provides a method for treating damage to the eye of a subject which comprises administering to said subject an effective amount of any of the compounds IV, V, VI, VII, or VIII.

In one embodiment of the method, said damage comprises retinal

or optic nerve head damage.

In another embodiment of the method, said damage is acute or chronic.

5

In another embodiment of the method, said damage is the result of glaucoma, edema, ischemia, hypoxia or trauma.

In another embodiment of the method, the subject is a human.

10

In another embodiment of the method, the compound is an antagonist of A3 adenosine receptors.

15

This invention also provide a pharmaceutical composition comprising a therapeutically effective amount of any of the compounds IV, V, VI, VII, or VIII and a pharmaceutically acceptable carrier.

20

In one embodiment of the pharmaceutical composition, said therapeutically effective amount is effective to treat a respiratory disorder or a gastrointestinal disorder.

25

In another embodiment of the pharmaceutical composition, said gastrointestinal disorder is diarrhea.

In another embodiment of the pharmaceutical composition, said respiratory disorder is asthma, allergic rhinitis, or chronic obstructive pulmonary disease.

30

In another embodiment of the pharmaceutical composition, said pharmaceutical composition is an ophthalmic formulation.

In another embodiment of the pharmaceutical composition, said pharmaceutical composition is an perocular, retrobulbar or intraocular injection formulation.

5 In another embodiment of the pharmaceutical composition, said pharmaceutical composition is a systemic formulation.

In another embodiment of the pharmaceutical composition, said pharmaceutical composition is a surgical irrigating solution.

10

This inventio also provides a packaged pharmaceutical composition for treating a disease associated with A₃ adenosine receptor in a subject, comprising: (a) a container holding a therapeutically effective amount of any of the compounds IV, V, VI, VII, or VIII; and (b) instructions for using said compound for treating said disease in a subject.

15

Compounds represented by the formula IV, V, VI, VII, and VIII can be synthesized by the Schemes I-IX.

20

As used herein, "A compound is A₃ selective." means that a compound has a binding constant to adenosine A₃ receptor of at least ten time higher then that to adenosine A₁, A_{2a}, or A_{2b}.

25

The invention is further illustrated by the following examples which in no way should be construed as being further limiting. The contents of all references, pending patent applications and published patent applications, cited throughout this application, including those referenced in the background section, are hereby incorporated by reference. It should be understood that the models used throughout the examples are accepted models and that the demonstration of efficacy in these

30

models is predictive of efficacy in humans.

A skilled artisan will know that metabolism of the compounds disclosed herein in a subject produces certain biologically active metabolites which can serve as drugs.

This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

Example 24: Adenosine A₃ Antagonist Experimentals

Compound 1700 (Table 17 below): MS (ES): 366.1 (M⁺+1).

Compound 1710 (Table 17 below): MS (ES): 381.1 (M⁺+1).

Compound 1316 (Table 17 below): MS (ES): 353.2 (M⁺+1).

Compound 1703 (Table 17 below): MS (ES): 357.1 (M⁺+1).

Compound 1719 (Table 17 below): ¹H-NMR (200MHz, d₆-DMSO) (1.75 (m, 2H), 3.11 (m, 2H), 3.35 (s, 3H), 3.59 (m, 2H), 5.72 (m, 1H), 5.96 (m, 1H), 6.55 (s, 1H), 7.15 (s, 1H), 7.49 (m, 2H), 8.32 (m, 2H).

Compound 1704 (Table 17 below): MS (ES): 367.0 (M⁺+1).

Compound 1706 (Table 17 below): ¹H-NMR (200MHz, CDCl₃) d 1.22 (m, 2H), 1.60-2.40 (m, 4H), 4.53 (m, 1H), 4.94 (m, 1H), 5.70 (d, 1H, J = 8.2 Hz), 6.35 (d, 1H, J = 2.8 Hz), 6.97 (d, 1H, J = 2.0 Hz), 7.50 (m, 3H), 8.40 (m, 2H), 10.83 (brs, 1H).

Compound 1707 (Table 17 below): MS(ES): 347.0 (M⁺+1).

Compound 1708 (Table 17 below): MS (ES) 399.0 (M+1).

Compound 1709 (Table 17 below): MS (ES) 385.9 (M+1).

5 Compound 1710 (Table 17 below): MS (ES) 434.0 (M++1).

Compound 1711 (Table 17 below): ²H-NMR (200MHz, CD₂OD) d 3.95 (d, 2H, J = 5.8Hz), 4.23 - 4.31 (m, 2H), 4.53 (t, 2H, J = 8.8Hz), 6.30 (d, 1H, J = 3.0Hz), 6.98 (d, 1H, J = 3.0Hz), 7.45 - 7.48 (m, 3H), 7.83 - 8.42 (m, 2H), 9.70 (brs, 1H). MS (ES): 281.1 (M⁺+1).

Compound 1712 (Table 17 below): ¹H-NMR (200MHz, CD₃OD) d 3.02 (m, 2H), 3.92 (m, 2H), 5.09 (2,2H), 6.53 (s, 1H), 6.92 (br s, 1H), 6.92 (m, 2H), 7.02 (m, 1H), 7.21 (dd, 1H, J = 8.2Hz), 7.40 (m, 3H), 7.50-7.80 (br s, 1H), 8.33 (m, 2H). MS (ES): 445.1 (M⁺+1).

Compound 1713 (Table 17 below): ¹H-NMR (200MHz, CDCl₃) d 1.65-1.80 (m, 7H), 1.88-2.00 (m, 1H), 2.10 - 2.40 (m, 1H), 2.70-3.05 (m, 3H), 3.09-3.14 (m, 2H), 3.16 - 3.38 (m, 1H), 3.45 (d, 1H, J = 14Hz), 3.53-3.60 (m, 2H), 3.84-3.92 (m, 2H), 3.97 (d, 1H, J = 14Hz), 5.55 (t, 1H, J = 5.8Hz), 6.17 (s, 1H), 6.55-6.59 (m, 2H), 6.64-6.71 (m, 1H), 7.11-7.19 (m, 2H), 7.43-7.46 (m, 3H), 8.38-8.42 (m, 2H), MS (ES): 484.0 (M⁺+1).

Compound 1714 (Table 17 below): MS (ES): 471.0 (M⁺+1)

Compound 1715 (Table 17 below): MS (ES): 505.0 (M⁺+1).

30 Compound 1716 (Table 17 below): ¹H-NMR (200MHz, CD₃OD) d 1.65 (m, 1H), 2.18 (m, 1H), 2.49 (br d, 2H, J = 6.2Hz), 2.64 (m, 1H), 3.38 (m, 1H), 3.69 (s, 3H), 3.72 (m, 1H), 3.93 (m, 1H), 4.10 (m, 1H), 5.06 (2, 2H), 6.58 (s, 1H), 6.92 (m, 2H), 7.02 (m, 1H), 7.23 (dd, 1H, J = 8.1Hz), 7.39 (m, 3H), 8.32 (m, 2H).

MS (ES): 477.1 (M^+1).

Compound 1717 (Table 17 below): ^1H -NMR (200MHz, CD_3OD) δ 1.69 (m, 1H), 2.26 (m, 1H), 2.42 (d, 2H, $J = 7.4\text{Hz}$), 2.72 (m, 1H),
5 3.53 (m, 1H), 3.83 (m, 1H), 4.02 (m, 1H), 4.14 (dd, 1H, $J = 10.6, 7.0\text{Hz}$), 5.14 (t, 2H), 6.69 (s, 1H), 6.96 (m, 2H), 7.06 (m, 1H), 7.25 (dd, 1H, $J = 8.0\text{Hz}$), 7.39 (m, 3H), 8.35 (m, 2H).
MS (ES): 462.2 (M^+1).

10 **Compound 1718 (Table 17 below):** ^1H -NMR (200MHz, CD_3OD) δ 1.40 - 2.00 (m, 5H), 3.52 (d, 2H, 7.6Hz), 3.80 - 4.00 (m, 1H), 4.00 - 4.20 (m, 3H), 4.50 (m, 2H), 6.36 - 6.50 (m, 2H), 6.54 (s, 1H), 6.84 - 6.92 (m, 1H), 7.05 (t, 1H, $J = 8.2\text{Hz}$), 7.30 - 7.45 (m, 3H), 8.24 (d, 2H, $J = 9.8\text{Hz}$). MS (ES): 449.0 (M^+1).

15

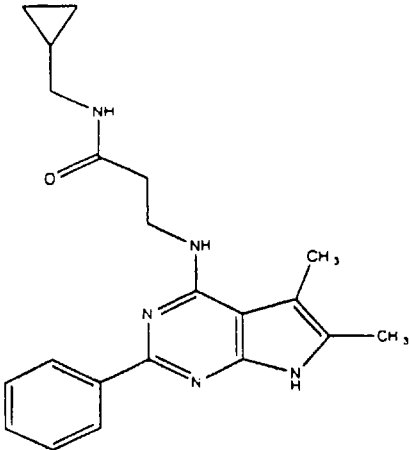
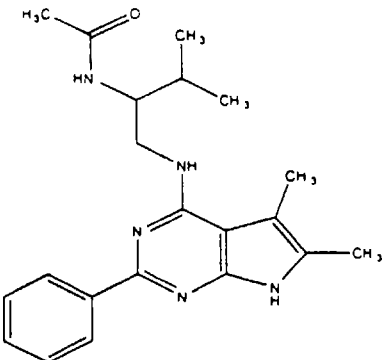
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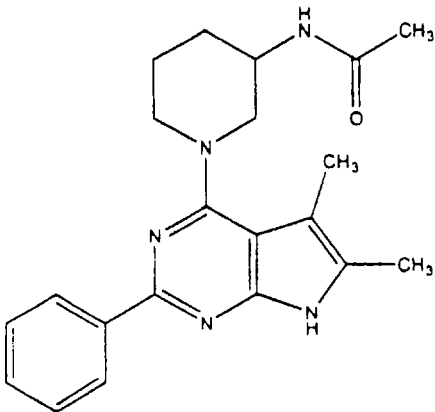
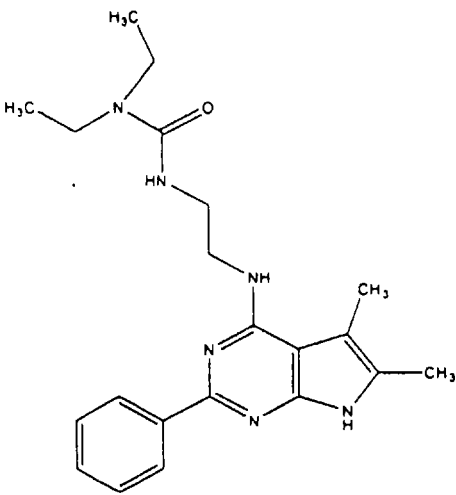
25

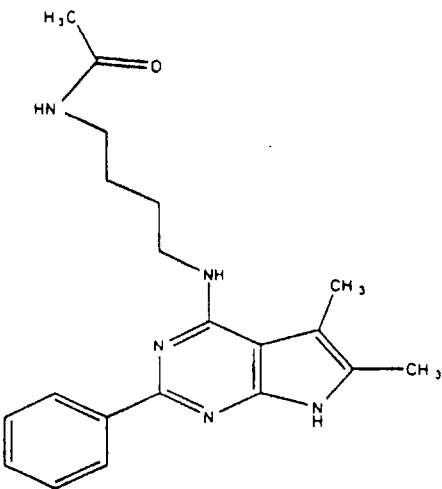
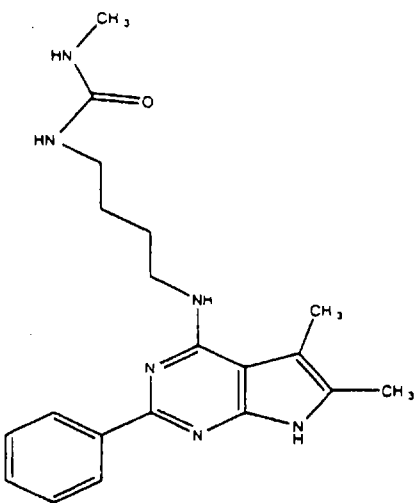
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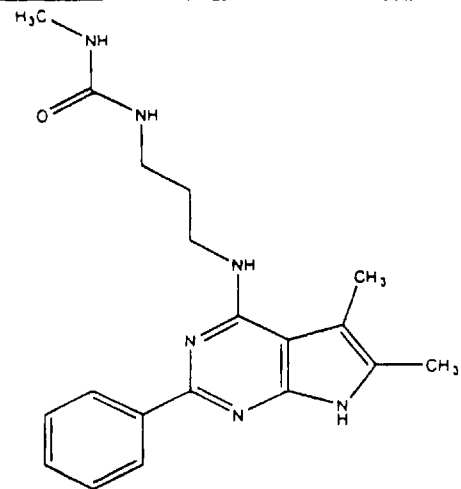
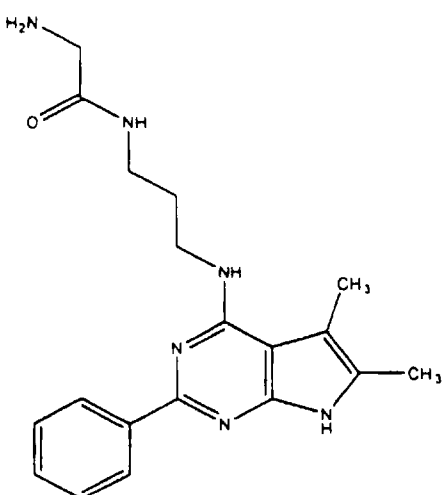
TABLE 17. Adenosine A₃ Receptor Selective Compounds

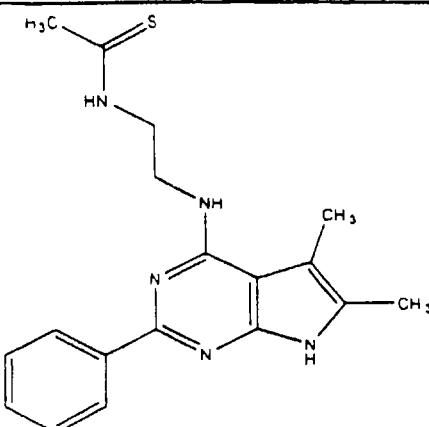
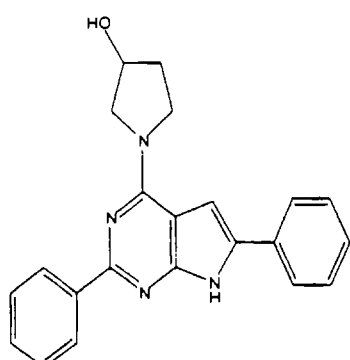
* at least 10 times more selective than other three subtypes.

