Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 16 (2008) 1861–1873
Bioorganic & Medicinal Chemistry

N^6-substituted C5′-modified adenosines as A_1 adenosine receptor agonists

T. D. Ashton,[a] Stephen P. Baker,[b] Sally A. Hutchinson[c] and Peter J. Scammells[a,*]

[a]*Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University, 381 Royal Parade, Parkville, Vic. 3052, Australia*
[b]*Department of Pharmacology & Therapeutics, University of Florida College of Medicine, Box 100267, Gainesville, FL 32610, USA*
[c]*CSIRO Textile and Fibre Technology, Henry street, Belmont, Vic. 3216, Australia*

Received 19 August 2007; revised 23 October 2007; accepted 1 November 2007
Available online 6 November 2007

Abstract—Adenosines bearing 5′-modification in conjunction with an N^6-substituent have previously been shown to act as partial agonists at the A_1 adenosine receptor. Our current work investigates the effect of modifying the 5′-position in conjunction with efficacious bicyclic and tricyclic N^6-substituents. Several highly potent agonists for the A_1 adenosine receptor were identified; however, all of these compounds behaved as full agonists. In keeping with previous reports, 5′-halogen and 5′-sulfide derivatives of N^6-(*endo*-norborn-2-yl)adenosine were, in general, low nanomolar agonists of the A_1 adenosine receptor. The known partial agonist, N^6-cyclopentyl-5′-deoxy-5′-ethylthioadenosine (**2**), also behaved as a full agonist in our assay.

1. Introduction

Adenosine is an endogenous hormone that mediates a variety of physiological and pathophysiological processes. The functions of adenosine are mediated through binding interactions with adenosine receptors (AR), which are part of the super-family of G-protein coupled receptors. Adenosine receptors consist of four known subtypes; A_1 and A_3, which inhibit adenylate cyclase activity, as well as A_{2A} and A_{2B}, which stimulate adenylate cyclase leading to an increase in intracellular cAMP. Adenosine receptors are widely distributed throughout the body including the heart, central nervous system, lymphocytes and kidneys.[1] Adenosine, marketed as Adenocard®, is currently used in the treatment of paroxysmal supraventricular tachycardia. However, adenosine also produces side effects as a result of the widespread distribution of adenosine receptors and its lack of receptor subtype selectivity. These side effects are limited by adenosine's short half-life which results from its rapid breakdown in plasma by adenosine deaminase.[2] However, the short half-life also limits adenosine's suitability for long-term control of ventricular rate in cases of atrial flutter or fibrillation.[2] These issues have stimulated interest in the development of agents which are both receptor subtype selective and have improved metabolic stability. Achieving selectivity for the A_1AR is well documented; in general, a cycloalkyl or heterocyclic substituent on the *exo*-cyclic nitrogen of adenosine will confer a degree of subtype selectivity. Certain 5′-modifications and/or the incorporation of a halogen in the 2-position are also known to improve A_1AR affinity and selectivity.[3]

There has also been interest in the development of partial agonists for the A_1AR. By definition, a partial agonist generates a sub-maximal response when there is full receptor occupancy. This sub-maximal response may prevent unwanted adverse events from occurring. For example, a partial A_1AR agonist may be able to slow conduction in the atrio-ventricular (A-V) node and provide ventricular rate control without producing high degrees of A-V block that may occur with a full agonist.[4] Diminished receptor desensitisation has also been observed for partial agonists.[3]

In the development of partial agonists, a series of N^6-substituted adenosines bearing carbamates and thiocarbamates (e.g., CVT-2759, **1**) (Fig. 1) in the 5′-position showed partial agonist profiles.[5,6] Furthermore, adenosine analogues possessing a 5′-sulfide and

Keywords: Adenosine; A_1AR agonist.
* Corresponding author. Tel.: +61 3 9903 9542; fax: +61 3 9903 9582; e-mail: peter.scammells@vcp.monash.edu.au

0968-0896/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2007.11.010

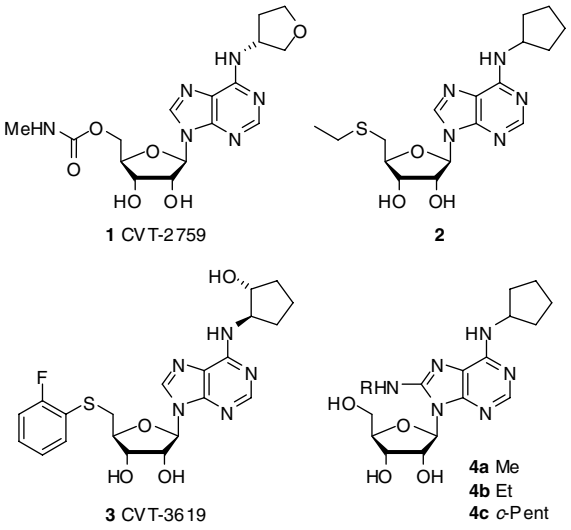


Figure 1. Partial agonists at the A_1 adenosine receptor.

