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Structure–activity relationships of adenosines with heterocyclic N^6-substituents

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Abstract—Two series of N^6-substituted adenosines with monocyclic and bicyclic N^6 substituents containing a heteroatom were synthesized in good yields. These derivatives were assessed for their affinity ([^{3}H]CPX), potency, and intrinsic activity (cAMP accumulation) at the A_1 adenosine receptor in DDT_1 MF-2 cells. In the monocyclic series, the N^6-tetrahydrofuran-3-yl and thiolan-3-yl adenosines (**1** and **26**, respectively) were found to possess similar activities, whereas the corresponding selenium analogue **27** was found to be more potent. A series of nitrogen containing analogues showed varying properties, N^6-((3*R*)-1-benzyloxycarbonylpyrrolidin-3-yl)adenosine (**30**) was the most potent at the A_1AR; IC_{50} = 3.2 nM. In the bicyclic series, the effect of a 7-azabicyclo[2.2.1]heptan-2-yl substituent in the N^6-position was explored. N^6-(7-Azabicyclo[2.2.1]heptan-2-yl)adenosine (**38**) proved to be a reasonably potent A_1 agonist (K_i = 51 nM, IC_{50} = 35 nM) while further substitution on the 7″-nitrogen with *tert*-butoxycarbonyl (**31**, IC_{50} = 2.5 nM) and 2-bromobenzyloxycarbonyl (**34**, IC_{50} = 9.0 nM) gave highly potent A_1AR agonists.

Adenosine is an endogenous ligand which acts in a non-selective manner upon the four subtypes of adenosine receptors (ARs), A_1, A_{2A}, A_{2B}, and A_3. All subtypes are connected to the cyclic adenosine monophosphate (cAMP) producing enzyme, adenylate cyclase, through G-protein coupling. Activation of the A_{2A} and A_{2B} subtypes leads to the stimulation of the cAMP production, whereas activation of the A_1 and A_3 leads to an inhibition of this second messenger.

The A_1AR has been implicated in many tissue types with various physiological effects. In the cardiovascular system, A_1ARs mediate negative chronotropic, dromotropic, and inotropic effects as well as having cardioprotective effects.[1–3] Activation decreases transmitter release and locomotor activity in the central nervous system (CNS); they also have anti-lipolytic effects.[1–3] Exploitation of the negative dromotropic effect of adenosine has seen its utilization in the treatment of paroxysmal supraventricular tachycardia (PSVT).[4] However, as a result of adenosine's short plasma half-life, up to 35% of tachycardias have been reported to recur within 2 min of termination. Accordingly, much research has been undertaken in the development of potent A_1AR agonists with longer plasma half-lives.[2,3] One of these agents, Tecadenoson (CVT-510, **1**), is currently in Phase III clinical trials for the treatment of PSVT.[5,6]

High potency and selectivity for the A_1AR can be achieved through mono-substitution of *exo*-cyclic nitrogen of adenosine with a hydrophobic group. Adenosine analogues with carbocyclic, heterocyclic or bicyclic N^6-substituents are among the more potent A_1AR agonists known [e.g., Tecadenoson (**1**) and ENBA (**2**),[7] Fig. 1]. Substitution of this position also renders the molecule more stable towards deamination by adenosine deaminase,[8] and subsequently, improves half-life. The incorporation of a halogen in the 2-position[9] and certain 5′-modifications such as the replacement of the hydroxyl group with fluoro or chloro[7] have also been found to

