2-Pyrazolyl-N^6-Substituted Adenosine Derivatives as High Affinity and Selective Adenosine A_3 Receptor Agonists

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We describe the synthesis of new high affinity and selective A_3-adenosine receptor (A_3-AdoR) agonists. Introduction of a methyl group at the N^6-position of the A_{2A}-AdoR selective 2-pyrazolyl-adenosine analogues (Figure 2) brought about a substantial increase in the A_3-AdoR binding affinity and selectivity. While the N^6-desmethyl analogues **3a** and **4** were inactive at the A_3-AdoR (K_i > 10 μM), the corresponding N^6-methyl analogues **5** and **22** showed good binding affinity at the A_3-AdoR (K_i = 73 and 97 nM, respectively). Replacement of the carboxamide group in **5** with different heteroaryl groups resulted in analogues with high affinities and selectivity for the A_3-AdoR. (2*R*,3*S*,4*R*)-tetrahydro-2-(hydroxymethyl)-5-(6-(methylamino)-2-(4-(pyridin-2-yl)-1*H*-pyrazol-1-yl)-9*H*-purin-9-yl)furan-3,4-diol (**15**, K_i = 2 nM) displayed high selectivity for the A_3-AdoR versus A_1- and A_{2A}-AdoRs (selectivity ratios of 1900 and >2000, respectively).

Introduction

Adenosine is a naturally occurring purine nucleoside that has a large variety of effects as a result of its activation of specific membrane bound adenosine receptors. There are four pharmacologically distinct adenosine receptor subtypes, defined as A_1, A_{2A}, A_{2B} and A_3.[1,2] Interaction of adenosine with its receptors initiates signal transduction pathways, including the adenylate cyclase effector system, which utilizes cAMP as a second messenger. The A_1 and A_3 adenosine receptors (A_1-AdoR, A_3-AdoR) are coupled to G_i proteins and therefore inhibit adenylate cyclase and lead to a decrease in intracellular levels of cAMP. The A_{2A}/A_{2B} adenosine receptors are coupled to G_s proteins and therefore stimulate adenylate cyclase and hence increase cAMP levels.[3] Acting through the A_{2A}-AdoR, adenosine elicits a number of physiological responses, including vasodilation[4] and inhibition of platelet aggregation.[5] Physiological effects mediated by adenosine action through the A_1-AdoR include negative dromotropic effects, negative chronotropic effects and reduction in lipolysis in adipose tissue.[1] Over the past few years, a considerable effort has been directed toward the discovery of potent and selective A_1- and A_{2A}-AdoR agonists. At the A_1-AdoR, the most active and selective agonists are the N^6-substituted adenosine analogues (e.g. CCPA),[6] whereas at the A_{2A}-AdoR, 2-substituted adenosine derivatives are the most potent and selective (e.g. YT-146).[7]

Among the four-adenosine receptor subtypes, the A_3-AdoR was the most recently identified. A_3-AdoR has been linked to several diseases such as cardiac ischemia,[8] cerebral ischemia,[9] inflammation,[10,11] and cancer[12] and therefore has been a primary target for new therapeutics. Since the discovery of the A_3-AdoR in 1991,[13,14] the development of potent and selective agonists for the A_3-AdoR has been an active area of research, but very few selective A_3-AdoR agonists have been identified to date. Cl−IB-MECA and IB-MECA (Figure 1) are among the most potent and selective A_3-AdoR agonists and are being used extensively as pharmacological tools for studying the A_3-AdoR.[15] However, the selectivity of IB-MECA is not evident in all pharmacological systems,[6] while the other selective agent, Cl-IB-MECA, has some adverse effects in vivo.[16] These drawbacks associated with both IB-MECA and Cl−IB-MECA have prompted the search for new high affinity and selective A_3-AdoR agonists.

Cristalli et al.[17] have shown that introducing a methyl group into the N^6 position of 2-alkynyl adenosine derivatives induces an increase in the affinity for the human A_3-AdoR and simultaneously decreases the affinity for the A_1- and A_{2A}-AdoRs, resulting in significant enhancement in A_3-AdoR selectivity (Figure 1, **1** versus **2**). Recently, we have reported the synthesis of 2-pyrazolyl adenosine analogues that were potent and selective A_{2A}-AdoR agonists (Figure 2).[18,19] Compounds **3a** and **4** (Figure 2) showed no affinity for HEK-hA_3-AdoR (K_i >10 μM). The goal of this study (and based on Cristalli's result) was to investigate the effect of introducing substituents at the N^6-position of 2-pyrazolyl adenosine analogues with the idea of identifying new high affinity and selective A_3-AdoR agonists.

Chemistry

The synthesis of compounds **9**−**21** is outlined in Scheme 1. The 2-chloro-N^6-substituted adenosine derivatives **25**−**28** were prepared by reacting **24** with the appropriate amine in ethanol. Treatment of **25**−**28** with hydrazine monohydrate at RT afforded the corresponding 2-hydrazino-N^6-substituted adenosine derivatives **29**−**32**. The new analogues **9**−**21** were then obtained by condensation of **29**−**32** with the appropriate malonaldehyde in ethanol at reflux. Compounds **5**−**8** were

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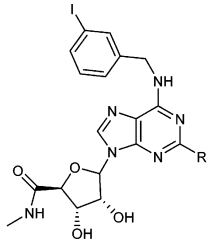
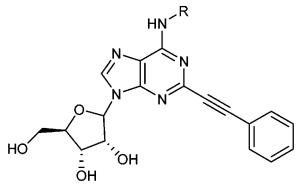


R = H, IB-MECA
K_i rA_3 = 1.1 nM
K_i rA_1 = 54 nM
K_i rA_{2A} = 56 nM

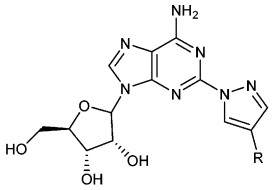
R = Cl, Cl-IB-MECA
K_i hA_3 = 1.4 nM
K_i hA_1 = 1240 nM
K_i hA_{2A} = 5360 nM



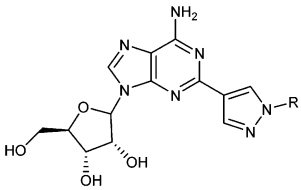
1, R = H
K_i hA_3 = 16 nM
K_i hA_1 = 391 nM
K_i hA_{2A} = 363 nM

2, R =Me
K_i hA_3 = 3.4 nM
K_i hA_1 = 1690 nM
K_i hA_{2A} = 8530 nM

Figure 1.



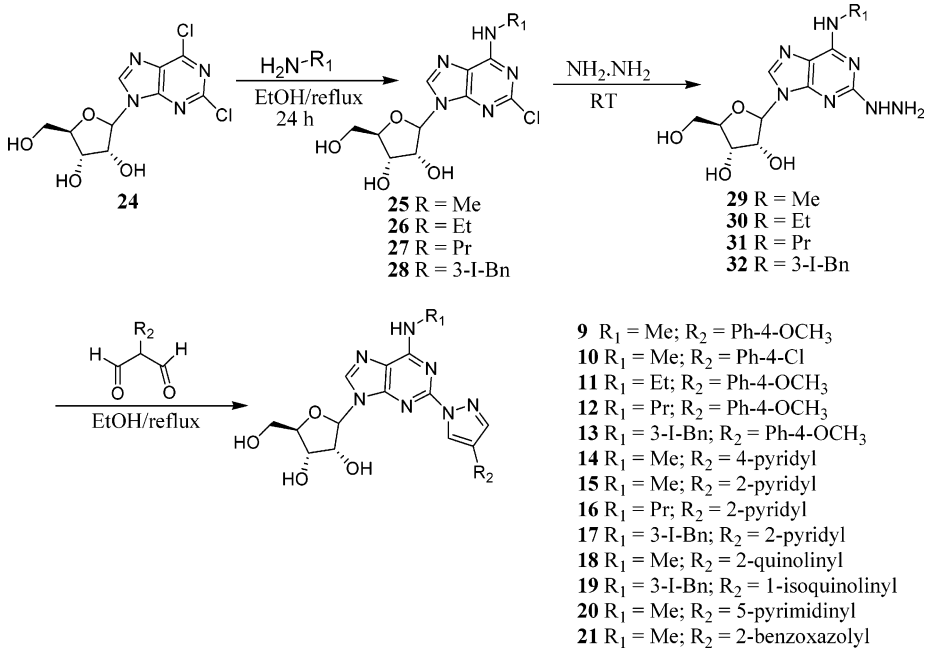
3a, R = -$CONHCH_3$
K_i, hA_{2A} = 297 nM, K_i hA_3 = > 10 μM
3b, R = -Ph-4-OCH_3
K_i, hA_{2A} = 190 nM, K_i hA_3 = > 6 μM



4, R = -benzyl, K_i, hA_{2A} =1.5 μM, Ki hA_3 = >10 μM

Figure 2.