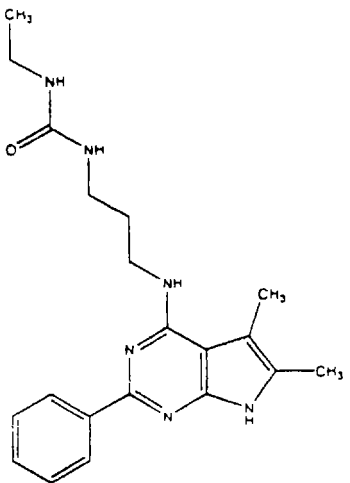
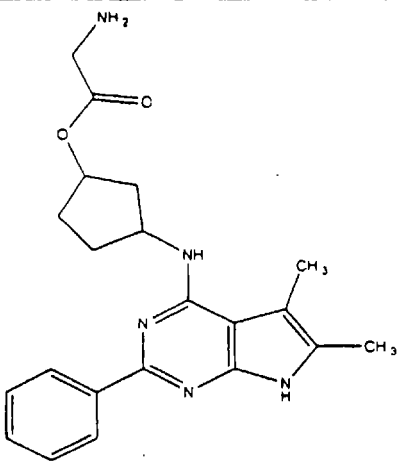
Compound	Structure	Ki-A1	Ki-A2a	Ki-A2b	Ki-A3
1202					*
1700					*

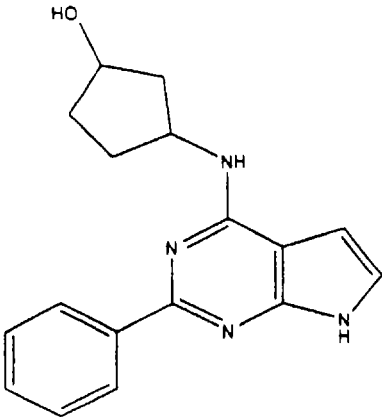
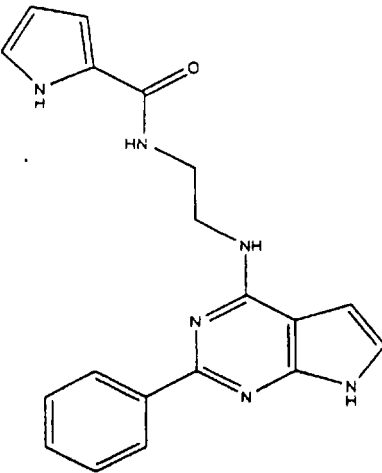
1309					*
1701					*

1311	 <chem>CC(=O)NCCCNc1nc2c(ncn2C)c3ccccc13</chem>				*
1312	 <chem>CC(=O)NCC(C)Nc1nc2c(ncn2C)c3ccccc13</chem>				*

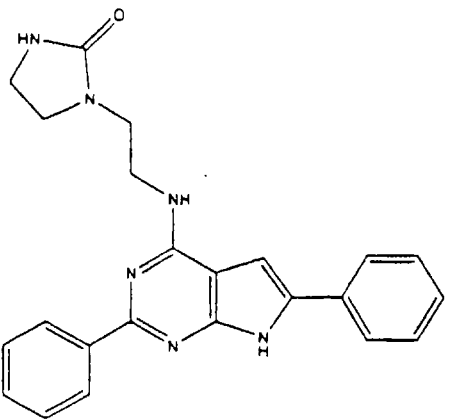
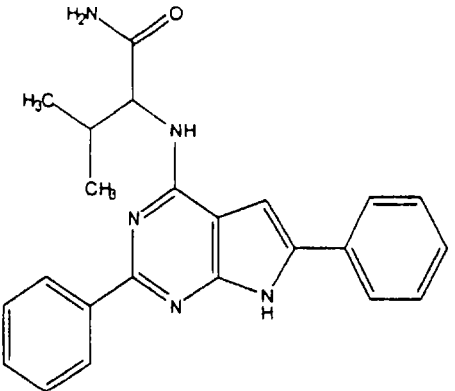
1310					*
1316					*

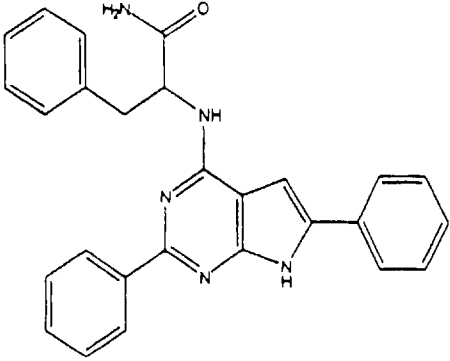
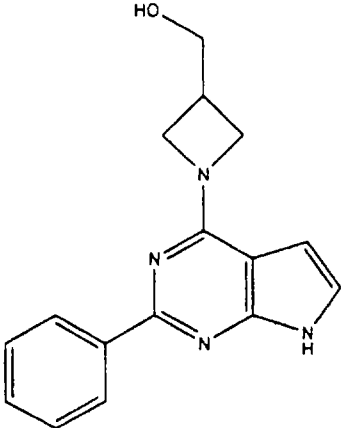
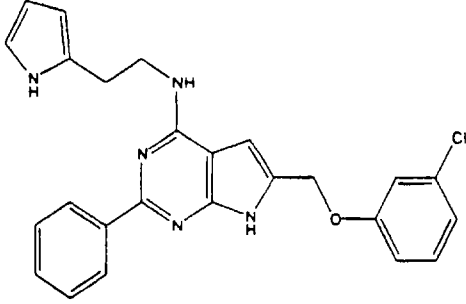
1702					*
1703					*

1704	 <chem>CCNC(=O)NCCCNc1nc2c(c1)c3c(nc2)ccccc3C</chem>				*
1705	 <chem>CC(C)C(=O)NCC1CCC1Nc2nc3c(c2)c4c(nc3)ccccc4C</chem>				*

1706					*
1707					*

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1708					*
1709					*

1710					*
1711					*
1712					*

5

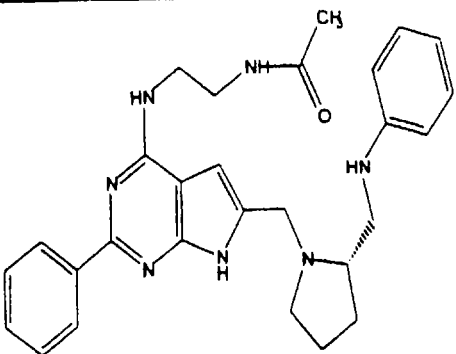
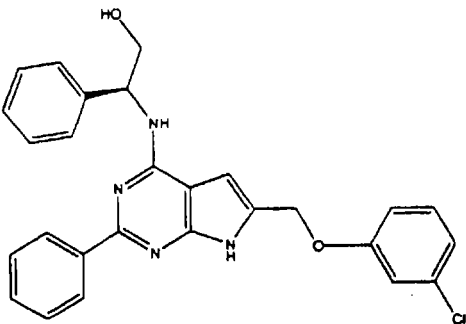
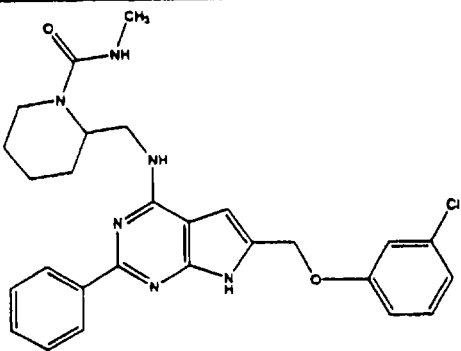
10

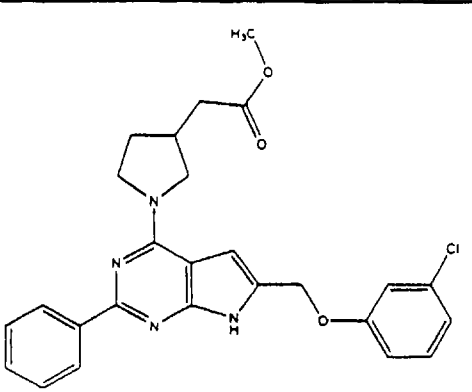
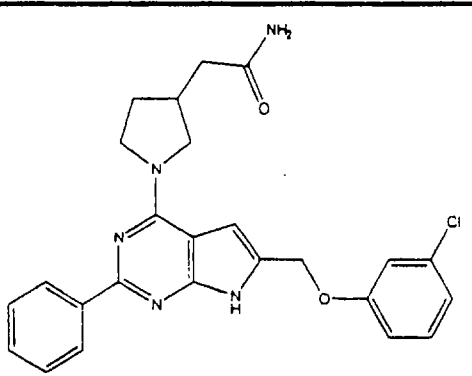
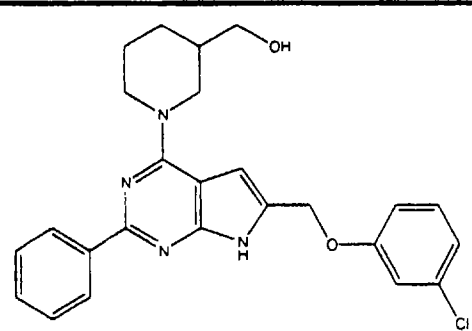
15

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25

30

1713					*
1714					*
1715					*

1716					*
1717					*
1718					*

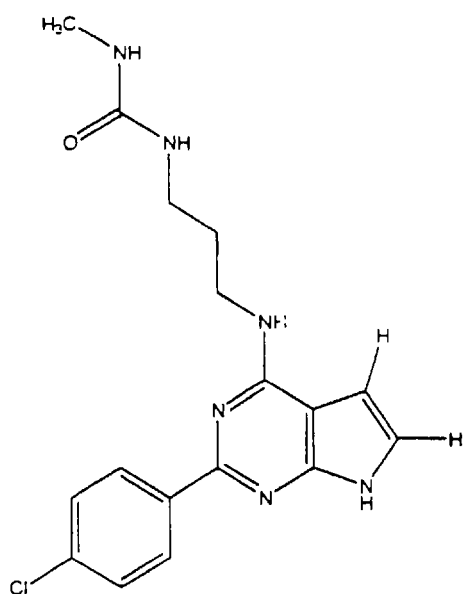
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20

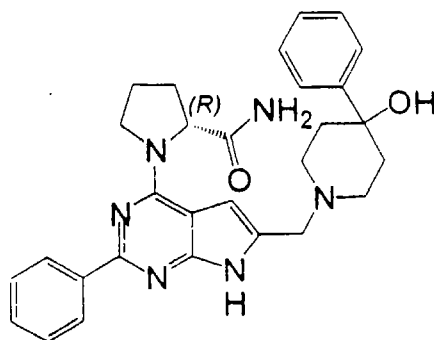
1719



*

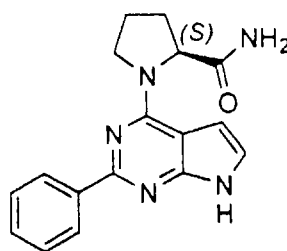
25

This invention provides a compound having the structure:



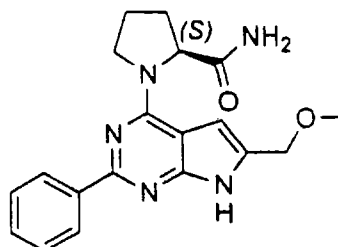
1505

This invention also provides a compound having the structure:



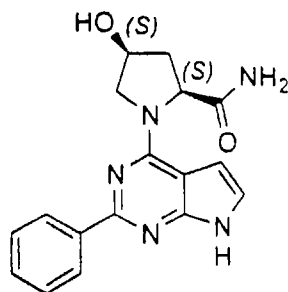
1506

This invention further provides a compound having the structure:



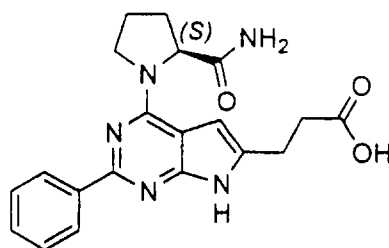
1507

This invention also provides a compound having the structure:



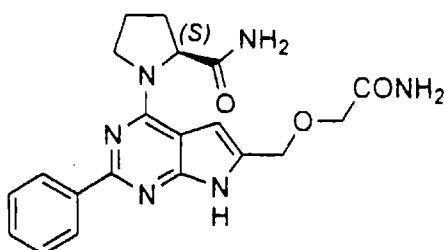
1508

15 This invention further provides a compound having the structure:



1509

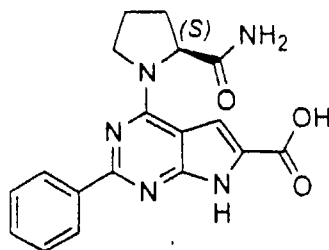
25 This invention also provides a compound having the structure:



1510

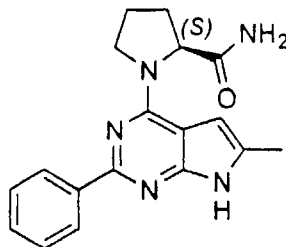
35

This invention also provides a compound having the structure:



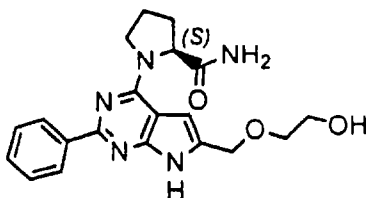
1511

This invention further provides a compound having the structure:



1512

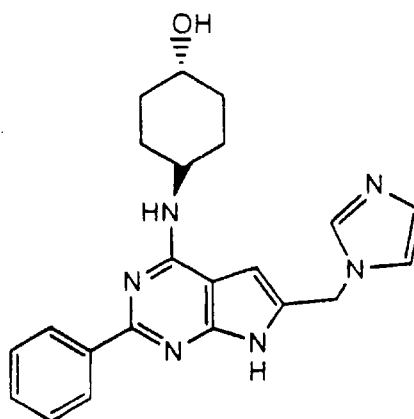
This invention also provides a compound having the structure:



1513

This invention further provides a compound having the structure:

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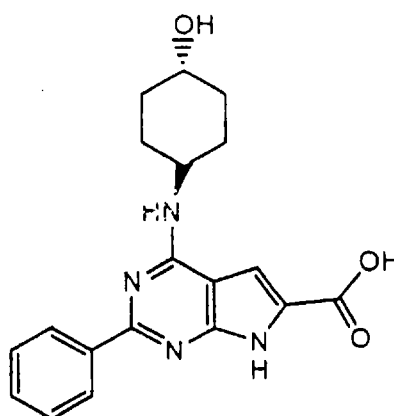


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1514

This invention further provides a compound having the structure:

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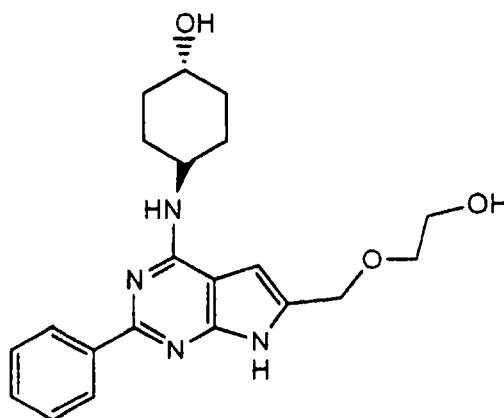


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1515

This invention also provides a compound having the structure:

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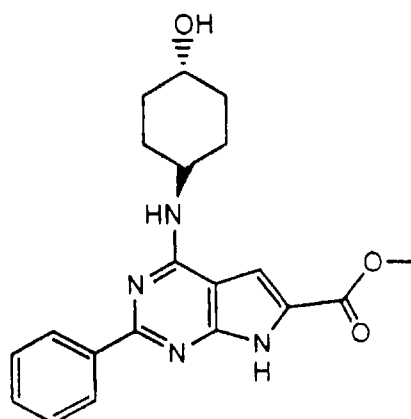


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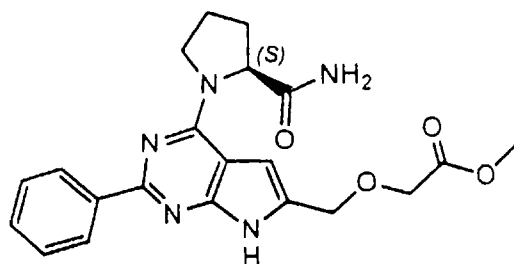
1516

261



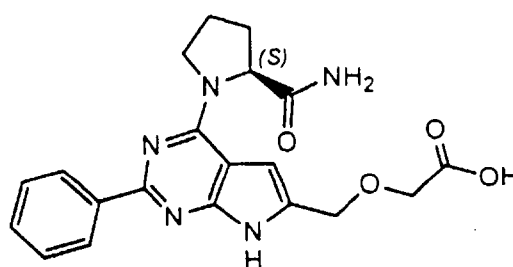
1517

This invention further provides a compound having the structure:



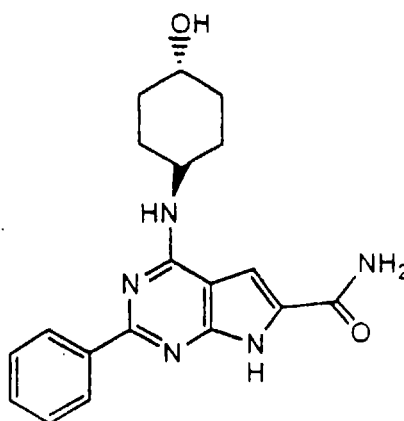
1518

This invention also provides a compound having the structure:



1519

This invention further provides a compound having the structure:



1520

In a further embodiment the invention provides a method for treating a disease associated with A₁ adenosine receptor in a subject, comprising administering to the subject a therapeutically effective amount of compounds 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1516, 1517, 1518, 1519, or 1520.

In a further embodiment the invention provides the above method, wherein the subject is a mammal.

In a further embodiment the invention provides the above method, wherein the mammal is a human.

In a further embodiment the invention provides the above method, wherein said A₁ adenosine receptor is associated with cognitive disease, renal failure, cardiac arrhythmias, respiratory epithelia, transmitter release, sedation, vasoconstriction, bradycardia, negative cardiac inotropy and dromotropy, bronchoconstriction, neutrophil chemotaxis, reflux condition, or ulcerative condition.