N^6-substituent (e.g., **2** and **3**) have been identified as A_1AR selective partial agonists.[7] In particular, CVT-3619 (**3**), a modified adenosine bearing a 5′-arylsulfide, has been shown to reduce lipolysis in epididymal and inguinal adipocytes whilst not effecting atrial rate.[8] Compounds possessing an N^6-cycloalkyl substituent and 8-alkylamino motif (**4a**–**c**) were also shown to have partial agonist activity at the A_1AR in rat brain slices or membranes.[9] The synthesis of N^6-norbornyl adenosine derivatives has been reported previously and several were shown to be potent, selective and full agonists for the A_1AR.[10–12] In an attempt to take advantage of the potency and selectivity conferred by an N^6-norbornyl group[13] in the development of new partial A_1AR agonists, a series of 5′-derivatives of N^6-(*endo*-norborn-2-yl)adenosine and N^6-(2*S*-*exo*-5,6-epithio-*endo*-norborn-2-yl)adenosine were prepared and examined for affinity, potency and intrinisic activity (IA, maximal response) at the A_1AR in DDT_1 MF-2 cells.

2. Results and discussion

In previous work, we have described the synthesis of 5′-deoxy-N^6-(*endo*-norborn-2-yl)-5′-fluoroadenosine (**5**)[14] (Fig. 2) and have also reported a convenient method of generating 5′-modified N^6-substituted adenosines from 2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)inosine.[15] This approach was applied to the synthesis of N^6-(*endo*-norbornyl)adenosine analogues containing methylthio (**6**), methylseleno (**7**), amino (**8**) and propylamino (**9**) moieties in the 5′-position. Continuation of this work has seen further elaboration of this series.

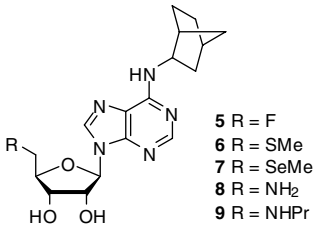


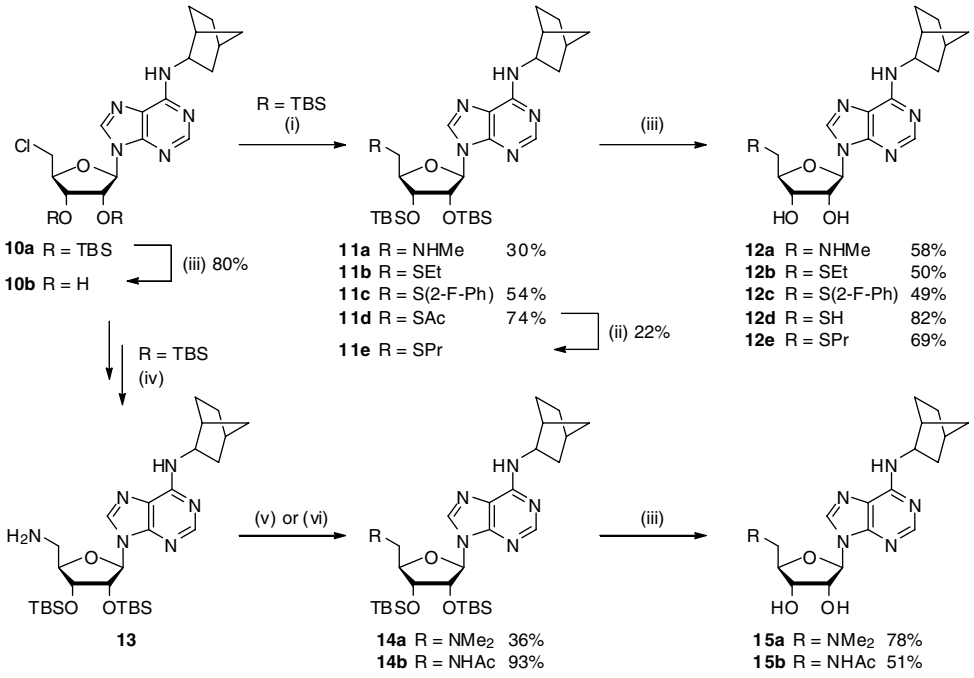
Figure 2. 5′-Modified N^6-nornorn-2-yladenosines.