Scheme 1

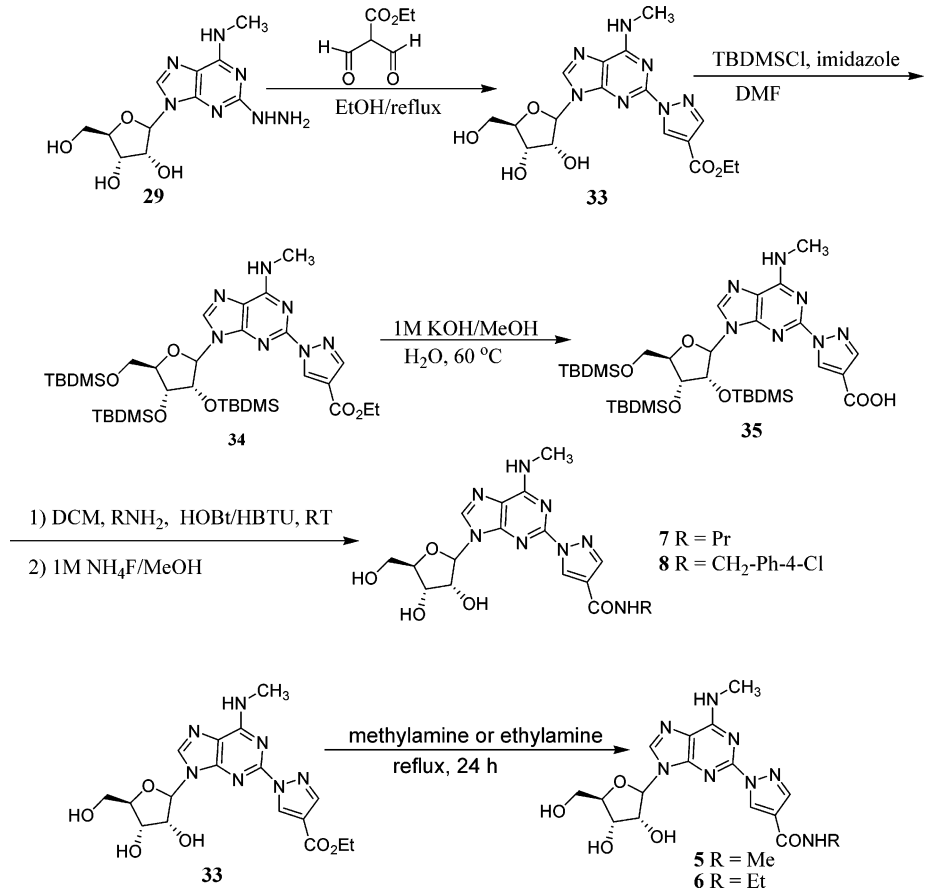


prepared as shown in Scheme 2. Reaction of 2-hydrazino-N^6-methyladenosine **29** with ethyl 2,2-diformylacetate[20] in ethanol yielded the ester **33**. To enhance the solubility of the acid **35** (resulting from hydrolysis of **34**) in organic solvents, the hydroxyl groups of **33** were protected with TBDMS groups using TBDMSCl and imidazole in DMF. Hydrolysis of the protected ester **34** was achieved in 1 M KOH/MeOH and water. Compounds **7** and **8** were then obtained from the acid **35** via standard amino acid coupling (HBTU/HOBt) in dichloromethane followed by removal of the TBDMS group using 1 M NH_4F in methanol. The ester **33** was converted directly to amides **5** and **6** by aminolysis with methyl and ethylamine, respectively. Preparation of the C-pyrazole analogues **22** and **23** (Scheme 3) was achieved by reacting 2-stannyl-4-chloroadenosine[21] derivative **38** with the corresponding *N*-alkyl-4-iodopyrazole utilizing a Stille coupling [tetrakis(triphenylphosphine) palladium-(0)] and cuprous iodide. Displacement of the 6-chloro group in **39** with methyl and propylamine in ethanol followed by cleavage of the TBDMS groups using 1 M NH_4F/MeOH afforded compounds **22** and **23**.

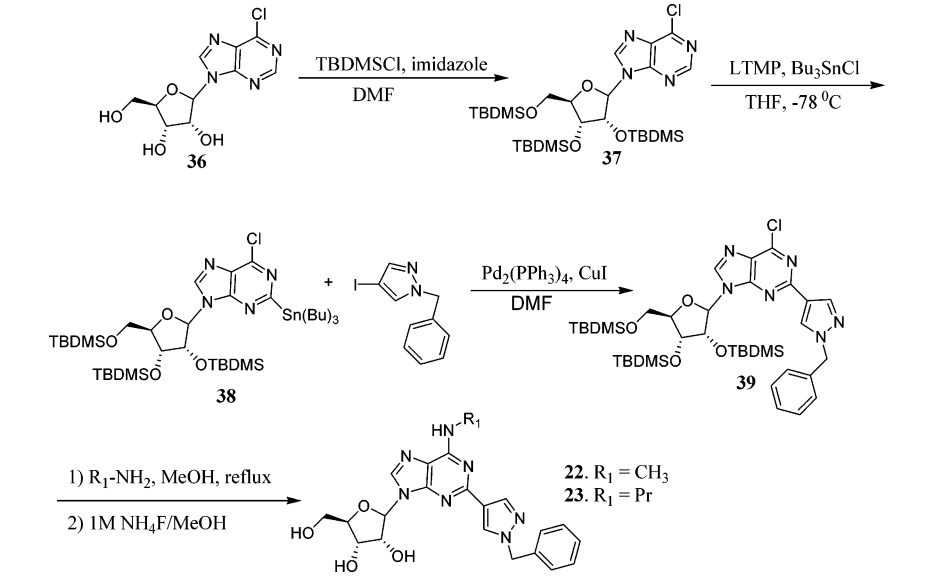
Results and Discussion

Binding affinities of compounds **5**−**23** for the A_3-, A_1- and A_{2A}-AdoRs were evaluated in radioligand binding assays using CHO cells stably expressing recombinant human A_1-AdoR receptor and HEK cells stably expressing recombinant human A_{2A}- and A_3-AdoRs. The radioligands for the A_3-, A_1- and A_{2A}-AdoRs were [^{125}I]AB-

Scheme 2

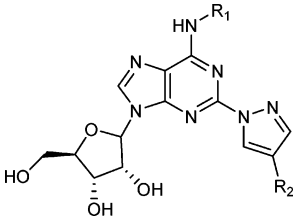


Scheme 3



MECA, [^{3}H]CCPA and [^{3}H]CGS-21680, respectively. As shown in Table 1, introducing a methyl group into the N^6-position of compound **3a** (Figure 2), which was inactive at the A_3-AdoR (K_i > 10 μM), indeed resulted in greater than 100-fold enhancement in A_3-AdoR binding affinity (**5**, K_i = 73 nM). Compound **5** showed no measurable affinity for both A_1- and A_{2A}-AdoRs at concentrations up to 6 μM and consequently displayed at least 80-fold selectivity for A_3-AdoR versus A_1-and A_{2A}-AdoRs. This result is in line with Cristalli's finding that introducing a methyl group in the N^6-position of 2-alkynyladenosine derivatives enhances A_3-AdoR binding affinity. Increasing the size of the alkyl amide from a methyl to an ethyl as in **6** resulted in moderate improvement in binding affinity for the A_3-AdoR (K_i = 49 nM). However, extending the alkyl amide chain to three carbons afforded >3-fold increase in binding affinity (**7**, K_i = 19 nM) and at least 2-fold increase in selectivity for the A_3-AdoR versus A_1- and A_{2A}-AdoRs, relative to **5**. It appears that for compounds **5**−**7** the A_3-AdoR binding affinity increases as the size of the amide alkyl chain increases. This prompted us to