In a further embodiment the invention provides a water-soluble prodrug of compound 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1516, 1517, 1518, 1519, or 1520, wherein the water-soluble prodrug is metabolized in vivo to produce an active drug which selectively inhibits A₁ adenosine receptor.

In a further embodiment the invention provides, wherein said prodrug is metabolized in vivo by esterase catalyzed hydrolysis.

In a further embodiment the invention provides a pharmaceutical composition comprising the above prodrug and a pharmaceutically acceptable carrier.

In a further embodiment the invention provides a method for inhibiting the activity of an A₁ adenosine receptor in a cell, which comprises contacting the cell with compounds 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1516, 1517, 1518, 1519, or 1520.

In a further embodiment the invention provides the above method for inhibiting the activity of an A₁ adenosine receptor in a cell, wherein the compound is an antagonist of the A₁ adenosine receptor.

In a further embodiment the invention provides the above method for inhibiting the activity of an A₁ adenosine receptor in a cell, wherein the cell is human cell.

In a further embodiment the invention provides the above method for inhibiting the activity of an A₁ adenosine receptor in a human cell, wherein the compound is an antagonist of A₁ adenosine receptors.

5 In a further embodiment the invention provides a method for treating a disease associated with A₁ adenosine receptor in a subject, wherein said disease is asthma, chronic obstructive pulmonary disease, allergic rhinitis, or an upper respiratory disorder.

10 In a further embodiment the invention provides a method for treating a disease associated with A₁ adenosine receptor in a subject, wherein said disease is asthma, chronic obstructive pulmonary disease, allergic rhinitis, or an upper respiratory disorder and wherein the subject is a human.

15 In a further embodiment the invention provides a method for treating the above disease, wherein said compound is an antagonist of A₁ adenosine receptors.

20 In a further embodiment the invention provides a combination therapy for asthma, comprising the compound 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1516, 1517, 1518, 1519, or 1520, and a steroid, β 2 agonist, glucocorticoid, lucotriene antagonist, or anticholinergic agonist.

25 In a further embodiment the invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1516, 1517, 1518, 1519, or 1520, and a pharmaceutically acceptable carrier.

30 In a further embodiment the invention provides a method for treating a respiratory disorder with the compound 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1516, 1517, 1518, 1519, or 1520, wherein said respiratory disorder is asthma, allergic rhinitis, or chronic obstructive pulmonary disease.

In a further embodiment the invention provides the above pharmaceutical composition(s), wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.

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In a further embodiment the invention provides the above pharmaceutical composition(s), wherein said pharmaceutical composition is a systemic formulation.

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In a further embodiment the invention provides the above pharmaceutical composition(s), wherein said pharmaceutical composition is a surgical irrigating solution.

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In a further embodiment the invention provides a packaged pharmaceutical composition for treating a disease associated with A1 adenosine receptor in a subject, comprising:

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(a) a container holding a therapeutically effective amount of the compounds 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1516, 1517, 1518, 1519, or 1520; and

25

(b) instructions for using said compound for treating said disease in a subject.

30

In a further embodiment the invention provides a pharmaceutically acceptable salt of the compound 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1516, 1517, 1518, 1519, or 1520.

In a further embodiment the invention provides the above pharmaceutically acceptable salt, wherein the pharmaceutically acceptable salt of the compound 1509, 1511, 1515, 1518, or 1519 contains a cation selected from the group consisting of sodium,

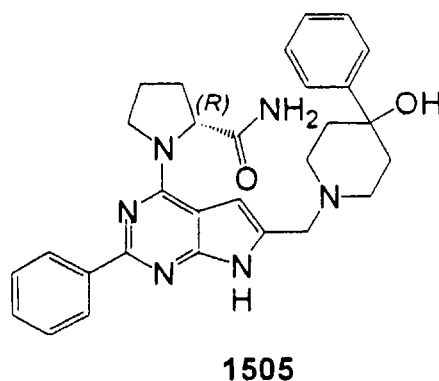
calcium and ammonium.

In yet a further embodiment the invention provides a method for treating a disease associated with A₁ adenosine receptor in a subject, wherein the A₁ adenosine receptor is associated with congestive heart failure.

Exemplification

Example 21: Synthesis of 1-[6-(4-Hydroxy-4-phenyl-piperidin-1-yl-methyl)-2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pyrrolidine-2-carboxylic acid amide (1505).

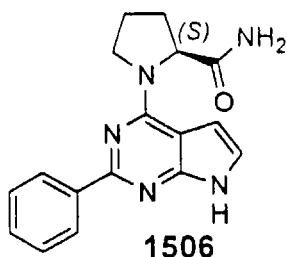
Compound **1505** was synthesized in a manner similar to that of Example 17 using synthesis scheme IX with L-prolineamide and 4-phenyl-piperidin-4-ol to obtain:



¹H-NMR (d₆-DMSO) δ 1.53 (s, 1H), 1.60 (s, 1H), 1.84-2.30 (m, 6H), 2.66 (m, 2H), 3.60 (s, 2H), 3.88 (m, 1H), 4.02 (m, 1H), 4.66 (d, 1H, J = 6.8Hz), 4.73 (s, 1H), 6.44 (s, 1H), 6.94 (s, 1H), 7.12 - 7.50 (m, 10H), 8.35 (m, 2H), 11.6 (brs, 1H); MS (ES): 305.1 (M⁺+1); mp = 234-235°C.

Example 22: Synthesis of [N-(2-Phenyl-7H-pyrrolo
[2,3-d]pyrimidin-4-yl) (L)-prolinamide (1506)

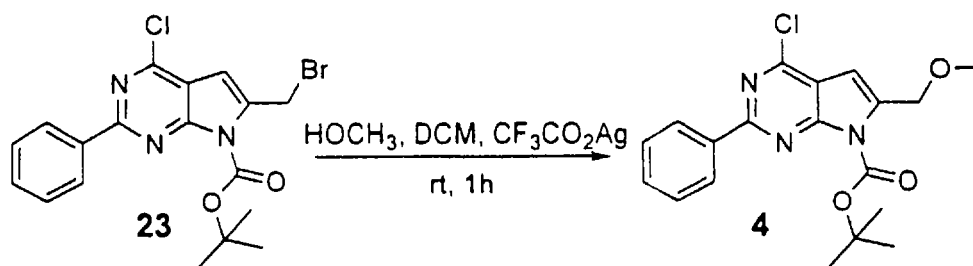
Compound **1506** was synthesized using synthesis scheme VII with
L-prolineamide to obtain:



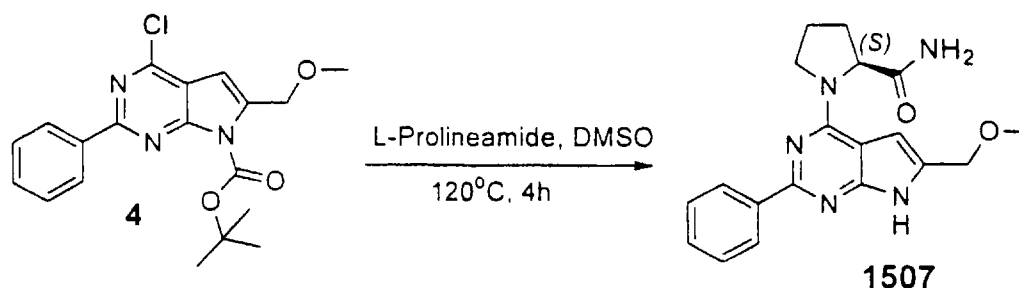
¹H-NMR (DMSO-*d*₆) δ 2.05 (m, 4H), 3.85 (m, 1H), 4.05 (m, 1H),
4.70 (d, 1H, J=8.0Hz), 6.58 (brs, 1H), 6.95 (brs, 1H), 7.15 (d,
1H, J=3.4Hz), 7.40 (m, 3H), 7.50 (brs, 1H), 8.40 (m, 2H), 11.6
(brs, 1H); MS (ES): 308.3 (M⁺+1). mp= 236-238°C.

Example 23: Synthesis of [N-(2-phenyl-6-methoxymethyl-7H-
pyrrolo[2,3-d]pyrimidin-4-yl)-(L)-prolinamide (1507)

Compound **1507** was synthesized using precursor compound 23 of
synthesis scheme IX to obtain:



Bromide **23** (4.23g, 10mmol) is dissolved in anhydrous methanol (60mL) and DCM (120mL) and treated with AgO_2CCF_3 under N_2 at rt for 1h. The solid is removed by filtration and washed with DCM (2x20mL). The filtrate is concentrated in vacuo. The residue is redissolved in DCM (80mL). The resulted solution is then washed with saturated NaHCO_3 solution and brine, dried over MgSO_4 , filtered and concentrated to give 3.71g (**4**, 99%) off white solid. $^1\text{H-NMR}$ (CDCl_3) δ 1.75 (s, 9H), 3.51 (s, 3H), 4.83 (s, 2H), 6.70 (s, 1H), 7.47 (m, 3H), 8.52 (m, 2H).

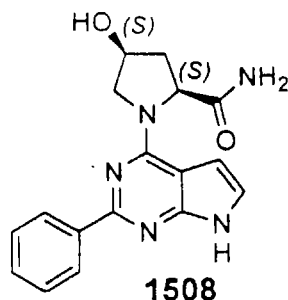


Aryl chloride **4** (2.448g, 6.55mmol), DMSO (15mL), L-prolineamide (4.0g, 35.0mmol) and NaHCO_3 (2.9g) are combined and heated to 120°C under nitrogen. After 4h, the reaction is cooled to room temperature and diluted with water (60ml). The resulted slurry is extracted with DCM (10x). The combined organic layers are washed with saturated NaHCO_3 solution and brine, dried over MgSO_4 , filtered and concentrated to give 2.48g brown solid. Pure product (1.86g, 81%) is obtained after flash column as white solid. White crystals are gotten from THF/hexane. M.p. = 213-215°C. $^1\text{H-NMR}$ (CDCl_3) δ 2.15 (m, 3H), 2.52 (m, 1H), 3.26 (s, 3H), 3.92 (m, 1H), 4.10 (m, 1H), 4.42 (s, 2H), 5.08 (d, 1H, $J=8.2\text{Hz}$), 5.49 (brs, 1H), 6.48 (s, 1H), 7.08 (brs, 1H), 7.42 (m, 3H), 8.38 (m, 2H), 9.78 (brs, 1H); MS (ES): 352.2 ($\text{M}^+ + 1$).

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Example 24: Synthesis of 4-Hydroxy-1-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-pyrrolidine-2-carboxylic acid amide (1508)

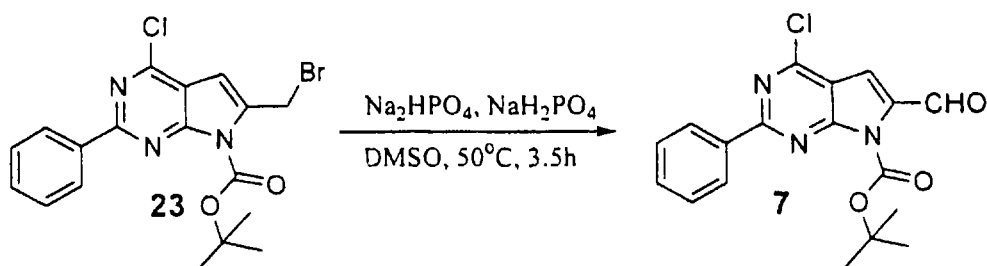
Compound **1508** was obtained with synthesis scheme VII using *cis*-hydroxy prolineamide to obtain:



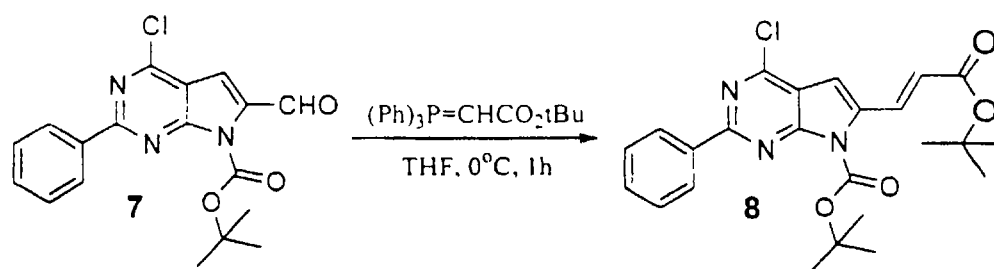
¹H-NMR (d₆-DMSO) δ 1.90 (m, 1H), 3.85 (d, 1H, J = 9.2Hz), 4.08 (m, 1H), 4.37 (s, 1H), 4.67 (dd, 1H, J = 8.8, 4.0Hz), 5.30 (s, 1H), 6.55 (s, 1H), 7.15 (s, 2H), 7.37 (m, 3H), 7.64 (s, 1H), 8.37 (m, 2H), 11.65 (brs, 1H); MS (ES): 324.2 (M⁺+1); mp = 268-271°C.

Example 25: Synthesis of 3-[4-((S)-2-Carbamoyl-pyrrolodin-1-yl)-2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-propionic acid (1509)

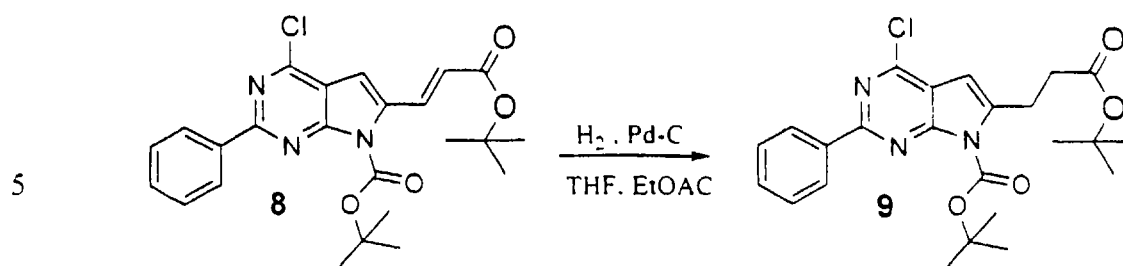
Compound **1509** was obtained using precursor compound 23 of synthesis scheme IX to obtain:



The tert-butoxycarbonyl protected aryl bromide **23** (4.0g, 9.5mmol), dry DMSO (25ml), NaH_2PO_4 (454mg, 3.79mmol) and Na_2HPO_4 (1.62g, 11.4mmol) were combined and heated to 50°C under argon for approximately 3.5h. The mixture was then poured into water (200ml) and extracted with three 100ml portions of EtOAc. The combined organic layers were thoroughly washed with water, brine, dried over MgSO_4 , filtered and concentrated to give a yellow solid which was purified by triturating with ethanol to give 1.55g of a pale yellow solid (**7**). The mother liquor was purified by flash chromatography (10% EtOAc in hexane) to give an additional 454mg (60%). $^1\text{H-NMR}$ (CDCl_3) δ 1.77 (s, 9H), 7.25 (s, 1H), 7.48 (m, 3H), 8.52 (m, 2H) 10.39 (s, 1H); m.p.= 156°C (dec).



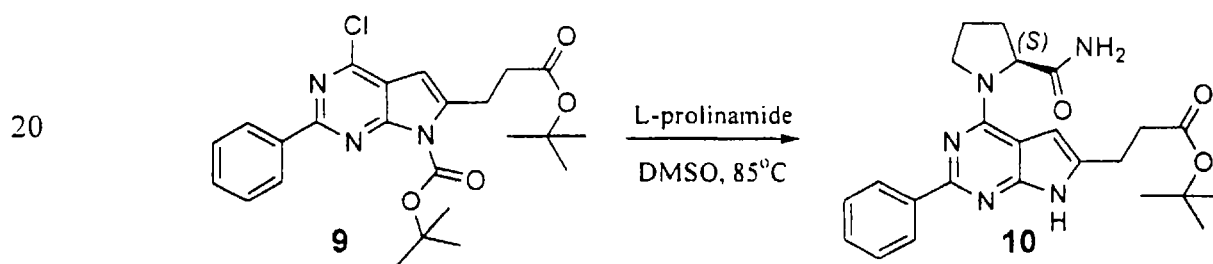
Aldehyde **7** (600mg, 1.7mmol) was dissolved in dry THF (20ml) and cooled to 0°C under argon. To this was added a 0°C solution of (tert-butoxycarbonylmethylene)-triphenylphosphorane (694mg, 1.8mmol) in 10ml of dry THF dropwise through a cannula. After 3h the mixture was concentrated and purified by triturating with ethanol to give 565mg (73%) of a white solid (**8**). $^1\text{HNMR}$ (CDCl_3) δ 1.58 (s, 9H), 1.79 (s, 9H), 6.46 (d, 1H), 6.95 (s, 1H), 7.48 (m, 3H), 8.09 (d, 1H), 8.56 (m, 2H).