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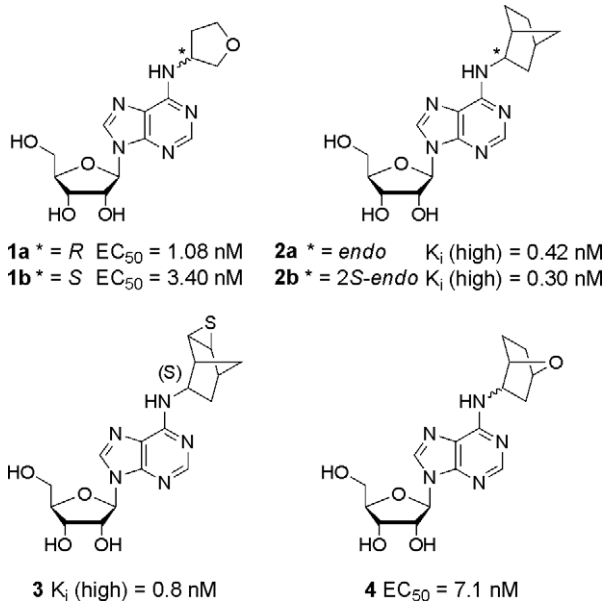


Figure 1. A_1 Adenosine receptor agonists.

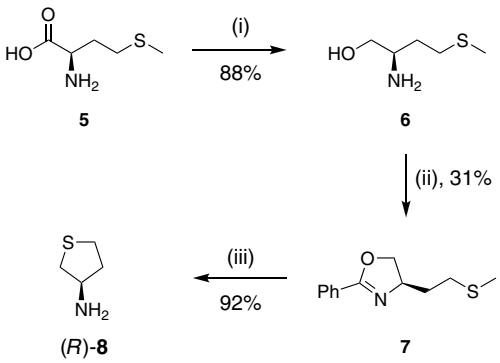
be favorable for A_1AR activity. Alternative substituent patterns are well known to confer selectivity for the other receptor subtypes.[10–12]

Previous work in our laboratory has demonstrated high activities at the A_1AR when a sulfur atom is present in the N^6-substituent (e.g. thiirane **3**).[13] Based on these findings we investigated sulfur, selenium, and nitrogen isosteres of other N^6-substituted adenosines with high affinity for the A_1AR. Isosteres of Tecadenoson (**1**) and 7-oxabicyclo[2.2.1]heptan-2-yl adenosine (**4**)[14] were targeted.

Adenosines bearing an N^6-substituent are readily synthesized from an appropriately functionalized purine riboside and the corresponding amine. Accordingly, we required the amines necessary to generate the target compounds.

The synthesis of optically pure (*R*)-3-aminothiolane (**8**) was prepared using the approach developed by Dehmlow and Westerheide for the synthesis of the corresponding (*S*)-isomer (Scheme 1).[15] (*R*)-Methioninol (**6**) was prepared smoothly in 88% yield via $NaBH_4/I_2$ reduction of D-methionine (**5**). Subsequent zinc bromide catalyzed condensation in neat benzonitrile gave the required 4,5-dihydrooxazole (**7**) in low yield (31%), however this gave sufficient quantities to continue. Reflux in harsh acidic conditions (conc. HCl in AcOH) cyclized **7** to give **8** as a phenyl amide which was subsequently hydrolyzed, in the same pot, under basic conditions to give the desired (*R*)-aminothiolane (**8**) in excellent yield (92%).

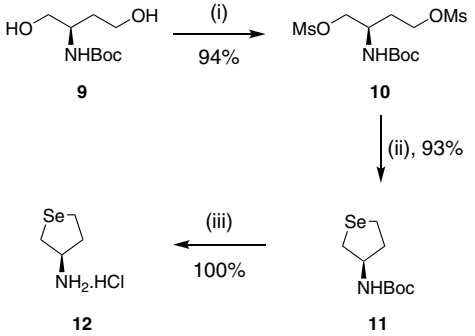
The analogous selenolane was also conveniently accessed from an amino acid precursor. The conversion of D-asparagine to the boc-protected D-asparagininol (**9**) was achieved via known procedures.[16–18] The diol was then mesylated at the two terminal hydroxy positions to give **10** in excellent yield (94%) using methanesulfonyl chloride and triethylamine in CH_2Cl_2 (Scheme 2).[19] Selenium was incorporated as a selenolane via tandem nucleophilic displacement of the mesylate groups using sodium selenide which was generated in situ from selenium powder and $NaBH_4$ in EtOH. Finally, the boc-group was removed using 2 M HCl in Et_2O to give the (*R*)-3-aminoselenolane (**12**) as the hydrochloride salt in quantitative yield.