2′,3′-Bis-*O*-(*tert*-butyldimethylsilyl)-5′-chloro-5′-deoxy-N^6-(*endo*-norborn-2-yl)adenosine (**10a**) was the starting point for our N^6-norbornyl series and was synthesised as previously reported.[15] When **10a** was treated with sodium ethanethiolate (10.0 equiv) we observed good conversion of the primary chloride; however, crude ^{1}H NMR and mass spectra indicated the formation of **11b** as well as concurrent deprotection (Scheme 1).[15] With this in mind we synthesised 5′-deoxy-N^6-(*endo*-norborn-2-yl)-5′-ethylthioadenosine (**12b**) by the treatment of **10a** with sodium ethanethiolate in DMF at ambient temperature. The TBS protecting groups were subsequently cleaved using ammonium fluoride in MeOH at elevated temperature to give **12b** in 50% yield over two steps. We found the conversion to the propylsulfide to also be problematic as full conversion was unable to be achieved, and the starting material and product were inseparable by chromatography (on silica). Consequently, we adopted a complimentary approach which involved the introduction and alkylation of a 5′-thiol. Thioacetates have been reported as a suitable precursor for the inclusion of 5′-sulfides.[16] Substitution of the primary chloride, **10a**, with potassium thioacetate in DMF at ambient temperatures gives the masked thiol in very good yield (74%). It is of note that performing this reaction at elevated temperatures led to the formation of a coloured impurity which was inseparable via column chromatography. Treatment of the thioester **11d** with *n*-bromopropane in MeOH with the addition of sodium deprotected the acetate in situ and subsequently alkylated the thiol that was formed to give the desired propylsulfide, **11e**.

Nitrogen analogues were also obtained from both nucleophilic and electrophilic processes. The 5′-methylamino analogue **11a** was synthesised in 30% yield by heating **10a** in a sealed in tube in 40% methylamine in MeOH solution. The bulk of the remaining material recovered was unreacted starting material (63%). The 5′-amino-N^6-substituted adenosine **13** was synthesised as previously reported and was used as the starting point for the preparation of other nitrogen analogues.[15] Reductive amination of **13**, using an excess of formaldehyde and sodium cyanoborohydride in MeCN at pH 7, gave the 5′-dimethyl analogue **14a** in a 36% yield. The secondary amide **14b** was established through treatment of the primary amine with acetic anhydride in pyridine at room temperature in excellent yield (93%).

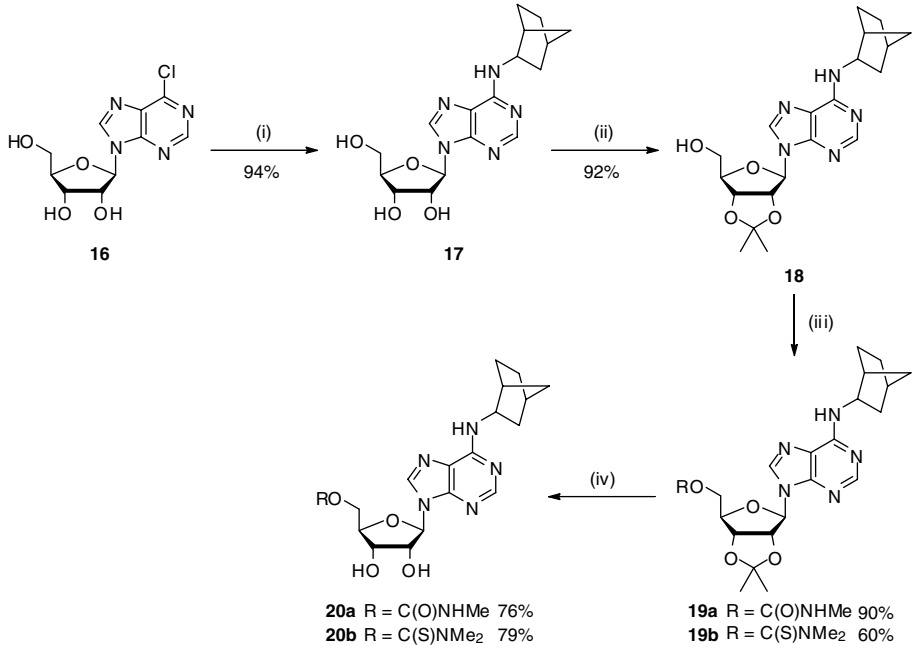
Removal of the TBS-ethers was achieved by warming with NH_4F in MeOH to give the target compounds **12a**, **12c**–**12e**, **15a** and **15b** in moderate to very good yields (49–82%). Reaction of **11d** with NH_4F led to the removal of the acetate group and extended reaction times allowed the 5′-thiol **12d** to be isolated as the sole product.