A solution of compound **8** (565mg 1.2mmol) in 5ml THF was diluted to 100ml with EtOAc. After adding 600mg of catalyst (5% wt Pd, 50% H₂O) and purging with argon, the mixture was hydrogenated under atmospheric pressure. After 8h the mixture was filtered, concentrated and purified with flash chromatography (10% EtOAc in hexane) to isolate 200mg (35%) of **9** as a clear oil that crystallized upon standing. ¹HNMR (CDCl₃) δ 1.42 (s, 9H), 1.75 (s, 9H), 2.65 (t, 2H), 3.32 (t, 2H), 6.41 (s, 1H) 7.45 (m, 3H), 8.51 (m, 2H).

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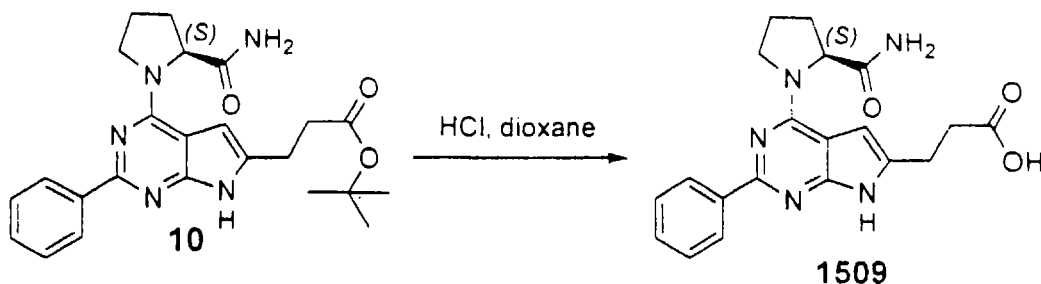


Aryl chloride **9** (200mg, 0.44mmol), DMSO (10ml) and L-prolinamide (440mg, 4.4mmol) were combined and heated to 85°C under argon. After 14 hours the mixture is cooled to room temperature and partitioned between water and ethyl acetate. The layers were separated and the aqueous layer washed with EtOAc (3x). The combined organic layers were thoroughly washed with water (3x), brine, dried over MgSO₄, filtered and concentrated to give **10** as a yellow film which was purified by flash chromatography (2.5% MeOH in CH₂Cl₂). 185mg (97%). MS (ES): 435.8 (M⁺+1).

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Ester **10** (30mg, mmol) in 5ml dioxane was hydrolyzed by adding 0.5ml concentrated HCl. After 3 hours the mixture was concentrated in vacuo and recrystallized in EtOH/ EtOAc to obtain **1509** as a white solid (20mg, 61%). MS (ES): 380 (M⁺+1).

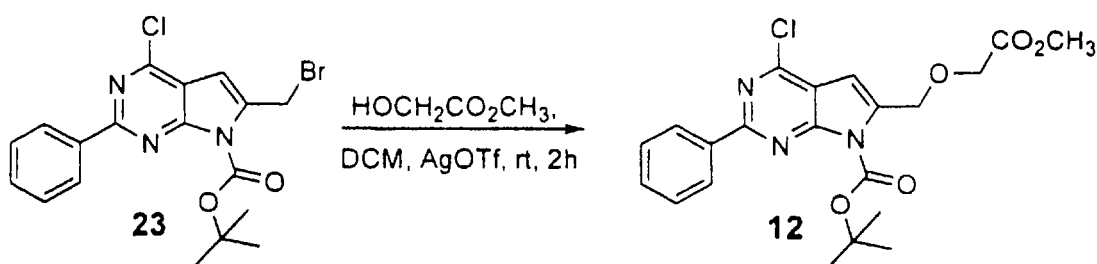
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Example 26: Synthesis of [N-(2-phenyl-6-aminocarbonyl methoxymethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(L)-prolinamide (**1510**)

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Compound **1510** was obtained using precursor compound **23** of synthesis scheme IX to obtain:

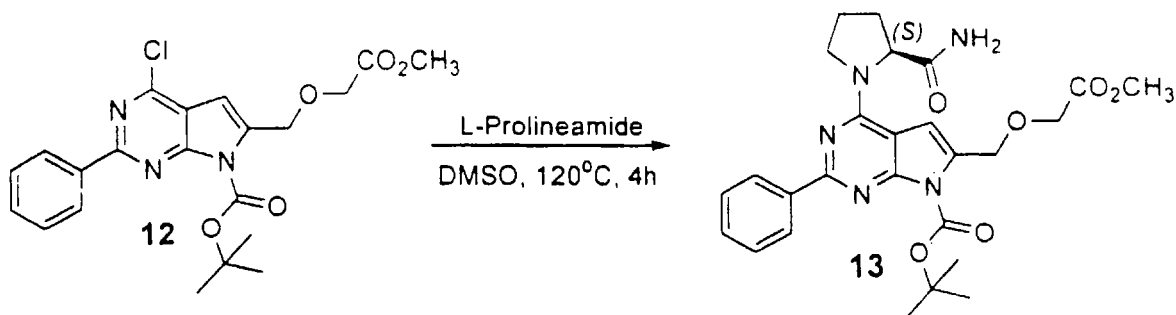
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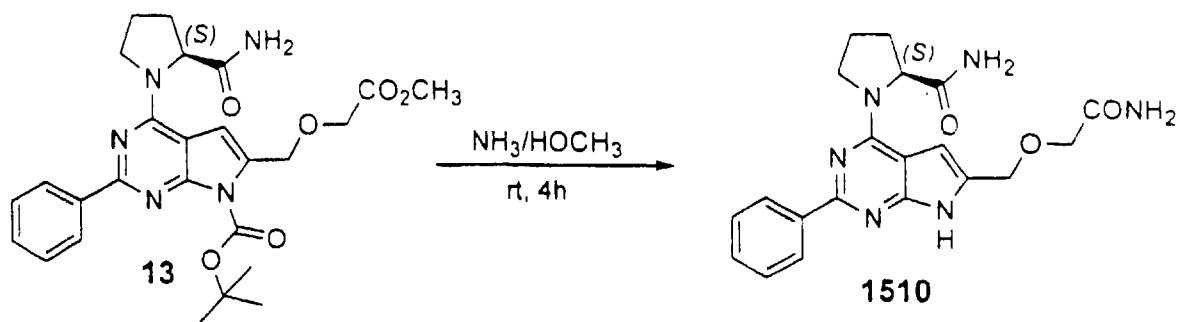
Bromide **23** (1.27g, 3mmol) and molecular sieve (5g) are stirred in anhydrous methyl glycolate (5.8g, 60mmol) and DCM (40mL). The solution is treated with AgOTf under N₂ and allowed to stir for 3h. The solid is removed by filtration and washed with DCM (2x20mL). The filtrate is concentrated in vacuo. The residue is

redissolved in DCM (80mL). The resulted solution is then washed with water, saturated NaHCO₃ solution and brine, dried over MgSO₄, filtered and concentrated to give 1.35g (99%) off white solid (**12**). ¹H-NMR (CDCl₃) δ 1.75 (s, 9H), 3.80 (s, 3H), 5.0 (s, 2H), 6.78 (s, 1H), 7.47 (m, 3H), 8.52 (m, 2H).



Aryl chloride **12** (177mg, 0.41mmol), DMSO (10mL), L-prolinamide (466mg, 4mmol) and NaHCO₃ (500mg) are combined and heated to 120°C under nitrogen. After 4h, the reaction is cooled to room temperature and diluted with water (60ml). The resulted slurry is extracted with DCM (5x30mL). The combined organic layers are washed with saturated NaHCO₃ solution and brine, dried over MgSO₄, filtered and concentrated to give brown solid. Pure product (154mg, 92%) is obtained after flash column as white solid (**13**). ¹H-NMR (CDCl₃) δ 2.15 (m, 3H), 2.52 (m, 1H), 3.55 (s, 3H), 4.58 (s, 2H), 5.08 (s, 1H), 5.85 (brs, 1H), 6.48 (s, 1H), 7.08 (brs, 1H), 7.42 (m, 3H), 8.40 (m, 2H), 10.58 (brs, 1H); MS (ES): 410.1 (M⁺+1).

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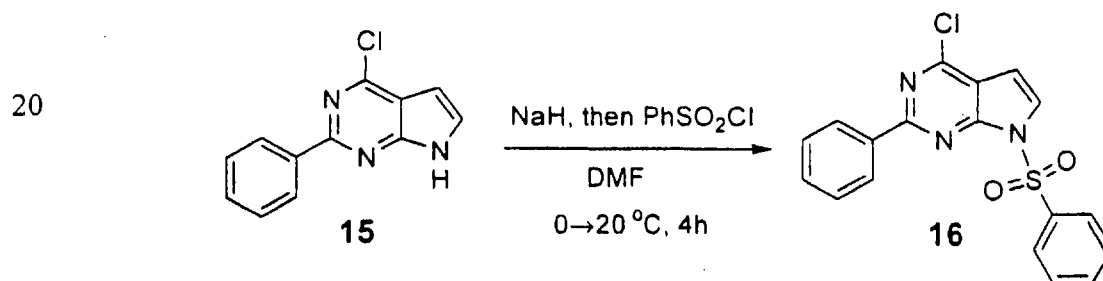


Methyl ester **13** (124mg, 0.3mmol) is dissolved in HOCH_3 (15mL). Ammonia is bubbled through the solution for 0.5h. The reaction mixture is then stirred for another 3h at rt. After removal of solvent 111mg of a white solid (**1510**, 93%) is obtained. $^1\text{H-NMR}$ (CDCl_3) δ 1.82 (m, 3H), 2.20 (m, 1H), 2.80 (m, 1H), 3.10 (m, 1H), 3.63 (dd, 2H, $J_1=13.8\text{Hz}$, $J_2=19.4\text{Hz}$), 3.87 (m, 1H), 4.07 (m, 1H), 4.97 (m, 1H), 5.96 (m, 2H), 6.35 (s, 1H), 6.86 (brs, 1H), 7.11 (brs, 1H), 7.37 (m, 3H), 8.28 (m, 2H), 11.46 (brs, 1H); MS (ES): 394.8 ($\text{M}^+ + 1$).

Example 27: Synthesis of [4-(2-Carbamoylpyrrolidin-1-yl)-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid] (**1511**)

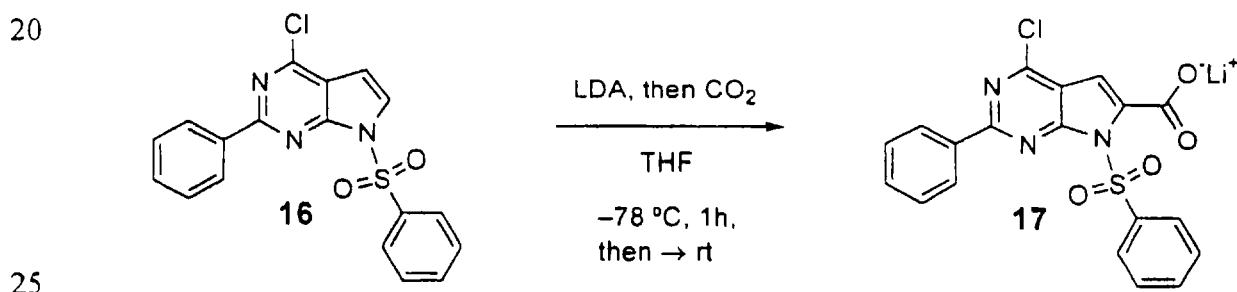
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Compound **1511** was synthesized using precursor compound **15** of synthesis scheme VII to obtain:



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To a suspension of sodium hydride (780mg of a 60% oil suspension, 19.5mmol) in dry DMF (20mL), cooled by an ice/water bath, under nitrogen, is added a solution of the pyrrolopyrimidine **15** (2.00g, 7.52mmol) in DMF (10mL) over 5 min. After 15 min, benzenesulfonyl chloride (1.2mL, 9.40mmol) is added, then the cooling bath is removed. After 4h, the reaction mixture is poured into a mixture of ice and sat. NaHCO₃ sol., the precipitated solid is filtered off and triturated with acetone (3) and methanol (2), yielding 2.37g of a beige solid. This solid (**16**) contains approx. 10mol-% DMF (based on that 83% yield) and can be used in the next step; a pure sample can be obtained by chromatography on silica gel using acetone as eluent. ¹H-NMR (CDCl₃): δ 6.70 (d, J = 4.2Hz, 1H), 7.47-7.68 (m, 6H), 7.76 (d, J = 4.2Hz, 1H), 8.24-8.32 (m, 2H), 8.48-8.56 (m, 2H); IR (solid): ν = 3146 cm⁻¹, 1585, 1539, 1506, 1450, 1417, 1386, 1370, 1186, 1176, 1154, 1111, 1015, 919, 726, 683, 616, 607; MS (ES): 372/370 (MH⁺); mp = 226-227 °C.



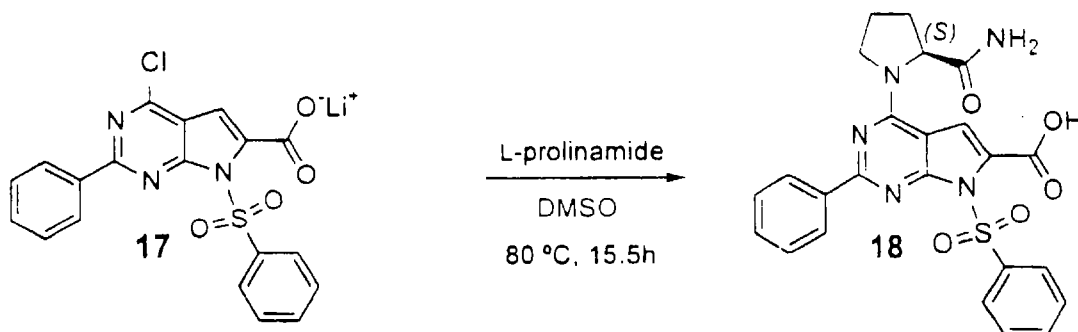
To a solution of the N-sulfonyl compound **16** (337mg, 0.911mmol) in dry THF (34mL), cooled by dry ice/acetone, is added LDA·THF (1.0mL, 1.5M solution in cyclohexane, 1.5mmol). After 45min, carbon dioxide is bubbled into the solution for 5min, then the cooling bath is removed. When the solution has reached ambient temp., the solvents are evaporated, yielding 398mg of the salt **17**, containing 0.5 equiv. of (iPr)₂NCO₂Li, as yellow solid. The

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salt is used without purification in the next step. $^1\text{H-NMR}$ ($\text{D}_2\text{-DMSO}$): δ = 6.44 (s, 1H), 7.50-7.75 (m, 6H), 8.33-8.40 (m, 2H), 8.53 (dd, J = 8.0, 1.6Hz, 2H).

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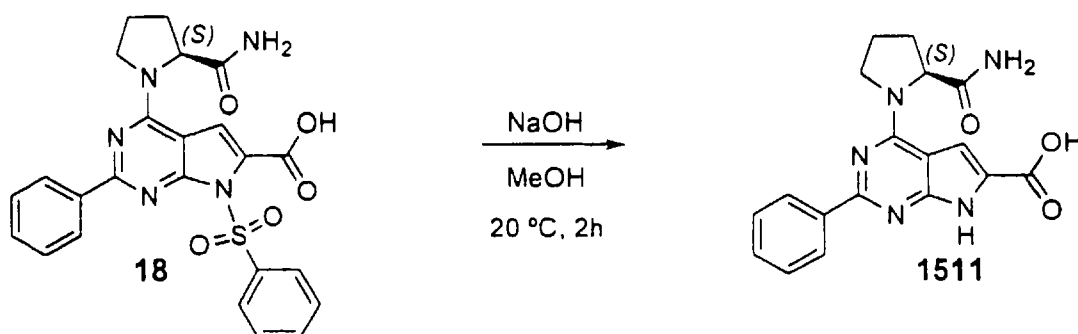
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A solution of the lithium salt **17** (50mg) and L-prolinamide (122mg, 1.07mmol) in DMSO (1.5mL) is heated under nitrogen to 80 °C for 15.5h. 4% aq. acetic acid (10mL) is added to the cooled solution, and the mixture is extracted with EtOAc (5'10mL). The combined organic layers are washed with 4% aq. acetic acid (10mL), water (10mL) and brine (10mL) and are dried over MgSO_4 . Filtration and concentration gives 40mg of **18** as a yellowish solid, which is used without purification in the next step. $^1\text{H-NMR}$ (CD_3OD): δ = 1.95-2.36 (m, 4H), 3.85-3.95 (m, 1H), 3.95-4.17 (m, 1H), 4.72 (brs, 1H), 7.14 (s, 1H), 7.35-7.45 (m, 3H), 7.45-7.70 (m, 3H), 8.33-8.50 (m, 4H).