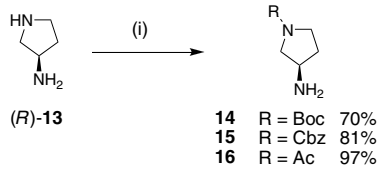
Scheme 1. Reagents and conditions: (i) $NaBH_4$, I_2, THF, 66 °C; (ii) $ZnBr_2$, PhCN, 120 °C; (iii) a—conc. HCl, AcOH, 100 °C; b—KOH, H_2O, 100 °C.

Commercially available (*R*)-3-aminopyrrolidine (**13**) was used for the preparation of nitrogen analogues of **1**. Conversion of the **13** to the corresponding Boc carbamate **14** was achieved as per Fujimoto and Hoshino (Scheme 3).[20] Replacement of di-*tert*-butyl dicarbonate with dibenzyl dicarbonate gave the benzyl carbamate **15**. The use of acetic anhydride gave the N-protected acetamide **16**. Due to the water solubility of acetyl amine and the bis-acetylated by-product it was necessary to purify this amine via column chromatography whereas the others were obtained from extraction.

The nitrogen isosteres of ENBA (**2**) required a slightly more involved synthesis of the amine synthons. The extensive SAR data available on A_1AR agonists indicate the norborn-2-yl N^6-substitution with the *endo*-conformation in the 2-position leads to higher affinities.[7] As a result, *endo*-7-azabicyclo[2.2.1]heptan-2-yl amines



Scheme 2. Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, rt; (ii) a—Se, $NaBH_4$, EtOH, 78 °C; b—**10**, THF, 66 °C; (iii) HCl, Et_2O, 30 °C.



Scheme 3. Reagents and condition: (i) R_2O, HCl, MeOH, 0 °C.

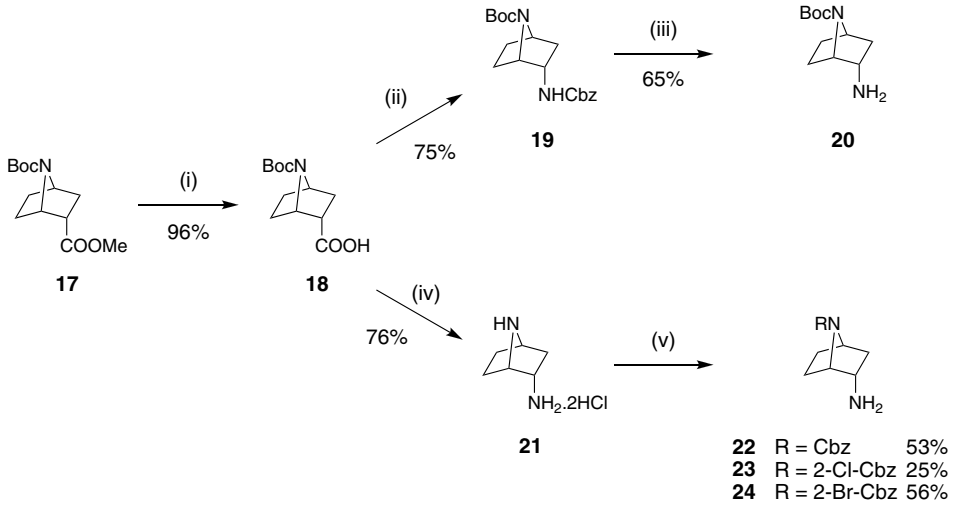
were targeted. The synthesis of the (±)-methyl *endo*-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]heptyl-2-carboxylate (**17**) has already been reported and provided an ideal starting point as it contains the aza-bridge and the 2-substituent in *endo*-stereochemistry.[21,22] Basic hydrolysis ($LiOH{\cdot}H_2O$ in $MeOH{:}H_2O$) of the methyl ester, **17**, followed by acidification gave the free carboxylic acid **18** in excellent yield (96%, Scheme 4). Further elaboration, through two complimentary synthetic routes, provided our desired amine synthons. The *tert*-butoxycarbonyl substituted amine **20** was prepared in two steps. This initially involved conversion of the carboxylic acid **18** to the corresponding acyl azide using diphenylphosphorylazide (DPPA) and Et_3N, followed by Curtius rearrangement and trapping of the intermediate isocyanate with benzyl alcohol to give the benzyl carbamate **19**. Selective cleavage of the benzyl carbamate (Pd–C under H_2 atmosphere) afforded the target amine (±)-**20** in 53% yield.