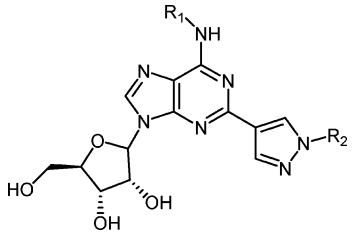
Table 1. Binding Affinities of Compounds **5**−**21** for A_3-, A_1-, and A_{2A}-Adenosine Receptors



			K_i, nM[a]				
compd	R_1	R_2	$(A_3)^b$	$(A_1)^c$	$(A_{2A})^d$	A_1/A_3	A_{2A}/A_3
5	CH_3	$CONHCH_3$	73	>6000	>6000	>80	>80
6	CH_3	$CONHCH_2CH_3$	49	NT	NT	NT	NT
7	CH_3	$CONH(CH_2)_2CH_3$	19	>4000	>4000	>200	>200
8	CH_3	$CONHCH_2$Ph-4-Cl	157	2000	4000	1	25
9	CH_3	Ph-4-OCH_3	15	>4000	>5000	>200	>300
10	CH_3	Ph-4-Cl	10	>6000	>5000	>600	>500
11	CH_2CH_3	Ph-4-OCH_3	41	3700	4000	90	100
12	$(CH_2)_2CH_3$	Ph-4-OCH_3	65	3000	3300	45	50
13	3-I−Bn	Ph-4-OCH_3	320	4500	4000	14	10
14	CH_3	4-pyridyl	6	3800	>5000	600	>800
15	CH_3	2-pyridyl	2	3800	>5000	1900	>2000
16	$(CH_2)_2CH_3$	2-pyridyl	107	1300	1800	12	17
17	3-I−Bn	2-pyridyl	170	4200	>3900	24	>22
18	CH_3	2-quinolinyl	3	>5000	>5000	>1600	>1600
19	3-I−Bn	1-isoquinolinyl	109	770	52	7	<1
20	CH_3	5-pyrimidinyl	2	1800	4100	900	2000
21	CH_3	2-benzoxazolyl	2	2600	2500	1300	1200
IBMECA			1	NT	NT	-	-

[a] 95% confidence limits were generally ±20% of the mean value. NT = not tested. [b] Displacement of specific binding of [^{125}I]AB-MECA in CHO-hA_3-AdoR; K_i values are average of $n = 3$. [c] Displacement of specific binding of [^{3}H]CCPA in CHO-hA_1-AdoR; K_i values are average of $n = 3$. [d] Displacement of specific binding of [^{3}H]CGS-21680 in HEK-hA_{2A}-AdoR; K_i values are average of $n = 3$.

Table 2. Binding Affinities of 2-(C)-Pyrazolyl-N^6-substituted Adenosine Derivatives at A_3-, A_1-, and A_{2A}-Adenosine Receptors



			K_i, nM[a]				
compd	R_1	R_2	$(A_3)^b$	$(A_1)^c$	$(A_{2A})^d$	A_1/A_3	A_{2A}/A_3
22	CH_3	benzyl	97	1300	>5000	13	>50
23	$(CH_2)_2CH_3$	benzyl	148	NT	NT	NT	NT

[a] 95% confidence limits were generally ±20% of the mean value. NT = not tested. [b] Displacement of specific binding of [^{125}I]AB-MECA in CHO-hA_3-AdoR; K_i values are average of $n = 3$. [c] Displacement of specific binding of [^{3}H]CCPA in CHO-hA_1-AdoR; K_i values are average of $n = 3$. [d] Displacement of specific binding of [^{3}H]CGS-21680 in HEK-hA_{2A}-AdoR; K_i values are average of $n = 3$.

introduce a benzylamide group in place of the alkyl amide with the idea of adding more steric bulk in this position. Compound **8** displayed markedly lower affinity and selectivity for A_3-AdoR ($K_i = 157$ nM) compared to **7**. Next we directed our attention to the optimization of compounds **5**−**7** with the goal of finding a suitable π bioisostere for the metabolically labile amide bond. Replacement of the carboxamide group in **5** with a Ph-4-OCH_3 directly attached to the 4-position of the pyrazole ring resulted in a considerable enhancement in A_3-AdoR binding affinity (**9**, $K_i = 15$ nM). Compound **9** showed >200- and >300-fold selectivity for A_3-AdoR versus A_1- and A_{2A}-AdoRs, respectively. It is noteworthy that the N^6-desmethyl analogue of **9**, compound **3b** (Figure 2) exhibited good affinity for the A_{2A}-AdoR (K_i, $A_{2A} = 0.19$ μM) and showed no measurable affinity for the hA_3-AdoR ($K_i > 6$ μM). Comparing **3b** and **9** clearly demonstrated that introducing a methyl group into the N^6-position of **3b** significantly enhances A_3-AdoR binding affinity while significantly decreasing A_{2A}-AdoR affinity resulting in a high A_{2A}/A_3 selectivity ratio. Replacing the 4-methoxy group in **9** with an electron-withdrawing group as in **10** has a slight effect on affinity ($K_i = 10$ nM). Compound **10** showed very weak binding affinity for both A_1- and A_{2A}-AdoRs ($K_i > 5$ μM) which in turn translated into >500-fold selectivity for A_3-AdoR relative to A_1- and A_{2A}-AdoRs. Increasing the alkyl size at the N^6-position of compound **9** from a methyl to an ethyl group as in **11** resulted in approximately 3-fold loss in binding affinity for the A_3-AdoR ($K_i = 41$ nM) accompanied by a drop in A_3 selectivity versus A_1- and A_{2A}-AdoRs (relative to **9**). Extending the size of the N^6-alkyl chain to a propyl group as in **12** resulted in 4-fold loss in A_3-AdoR binding affinity ($K_i = 65$ nM) and at least 5-fold drop in A_1/A_3 and A_{2A}/A_3 selectivity ratios compared to **9**. Compound **9** gradually loses its high binding affinity and selectivity for the A_3-AdoR as the size of the alkyl chain on the N^6- position increases from one to three carbon atoms. It is believed that the 3-I-benzyl group at the N^6-position of IB-MECA is responsible for the high binding affinity and selectivity of this compound for the A_3-AdoR. We wanted to explore the effect of introducing the 3-I-benzyl group at the N^6-position of compound **9** (in place of the N^6-methyl group) with the goal of further enhancing its A_3-AdoR binding affinity and selectivity. This resulted in compound **13**, which showed dramatic loss in affinity and selectivity