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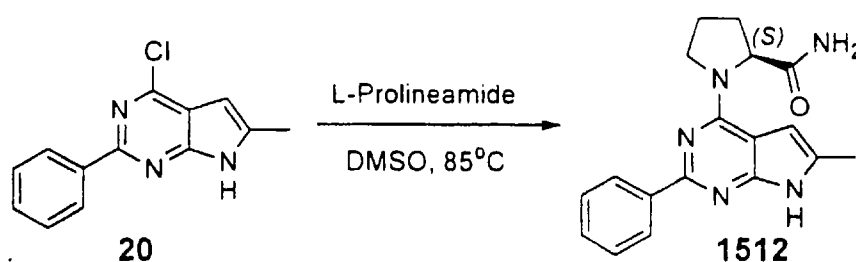
A solution of sodium hydroxide in methanol (1.5mL, 5M, 7.5mmol) is added to a solution of the pyrrolopyrimidine **18** (40mg, 0.081mmol) in methanol (2mL). After 2h, the pH is adjusted to 5, most of the methanol is evaporated, the mixture is extracted with EtOAc (5 10mL), the combined organic layers are washed with brine and dried over MgSO₄. Filtration and concentration yields 24mg of a pale yellow solid, which is triturated with toluene/EtOAc/MeOH to yield 15.6mg (55%) of the acid **1511** as slightly yellowish solid. ¹H-NMR (CD₃OD): δ = 2.05-2.20 (m, 4H), 3.95-4.10 (m, 1H), 4.15-4.25 (m, 1H), 4.85 (brs, 1H), 7.14 (s, 1H), 7.35-7.42 (m, 3H), 8.38-8.45 (m, 2H); IR (solid): ν = 3192 cm⁻¹, 2964, 2923, 2877, 1682, 1614, 1567, 1531, 1454, 1374, 1352, 1295, 1262, 1190, 974, 754, 700; MS (ES): 352 (M⁺+1); m.p. = 220 °C (decomp.).

15

Example 28: Synthesis of 1-(6-methyl-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-(S)-pyrrolidine-2-carboxylic acid amide (**1512**)

20 Compound **1512** was synthesized by the following steps:

25



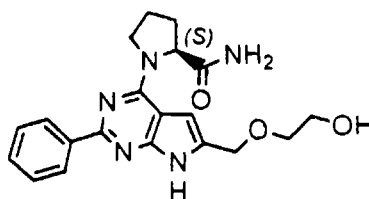
30

Aryl chloride **20** (3g, 10.7 mmol), DMSO (50ml) and (S)-prolinamide were combined and heated to 85°C under argon. After stirring overnight (14hrs), the mixture was cooled to room

temperature and poured into 800ml of water. This was extracted with three 200ml portions of EtOAc. The combined organic layers were thoroughly washed with water (3 x 300 ml), brine, dried over MgSO_4 , filtered and concentrated to give a dark brown solid. The solid was recrystallized twice from EtOAc to yield 1.95g (57%) of a tan solid (**1512**). $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 1.8-2.2 (m, 4H), 2.3 (s, 3H), 3.8 (m, 1H), 4.0 (m, 1H), 4.6 (d, 1H) 6.2 (s, 1H), 6.9 (s, 1H), 7.2 (m, 3H), 7.3 (s, 1H), 8.4 (m, 2H), 11.5 (s, 1H); MS (ES): 322 ($\text{M}^+ + 1$)

Example 29: Synthesis of 1-[6-(2-Hydroxy-ethoxymethyl)-2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pyrrolidine-2-carboxylic acid amide (**1513**)

Compound **1513** was synthesized in a manner similar to that of Example 17 using synthesis scheme IX with L-prolineamide and ethane-1,2-diol to obtain:

**1513**

MS (ES): 382 ($\text{M}^+ + 1$).

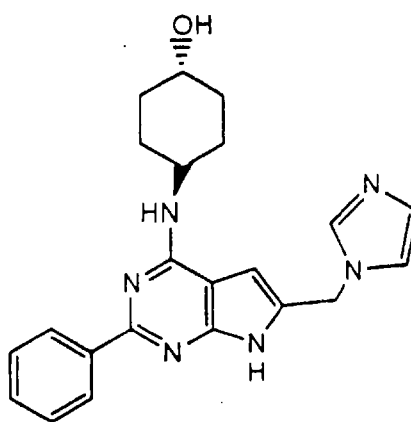
Example 30: Synthesis of 4-(6-Imidazol-1-ylmethyl-2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-cyclohexanol (1514).

5

Compound **1514** was synthesized in a manner similar to that of Example 17 using synthesis scheme IX with N-6 amino cyclohexanol and imidazole to obtain:

10

15



20

1514

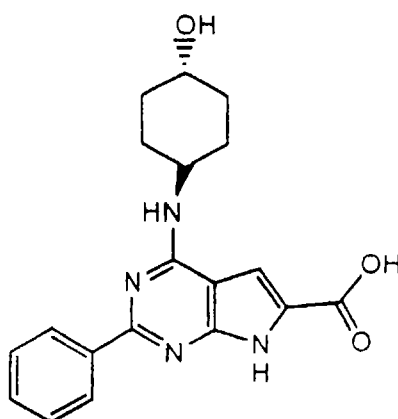
MS (ES): 389 (M⁺+1)

25

Example 31: Synthesis of 4-(4-Hydroxy-cyclohexylamino)-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid (1515)

30

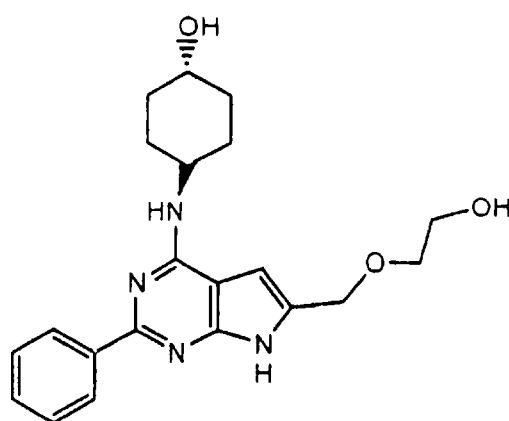
Compound **1515** was synthesized in a manner similar to that of Example 27 using synthesis scheme IX with N-6 amino cyclohexanol to obtain:

**1515**

MS (ES): 353 ($M^+ + 1$)

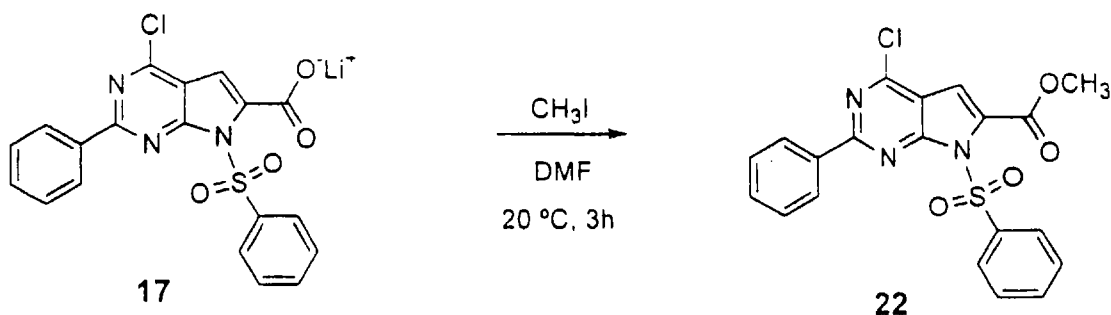
Example 32: Synthesis of 4-[6-(2-Hydroxy-ethoxymethyl)-2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-cyclohexanol (1516)

Compound **1516** was synthesized in a manner similar to that of Compound **1513** using synthesis scheme IX with N-6 amino cyclohexanol to obtain:

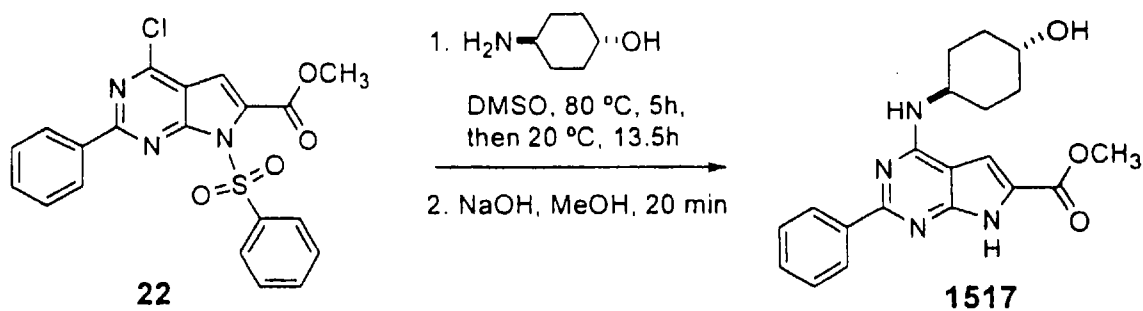
**1516**

MS (ES): 383 ($M^+ + 1$)

Example 33: Synthesis of 4-(4-Hydroxy-cyclohexylamino)-
-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid methyl
ester (1517)



A solution of the lithium salt **17** (0.13mmol) in dry DMF (4mL) is stirred with methyl iodide (0.1mL, 1.6mmol) at 20°C under argon for 3h. DMF is evaporated, and aqueous ammonium chloride solution is added (15mL). The mixture is extracted with EtOAc (3'15mL), the combined organic layers are washed with water (2'10mL) and brine (10mL) and are dried over MgSO_4 . Filtration and concentration gives 21mg (38%) of the methyl ester **22**.

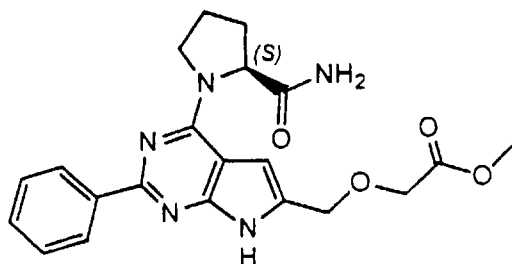


A solution of the methyl ester **22** (24.5mg, 0.057mmol) and 4-*trans*-aminocyclohexanol (66mg, 0.57mmol) in DMSO (1.5mL) is heated under nitrogen to 80 °C for 5h, then the heating is stopped, and stirring at 20 °C is continued for 13.5h. 4% aq. acetic acid (10mL) is added to the cooled solution, and the mixture is extracted with EtOAc (3x10mL). The combined organic layers are washed with 4% aq. acetic acid (10mL), water (10mL) 2N NaOH (10mL), water (10mL), and brine (10mL) and are dried over MgSO₄. To a solution of the crude material obtained after filtration and concentration (1H NMR indicates about 50% removal of the benzenesulfonyl group) in THF (2mL) is added a solution of NaOH in MeOH (0.5mL of 5M solution, 2.5mmol) at ambient temperature. After 20min, water and sat. NaHCO₃ solution (5mL each) are added, and the mixture is extracted with EtOAc (4x15mL). The combined organic layers are washed with 2N NaOH (10mL), water (10mL), and brine (10mL) and are dried over MgSO₄. Chromatography of the crude material obtained after filtration and concentration on silica gel, eluting with hexanes/EtOAc 1:1 @ 1:2 yields 8.6mg (41%) of **1517** as a white solid, mp. 225-227 °C. ¹H-NMR (CD₃OD): δ = 1.38-1.62 (m, 4H), 1.95-2.10 (m, 2H), 2.10-2.25 (m, 2H), 3.55-3.70 (m, 1H), 3.91 (s, 3H), 4.20-4.35 (m, 1H), 7.32 (s, 1H), 7.35-7.47 (m, 3H), 8.35-8.42 (m, 2H); IR (solid): ν = 3352 cm⁻¹, 3064, 2935, 2860, 1701, 1605, 1588, 1574, 1534, 1447, 1386, 1333, 1263, 1206, 1164, 1074, 938, 756, 705; MS (ES): 367 (MH⁺).

Example 34: Synthesis of [4-(2-Carbamoyl-pyrrolidin-1-yl)-2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-6-ylmethoxy]-acetic acid methyl ester (**1518**)

5 Compound **1518** was synthesized in a manner similar to example 26 using precursor compound **12** to obtain:

10



15

1518

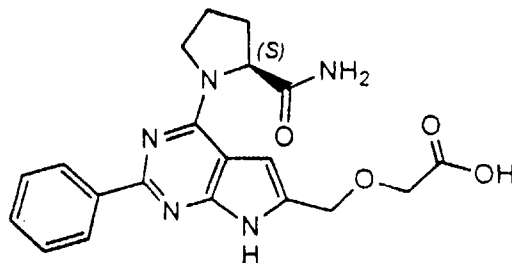
MS (ES): 410 (M⁺+1)

Example 35: Synthesis of [4-(2-Carbamoyl-pyrrolidin-1-yl)-2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-6-ylmethoxy]-acetic acid (**1519**)

20

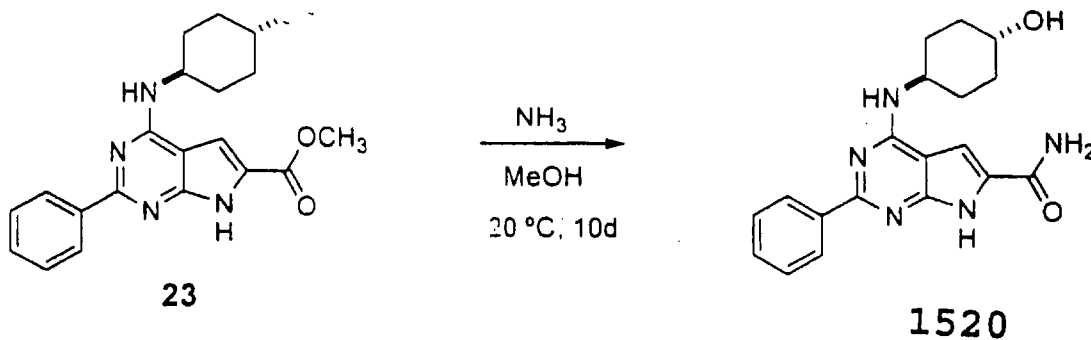
25

Compound **1519** was synthesized in a manner similar to compound **1518** wherein the methyl ester group was hydrolyzed with a base to obtain:

**1519**

MS : 396 ($M^+ + 1$)

Example 2: Synthesis of 4-(4-Hydroxy-cyclohexylamino)-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid amide (**1520**)



Gaseous ammonia is condensed into a solution of the pyrrolopyrimidine **23** (7.8mg, 0.021mmol) in methanol (6mL), cooled by dry ice/acetone, until a total volume of 12mL is reached. After stirring for 10d at 20 °C, the solvents are evaporated, and the residue is purified by preparative TLC on silica gel, eluting with 5% MeOH in CH₂Cl₂. The material thus obtained is triturated with ether to yield 6.5mg (88%) of the amide **1520** as white solid, mp. 210-220 °C (decomp.). ¹H-NMR (CD₃OD): δ = 1.40-1.60 (m, 4H), 2.00-2.15 (m, 2H), 2.15-2.25 (m, 2H), 3.55-3.70 (m, 1H), 4.20-4.35 (m, 1H), 7.16 (s, 1H), 7.35-7.47 (m, 3H), 8.34-8.40 (m, 2H); IR (solid): ν = 3358 cm⁻¹, 3064, 3025, 2964, 2924, 2853, 1652, 1593, 1539, 1493, 1452, 1374, 1326, 1251, 1197, 1113, 1074, 1028, 751, 699; MS (ES): 352 (MH⁺).

15

Activity of Compounds

Adenosine 1 (A₁) receptor subtype saturation and competition radio ligand binding were carried out for compounds **1505**, **1506**, **1507**, **1508**, **1509**, **1510**, **1511**, **1512**, **1513**, **1514**, **1516**, **1517**, **1518**, **1519**, and **1520** as described herein and *inter alia*, on pages 152-153 of this specification. All of the above-referenced compounds equaled or surpassed the A₁ receptor binding affinity of reference compounds **1318** or **1319** as described herein and, *inter alia*, in Table 13, on page 171 of the specification.