Benzyloxycarbonyl substituted amines **22**–**24** were also prepared from the carboxylic acid **18**. In this case it was envisaged that acid hydrolysis of the isocyanate formed in the Curtius rearrangement would also lead to the removal of the boc-group from the 7-position to give the diamine, **21**. Our initial attempts at heating in 1 M HCl solution overnight were sufficient for removal of the protecting group, but not harsh enough to fully convert the isocyanate to the corresponding amine. Eventually, full conversion to the 2-amine was achieved using 4 M HCl, heating at 130 °C under microwave irradiation for 2 h. In instances when pressure in the microwave vessel exceeded 13 bar, heating was ceased and the reaction vessel was cooled and vented before being heated again. This was sufficient to avoid a cumulative build up in pressure. Benzyloxycarbonyl substituents were subsequently introduced using either Cbz_2O (for **22**) or the relevant succinimide carbamate reagent (for **23** and **24**).

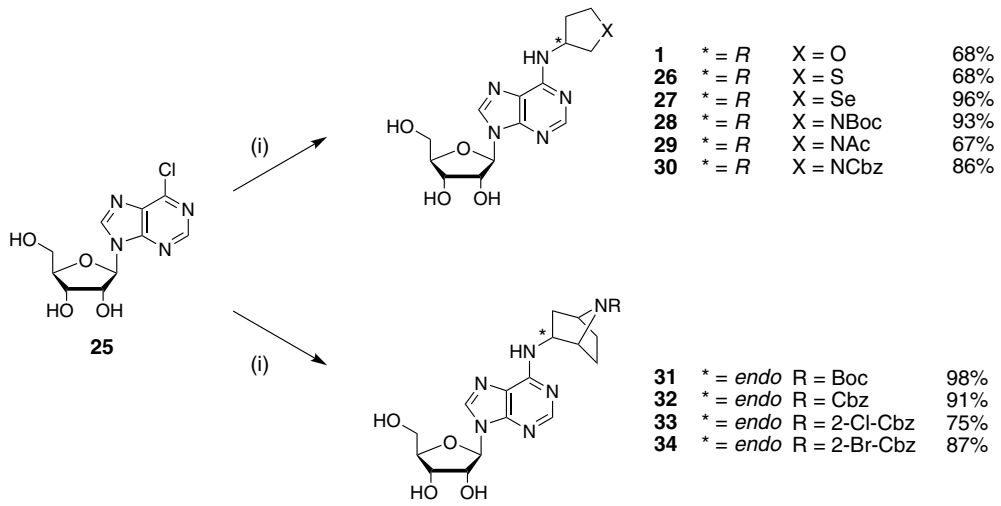
With the required amine synthons in hand, the corresponding N^6-substituted adenosines could be routinely prepared from the commercially available 6-chloropurine riboside (**25**) using standard S_NAr conditions [$N(i\text{-}Pr)_2Et$, *t*-BuOH, Scheme 5]. Tecadenoson (**1**) was synthesized using the aforementioned conditions with commercially available (*R*)-(+)-3-aminotetrahydrofuran toluene-4-sulfonate. In the case of the acetamide analogue **29**, difficulties with the separation of the $N(i\text{-}Pr)_2Et$ from the product lead to the use of NH_4OH solution as an alternative acid scavenger. Yields of the S_NAr reactions ranged from 67% to 99%.