for the A_3-AdoR (K_i = 320 nM). Introducing a heteroaryl group (pyridyl, quinolinyl, isoquinolinyl, pyrimidinyl and benzoxazole) in place of the phenyl group in **9** resulted in compounds **14**−**21**. Compounds **15**, **20** and **21** displayed high binding affinities (K_i = 2 nM) and selectivity for the A_3-AdoR ($A_1/A_3 \geq 900$ and $A_{2A}/A_3 \geq 1200$). In addition to its high binding affinity (K_i = 2 nM), the 2-pyridyl analogue **15** also showed extremely high selectivity for the A_3-AdoR versus A_1- and A_{2A}-AdoRs (selectivity ratios of 1900 and >2000, respectively). Increasing the alkyl size at the N^6-position of **15** to a propyl or 3-I-benzyl groups as in **16** and **17** resulted in markedly lower binding affinity and selectivity for the A_3-AdoR (K_i = 107 and 170 nM, respectively). This trend is similar to the one that was observed when the same structural changes were applied to compound **9**. The low A_3-AdoR affinity and selectivity of **12**, **13** relative to **9** and of **16**, **17** relative to **15** suggest that the steric factor at the N^6-position may play a crucial role in determining the binding affinity and selectivity for the A_3-AdoR. It appears that at the N^6-position of the 2-pyrazolyladenosine analogues, the methyl group is optimal for high A_3-AdoR binding affinity and selectivity. Compound **4** (Figure 2) a 2-C-pyrazolyladenosine analogue was essentially inactive at the A_3-AdoR (K_i > 10 μM). As anticipated, introducing a methyl group at the N^6-position of **4** resulted in substantial enhancement in A_3-AdoR affinity (Table 1, **22**, K_i = 97 nM). Similar to the N-pyrazole analogues, increasing the N^6-alkyl side chain from methyl to propyl as in **23** led to a decrease in binding affinity (K_i = 148 nM). The agonistic effect of compound **9** on forskolin-induced cAMP levels in HEK-hA_3-AdoR was evaluated relative to the A_3-AdoR agonist IB-MECA. Compound **9** showed inhibition of cAMP levels similar to that of IB-MECA (27% inhibition at 1 nM and 35% inhibition at 10 nM).

Conclusion

In summary, we have shown that introduction of a methyl group at the N^6-position of the A_{2A} selective 2-pyrazolyladenosine analogues brought about a substantial increase in the A_3-AdoR binding affinity and selectivity. While the N^6-desmethyl analogues **3a** and **4** were inactive at the A_3-AdoR (K_i > 10 μM), the N^6-methyl analogues **5** and **22**, showed good binding affinity at the A_3-AdoR (K_i = 73 and 97 nM, respectively). Replacement of the carboxamide group in **5** with different heteroaryl groups (**15**, **18**, **20** and **21**) resulted in analogues with high binding affinities and selectivity for the A_3-AdoR. Compound **15** (K_i = 2 nM) showed extremely high selectivity for the A_3-AdoR versus A_1- and A_{2A}-AdoRs (selectivity ratios of 1900 and >2000, respectively). Considering the fact that only a few high affinity and selective A_3-AdoR agonists are available to date, this new class of 2-pyrazolyl-N^6-substituted adenosine analogues constitutes a significant addition to the field and might be useful as pharmacological tools. In addition, these new analogues may serve as leads to discover additional potent and selective A_3-AdoR agonists that may have potential use as therapeutic agents.[9−12]

Experimental Section

Commercial chemicals and solvents were of reagent grade and were used without further purification. The following abbreviations are used for reagents and solvents: DCM, dichloromethane; DMF, dimethyl formamide; DMSO, dimethyl sulfoxide; EtOAc, ethyl acetate; Hex, hexane; EtOH, ethanol; MeOH, methanol; HOBt, *N*-hydroxybenzotriazole; HBTU, 2-(1*H*-benzotiazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; DMAP, 4-(dimethylamino)pyridine. Whatman silica gel (60 Å, 230−400 mesh) was used for column chromatography. Analtech thin-layer chromatography plates (20 × 20 cm, 2000 μm) were used for preparative thin-layer chromatography. Proton NMR (^{1}H NMR) spectra were recorded on a Varian Gemini-400 spectrometer (400 MHz). Chemical shifts are reported in δ units (parts per million) downfield from tetramethylsilane and are assigned as singlets (s), doublets (d), doublet of doublets (dd), triplets (t), quartet (q), multiplets (m). Coupling constants (J) are reported in hertz (Hz). Mass spectra (MS) were recorded on Micromass LCZ. Elemental analysis data for final compounds were obtained from Galbraith Laboratories and were within ±0.4% of the theoretical values for formulas given.

General Procedure for the Amination of 24 into Compounds 25−28. To a solution of **24** (1.0 g, 3.13 mmol) in absolute ethanol (40 mL) were added the corresponding amine (6.26 mmol) and triethylamine (6.52 mmol), and the mixture was heated at 80 °C for 24 h. The solution was allowed to cool and was then concentrated under reduced pressure. Water (50 mL) was added to the residue, and the aqueous layer was extracted with three portions of ethyl acetate (50 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The product was crystallized from ethanol/ethyl acetate.

2-Chloro-*N*^{6}-methyladenosine (25). This reaction was carried out using 40% aqueous methylamine (6.26 mmol); yield 86%; ^{1}H NMR (CD_3OD) δ 2.97 (s, 3H, CH_3), 3.18−3.25 (m, 2H, H-5′), 3.58−3.67 (m, 1H, H-4′), 3.68−3.80 (m, 1H, H-3′), 4.00−4.15 (m, 1H, H-2′), 5.78 (d, 1H, H-1′), 8.15 (s, 1H, H-8); MS m/z 316.1 $(M + H)^+$.

2-Chloro-*N*^{6}-ethyladenosine (26). This reaction was carried out using ethylamine (6.26 mmol, 0.40 mL); yield 81%; ^{1}H NMR (DMSO) δ 1.08−1.12 (t, 3H, CH_3), 3.27−3.35 (m, 2H, CH_2CH_3), 3.42−3.60 (m, 2H, H-5′), 3.81−3.85 (m,1H, H-4′), 4.11−4.14 (m, 1H, H-3′), 4.50−4.54 (m, 1H, H-2′), 4.91 (d, 1H, 3′-OH), 5.15 (d, 1H, 5′-OH), 5.43 (d, 1H, 2′-OH), 5.85 (d, 1H, H-1′), 8.15−8.23 (bs, 1H, N^6-H), 8.35 (s, 1H, H-8); MS m/z 330.2 $(M + H)^+$.

2-Chloro-*N*^{6}-propyladenosine (27). This reaction was carried out using propylamine hydrochloride (6.26 mmol, 0.60 g); yield 78%; ^{1}H NMR (DMSO) δ 0.85−0.89 (t, 3H, CH_3), 1.54−1.63 (m, 2H, CH_2CH_3), 3.12−3.27 (m, 2H, $NHCH_2CH_2CH_3$), 3.44−3.61 (m, 2H, H-5′), 3.83−3.87 (m, 1H, H-4′), 4.12−4.15 (m, 1H, H-3′), 4.50−4.55 (m, 1H, H-2′), 4.93 (d, 1H, 3′-OH), 5.17 (d, 1H, 5′-OH), 5.44 (d, 1H, 2′-OH), 5.87 (d, 1H, H-1′), 8.15−8.22 (bs, 1H, N^6-H), 8.31 (s, 1H, H-8); MS m/z 344.2 $(M + H)^+$.

2-Chloro-*N*^{6}-(3-iodobenzyl)adenosine (28). This reaction was carried out using 3-iodobenzylamine hydrochloride (6.26 mmol, 0.83 mL); yield 82%; ^{1}H NMR (DMSO) δ 3.46−3.65 (m, 2H, H-5′), 3.91−3.94 (m, 1H, H-4′), 4.12−4.14 (m, 1H, H-3′), 4.50−4.55 (m, 1H, H-2′), 4.6 (s, 2H, Bn-CH_2), 4.91 (d, 1H, 3′-OH), 5.22 (d, 1H, 5′-OH), 5.40 (d, 1H, 2′-OH), 5.85 (d, 1H, H-1′), 7.10 (t, 1H, CCHC*H*), 7.35 (d, 1H, CC*H*CH), 7.56 (d, 1H, CCHCIC*H*), 7.71 (s, 1H, $NHCH_2CC$*H*CI), 8.4−8.55 (bs, 1H, N^6-H), 8.37 (s, 1H, H-8); MS m/z 518.1 $(M + H)^+$.