Examples of 5′-carbamates and thiocarbamates were also prepared based on reports of this functionality lead-



Scheme 1. Reagents and conditions: (i) for **11a**, $MeNH_2$, MeOH, 60 °C; for **11b**, NaSEt, DMF, rt; for **11c**, 2-fluorothiophenol, NaH, THF then **10a**, 0 °C—rt; for **11d**, KSAc, DMF, rt; (ii) *n*-PrBr, Na, MeOH, −20 °C—rt; (iii) NH_4F, MeOH, 50 °C; (iv) Ref. 15; (v) H_2CO, H_2O, $NaBH_3CN$, pH 7, MeCN, rt; (vi) Ac_2O, pyridine, 0 °C—rt.

ing to attenuated intrinsic activities.[5] Isopropylidenated N^6-(*endo*-norborn-2-yl)adenosine (**18**) was prepared in two steps from 6-chloropurine riboside (**16**) (Scheme 2). Firstly, the N^6-substituted adenosine **17** was prepared in excellent yield (94%) from **16** using (±)-*endo*-norborn-2-yl amine.HCl in the presence of Hünigs base [$N(i\text{-}Pr)_2Et$] in refluxing *t*-BuOH. Protection of **17** as the acetonide **18** was achieved using *para*-toluenesulphonic acid and 2,2-dimethoxypropane in acetone at room temperature in 92% yield. The carbamate derivative **19a** was then prepared via a sodium hydride generated alkoxide which was treated with carbonyl-1,1′-diimidazole (CDI), followed by a $MeNH_2$/MeOH solution to give the methylcarbamate in very good yield (90%). Following the method of Barma et al., the thiocarbamate derivative **19b** was formed in 60% yield by treating **18** with

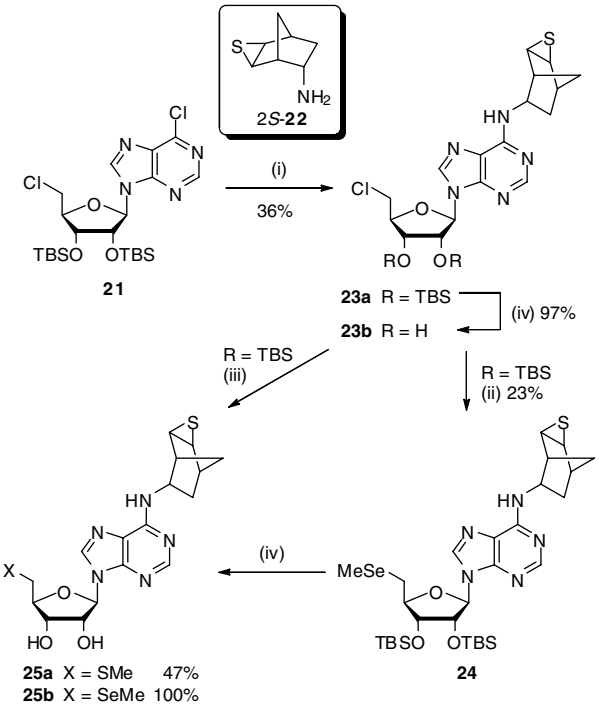


Scheme 2. Reagents and conditions: (i) (±)-*endo*-norborn-2-yl amine·HCl, $N(i\text{-}Pr)_2Et$, *t*-BuOH, 83 °C; (ii) *p*-TsOH, 2,2-dimethoxypropane, acetone, rt; (iii) for **19a**, NaH, THF, CDI, $MeNH_2$, MeOH, rt; for **19b**, NaH, NaI (cat.), DMTC-Cl, solvent, 0 °C—rt; (iv) 80% AcOH, 70–80 °C.

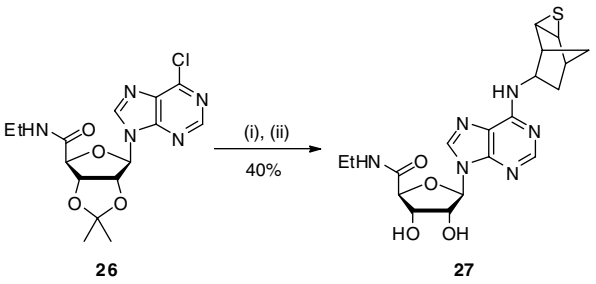
NaH followed dimethylthiocarbamoyl chloride (DMTC-Cl) and catalytic sodium iodide.[17] Deprotection was performed using 80% AcOH at 70–80 °C to give the target compounds, **20a** and **20b**, in good yield.