25

The water solubilities of the above compounds listed in Table 18 are expected to be better than reference compounds **1318** or

1319 due to their cLogP values, which were calculated using the computer program CS ChemDraw, ChemDraw Ultra ver. 6.0 ©1999 as provided by CambridgeSoft Corporation, 100 Cambridge Park Drive, Cambridge, MA 02140.

5

The compounds specific to the A₂ receptor listed in Table 18 had lower cLogP values, between about 1.5 to about 3.4, as compared to reference compounds 1318 or 1319 with a cLogP value about 3.8. It was not predicted that the more polar A₂ receptor compounds listed in Table 18 having lower cLogP values than the reference compounds 1318 or 1319 would still retain the potency and A₁ receptor binding selectivity as compared to those reference compounds.

10

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20

25

Table 18

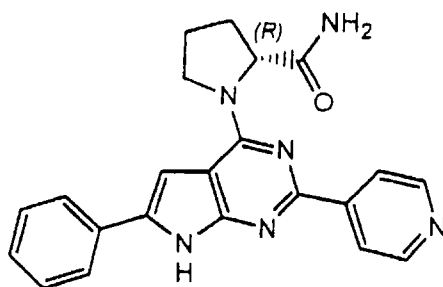
Compound	cLogP
1505	4.1
1506	3.0
1507	2.88
1508	2.1
1509	2.9
1510	1.5
1511	2.7
1512	3.37
1513	2.4
1514	2.8
1515	3.1
1516	2.8
1517	3.4
1518	2.4
1519	2.2
1520	2.4

Pages 288-293 relate to additional compounds specific to A_{2a} receptor

This invention provides a compound having the structure:

5

10



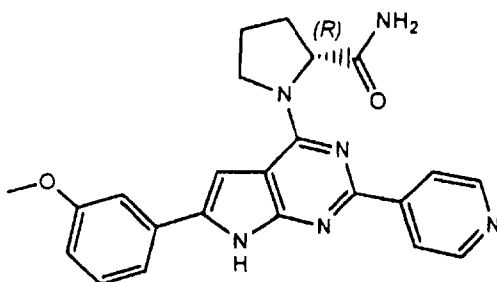
15

1609

This invention also provides a compound having the structure:

20

25



1610

In a further embodiment the invention provides a method for treating a disease associated with A_{2a} adenosine receptor in a subject, comprising administering to the subject a

30

therapeutically effective amount of compounds 1609 or 1610.

The invention also provides the above method, wherein the subject is a mammal.

5

The invention further provides the above method, wherein the mammal is a human.

10 The invention also provides the method for treating a disease associated with A_{2a} adenosine receptor in a subject, wherein the A_{2a} adenosine receptor is associated with locomotor activity, vasodilation, platelet inhibition, neutrophil superoxide generation, cognitive disorder, senile dementia, or Parkinson's disease.

15

The invention provides the above method, wherein the compound treats the diseases by stimulating adenylate cyclase.

20 The invention also provides a water-soluble prodrug of the compound 1609 or 1610, wherein the water-soluble prodrug is metabolized in vivo to an active drug to selectively inhibit an A_{2a} adenosine receptor.

25 The invention also provides a water-soluble prodrug of the compound 1609 or 1610, wherein the prodrug is metabolized in vivo by esterase catalyzed hydrolysis.

30 The invention also provides a pharmaceutical composition comprising the water-soluble prodrug of the compound 1609 or 1610, and a pharmaceutically acceptable carrier.

The invention also provides a method for inhibiting the activity of an A_{2a} adenosine receptor in a cell, which comprises contacting the cell with compound 1609 or 1610.

5 The invention also provides a method for inhibiting the activity of an A_{2a} adenosine receptor in a cell, which comprises contacting the cell with compound 1609 or 1610, wherein the compound is an antagonist of said A_{2a} adenosine receptor.

10 The invention also provides the above method, wherein the cell is a human cell.

The invention also provides the above method, wherein the cell is a human cell and the compound is an antagonist of A_{2a} adenosine receptors.

15 The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of the compound 1609 or 1610 and a pharmaceutically acceptable carrier.

20 The invention also provides the above pharmaceutical composition, wherein the therapeutically effective amount is effective to treat Parkinson's disease and diseases associated with locomotor activity, vasodilation, platelet inhibition, neutrophil superoxide generation, cognitive disorder, or senile
25 dementia.

The invention also provides the above pharmaceutical composition, wherein the pharmaceutical composition is an ophthalmic formulation.

30 The invention also provides the above pharmaceutical

composition, wherein the pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.

5 The invention also provides the above pharmaceutical composition, wherein the pharmaceutical composition is a systemic formulation.

10 The invention also provides the above pharmaceutical composition, wherein the pharmaceutical composition is a surgical irrigating solution.

The invention also provides a combination therapy for Parkinson's disease, comprising the compounds 1609 or 1610, and any of the dopamine enhancers.

15 The invention also provides a combination therapy for cancer, comprising the compound 1609 or 1610, and any of the cytotoxic agents.

20 The invention also provides a combination therapy for glaucoma, comprising the compound 1609 or 1610, and a prostaglandin agonist, a muscrinic agonist, or a β -2 antagonist.

25 The invention also provides a packaged pharmaceutical composition for treating a disease associated with A_{2a} adenosine receptor in a subject, comprising:

(a) a container holding a therapeutically effective amount of the compound 1609 or 1610; and

30

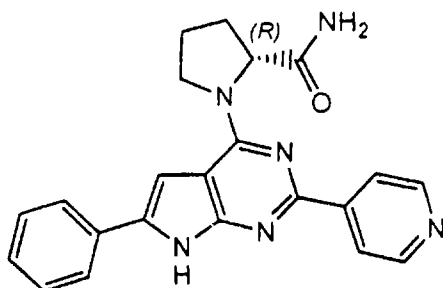
(b) instructions for using the compound for treating said disease in a subject.

Exemplification

5 **Example 41:** Synthesis of 1-(6-Phenyl-2-pyridin-4-yl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-pyrrolidine-2-carboxylic acid amide (1609).

10 Compound 1609 was synthesized by reacting L-prolinamide with the appropriate chloride intermediate described in synthesis scheme II on page 82 to obtain:

15



1609

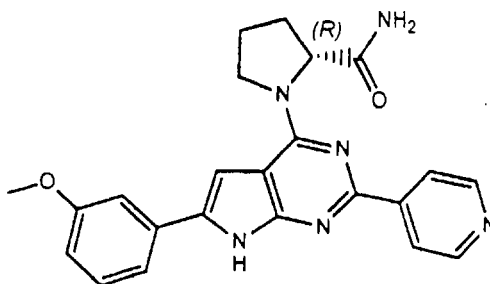
20 ¹H-NMR (d₆-DMSO) δ 1.95-2.15 (m, 4H), 4.00 (brs, 1H), 4.15 (brs, 1H), 4.72 (brs, 1H), 6.90 (brs, 1H), 7.19 (brs, 1H), 7.30 (t, 1H, J = 7.0Hz), 7.44 (t, 2H, J = 7.0Hz), 7.59 (s, 1H), 7.92 (brs, 2H), 8.26 (d, 2H, J = 6.2Hz), 8.65 (d, 2H, J = 6.2Hz); MS (ES): 384.9 (M⁺+1); Mpt = 280-316°C (decomp.).

25

Example 42: Synthesis of 1-[6-(3-Methoxy-phenyl)-2-pyridin-4-yl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pyrrolidine-2-carboxylic acid amide (1610).

5 Compound 1610 was synthesized by reacting L-prolinamide with the appropriate chloride intermediate described in synthesis scheme II on page 82 to obtain:

10



15

1610

$^1\text{H-NMR}$ (d_6 -DMSO) δ 2.07 (m, 4H), 3.85 (s, 3H), 4.02 (m, 1H), 4.17 (m, 1H), 4.75 (m, 1H), 6.89 (m, 1H), 7.00 (s, 1H), 7.23 (s, 1H), 7.35 (t, 1H, $J=8.2\text{Hz}$), 7.53 (s, 2H), 7.60 (s, 1H), 8.28 (d, 2H, $J=5.8\text{Hz}$), 8.67 (d, 2H, $J=5.8\text{Hz}$), 12.37 (s, 1H); MS (ES): 415.0 ($M^+ + 1$).

20

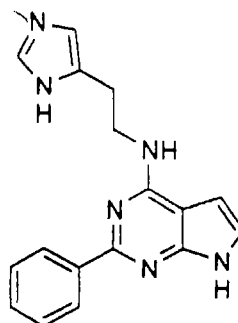
Activity of Compounds

Adenosine 2a (A_{2a}) receptor subtype competition radio ligand binding were carried out for compounds 1609 and 1610 as described herein and *inter alia*, on page 153 of this specification. Compounds 1609 and 1610 were found have A_{2a} receptor binding affinity and selectivity.

25

Pages 294-300 relate to additional compounds specific to A₃ receptor

This invention also provides a compound having the structure:



1720

In a further embodiment the invention provides a method for inhibiting the activity of an A₃ adenosine receptor in a cell, which comprises contacting the cell with the compound 1720.

In a further embodiment the invention provides a method for inhibiting the activity of an A₃ adenosine receptor in a cell, wherein the compound is an antagonist of the A₃ adenosine receptor.

In a further embodiment the invention provides the above method for inhibiting the activity of an A₃ adenosine receptor in a cell, wherein the cell is human cell.

In a further embodiment the invention provides the above method for inhibiting the activity of an A₃ adenosine receptor in a cell, wherein the cell is a human cell and wherein the compound

is an antagonist of A₃ adenosine receptors.

5 In a further embodiment the invention provides a method of treating damage to the eye of a subject which comprises administering to the subject a composition comprising a therapeutically effective amount of the compound 1720.

10 In a further embodiment the invention provides the above method, wherein the damage comprises retinal or optic nerve head damage.

15 In a further embodiment the invention provides a therapy for glaucoma, comprising administering to a subject a therapeutically effective amount of the compound 1720.

20 In a further embodiment the invention provides a therapy for glaucoma comprising one or more adenosine receptor antagonists, preferably comprising an adenosine receptor A₃ antagonist (preferably an N-6 substituted 7-deazapurine, most preferably [2-(3H-Imidazol-4-yl)-ethyl]-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine).

25 In an alternative embodiment the invention provides a combination therapy for glaucoma comprising an adenosine receptor A₃ antagonist (preferably an N-6 substituted 7-deazapurine, most preferably [2-(3H-Imidazol-4-yl)-ethyl]-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine)) and one or more other compounds selected from the group consisting of beta adrenoceptor antagonists (i.e. beta adrenergic antagonists or

b-blockers) (e.g. timolol maleate, betaxolol, carteolol, levobunolol, metipranolol, L-653328 (the acetate ester of L-652698), beta 1 adrenoceptor antagonists), alpha-2 adrenoceptor agonists (e.g. apraclonidine, brimonidine, AGN-195795, AGN-190837 (an analog of Bay-a-6781)), carbonic anhydrase inhibitors (brinzolamide, dorzolamide, MK-927 (an inhibitor of the human carbonic anhydrase II isoenzyme), inhibitors of carbonic anhydrase IV isoenzyme), cholinergic agonists (e.g. muscarinic cholinergic agonists, carbachol, pilocarpine HCl, pilocarpine nitrate, pilocarpine, pilocarpine prodrugs (e.g. DD-22A)), prostaglandins and prostaglandin receptor agonists (e.g. latanoprost, unoprostone isopropyl, PGF2 alpha agonists, prostanoid-selective FP receptor agonists, PG agonists such as the hypotensive prostamides), angiotensin converting enzyme (ACE) inhibitors (e.g. Spirapril, spiraprilat), AMPA receptor antagonists, 5-HT agonists (e.g. a selective 5-HT 1A receptor agonist such as MKC-242 (5-3-(((2S)-1,4-benzodioxan-2-ylmethyl)amino)propoxy-1,3-benzodioxole HCl)), angiogenesis inhibitors (e.g. the steroid anecortave), NMDA antagonists (e.g. HU-211, memantine, the cannabinoid NMDA-receptor agonist dexamabinol, prodrugs and analogs of dexamabinol, NR2B-selective antagonists (e.g. eliprodil (SL-82.0715)), renin inhibitors (e.g. CGP-38560, SR-43845), cannabinoid receptor agonists (e.g. tetrahydrocannabinol (THC) and THC analogs, selective CB2 cannabinoid receptor agonists (e.g. L-768242, L-759787), compounds such as anandamide that bind to both brain-specific CB1 receptors and peripheral CB2 receptors), angiotensin receptor antagonists (e.g., angiotensin II receptor antagonists (e.g. CS-088), selective angiotensin II AT-I

receptor antagonists, such as losartan potassium, hydrochlorothiazide (HCTZ), somatostatin agonists (e.g. the non-peptide somatostatin agonist NNC-26-9100), glucocorticoid antagonists, mast cell degranulation inhibitors (e.g. nedocromil), alpha-adrenergic receptor blockers (e.g. dapiprazole, alpha-2 adrenoceptor antagonists, alpha 1 adrenoceptor antagonists (e.g. bunazosin)), alpha-2 adrenoceptor antagonists, thromboxane A2 mimetics, protein kinase inhibitors (e.g. H7), prostaglandin F derivatives (e.g. S-1033), prostaglandin-2 alpha antagonists (e.g. PhXA-34), dopamine D1 and 5-HT2 agonists (fenoldopam), nitric-oxide-releasing agents (e.g. NCX-904 or NCX-905, nitric-oxide-releasing derivatives of timolol), 5-HT 2 antagonists (e.g. sarpogrelate), NMDA antagonists (e.g. prodrugs and analogs of dexanabinol), alpha 1 adrenoceptor antagonists (e.g. bunazosin), cyclooxygenase inhibitors (e.g. diclofenac, or the non-steroidal compound nepafenac), inosine, dopamine D2 receptor and alpha 2 adrenoceptor agonists (e.g. talipexole), dopamine D1 receptor antagonist and D2 receptor agonists (e.g. SDZ-GLC-756), vasopressin receptor antagonists (e.g. vasopressin V2 receptor antagonists (e.g. SR-121463)), endothelin antagonists (e.g. TBC-2576), 1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) and related analogs and prodrugs, thyroid hormone receptor ligands (e.g. KB-130015), muscarinic M1 agonists, NMDA-receptor antagonists (e.g. the cannabinoid NMDA-receptor antagonist dexanabinol), PG agonists such as the hypotensive lipids, prostamides, sodium channel blockers, NMDA antagonists, mixed-action ion channel blockers, beta adrenoceptor antagonist and PGF2 alpha agonist

combinations (e.g. latanoprost and timolol), guanylate cyclase activators (e.g. atrial natriuretic peptide (ANP) or non-peptide mimetics, inhibitors of ANP neutral endopeptidase, nitrovasodilators (e.g. nitroglycerin, hydralazine, sodium nitroprusside), endothelin receptor modulators (e.g. ET-1 or non-peptide mimetics, sarafotoxin-S6c), ethacrynic acid, other phenoxyacetic acid analogs (e.g. indacrinone, ticrynafen), actin disrupters (e.g. latrunculin), calcium channel blockers (e.g. verapamil, nifedipine, brovincamine, nivaldipine) and neuroprotective agents.

A combination therapy for glaucoma, comprising the compound of 1702, and one or more compounds selected from the group consisting of beta adrenoceptor antagonists, alpha-2 adrenoceptor agonists, carbonic anhydrase inhibitors, cholinergic agonists and prostaglandin receptor agonists.

In a further embodiment the invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound 1720 and a pharmaceutically acceptable carrier.

In a further embodiment the invention provides a packaged pharmaceutical composition for treating a disease associated with A3 adenosine receptor in a subject, comprising:

- (a) a container holding a therapeutically effective amount of the compound 1720; and
- (b) instructions for using said compound for treating said disease in a subject.

In a further embodiment the invention provides a method of making a composition which comprises the compound 1720, the method comprising admixing the compound 1702 with a suitable carrier.

5

In a further embodiment the invention provides a pharmaceutically acceptable salt of compound 1720, wherein the pharmaceutically acceptable salt contains an anion selected from the group consisting of maleic, fumaric, tartaric, acetate, phosphate and mesylate.