Successful deprotection of the secondary amine was often precluded by the sensitivity of the glycosidic bond. Consequently, 6-chloro-9-(2,3,5-tris-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl)-9*H*-purine (**35**)[23] was used to form the per-silylated adenosine derivative **36** under standard S_NAr conditions (Scheme 6). The use of the TBS-protecting groups facilitated $ZnBr_2$ promoted deprotection of the boc-group by instating solubility in the reaction media (CH_2Cl_2).[24] This gave the free amine **37** in good yield (78%) following partitioning between CH_2Cl_2 and satd $NaHCO_3$. Full deprotection, to give the adenosine analogue **38**, was then achieved in 85% yield by warming in MeOH in the presence of ammonium fluoride.

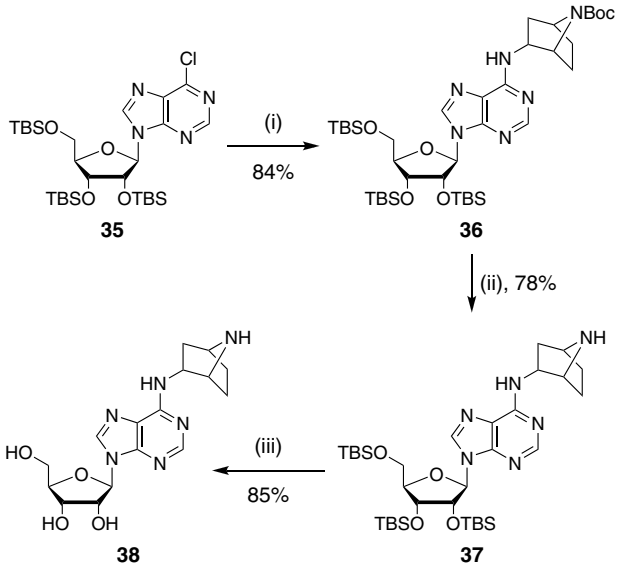
The affinity of the compounds was determined by their ability to displace [^{3}H]CPX binding at the A_1AR in DDT_1 MF-2 cell membranes and also [^{3}H]ZM241385



Scheme 4. Reagents and conditions: (i) $LiOH{\cdot}H_2O$, $MeOH{:}H_2O$ (1:1), rt; (ii) a—DPPA, Et_3N, Toluene 100 °C; b—BnOH, 100 °C; (iii) H_2, Pd–C (10%), MeOH, rt; (iv) a—DPPA, Et_3N, MeCN; b—4 M HCl, MW, 130 °C, 2 h; (v) $NaHCO_3$, $MeOH{:}H_2O$ (2:1), 0 °C, Cbz_2O for **22**; Z[2-Cl]-OSu for **23**; Z[2-Br]-OSu for **24**.



Scheme 5. Reagents and conditions: (i) amine or amine salt, N(*i*-Pr)$_2$Et, *t*-BuOH, 83 °C (for **29**; NH_4OH, *t*-BuOH, 83 °C).



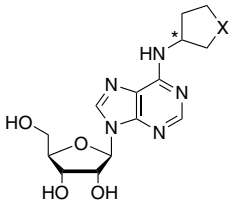
Scheme 6. Reagents and conditions: (i) **20**, N(*i*-Pr)$_2$Et, *t*-BuOH, 83 °C; (ii) $ZnBr_2$, CH_2Cl_2, rt; (iii) NH_4F, MeOH, 55 °C.

binding at the A_{2A}AR in PC-12 membranes (Tables 1 and 2).[25,26] These assays contained 5′-guanylyl-imidodiphosphate to maintain the receptor in the agonist low affinity state. Using intact DDT cells, each compound was tested for potency to inhibit (−)-isoproterenol-stimulated cAMP accumulation. The maximal inhibition of cAMP accumulation (intrinsic activity) by the compounds was also determined by comparison to the classical A_1 agonist, N^6-cyclopentyladenosine (CPA).