Adenosine analogues with tricyclic N^6-substituents bearing an epithiirane in the 5,6-position of a norbornane ring have proven to be highly potent A_1AR agonists.[18] As a result we were interested in exploring the effect of 5′-modification on the activity of N^6-(5,6-epithionorborn-2-yl)adenosine. The key intermediate required for this synthesis (compound **23a**) was generated in 36% yield using 9-(2,3-bis-*O*-(*tert*-butyldimethylsilyl)-5-chloro-5-deoxy-β-D-ribofuranosyl)-6-chloropurine (**21**)[15] and 2*S*-*endo*-amino-5,6-*exo*-epithiobicyclo[2.2.1]heptane (2*S*-**22**)[18] in the presence of Hünigs base [N(*i*-Pr)$_2$Et] in refluxing *t*-BuOH (Scheme 3). Similar to the N^6-(*endo*-norborn-2-yl)-series, the 5′-chloro proved to be a suitable precursor for nucleophilic displacement. Introduction of the methylsulfide and concurrent TBS-deprotection was achieved using sodium thiomethoxide in DMF at ambient temperatures to give **25a** in a moderate yield of 47%. Potassium selenomethoxide was generated in situ using potassium hydride and dimethyldiselenide in DMF at 0 °C,[19] and subsequent addition of **23a** led to the formation of the desired dialkyl selenide **24b** in low yield (24%). Deprotection of **23a** and **24** was achieved using NH_4F in MeOH to give the 5′-chloride **23b** and 5′-methylselenide **25b** in excellent yields (97% and 100%, respectively).

The *N*-ethyl-5′-uronamide **26** was prepared as per the method of Olsson and co-workers.[20] Deprotection of the acetonide moiety was achieved using Dowex-50W (H^+) resin (Scheme 4). Substitution was performed on the crude material with 2*S*-**22** using the standard S_NAr conditions to give **27** in a 40% yield over two steps.



Scheme 3. Reagents and conditions: (i) 2*S*-**22**, N(*i*-Pr)$_2$Et, *t*-BuOH, 83 °C; (ii) Me_2Se_2, KH, DMF, then **23a**, 0 °C—rt; (iii) NaSMe, DMF, rt; (iv) NH_4F, MeOH, 50–60 °C.

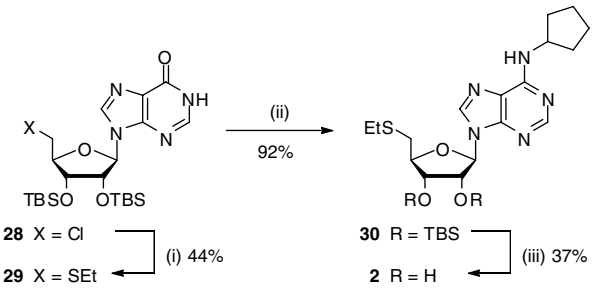


Scheme 4. Reagents and conditions: (i) Dowex-50W (H^+), H_2O, rt; (ii) **22**, N(*i*-Pr)$_2$Et, *t*-BuOH, 83 °C.

IJzerman and co-workers identified N^6-cyclopentyl-5′-deoxy-5′-ethylthioadenosine (**2**) as a high affinity partial agonist at the A_1AR.[7] For use as a standard in our assay, we also required a sample of **2**. 2′,3′-Bis-*O*-(*tert*-butyldimethylsilyl)-5′-chloro-5′-deoxyinosine (**28**)[15] was converted to the corresponding 5′-ethylthio analogue **29** using NaSEt in DMF in 44% yield (Scheme 5). We were able to form the silylated adenosine analogue **30** in excellent yield (92%) using a procedure modified from Wan et al.[21] The silylated inosine **29** was heated at reflux in the presence of cyclopentyl amine and bromo-tri-(1-pyrrolidinyl)phosphonium hexafluorophosphate (PyBroP) and N(*i*-Pr)$_2$Et in dichloroethane. Removal of the protecting groups using NH_4F in MeOH afforded **2** in 37% yield.

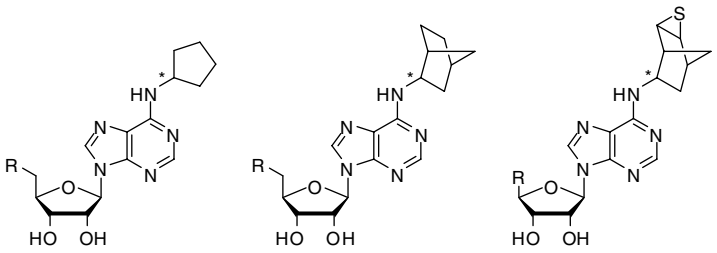
The 5′-modified derivatives of N^6-(*endo*-norborn-2-yl)adenosines were tested for A_1AR affinity by displacement of specific [^{3}H]CPX binding in DDT cell membranes. These assays were performed in the presence of 10 μM 5′-guanylyl-imidodiphosphate to maintain the receptors in the agonist low affinity state. The potency and intrinsic activity of the compounds were determined by their ability to inhibit (−)-isoproterenol-stimulated cAMP accumulation in DDT cells (Table 1).