10

Exemplification

Example 43: Synthesis of [2-(3H-Imidazol-4-yl)-ethyl]-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine (1720)

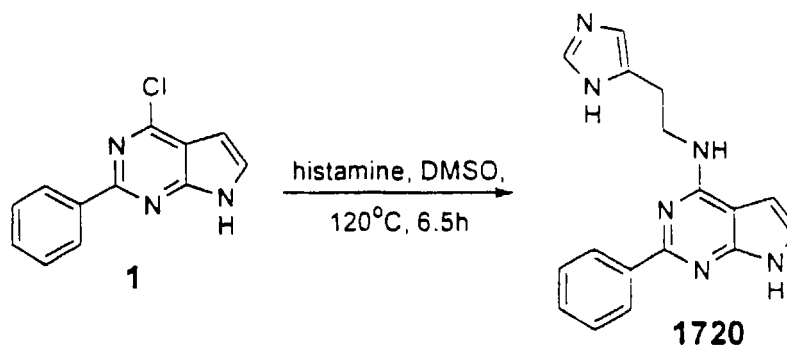
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Compound 1720 was synthesized using precursor compound 1 of synthesis scheme VII to obtain:

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Aryl chloride **1** (400mg, 1.50mmol), DMSO (10mL) and histamine (1.67g, 15.0mmol) are combined and heated to 120°C under nitrogen. After 6.5h, the reaction is cooled to room temperature and partitioned between EtOAc and water. The layers are separated and the aqueous layer is extracted with EtOAc (3x). The combined organic layers are washed with brine (2x), dried over MgSO_4 , filtered and concentrated to yield 494mg of a brown solid. The solid is washed with cold MeOH and recrystallized from MeOH to yield 197mg (43%) of an off white solid (**1720**). $^1\text{H-NMR}$ (CD_3OD) δ 3.05 (t, 2H, $J = 7.0\text{Hz}$), 3.94 (t, 2H, $J = 7.0\text{Hz}$), 6.50 (d, 1H, $J = 3.5\text{Hz}$), 6.88 (brs, 1H), 7.04 (d, 1H, $J = 3.5\text{Hz}$), 7.42 (m, 3H), 7.57 (s, 1H), 8.34 (m, 2H); MS (ES): 305.1 ($\text{M}^+ + 1$); Mpt = 234-235°C.

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Activity of Compounds

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Adenosine 3 (A_3) receptor competition radio ligand binding was carried out for compound 1720 as described herein and *inter alia*, on pages 153-154 of this specification. Compound 1720 was found to have an A_3 receptor binding affinity greater than 10 times that of reference compound 1308 as described herein and, *inter alia*, in Table 13, on page 169 of the specification.

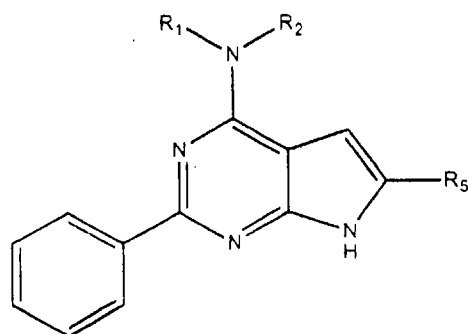
Incorporation by Reference

5 All patents, published patent applications and other references disclosed herein are hereby expressly incorporated herein by reference.

Equivalents

10 Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to specific embodiments of the invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

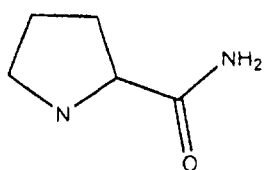
This invention further provides compounds having the formula:



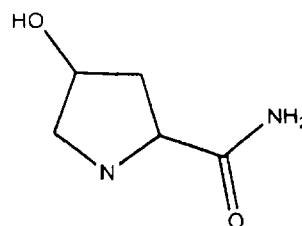
XI

wherein

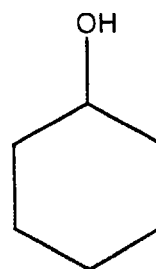
R_1NR_2 together form a ring having the structure:



or



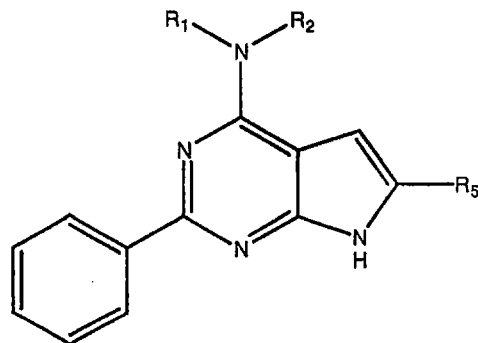
or R_1 is H and R_2 is:



R_5 is H, or substituted or unsubstituted alkyl or alkylaryl.

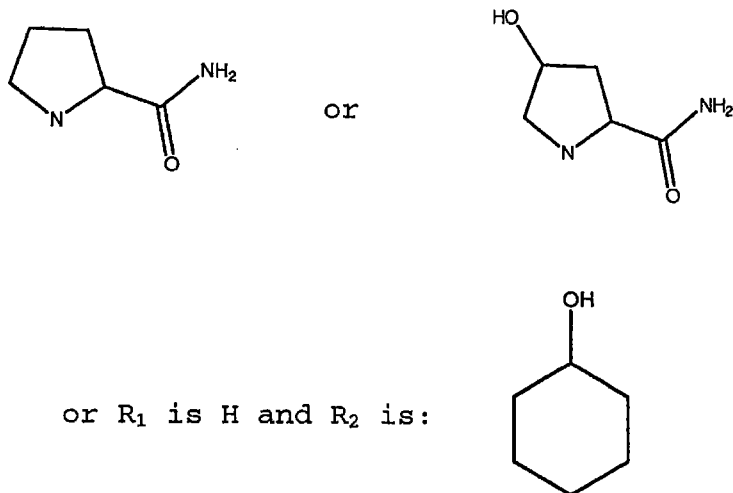
What is claimed is:

1. A compound having the structure:

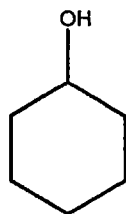


wherein

R₁NR₂ together form a ring having the structure:

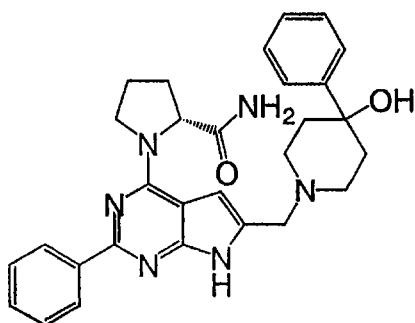


or R₁ is H and R₂ is:

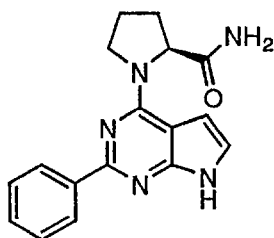


R₅ is H, or substituted or unsubstituted alkyl or alkylaryl.

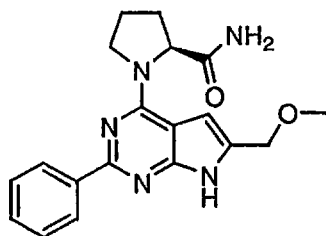
2. The compound of claim 1, having the structure:



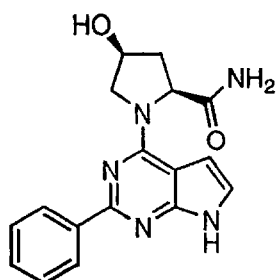
3. The compound of claim 1, having the structure:



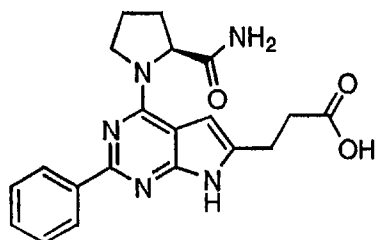
4. The compound of claim 1, having the structure:



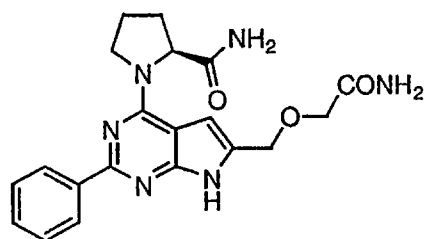
5. The compound of claim 1, having the structure:



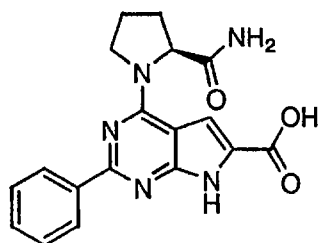
6. The compound of claim 1, having the structure:



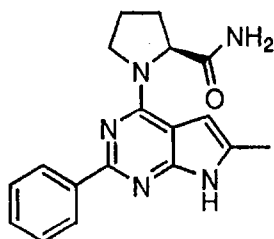
7. The compound of claim 1, having the structure:



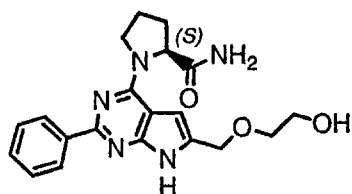
8. The compound of claim 1, having the structure:



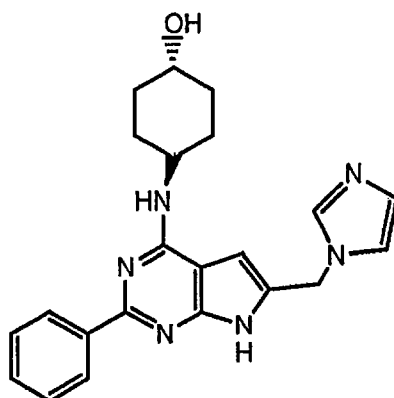
9. The compound of claim 1, having the structure:



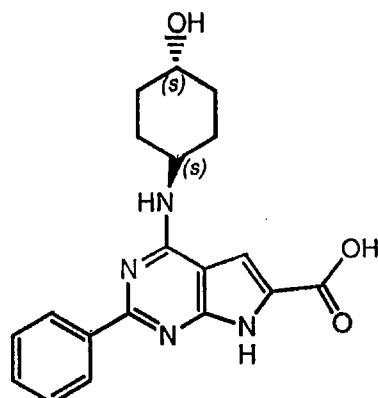
10. The compound of claim 1, having the structure:



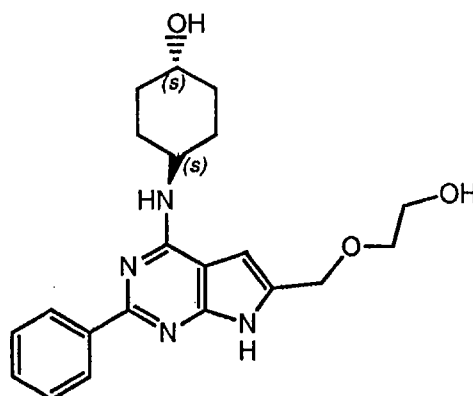
11. The compound of claim 1, having the structure:



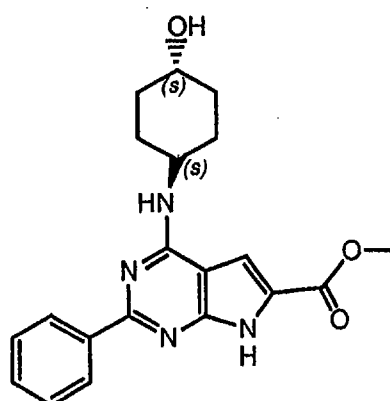
12. The compound of claim 1, having the structure:



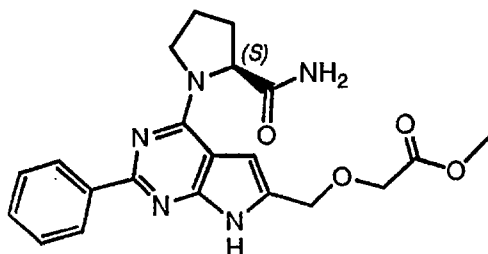
13. The compound of claim 1, having the structure:



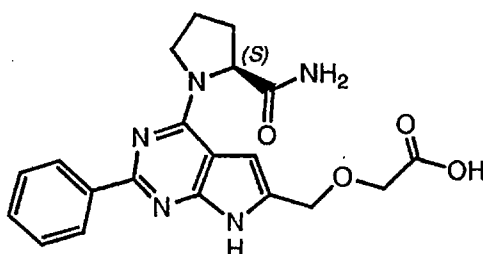
14. The compound of claim 1, having the structure:



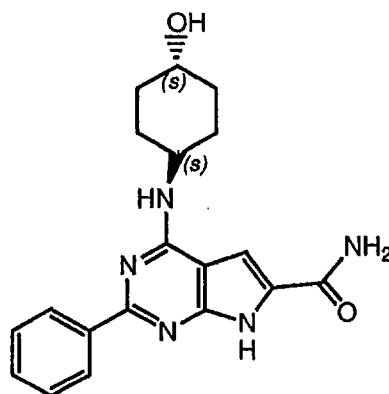
15. The compound of claim 1, having the structure:



16. The compound of claim 1, having the structure:



17. The compound of claim 1, having the structure:



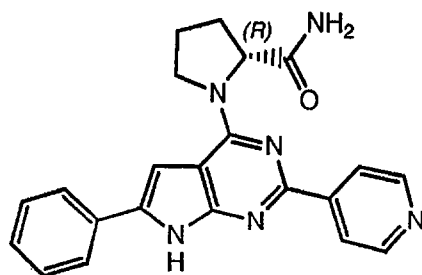
18. A method for treating a disease associated with A₁ adenosine receptor in a subject, comprising administering to the subject a therapeutically effective amount of a compound of claim 1.

19. The method of claim 18, wherein the subject is a mammal.
20. The method of claim 19, wherein the mammal is a human.
21. The method of claim 18, wherein said A₁ adenosine receptor is associated with cognitive disease, renal failure, cardiac arrhythmias, respiratory epithelia, transmitter release, sedation, vasoconstriction, bradycardia, negative cardiac inotropy and dromotropy, bronchoconstriction, neutrophil chemotaxis, reflux condition, or ulcerative condition.
22. A water-soluble prodrug of the compounds of claim 1, wherein the water-soluble prodrug is metabolized in vivo to produce an active drug which selectively inhibits A₁ adenosine receptor.
23. The prodrug of claim 22, wherein said prodrug is metabolized in vivo by esterase catalyzed hydrolysis.
24. A pharmaceutical composition comprising the prodrug of claim 22 and a pharmaceutically acceptable carrier.
25. A method for inhibiting the activity of an A₁ adenosine receptor in a cell, which comprises contacting the cell with a compound of claim 1.
26. The method of claim 25, wherein the compound is an antagonists of the A₁ adenosine receptor.
27. The method of claim 25, wherein the cell is a human cell.

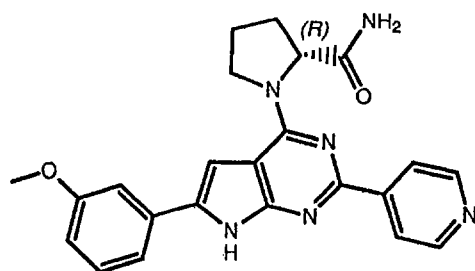
28. The method of claim 27, wherein the compound is an antagonist of A1 adenosine receptors.
29. The method of claim 18, wherein said disease is asthma, chronic obstructive pulmonary disease, allergic rhinitis, or an upper respiratory disorder.
30. The method of claim 29, wherein the subject is human.
31. The method of claim 30, wherein said compound is an antagonist of A1 adenosine receptors.
32. A combination therapy for asthma, comprising the compound of claim 1, and a steroid, β 2 agonist, glucocorticoid, leukotriene antagonist, or an anticholinergic agonist.
33. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1, and a pharmaceutically acceptable carrier.
34. The method of claim 29, wherein said respiratory disorder is asthma, allergic rhinitis, or chronic obstructive pulmonary disease.
35. The pharmaceutical composition of claim 33, wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.
36. The pharmaceutical composition of claim 33, wherein said pharmaceutical composition is a systemic formulation.

37. The pharmaceutical composition of claim 33, wherein said pharmaceutical composition is a surgical irrigating solution.
38. A packaged pharmaceutical composition for treating a disease associated with an A₁ adenosine receptor in a subject, comprising:
 - (a) a container holding a therapeutically effective amount of the compound of claim 1; and
 - (b) instructions for using said compound for treating said disease in a subject.
39. The pharmaceutically acceptable salt of the compound of claim 1.
40. The pharmaceutically acceptable salt of the compound of claim 39, wherein the pharmaceutically acceptable salt of the compound of claims 6, 8, 12, 15, or 16 contains a cation selected from the group consisting of sodium, calcium and ammonium.
41. The method of claim 18, wherein the A₁ adenosine receptor is associated with congestive heart failure.