2-Hydrazino-*N*^{6}-methyladenosine (29). A solution of **25** (0.7 g, 2.2 mmol) in 5 mL hydrazine monohydrate was allowed to stir at ambient temperature for 24 h. To the solution was added 2-propanol (10 mL), and the gummy residue formed was separated by decantation and treated with water (10 mL). The mixture was then allowed to stir at ambient temperature for 24 h. The white precipitate formed was collected by filtration, washed with water and air-dried to afford 0.57 g (83%) of **29**. MS m/z 312.2 $(M + H)^+$.

2-Hydrazino-*N*^{6}-ethyladenosine (30). A solution of **26** (0.5 g, 1.5 mmol) in 5 mL of hydrazine monohydrate was allowed to stir at ambient temperature for 24 h. To the solution

was added 2-propanol (10 mL), and the gummy residue formed was separated by decantation and treated with water (10 mL). The mixture was then allowed to stir at ambient temperature for 24 h. The white precipitate formed was collected by filtration, washed with water and air-dried to afford 0.39 g (79%) of **30**. MS *m*/*z* 326.1 $(M + H)^+$.

2-Hydrazino-N^6-propyladenosine (31). A solution of **27** (0.5 g, 1.5 mmol) in 5 mL of hydrazine monohydrate was allowed to stir at ambient temperature for 24 h. To the solution was added 2-propanol (10 mL), and the gummy residue formed was separated by decantation and treated with water (10 mL). The mixture was then allowed to stir at ambient temperature for 24 h. The white precipitate formed was collected by filtration, washed with water and air-dried to afford 0.40 g (84%) of **31**. MS *m*/*z* 340.1 $(M + H)^+$.

2-Hydrazino-N^6-(3-iodobenzyl)adenosine (32). A solution of **28** (0.5 g, 0.96 mmol) in 5 mL of hydrazine monohydrate was allowed to stir at ambient temperature for 24 h. To the solution was added 2-propanol (10 mL), and the gummy residue formed was separated by decantation and treated with water (10 mL). The mixture was then allowed to stir at ambient temperature for 24 h. The white precipitate formed was collected by filtration, washed with water and air-dried to afford 0.38 g (76%) of **31**. MS *m*/*z* 514.2 $(M + H)^+$.

General Procedure for the Synthesis of Compounds 9−21 and 33. To a suspension of 2-hydrazino-N^6-substituted adenosine derivatives (**29**−**32**, 0.30 mmol) in EtOH was added the appropriate malondialdehyde (0.40 mmol), and the mixture was heated at 80 °C for 3−5 h. The precipitate formed was then collected by filtration and washed with EtOH, ether and air-dried. The final product was then crystallized from MeOH.

(2*R*,3*S*,4*R*)-Tetrahydro-2-(hydroxymethyl)-5-(2-(4-(4-methoxyphenyl)-1*H*-pyrazol-1-yl)-6-(methylamino)-9*H*-purin-9-yl)furan-3,4-diol (9). This compound was prepared using 2-hydrazino-N^6-methyladenosine (**29**, 0.09 g, 0.30 mmol) and 2-(4-methoxyphenyl)malonaldehyde (0.07 g, 0.4 mmol) following the general procedure described above to afford 0.08 g (58%) of **9**. ^{1}H NMR (DMSO) δ 2.90 (d, 3H, CH_3), 3.40−3.58 (m, 2H, H-5′), 3.65 (s, 3H, OCH_3), 3.80−3.85 (m, 1H, H-4′), 4.11−4.15 (m, 1H, H-3′), 4.50−4.54 (m, 1H, H-2′), 4.91 (d, 1H, 3′-OH), 5.15 (d, 1H, 5′-OH), 5.33 (d, 1H, 2′-OH), 5.78 (d, 1H, H-1′), 6.8 (d, 2H), 7.55 (d, 2H), 8.0−8.10 (m, 2H, NH), 8.20 (s, 1H, H-8), 8.8 (s, 1H); MS *m*/*z* 455.43 $(M + H)^+$. Anal. ($C_{21}H_{23}N_7O_5$): C, H, N.

(3*R*,4*S*,5*R*)-2-(2-(4-(4-Chlorophenyl)-1*H*-pyrazol-1-yl)-6-(methylamino)-9*H*-purin-9-yl)-tetrahydro-5-(hydroxymethyl)furan-3,4-diol (10). This compound was prepared using 2-hydrazino-N^6-methyladenosine (**29**, 0.09 g, 0.30 mmol) and 2-(4-chlorophenyl)malonaldehyde (0.07 g, 0.4 mmol) following the general procedure described above to afford 0.10 g (72%) of **10**. ^{1}H NMR (DMSO) δ 2.95 (d, 3H, CH_3), 3.42−3.60 (m, 2H, H-5′), 3.81−3.85 (m, 1H, H-4′), 4.08−4.15 (m, 1H, H-3′), 4.44−4.54 (m, 1H, H-2′), 4.90 (d, 1H, 3′-OH), 5.13 (d, 1H, 5′-OH), 5.40 (d, 1H, 2′-OH), 5.81 (d, 1H, H-1′), 7.3 (d, 2H), 7.7 (d, 2H), 8.03−8.15 (m, 2H, H-8, NH), 8.3 (s, 1H), 8.89 (s, 1H); MS *m*/*z* 458.1 $(M + H)^+$. Anal. ($C_{20}H_{20}N_7O_4Cl\cdot0.5H_2O$): C, H, N.

(3*R*,4*S*,5*R*)-2-(6-(Ethylamino)-2-(4-(4-methoxyphenyl)-1*H*-pyrazol-1-yl)-9*H*-purin-9-yl)-tetrahydro-5-(hydroxymethyl)furan-3,4-diol (11). This compound was prepared using 2-hydrazino-N^6-ethyladenosine (**30**, 0.09 g, 0.30 mmol) and 2-(4-methoxyphenyl)malonaldehyde (0.07 g, 0.4 mmol) following the general procedure described above to afford 0.12 g (86%) of **11**. ^{1}H NMR (DMSO) δ 1.10−1.13 (t, 3H, CH_3), 3.25−3.35 (m, 2H, CH_2CH_3), 3.40−3.58 (m, 2H, H-5′), 3.66 (s, 3H, OCH_3), 3.81−3.85 (m, 1H, H-4′), 4.11−4.16 (m, 1H, H-3′), 4.51−4.54 (m, 1H, H-2′), 4.90 (d, 1H, 3′-OH), 5.15 (d, 1H, 5′-OH), 5.34 (d, 1H, 2′-OH), 5.80 (d, 1H, H-1′), 6.81 (d, 2H), 7.54 (d, 2H), 8.0−8.10 (m, 2H,), 8.21 (s, 1H, H-8), 8.81 (s, 1H); MS *m*/*z* 468.1 $(M + H)^+$. Anal. ($C_{22}H_{25}N_7O_5$): C, H, N.

(2*R*,3*S*,4*R*)-Tetrahydro-2-(hydroxymethyl)-5-(2-(4-(4-methoxyphenyl)-1*H*-pyrazol-1-yl)-6-(propylamino)-9*H*-purin-9-yl)furan-3,4-diol (12). This compound was prepared using 2-hydrazino-N^6-propyladenosine (**31**, 0.10 g, 0.30 mmol) and 2-(4-methoxyphenyl)malonaldehyde (0.07 g, 0.4 mmol) following the general procedure described above to afford 0.11 g (77%) of **12**. ^{1}H NMR (CD_3OD) δ 1.09−1.15 (m, 3H), 1.79−1.86 (m, 2H), 3.71−3.79 (m, 2H), 3.83−3.87 (m, 1H), 3.86 (s, 3H), 3.97−4.01 (m, 1H), 4.18−4.21 (m, 1H), 4.37−4.40 (m, 1H), 4.67 (t, 1H, *J* = 4.8 Hz), 6.13 (d, 1H, *J* = 4.4 Hz), 7.01−7.04 (m, 2H), 7.63−7.66 (m, 2H), 8.14 (s, 1H), 8.44 (s, 1H), 8.87 (s, 1H); MS *m*/*z* 482.2 $(M + H)^+$. Anal. ($C_{23}H_{27}N_7O_5\cdot1.2H_2O$): C, H, N.