As shown in Table 1, the 5′-fluoro and chloro derivatives (**5** and **10b**, respectively) have affinities and potencies similar to the classical A_1AR agonist, CPA.



Scheme 5. Reagents and conditions: (i) NaSEt, DMF, rt; (ii) PyBroP, *c*-PentNH$_2$, N(*i*-Pr)$_2$Et, DCE, 86 °C; (iii) NH_4F, MeOH, 50–60 °C.

Table 1. K_i, IC_{50} and intrinsic activity (IA) of adenosine derivatives at the A_1AR in DDT_1 MF-2 cells



Entry	Compound	*	R	K_i (nM)	IC_{50} (nM)	IA
1	CPA	—	OH	21.5 ± 5.7 (4)	2.7 ± 0.6 (4)	1.00
2	**2**	—	SEt	173 ± 35 (5)	21 ± 8 (4)	1.02 ± 0.02 (4)
3	**5**	*endo*	F	17 ± 6 (3)	7 ± 3 (3)	0.97 ± 0.04 (3)
4	**10b**	*endo*	Cl	9.8 ± 3.4 (3)	2.6 ± 1.6 (5)	1.03 ± 0.03 (3)
5	**12d**	*endo*	SH	283 ± 19 (4)	224 ± 69 (4)	1.00 ± 0.01 (4)
6	**6**	*endo*	SMe	120 ± 37 (5)	68 ± 13 (3)	0.95 ± 0.01 (3)
7	**12b**	*endo*	SEt	122 ± 42 (5)	28 ± 15 (3)	1.04 ± 0.03 (3)
8	**12e**	*endo*	SPr	383 ± 21 (3)	15 ± 4 (5)	0.92 ± 0.03 (5)
9	**12c**	*endo*	S(2-F-Ph)	431 ± 15 (3)	21 ± 13 (4)	0.90 ± 0.01 (4)
10	**7**	*endo*	SeMe	285 ± 68 (3)	48 ± 13 (5)	0.89 ± 0.02 (5)
11	**8**	*endo*	NH_2	3933 ± 1008 (3)	351 ± 135 (3)	0.92 ± 0.06 (3)
12	**12a**	*endo*	NHMe	>10,000 (4)	867 ± 135 (3)	0.83 ± 0.07 (3)
13	**9**	*endo*	NHPr	7200 ± 1700 (4)	4950 ± 1800 (6)	0.91 ± 0.12 (6)
14	**15b**	*endo*	NHAc	5865 ± 1309 (3)	605 ± 209 (5)	0.97 ± 0.04 (5)
15	**15a**	*endo*	NMe_2	11716 ± 1563 (3)	4279 ± 1196 (5)	0.97 ± 0.04 (5)
16	**20a**	*endo*	OC(O)NHMe	590 ± 110 (4)	410 ± 50 (4)	1.03 ± 0.02 (4)
17	**20b**	*endo*	$OC(S)NMe_2$	2200 ± 500 (4)	710 ± 200 (4)	0.96 ± 0.02 (4)
18	**27**	*S-endo*	C(O)NHEt	0.9 ± 0.2 (3)	0.12 ± 0.03 (3)	0.98 ± 0.02 (3)
19	**23b**	*S-endo*	CH_2Cl	2.8 ± 0.8 (3)	0.3 ± 0.1(6)	1.05 ± 0.03 (6)
20	**25a**	*S-endo*	CH_2SMe	5.0 ± 0.2 (3)	0.9 ± 0.3 (5)	0.93 ± 0.04 (5)
21	**25b**	*S-endo*	CH_2SeMe	30 ± 3 (3)	12 ± 3 (4)	0.96 ± 0.03 (4)

The K_i values were calculated from the concentration of the compounds that initiated [^{3}H]CPX binding by 50%. The IC_{50} values are the concentration 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*.