Consistent with a previous report, Tecadenoson (**1**) showed nanomolar affinity and potency at the A_1AR and was a full agonist as compared to CPA.[5] When a chalcogen is present as part of the cyclic N^6-substituent high affinity for the A_1AR is observed. N^6-(*R*-Thiolan-3-yl)adenosine (**26**) possessed similar affinity and potency to **1**. The corresponding selenolane **27** also showed low nanomolar affinity with a K_i = 8 nM as well as high potency (IC_{50} = 1.9 nM). Pyrrolidine based N^6-substituents exhibited a larger range and interesting properties at the A_1AR. When the secondary amine of the N^6-pyrrolidinyl group was *tert*-butoxycarbonyl substituted (compound **28**), it displayed poor affinity and potency (K_i = 929 nM, IC_{50} = 380 nM). However, when an acetamide was present (compound **29**), the affinity was similar (K_i = 803 nM) but the potency increased five-fold (IC_{50} = 85 nM). Even more significant, the benzyl carbamate **30** showed a three-fold improvement in affinity (K_i = 288 nM, cf. **28**) and over two orders of magnitude enhancement in potency, with an IC_{50} of 3.2 nM. The differential between affinity and potency may be due to structurally related alterations in the efficacy of the compounds. According to receptor occupation theory, the potency of an agonist is dependent upon both affinity and efficacy where the latter is estimated from the relationship between receptor occupancy and response. Thus there will be an increase in efficacy and hence potency when a fewer number of receptors are activated to produce a given level of response. All of the pyrrolidine derivatives were full agonists at the A_1AR as they produced the same maximal inhibition of (−)-isoproterenol-stimulated cAMP accumulation as did CPA. The N^6-monocyclic adenosine analogues had relatively weak affinity for the A_{2A}AR, with only **26** and **27** (K_i = 9700 and 5500 nM, respectively) possessing a K_i below 100,000 nM. Thus the A_1AR selectivity versus the A_{2A}AR ranged from about 140-fold for **26** to over 4700-fold for compounds **1** and **28**–**30**.

The N^6-aza-bicyclic analogues showed considerable variation in interaction with and agonist effect at the A_1AR (Table 2). The free amine analog **38** exhibited relatively high affinity and potency (51 and 35 nM, respectively). The *tert*-butyl carbamate **31** has about the same affinity as **38** but a 14-fold higher potency whereas the Cbz analogue **32** has a two- to three-fold decrease in both affinity and potency as compared to **38**. 2-Chloro substitution of Cbz (compound **33**) resulted in a 4.8- and 3.7-fold decrease in affinity and potency, respectively, in relation to the unsubstituted analogue **32**. In contrast, 2-bromo substitution of Cbz (**34**) showed a 7.8-fold increase in affinity and

Table 1. K_i, IC_{50} and intrinsic activity (IA) of N^6-monocyclic adenosine derivatives

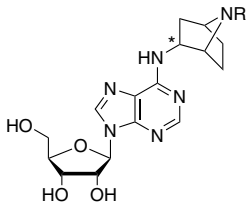


Entry	X	No.	A_1AR Data[a]			A_{2A}AR Data[b]
			K_i (nM)	IC_{50} (nM)	IA	K_i (nM)
1	O	**1**	65 ± 16 (3)	8.2 ± 1.2 (3)	1.00 ± 0.02 (3)	>100,000 (4)
2	S	**26**	70 ± 9 (3)	5.3 ± 2 (4)	0.98 ± 0.01 (4)	9700 ± 1200 (4)
3	Se	**27**	8 ± 2 (4)	1.9 ± 0.1 (4)	1.01 ± 0.02 (4)	5500 ± 500 (3)
4	NBoc	**28**	929 ± 397 (3)	380 ± 84 (3)	0.99 ± 0.04 (3)	>100,000 (4)
5	NAc	**29**	803 ± 341 (4)	85 ± 24 (4)	1.00 ± 0.05 (4)	>100,000 (4)
6	NCbz	**30**	288 ± 127 (3)	3.2 ± 0.4 (3)	0.99 ± 0.03 (3)	>100,000 (4)

[a] The K_i values were calculated from the concentration of the compounds that initiated [^{3}H]CPX binding by 50%. The assays were performed in the presence of Gpp(NH)p and therefore the K_i values represent the agonist low affinity binding state. IC_{50} values are concentrations of compounds that inhibited (−)-isoproterenol (1 μM)-stimulated cAMP accumulation by 50% in DDT cells. The IA is the maximal inhibition of (−)-isoproterenol-stimulated cAMP accumulation as compared to the maximum inhibition by CPA which was set at 1.00. Numbers in parentheses are the *n*.