(3*R*,4*S*,5*R*)-2-(6-(3-Iodobenzylamino)-2-(4-(4-methoxyphenyl)-1*H*-pyrazol-1-yl)-9*H*-purin-9-yl)-tetrahydro-5-(hydroxymethyl)furan-3,4-diol (13). This compound was prepared using 2-hydrazino-N^6-(3-iodobenzyl)adenosine (**32**, 0.15 g, 0.30 mmol) and 2-(4-methoxyphenyl)malonaldehyde (0.07 g, 0.4 mmol) following the general procedure described above to afford 0.14 g (73%) of **13**. ^{1}H NMR (DMSO) δ 3.43−3.62 (m, 2H), 3.58−3.81 (s, 3H), 3.97−3.99 (m, 1H), 4.20−4.22 (m, 1H), 4.65−4.69 (m, 1H), 5.96 (d, 1H, *J* = 6.0 Hz), 6.70−7.02 (m, 2H), 7.13−7.17 (m, 1H), 7.50−7.54 (m, 1H), 7.60−7.62 (m, 1H), 7.69−7.72 (m, 2H), 7.95 (s, 1H), 8.17−8.22 (m, 1H), 8.43 (s, 1H), 8.83 (s, 1H). Anal. ($C_{27}H_{26}IN_7O_5\cdot0.7H_2O$): C, H, N.

(2*R*,3*S*,4*R*)-Tetrahydro-2-(hydroxymethyl)-5-(6-(methylamino)-2-(4-(pyridin-4-yl)-1*H*-pyrazol-1-yl)-9*H*-purin-9-yl)furan-3,4-diol (14). This compound was prepared using 2-hydrazino-N^6-methyladenosine (**29**, 0.09 g, 0.30 mmol) and 2-(pyridin-4-yl)malonaldehyde (0.06 g, 0.4 mmol) following the general procedure described above to afford 0.10 g (78%) of **14**. ^{1}H NMR (CD_3OD) δ 3.11 (s, 3H), 3.65−3.70 (m, 1H), 3.78−3.82 (m, 1H), 4.00−4.05 (m, 1H), 4.20−4.25 (m, 1H), 4.50−4.55 (m, 1H), 5.95−5.99 (m, 1H), 8.17−8.27 (m, 3H), 8.44−8.46 (m, 1H), 8.58−8.64 (m, 2H), 9.42 (s, 1H); MS *m*/*z* 425 $(M + H)^+$. Anal. ($C_{19}H_{20}N_8O_4$): C, H, N.

(2*R*,3*S*,4*R*)-Tetrahydro-2-(hydroxymethyl)-5-(6-(methylamino)-2-(4-(pyridin-2-yl)-1*H*-pyrazol-1-yl)-9*H*-purin-9-yl)furan-3,4-diol (15). This compound was prepared using 2-hydrazino-N^6-methyladenosine (**29**, 0.09 g, 0.30 mmol) and 2-(pyridin-2-yl)malonaldehyde (0.06 g, 0.4 mmol) following the general procedure described above to afford 0.09 g (70%) of **15**. ^{1}H NMR (CD_3OD) δ 3.10 (s, 3H), 3.65−3.70 (m, 1H), 3.78−3.82 (m, 1H), 4.00−4.05 (m, 1H), 4.20−4.25 (m, 1H), 4.49−4.53 (m, 1H), 5.96−5.98 (m, 1H), 7.69−7.73 (m, 1H), 8.22−8.42 (m, 4H), 8.58−8.61 (m, 1H), 9.50 (s, 1H); MS *m*/*z* 425 $(M + H)^+$. Anal. ($C_{19}H_{20}N_8O_4$): C, H, N.

(2*R*,3*S*,4*R*)-Tetrahydro-2-(hydroxymethyl)-5-(6-(propylamino)-2-(4-(pyridin-2-yl)-1*H*-pyrazol-1-yl)-9*H*-purin-9-yl)furan-3,4-diol (16). This compound was prepared using 2-hydrazino-N^6-propyladenosine (**31**, 0.10 g, 0.30 mmol) and 2-(pyridin-2-yl)malonaldehyde (0.06 g, 0.4 mmol) following the general procedure described above to afford 0.11 g (81%) of **16**. ^{1}H NMR (CD_3OD) δ 1.11 (t, 3H, *J* = 7.2 Hz), 1.80−1.85 (m, 2H), 3.73−3.78 (m, 2H), 3.82−3.86 (m, 1H), 3.97−4.01 (m, 1H), 4.18−4.21 (m, 1H), 4.37−4.40 (m, 1H), 4.68 (t, 1H, *J* = 4.8 Hz), 6.12 (d, 1H, *J* = 4.8 Hz), 7.33−7.36 (m, 1H), 7.42−7.46 (m, 1H), 7.87−7.92 (m, 1H), 8.20−8.25 (m, 1H), 8.37 (s, 1H), 8.58−8.59 (m, 1H), 9.26 (s, 1H); MS *m*/*z* 453.1 $(M + H)^+$. Anal. ($C_{21}H_{24}N_8O_4\cdot0.5H_2O$): C, H, N.

(3*R*,4*S*,5*R*)-2-(6-(3-Iodobenzylamino)-2-(4-(pyridin-2-yl)-1*H*-pyrazol-1-yl)-9*H*-purin-9-yl)-tetrahydro-5-(hydroxymethyl)furan-3,4-diol (17). This compound was prepared using 2-hydrazino-N^6-(3-iodobenzyl)adenosine (**32**, 0.15 g, 0.30 mmol) and 2-(pyridin-2-yl)malonaldehyde (0.06 g, 0.4 mmol) following the general procedure described above to afford 0.13 g (69%) of **17**. ^{1}H NMR (CD_3OD) δ 3.49−3.65 (m, 2H), 3.87−3.91 (m, 1H), 4.09−4.11 (m, 1H), 4.48−4.52 (m, 1H), 4.58 (s, 2H), 5.74 (d, 1H), 7.09−7.13 (m, 1H), 7.20 (s, 1H), 7.39−7.51 (m, 3H), 7.69−7.74 (m, 2H), 8.00−8.03 (m, 2H), 8.92 (d, 1H); MS *m*/*z* 627.1 $(M + H)^+$. Anal. ($C_{25}H_{23}IN_8O_4\cdot0.5H_2O$): C, H, N.

(2*R*,3*S*,4*R*)-Tetrahydro-2-(hydroxymethyl)-5-(6-(methylamino)-2-(4-(quinolin-2-yl)-1*H*-pyrazol-1-yl)-9*H*-purin-9-yl)furan-3,4-diol (18). This compound was prepared using 2-hydrazino-N^6-methyladenosine (**29**, 0.09 g, 0.30 mmol) and 2-(quinolin-2-yl)malonaldehyde (0.08 g, 0.4 mmol) following the general procedure described above to afford 0.11 g (77%) of

18. ^{1}H NMR (CD_3OD) δ 3.31 (s, 3H), 3.84−3.88 (m, 1H), 3.97−4.01 (m, 1H), 4.20−4.22 (m, 1H), 4.40−4.42 (m, 1H), 4.70 (t, 1H, J = 5.2 Hz), 6.14 (d, 1H, J = 5.6 Hz), 7.87−7.91 (m, 1H), 8.09−8.14 (m, 1H), 8.24−8.29 (m, 2H), 8.41−8.44 (m, 2H), 8.76 (s, 1H), 8.95−8.99 (m, 1H), 9.82 (s, 1H); MS m/z 475 $(M + H)^+$. Anal. ($C_{23}H_{22}N_8O_4$): C, H, N.