Furthermore, these two derivatives are full agonists as they produced the same maximal response (inhibition of cAMP formation) as CPA. The 5′-thio derivatives including the 5′-thio (**12d**), methylthio (**6**), ethylthio (**12b**), propylthio (**12e**) and (2-fluorophenyl)thio (**12c**) compounds have affinities that ranged from 5.6- to 20-fold lower and functional potencies that are 5.5- to 83-fold lower than CPA. All of these derivatives retained the same intrinsic activity as CPA. The 5′-amino (**8**), methylamino (**12a**), propylamino (**9**), acetamido (**15b**) and dimethylamino (**15a**) analogues all have affinities for the A_1AR in the low to mid micromolar range and potencies in the mid nanomolar to low micromolar range. However, the intrinsic activities for the inhibition of cAMP formation for all of these compounds did not differ from CPA. The affinity of the 5′-methylcarbamate derivative **20a** for the A_1AR is 27-fold lower than CPA, whereas the affinity for 5′-dimethylthiocarbamate **20b** is 102-fold lower. With respect to cAMP accumulation, both of these derivatives had the same intrinsic activity as CPA but with less potency. The 5′-methylseleno derivative **7** has an affinity and IC_{50} that are 13- and 18-fold lower than CPA, respectively, but with the same intrinsic activity. Finally, the 5′-modified N^6-(2*S*-*exo*-5,6-epithio-*endo*-norborn-2-yl)adenosine derivatives have high affinity and potency for the A_1AR. The *N*-ethyl-5′-uronamide **27** (K_i = 0.9 nM, IC_{50} = 0.12 nM), 5′-chloro **23** (K_i = 2.8 nM, IC_{50} = 0.3 nM) and 5′-methylthio **25a** (K_i = 5.0 nM, IC_{50} = 0.9 nM) derivatives have affinities and potencies greater than that of CPA, whereas the 5′-methylseleno derivative **25b** has an affinity (30 nM) and potency (12 nM) similar to that for CPA. All of the N^6-(2*S*-*exo*-5,6-epithio-*endo*-norborn-2-yl)adenosine 5′-derivatives have the same intrinsic activity as CPA indicating that they are full A_1 agonists.

In general, the data from the present study show an affinity (K_i) and potency (IC_{50}) series for 5′-modified N^6-(*endo*-norborn-2-yl)adenosines where halogens > alkylthio > carbamate > alkylamino. With the exception of the carbamates, which were not reported, this series is similar to the corresponding 5′-modified N^6-cyclopentyladenosines. However, the 5′-substituted N^6-cyclopentyladenosines were largely partial agonists,[7] whereas the 5′-substituted N^6-(*endo*-norborn-2-yl)adenosines are all full agonists as compared to CPA. Furthermore,

compound **2** acted as a full A_1AR agonist, whereas it has previously been reported to be a partial A_1 agonist using different functional assays.[7] The 5′-substituted carbamate and 5′-substituted thiocarbamate which showed reduced affinities and potencies at the A_1AR compared to CPA also acted as full agonists in the cAMP inhibition assay. This contrasts to the reported partial A_1AR activity of CVT-2759 (**1**) which contains a 5′-substituted carbamate on a N^6-substituted adenosine.[22] The difference between full and partial agonist activity of the 5′-substituted compounds may have several explanations including differences in biological preparations where receptor densities and/or coupling efficiencies may be different and in the functional assays used to determine the intrinsic activity. In the previous reports,[7,22] stimulation of [^{35}S]GTPγS binding in rat brain or DDT cell membranes was used as a functional assay, whereas in the present study the inhibition of cAMP accumulation in DDT cells was employed. The 5′-(2-fluorophenyl)thio analogue of N^6-(*endo*-norborn-2-yl)adenosine (**12c**) is a full agonist for cAMP inhibition as compared to CPA. CVT-3619, which also contains a 5′-(2-fluorophenyl)thio substitutent, was also reported to act as a full agonist for the inhibition of cAMP accumulation in rat epididymal and inguinal adipocytes, but as a partial agonist for the stimulation of non-esterified fatty acid release from the same cells.[6] Thus full or partial agonism may partly depend upon the cellular response measured which suggests the possibility that some of the 5′-substituted N^6-norbornyladenosines may have partial agonist activity at the A_1AR for responses other than cAMP accumulation. Finally, N^6-substituted adenosines have been shown to mainly affect affinity and selectivity towards the A_1AR,[4,23] although it is possible that these substitutions in conjunction with 5′-alterations could also modify the intrinsic activity of the molecule at the A_1AR. Further studies will be needed to specifically address the validity of this issue.

The K_i/IC_{50} ratio can be used to indicate the presence of a receptor reserve or as a relative indicator of the signalling amplification between the receptor and the response induced by the ligand. Thus a ratio of 1 would indicate that the concentration of agonist that occupies half the receptors produces the half-maximal response. Ratios greater than one indicate that the half-maximal response occurs with less than half-maximal receptor occupancy. The latter case would indicate the presence of a receptor reserve or a relatively higher signalling amplification. For the 5′-substituted N^6-norbornyladenosines, the K_i/IC_{50} ratios ranged from 1.3 to 25.5 with the 5′-methylthio and 5′-(2-fluorophenyl)thio analogues having the largest ratio. Although there appears to be no obvious structural pattern, the data suggest that substitutions in the 5′-position may contribute to a ligand's receptor reserve or signal amplification capability.