[b] The K_i values were calculated from the concentration of compounds that inhibited [^{3}H]ZM241385 binding by 50%. Numbers in parentheses are the *n*. The notation of >100,000 indicates that at the highest concentration of the compounds used (100,000 nM), less than 50% inhibition of [^{3}H]ZM241385 binding was observed. NECA was included as a standard and was found to have a K_i of 110 ± 10 nM in this assay.

Table 2. K_i, IC_{50} and intrinsic activity (IA) of N^6-bicyclic adenosine derivatives



Entry	R	No.	A_1AR Data[a]			A_{2A}AR Data[b]
			K_i (nM)	IC_{50} (nM)	IA	K_i (nM)
1	H	**38**	51 ± 16 (5)	35 ± 9 (4)	1.02 ± 0.04 (4)	7800 ± 1500 (3)
2	Boc	**31**	32 ± 8 (5)	2.5 ± 0.5 (4)	1.01 ± 0.02 (4)	34,700 ± 3,900 (3)
3	Cbz	**32**	164 ± 9 (3)	68 ± 13 (6)	1.01 ± 0.02 (6)	>100,000
4	2-Cl-Cbz	**33**	783 ± 73 (3)	254 ± 58 (6)	0.86 ± 0.04 (6)	>100,000
5	2-Br-Cbz	**34**	21 ± 4 (3)	9.0 ± 2.7 (6)	0.97 ± 0.02 (6)	>100,000

[a] The K_i values were calculated from the concentration of the compounds that initiated [^{3}H]CPX binding by 50%. The assays were performed in the presence of Gpp(NH)p and therefore the K_i values represent the agonist low affinity binding state. IC_{50} values are concentrations of compounds that inhibited (−)-isoproterenol (1 μM)-stimulated cAMP accumulation by 50% in DDT cells. The IA is the maximal inhibition of (−)-isoproterenol-stimulated cAMP accumulation as compared to the maximum inhibition by CPA which was set at 1.00. Numbers in parentheses are the *n*.

[b] The K_i values were calculated from the concentration of compounds that inhibited [^{3}H]ZM241385 binding by 50%. Numbers in parentheses are the *n*. The notation of >100,000 indicates that at the highest concentration of the compounds used (100,000 nM), less than 50% inhibition of [^{3}H]ZM241385 binding was observed. NECA was included as a standard and was found to have a K_i of 110 ± 10 nM in this assay.

7.6-fold increase in potency as compared to **32**. As with the pyrrolidine analogues, all of the N^6-aza-bicyclic derivatives produced the same maximal inhibition of cAMP accumulation as CPA indicating that these compounds acted as full agonists at the A_1AR. As observed for the monocyclic series, the adenosines with bicyclic N^6-substituents also proved to be selective for the A_1AR over the A_{2A}AR.

In summary, two series of N^6-substituted adenosines with monocyclic and bicyclic N^6-substituents containing a heteroatom were synthesized and evaluated as A_1AR agonists. In the monocyclic series, it was found that N^6-((*R*)-seleolan-3-yl)adenosine (**27**) had the highest affinity, potency and selectivity. In the bicyclic series, N^6-(7-azabicyclo[2.2.1]heptan-2-yl)adenosine (**38**) proved to be a reasonably potent A_1 agonist (K_i = 51 nM, IC_{50} = 35 nM) while further substitution on the bridging nitrogen with *tert*-butoxycarbonyl (**31**, IC_{50} = 2.5 nM) and 2-bromobenzyloxycarbonyl (**34**, IC_{50} = 9.0 nM) gave highly potent and selective (as compared to the A_{2A}) A_1AR agonists.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.10.028.

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