42. A compound having the structure:



43. A compound having the structure:



44. A method for treating a disease associated with A_{2a} adenosine receptor in a subject, comprising administering to the subject a therapeutically effective amount of a compound of claim 42 or 43.
45. The method of claim 44, wherein the subject is a mammal.
46. The method of claim 45, wherein the subject is a human.
47. The method of claim 46, wherein said A_{2a} adenosine receptor is associated with locomotor activity,

vasodilation, platelet inhibition, neutrophil superoxide generation, cognitive disorder, senile dementia, or Parkinson's disease.

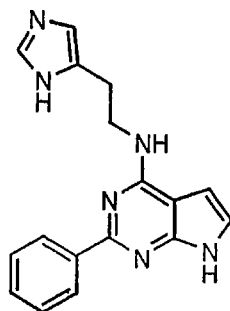
48. The method of claim 44, wherein the compound treats said diseases by stimulating adenylate cyclase.
49. A water-soluble prodrug of the compound of claim 42 or 43, wherein said water-soluble prodrug that is metabolized *in vivo* to an active drug which selectively inhibit A_{2a} adenosine receptor.
50. The prodrug of claim 49, wherein said prodrug is metabolized *in vivo* by esterase catalyzed hydrolysis.
51. A pharmaceutical composition comprising the prodrug of claim 49 and a pharmaceutically acceptable carrier.
52. A method for inhibiting the activity of an A_{2a} adenosine receptor in a cell, which comprises contacting said cell with a compound of claims 42 or 43.
53. The method of claim 52, wherein the compound is an antagonist of said A_{2a} adenosine receptor.
54. The method of claim 53, wherein the cell is a human cell.
55. The method of claim 53, wherein the compound is an antagonist of A_{2a} adenosine receptors.
56. A pharmaceutical composition comprising a therapeutically effective amount of the compound of

claim 42 or 43 and a pharmaceutically acceptable carrier.

57. The pharmaceutical composition of claim 56, wherein said therapeutically effective amount is effective to treat Parkinson's disease and diseases associated with locomotor activity, vasodilation, platelet inhibition, neutrophil superoxide generation, cognitive disorder, or senile dementia.
58. The pharmaceutical composition of claim 56, wherein said pharmaceutical composition is an ophthalmic formulation.
59. The pharmaceutical composition of claim 56, wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.
60. The pharmaceutical composition of claim 56, wherein said pharmaceutical composition is a systemic formulation.
61. The pharmaceutical composition of claim 56, wherein said pharmaceutical composition is a surgical irrigating solution.
62. A combination therapy for Parkinson's disease, comprising the compounds of claim 42 or 43, and any of the dopamine enhancers.
63. A combination therapy for cancer, comprising the compound of claim 42 or 43, and any of the cytotoxic agents.

64. A combination therapy for glaucoma, comprising the compound of claim 42 or 43, and a prostaglandin agonist, a muscrinic agonist, or a β -2 antagonist.
65. A packaged pharmaceutical composition for treating a disease associated with A_{2a} adenosine receptor in a subject, comprising:
 - (a) a container holding a therapeutically effective amount of the compound of claim 42 or 43; and
 - (b) instructions for using said compound for treating said disease in a subject.
66. A pharmaceutically acceptable salt of the compound of claim 42 or 43.
67. The pharmaceutically acceptable salt of claim 66, wherein the pharmaceutically acceptable salt of the compound of claim 41 or 42 contains anion selected from the group consisting of maleic, fumaric, tartaric, acetate, phosphate and mesylate.

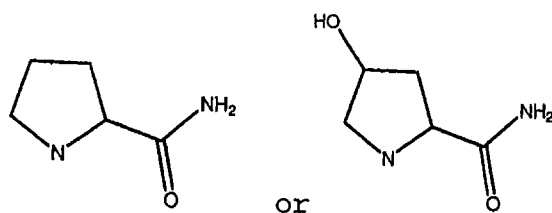
68. A compound having the structure:



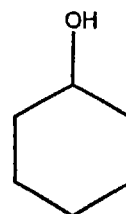
69. A method for inhibiting the activity of an A₃ adenosine receptor in a cell, which comprises contacting the cell with a compound of claim 68.
70. The method of claim 69, wherein the compound is an antagonist of the A₃ adenosine receptor.
71. The method of claim 69, wherein the cell is human cell.
72. The method of claim 71, wherein the compound is an antagonist of A₃ adenosine receptors.
73. A method of treating damage to the eye of a subject which comprises administering to the subject a composition comprising a therapeutically effective amount of the compound of claim 68.
74. The method of claim 73, wherein the damage comprises retinal or optic nerve head damage.
75. A therapy for glaucoma, comprising administering to a subject a therapeutically effective amount of the compound of claim 68.

76. A combination therapy for glaucoma, comprising the compound of claim 68, and one or more compounds selected from the group consisting of beta adrenoceptor antagonists, alpha-2 adrenoceptor agonists, carbonic anhydrase inhibitors, cholinergic agonists, prostaglandins and prostaglandin receptor agonists, angiotensin converting enzyme (ACE) inhibitors, AMPA receptor antagonists, 5-HT agonists, angiogenesis inhibitors, NMDA antagonists, renin inhibitors, cannabinoid receptor agonists, angiotensin receptor antagonists, hydrochlorothiazide (HCTZ), somatostatin agonists, glucocorticoid antagonists, mast cell degranulation inhibitors, alpha-adrenergic receptor blockers, alpha-2 adrenoceptor antagonists, thromboxane A2 mimetics, protein kinase inhibitors, prostaglandin F derivatives, prostaglandin-2 alpha antagonists, dopamine D1 and 5-HT2 agonists, nitric-oxide-releasing agents, 5-HT 2 antagonists, cyclooxygenase inhibitors, inosine, dopamine D2 receptor and alpha 2 adrenoceptor agonists, dopamine D1 receptor antagonist and D2 receptor agonists, vasopressin receptor antagonists, endothelin antagonists, 1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) and related analogs and prodrugs, thyroid hormone receptor ligands, muscarinic M1 agonists, sodium channel blockers, mixed-action ion channel blockers, beta adrenoceptor antagonist and PGF2 alpha agonist combinations, guanylate cyclase activators, nitrovasodilators, endothelin receptor modulators, ethacrynic acid, other phenoxyacetic acid analogs, actin disrupters, calcium channel blockers and neuroprotective agents.

77. A combination therapy for glaucoma, comprising the compound of claim 68, and one or more compounds selected from the group consisting of beta adrenoceptor antagonists, alpha-2 adrenoceptor agonists, carbonic anhydrase inhibitors, cholinergic agonists and prostaglandin receptor agonists.
78. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 68 and a pharmaceutically acceptable carrier.
79. A packaged pharmaceutical composition for treating a disease associated with an A3 adenosine receptor in a subject, comprising:
 - (a) a container holding a therapeutically effective amount of the compound of claim 68; and
 - (b) instructions for using said compound for treating said disease in a subject.
80. A method of making a composition which comprises the compound of claim 68, the method comprising admixing the compound of claim 68 with a suitable carrier.
81. A pharmaceutically acceptable salt of the compound of claim 68.
82. The pharmaceutically acceptable salt of claim 81, wherein the pharmaceutically acceptable salt contains an anion selected from the group consisting of maleic, fumaric, tartaric, acetate, phosphate and mesylate.
83. The compound of claim 1, wherein when R_1NR_2 together form a ring having the structure:



R₅ is H, -CH₂(NC₅H₈)(OH)(C₆H₅), -CH₂OCH₃,
 -(CH₂)₂C(O)OH, -CH₂OCH₂C(O)NH₂, -C(O)OH, -CH₃,
 -CH₂O(CH₂)₂OH, -CH₂OCH₂C(O)OCH₃, or -CH₂OCH₂C(O)OH;
 or



when R₁ is H and R₂ is:

R₅ is H, -CH₂(N₂C₃H₃), -C(O)OH, -CH₂O(CH₂)₂OH, -C(O)OCH₃, or
 -C(O)NH₂,
 or a pharmaceutically acceptable salt thereof.

84. Use of the compound of claim 1 for manufacturing a medicament useful for treating a disease associated with an A₁ adenosine receptor in a subject.

85. Use of the compound of claim 1 for manufacturing a medicament useful for inhibiting the activity of an A₁ adenosine receptor in a cell.

86. A pharmaceutical composition comprising the compound of claim 1, a pharmaceutically acceptable carrier and at least one of steroid, β₂ agonist, glucocorticoid, leukotriene antagonist, or an anticholinergic agonist.

87. Use of the compound of claim 42 or 43 for manufacturing a medicament useful for treating a disease associated with an A_{2a} adenosine receptor in a subject.
88. Use of the compound of claim 42 or 43 for manufacturing a medicament useful for inhibiting the activity of an A_{2a} adenosine receptor in a cell.
89. A pharmaceutical composition comprising the compounds of claim 42 or 43, a pharmaceutically acceptable carrier and any of the dopamine enhancers.
90. A pharmaceutical composition comprising the compound of claim 42 or 43, a pharmaceutically acceptable carrier and any of the cytotoxic agents.
91. A pharmaceutical composition comprising the compound of claim 42 or 43, a pharmaceutically acceptable carrier and a prostaglandin agonist, a muscrinic agonist, or a β -2 antagonist.
92. Use of the compound of claim 50 for manufacturing a medicament useful for inhibiting the activity of an A₃ adenosine receptor in a cell.
93. Use of the compound of claim 50 for manufacturing a medicament useful for treating damage to the eye of a subject.
94. Use of the compound of claim 50 for manufacturing a medicament useful for glaucoma in a subject.

95. The use of claim 94, wherein the medicament further comprises one or more compounds selected from the group consisting of beta adrenoceptor antagonists, alpha-2 adrenoceptor agonists, carbonic anhydrase inhibitors, cholinergic agonists, prostaglandins and prostaglandin receptor agonists, angiotensin converting enzyme (ACE) inhibitors, AMPA receptor antagonists, 5-HT agonists, angiogenesis inhibitors, NMDA antagonists, renin inhibitors, cannabinoid receptor agonists, angiotensin receptor antagonists, hydrochlorothiazide (HCTZ), somatostatin agonists, glucocorticoid antagonists, mast cell degranulation inhibitors, alpha-adrenergic receptor blockers, alpha-2 adrenoceptor antagonists, thromboxane A2 mimetics, protein kinase inhibitors, prostaglandin F derivatives, prostaglandin-2 alpha antagonists, dopamine D1 and 5-HT2 agonists, nitric-oxide-releasing agents, 5-HT 2 antagonists, cyclooxygenase inhibitors, inosine, dopamine D2 receptor and alpha 2 adrenoceptor agonists, dopamine D1 receptor antagonist and D2 receptor agonists, vasopressin receptor antagonists, endothelin antagonists, 1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) and related analogs and prodrugs, thyroid hormone receptor ligands, muscarinic M1 agonists, sodium channel blockers, mixed-action ion channel blockers, beta adrenoceptor antagonist and PGF2 alpha agonist combinations, guanylate cyclase activators, nitrovasodilators, endothelin receptor modulators, ethacrynic acid, other phenoxyacetic acid analogs, actin disrupters, calcium channel blockers and neuroprotective agents.

96. The use of claim 94, wherein the medicament further comprises one or more compounds selected from the group consisting of beta adrenoceptor antagonists, alpha-2 adrenoceptor agonists, carbonic anhydrase inhibitors, cholinergic agonists and prostaglandin receptor agonists.
97. The pharmaceutical composition of claim 78, further comprising one or more compounds selected from the group consisting of beta adrenoceptor antagonists, alpha-2 adrenoceptor agonists, carbonic anhydrase inhibitors, cholinergic agonists, prostaglandins and prostaglandin receptor agonists, angiotensin converting enzyme (ACE) inhibitors, AMPA receptor antagonists, 5-HT agonists, angiogenesis inhibitors, NMDA antagonists, renin inhibitors, cannabinoid receptor agonists, angiotensin receptor antagonists, hydrochlorothiazide (HCTZ), somatostatin agonists, glucocorticoid antagonists, mast cell degranulation inhibitors, alpha-adrenergic receptor blockers, alpha-2 adrenoceptor antagonists, thromboxane A2 mimetics, protein kinase inhibitors, prostaglandin F derivatives, prostaglandin-2 alpha antagonists, dopamine D1 and 5-HT2 agonists, nitric-oxide-releasing agents, 5-HT 2 antagonists, cyclooxygenase inhibitors, inosine, dopamine D2 receptor and alpha 2 adrenoceptor agonists, dopamine D1 receptor antagonist and D2 receptor agonists, vasopressin receptor antagonists, endothelin antagonists, 1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) and related analogs and prodrugs, thyroid hormone receptor ligands, muscarinic M1 agonists, sodium channel blockers, mixed-action ion channel blockers, beta adrenoceptor

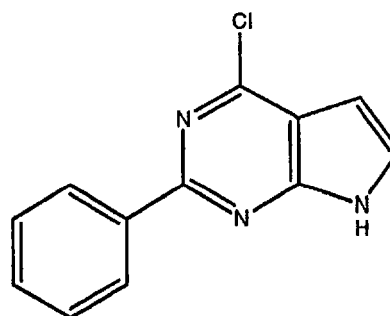
antagonist and PGF2 alpha agonist combinations, guanylate cyclase activators, nitrovasodilators, endothelin receptor modulators, ethacrynic acid, other phenoxyacetic acid analogs, actin disrupters, calcium channel blockers and neuroprotective agents.

98. The pharmaceutical composition of claim 78, further comprising one or more compounds selected from the group consisting of beta adrenoceptor antagonists, alpha-2 adrenoceptor agonists, carbonic anhydrase inhibitors, cholinergic agonists and prostaglandin receptor agonists.

99. Use of the compound of claim 68 for manufacturing a medicament useful for treating a disease associated with an A3 adenosine receptor in a subject in need of such treatment, wherein the disease associated with the A3 adenosine receptor is asthma, bronchitis, chronic obstructive pulmonary disorder, or bronchoconstriction.

100. A process of manufacturing the compound of claim 68, comprising the steps of:

(a) reacting the compound



with histamine in the presence of dimethyl sulfoxide;

(b) heating the reaction mixture under an inert atmosphere;

(c) cooling the reaction mixture and separating the organic layer from the aqueous layer;

(d) washing the organic layer with brine, drying, and filtering, to yield the compound.

101. The process of claim 100, wherein in step (b) the reaction mixture is heated under a nitrogen atmosphere.

102. The process of claim 100, wherein in step (d) the organic layer is dried with MgSO_4 .

103. Use of the compound of any of claims 1-17 for manufacturing a medicament useful for treating a disease associated with an A1 adenosine receptor in a subject in need of such treatment, wherein the disease is antidiuresis, bradycardia, bronchitis, bronchoconstriction, Alzheimer's disease, cardiac arrhythmias, cardiac hypoxia, hypertension, inflammation, negative cardiac inotropy and dromotropy, renal failure, sedation or is associated with transmitter release, respiratory epithelia, contraction of smooth muscle underlying respiratory epithelia, vasoconstriction or mast cell degranulation.

104. Use of the compound of any of claims 1-17 for enhancing the memory of a subject.
105. Use of the compound of claim 42 or 43 for manufacturing a medicament useful for treating a disease associated with an A2a adenosine receptor in a subject in need of such treatment, wherein the disease associated with the A2a adenosine receptor is Parkinson's disease or glaucoma.
106. Use of the compound of claim 68 for manufacturing a medicament useful for treating a disease associated with an A3 adenosine receptor in a subject in need of such treatment, wherein the disease associated with the A3 adenosine receptor is myocardial ischemia, bronchitis, or bronchoconstriction.
107. Use of the compound of claim 68 for manufacturing a medicament useful for treating inflammation of the eye associated with an A3 adenosine receptor in a subject.
108. Use of the compound of claim 68 for manufacturing a medicament useful for treating a disease associated with an A3 adenosine receptor in a subject in need of such treatment, wherein the disease associated with the A3 adenosine receptor is associated with mast cell degranulation.
109. Use of the compound of claim 68 for manufacturing a medicament useful for treating a disease associated with an A3 adenosine receptor in a subject in need of such treatment, wherein the disease associated with the

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A3 adenosine receptor is asthma, glaucoma, retinopathy,
ocular ischemia, or macular degeneration.