(3*R*,4*S*,5*R*)-2-(6-(3-Iodobenzylamino)-2-(4-(isoquinolin-1-yl)-1*H*-pyrazol-1-yl)-9*H*-purin-9-yl)-tetrahydro-5-(hydroxymethyl)furan-3,4-diol (19). This compound was prepared using 2-hydrazino-N^6-(3-iodobenzyl)adenosine (**32**, 0.15 g, 0.30 mmol) and 2-(isoquinolin-3-yl)malonaldehyde (0.08 g, 0.4 mmol) following the general procedure described above to afford 0.12 g (84%) of **19**. ^{1}H NMR (CD_3OD) δ 3.84−3.88 (m, 1H), 3.97−4.01 (m, 1H), 4.20−4.22 (m, 1H), 4.40−4.42 (m, 1H), 4.70−4.72 (m, 1H), 4.98 (s, 2H), 6.16 (d, 1H, J = 5.2 Hz), 7.14−7.18 (m, 1H), 7.52−7.55 (m, 1H), 7.64−7.67 (m, 1H), 7.82−7.87 (m, 1H), 7.96−7.98 (m, 1H), 8.04−8.10 (m, 1H), 8.20−8.26 (m, 2H), 8.33−8.38 (m, 1H), 844 (s, 1H), 8.74 (s, 1H), 8.87−8.93 (m, 1H), 9.67 (s, 1H); MS m/z 475 $(M + H)^+$. Anal. ($C_{29}H_{25}IN_8O_4$): C, H, N.

(2*R*,3*S*,4*R*)-Tetrahydro-2-(hydroxymethyl)-5-(6-(methylamino)-2-(4-(pyrimidin-5-yl)-1*H*-pyrazol-1-yl)-9*H*-purin-9-yl)furan-3,4-diol (20). This compound was prepared using 2-hydrazino-N^6-methyladenosine (**29**, 0.09 g, 0.30 mmol) and 2-(pyrimidin-5-yl)malonaldehyde (0.06 g, 0.4 mmol) following the general procedure described above to afford 0.09 g (71%) of **20**. ^{1}H NMR (DMSO) δ 3.11 (s, 3H), 3.58−3.62 (m, 1H), 3.69−3.74 (m, 1H), 3.98−4.00 (m, 1H), 4.20−4.22 (m, 1H), 4.65 (t, 1H, J = 5.2 Hz), 5.98 (d, 1H, J = 6.4 Hz), 8.08 (d, 1H, J = 5.2 Hz), 8.31 (d, 1H, J = 4.0 Hz), 8.45 (s, 1H), 8.50 (s, 1H), 8.83 (d, 1H, J = 5.6 Hz), 9.19 (d, 1H, J = 1.2 Hz), 9.40 (s, 1H); MS m/z 426 $(M + H)^+$. Anal. ($C_{18}H_{19}N_9O_4$): C, H, N.

(3*R*,4*S*,5*R*)-2-(2-(4-(Benzo[*d*]oxazol-2-yl)-1*H*-pyrazol-1-yl)-6-(methylamino)-9*H*-purin-9-yl)-tetrahydro-5-(hydroxymethyl)furan-3,4-diol (21). This compound was prepared using 2-hydrazino-N^6-methyladenosine (**29**, 0.09 g, 0.30 mmol) and 2-(benzo[*d*]oxazol-2-yl)malonaldehyde (0.08 g, 0.4 mmol) following the general procedure described above to afford 0.12 g (86%) of **21.** ^{1}H NMR (DMSO) δ 3.40−3.80 (m, 5H), 3.98−4.01 (m, 1H), 4.19−4.23 (m, 1H), 4.64−4.68 (m, 1H), 5.99 (d, 1H, J = 5.6 Hz), 7.14−7.19 (m, 1H), 7.42−7.44 (m, 2H), 7.77−7.81 (m, 2H), 8.50 (s, 1H), 9.26 (s, 1H); MS m/z 465.1 $(M + H)^+$. Anal. ($C_{21}H_{20}N_8O_5 \cdot 0.5H_2O$): C, H, N.

Ethyl 1-(9-((3*R*,4*S*,5*R*)-Tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-6-(methylamino)-9*H*-purin-2-yl)-1*H*-pyrazole-4-carboxylate (33). This compound was prepared using 2-hydrazino-N^6-methyladenosine (**29**, 1.0 g g, 3.2 mmol) and ethyl 2,2-diformylacetate (0.60 g, 4.2 mmol) following the general procedure described above to afford 1.1 g (85%) of **33**. ^{1}H NMR (CD_3OD) δ 1.34−1.40 (m, 3H), 1.94−1.99 (m, 2H), 3.15 (s, 3H), 3.72−3.79 (m, 1H), 3.87−3.91 (m, 1H), 4.07−4.13 (m, 1H), 4.28−4.34 (m, 1H), 4.55−4.60 (m, 1H), 6.02−6.07 (m, 1H), 8.12 (s, 1H), 8.31 (s, 1H), 9.06 (s, 1H); MS m/z 420 $(M + H)^+$.

1-(9-((3*R*,4*S*,5*R*)-Tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-6-(methylamino)-9*H*-purin-2-yl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (5). Compound **33** (0.05 g, 0.12 mmol) was added to 4 mL methylamine (40% aqueous solution). The mixture was heated at 65 °C for 24 h. After concentration in vacuo, the residue was purified using prep. TLC (10% MeOH:DCM) to afford 0.04 g (72%) of compound **5.** ^{1}H NMR (DMSO) δ 2.78 (s, 3H), 3.08 (s, 3H), 3.56−3.59 (m, 1H), 3.65−3.72 (m, 1H), 3.96−3.98 (m, 1H), 4.17−4.20 (m, 1H), 4.62−4.65 (m, 1H), 5.96 (d, 1H, J = 6.0 Hz), 8.09 (s, 1H), 8.42 (s, 1H), 9.10 (s, 1H); MS m/z 405 $(M + H)^+$. Anal. ($C_{16}H_{20}N_8O_5$): C, H, N.

***N*-Ethyl-1-(9-((3*R*,4*S*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-6-(methylamino)-9*H*-purin-2-yl)-1*H*-pyrazole-4-carboxamide (6).** Compound **33** (0.05 g, 0.12 mmol) was added to 4 mL of ethylamine (70% aqueous solution). The mixture was heated at 65 °C for 24 h. After concentration in vacuo, the residue was purified using prep TLC (10% MeOH:DCM) to afford 0.03 g (60%) of compound **6**. ^{1}H NMR (CD_3OD) δ 1.00 (t, 3H), 2.97 (s, 3H), 3.17 (q, 2H), 3.55−3.58 (m, 1H), 3.63−3.70 (m, 1H), 3.97−3.99 (m, 1H), 4.16−4.20 (m, 1H), 4.60−4.65 (m, 1H), 5.95 (d, 1H, J = 6.0 Hz), 8.08 (s, 1H), 8.41 (s, 1H), 9.10 (s, 1H); MS m/z 419 $(M + H)^+$. Anal. ($C_{17}H_{22}N_8O_5$): C, H, N.

1-(9-((3*R*,4*S*,5*R*)-Tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-6-(methylamino)-9*H*-purin-2-yl)-*N*-propyl-1*H*-pyrazole-4-carboxamide (7). The ester **33** (0.5 g, 1.2 mmol) was dissolved in dry DMF (5 mL), TBDMSCl (1.5 g, 10 mmol) and imidazole (0.07 g, 10 mmol) was added, and the mixture was heated at 80 °C for 24 h. The solvent was evaporated, and the residue was purified by flash column chromatography (20:1, DCM:MeOH) to afford the protected ester derivative **34** in 88% yield.

The ester derivative **34** (0.8 g, 1 mmol) was suspended in 1 mL of water and treated with 4 mL of 1 M KOH/MeOH. The mixture was allowed to stir at RT for 72 h. The solvent was removed under reduced pressure. The residue was dissolved in 5 mL of water and acidified to pH 5 with 1 M HCl. The resulting precipitate was filtered and washed with water and ethyl ether to afford the acid derivative **35** which was used without further purification. ^{1}H NMR (DMSO) δ 0.24−0.50 (m, 18H), 1.07 (s, 9H), 1.23 (s, 9H), 1.28 (s, 9H), 3.39 (d, 3H, J = 4.8 Hz), 4.05−4.10 (m, 1H), 4.32−4.37 (m, 1H), 4.42−4.47 (m, 1H), 4.70−4.72 (m, 1H), 5.45−5.48 (m, 1H), 6.27 (d, 1H, J = 4.0 Hz), 8.38 (s, 1H), 8.76 (s, 1H), 9.31 (s, 1H), 13.09 (s, 1H).

The protected acid derivative (**35**, 0.14 g, 0.2 mmol) was dissolved in 10 mL DCM. To the solution were added propylamine hydrochloride (0.04 g, 0.4 mmol), HBTU (0.19 g, 0.4 mmol), HOBt (0.076 g, 0.4 mmol), *N*-methylmorpholine (0.04 g, 0.4 mmol) and cat. DMAP. The mixture was allowed to stir at RT for 24 h. The mixture was then washed with 10% citric acid, saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed, and the residue (without further purification) was treated with 5 mL of 1 M NH_4F/MeOH. The solution was heated at reflux for 24 h. The solvent was evaporated, and the residue was purified by preparative TLC (10:1, DCM:MeOH) to afford 0.06 g (75%) of compound **7** in 70% yield**.** ^{1}H NMR (CD_3OD) δ 0.94 (t, 3H), 1.56−1.63 (m, 2H), 2.97 (s, 3H), 3.21 (q, 2 H), 3.53−3.56 (m, 1H), 3.63−3.70 (m, 1H), 3.97−3.99 (m, 1H), 4.16−4.21 (m, 1H), 4.60−4.66 (m, 1H), 5.95 (d, 1H, J = 6.0 Hz), 8.08 (s, 1H), 8.42 (s, 1H), 9.11 (s, 1H); MS m/z 433 $(M + H)^+$. Anal. ($C_{18}H_{24}N_8O_5$): C, H, N.

***N*-(4-Chlorobenzyl)-1-(9-((3*R*,4*S*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-6-(methylamino)-9*H*-purin-2-yl)-1*H*-pyrazole-4-carboxamide (8).** The acid derivative (**35**, 0.14 g, 0.2 mmol) was dissolved in 10 mL of DCM. To the solution were added 4-Cl-benzylamine (0.06 g, 0.4 mmol), HBTU (0.19 g, 0.4 mmol), HOBt (0.076 g, 0.4 mmol), *N*-methylmorpholine (0.04 g, 0.4 mmol) and cat. DMAP. The mixture was allowed to stir at RT for 24 h. The mixture was then washed with 10% citric acid, saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed, and the residue (without further purification) was treated with 5 mL of 1 M NH_4F/MeOH. The solution was heated at reflux for 24 h. The solvent was evaporated, and the residue was purified by preparative TLC (10:1, DCM:MeOH) to afford 0.08 g (78%) of compound **8**. ^{1}H NMR (CD_3OD) δ 2.95 (d, 3H, CH_3), 3.49−3.65 (m, 2H, H-5′), 3.87−3.91 (m, 1H, H-4′), 4.09−4.11 (m, 1H, H-3′), 4.43 (s, 2H, CH_2−Bn), 4.48−4.51 (m, 1H, H-2′), 5.88 (s, 1H, H-1′), 7.15 (d, 2H, ArH), 7.25 (d, 2H, ArH), 7.91 (s, 1H, H-8), 8.26 (s, 1H, pyrazole), 9.93 (s, 1H, pyrazole); MS m/z 515.1 $(M + H)^+$. Anal. ($C_{22}H_{23}ClN_8O_5 \cdot 0.5H_2O$): C, H, N.

1-((3*R*,4*R*,5*R*)-2-{6-Chloro-2-[1-benzylpyrazol-4-yl]purin-9-yl}-4-(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-3-yloxy)-1,1,2,2-tetramethyl-1-silapropane (39). To a solution of **38** (0.5 g, 0.7 mmol) in 10 mL of DMF were added 1-benzyl-4-iodo-1*H*-pyrazole (0.28 g, 1.0 mmol), [tetrakis(triphenylphosphine)-palladium(0), 0.010 g] and cuprous iodide (0.005 g). The mixture was heated at 80 °C for 16 h. DMF was removed, and the residue was purified using column chromatography (50% EtOAc:Hex) to afford 0.3 g (56%) of **39**. ^{1}H NMR (DMSO) δ 0.24−0.51 (m, 18H), 1.08 (s, 9H), 1.22 (s, 9H), 1.28 (s, 9H),

4.06−4.10 (m, 1H), 4.32−4.37 (m, 1H), 4.42−4.47 (m, 1H), 4.70−4.72 (m, 1H), 4.88 (s, 2H), 5.45−5.48 (m, 1H), 6.27 (d, 1H, J = 4.0 Hz), 7.15 (m, 5H), 7.55 (s, 1H), 7.76 (s, 1H), 8.87 (s, 1H).

(9-{(3*R*,4*R*,5*R*)-3,4-Bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]-oxolan-2-yl}-2-[1-benzylpyrazol-4-yl]purin-6-yl)methylamine (22). To a solution of **39** (0.10 g, 0.13 mmol) in 1 mL of MeOH was added methylamine (40% aqueous solution, 3 mL), and the mixture was heated at 80 °C for 24 h. The solvent was removed under reduced pressure, and the residue was treated with 5 mL of 1 M NH_4F/MeOH, and the solution was heated at 80 °C for 24 h. The solvent was removed and the residue was purified using prep TLC (10:1, DCM:MeOH) to afford 0.034 g (60%) of compound **22**. ^{1}H NMR (DMSO) δ 3.04 (s, 3H), 3.55−3.62 (m, 1H), 3.68−3.74 (m, 1H), 3.98−4.00 (m, 1H), 4.20−4.22 (m, 1H), 4.69−4.72 (m, 1H), 5.41 (s, 2H), 5.92 (d, 1H, J = 6.4 Hz), 7.30−7.40 (m, 5H), 8.07 (s, 1H), 8.28 (s, 1H), 8.41 (s, 1H); MS m/z 438.2 $(M + H)^+$. Anal. ($C_{21}H_{23}N_7O_4 \cdot 0.5H_2O$): C, H, N.

(9-{(3*R*,4*R*,5*R*)-3,4-Bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl}-2-[1-benzylpyrazol-4-yl]purin-6-yl)propylamine (23). To a solution of **39** (0.10 g, 0.13 mmol) in 1 mL of MeOH was added propylamine (3 mL), and the mixture was heated at 60 °C for 24 h. The solvent was removed under reduced pressure, and the residue was treated with 5 mL of 1 M NH_4F/MeOH and the solution was heated at 80 °C for 24 h. The solvent was removed, and the residue was purified using prep TLC (10:1, DCM:MeOH) to afford 0.042 g (75%) of compound **23**. ^{1}H NMR (DMSO) δ 0.93 (t, 3H, J = 7.2 Hz), 1.62−1.69 (m, 2H), 3.52−3.62 (m, 3H), 3.68−3.74 (m, 1H), 3.98−4.00 (m, 1H), 4.20−4.22 (m, 1H), 4.69−4.73 (m, 1H), 5.41 (s, 2H), 5.91 (d, 1H, J = 6.4 Hz), 7.29−7.40 (m, 5H), 8.05 (s, 1H), 8.28 (s, 1H), 8.39 (s, 1H); MS m/z 66.2 $(M + H)^+$. Anal. ($C_{23}H_{27}N_7O_4 \cdot 0.3H_2O$): C, H, N.

Competition Binding Assays. Binding affinities of compounds **5**−**23** for the A_3-, A_1-, and A_{2A}-AdoRs were evaluated in radioligand binding assays using CHO cells stably expressing recombinant human A_1-AdoR and HEK cells stably expressing recombinant human A_{2A}- and A_3-AdoRs. The radioligands for the A_3, A_1- and A_{2A}-AdoRs were [^{125}I]AB-MECA, [^{3}H]CCPA and [^{3}H]CGS-21680, respectively.

Supporting Information Available: Elemental analysis table for compounds **5**−**23** and detailed binding and functional assays. This material is available free of charge via the Internet at http://pubs.acs.org

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