In summary, a range of 5′-modified N^6-(*endo*-norborn-2-yl)adenosine derivatives were synthesised and evaluated as A_1AR agonists. The pharmacological data indicate that modification of the 5′-position can have relatively large effects on the affinity, potency and receptor reserve for the A_1AR. Of particular interest are several of the 5′-modified N^6-(2*S*-*exo*-epithio-*endo*-norborn-2-yl)adenosine derivatives that have high affinity and subnanomolar potency. All of the 5′-derivatives tested in the present study were full agonists for cAMP inhibition as compared to CPA.

3. Experimental

3.1. General experimental

All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 WB spectrometer with Avance console. Unless otherwise stated, spectra were acquired in $CDCl_3$. Chemical shifts are recorded in parts per million (ppm). For ^{1}H NMR spectra the residual solvent peak was used as an internal reference ($CHCl_3$ 7.26). For ^{13}C NMR spectra the central peak of the $CDCl_3$ triplet was used as the internal reference (77.0). Signal multiplicities are abbreviated as follows; s singlet, d doublet, t triplet, q quartet, m multiplet, br broad, app. apparent. Signal multiplicities and connectivities were assigned using attached proton test (APT), homonuclear correlation spectroscopy (COSY) and heteronuclear single-quantum correlation (HSQC) experiments. ^{1}H NMR data were reported as follows: chemical shift (signal multiplicity, coupling constant, integration, assignment). ^{13}C NMR data were reported as follows; chemical shift (C=O, C, CH, CH_2, CH_3). For instances when fluorine is attached to carbon, chemical shift is followed by multiplicity, and coupling constant instances where 2 resonances were observed for a particular carbon due to diastereotopicity (1:1 mixtures), they are both reported with a single characterisation for both. High resolution electrospray mass spectra (HRMS) utilised electrospray ionisation (ESI) and were obtained on a Bruker BioApex II FTMS. Low resolution electrospray mass spectra (LRMS) using electrospray ionisation (ESI) were obtained on a Micromass Platform II. Unless otherwise stated, cone voltage was 20 V. MS data are listed as mass-to-charge (*m*/*z*) with assignment (where appropriate), isotopes and relative intensity in parentheses. Reactions were monitored by TLC on pre-coated silica gel 60 F_{254} aluminium plates (Merck). Visualisations were achieved using UV light at 254 nm and phosphomolbdic acid staining (4.8 g in 100 mL of EtOH) followed by heating. Column chromatography was carried out on silica gel 60 (0.063–0.200 mm; Merck). Dry THF was distilled from a blue sodium benzophenone ketyl solution under N_2. Dry MeOH was refluxed and distilled from Mg and I_2 and stored under N_2. Dry acetone was refluxed over and distilled from Drierite. Anhydrous DMF and DCE were purchased from Sigma–Aldrich Chemical Co. Ltd. NaH (60% dispersion in mineral oil) was used as supplied. Unless otherwise stated, reagents were purchased and used without further purification from Sigma–Aldrich Chemical Co. Ltd.

3.1.1. 2′,3′-Bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-N^6-(*endo*-norborn-2-yl)-5′-methylaminoadenosine (11a). A sealed tube containing **10a** (214.5 mg, 0.353 mmol) in

40% $MeNH_2$ in MeOH (1 mL) was heated at 60 °C for 8 days. The crude reaction mixture was concentrated under reduced pressure and purified via column chromatography ($CHCl_3$ to $CHCl_3$/MeOH; 95:5) to give **11a** (63 mg, 29.6%) and unreacted **10a** (135 mg, 63.4%), both as clear oils. ^{1}H NMR δ 8.30 (s, 1H, H-2/8), 7.80 (s, 1H, H-8/2), 5.86, 5.84 (br s, 1H, N^6H), 5.79, 5.78 (d, J = 6.6 Hz, 1H, H-1′), 4.96–4.94 (m, 1H, H-2′), 4.50 (br s, 1H, H-2″), 4.43–4.41 (m, 1H, H-3′), 4.25–4.21 (m, 1H, H-4′), 3.04 (m, 1H, H-5a′/b′), 2.91–2.90 (m, 1H, H-5b′/a′), 2.62 (br s, 1H, H-1″), 2.54 (s, 3H, $NHCH_3$), 2.27 (br s, 1H, H-4″), 2.23–2.22 (m, 1H, H-3x″), 1.65–1.29 (m, 6H, H-5″, H-6″, H-7″), 0.92 (s, 10H, H-3n″, *t*-Bu), 0.76 (s, 9H, *t*-Bu), 0.11 (s, 6H, $2\times CH_3$), −0.05 (s, 3H, CH_3), −0.43, −0.44 (s, 3H, CH_3). ^{13}C NMR δ 155.2 (C), 152.8 (CH), 148.1 (C), 139.9, 139.8 (CH), 121.0 (C), 90.0 (CH), 84.9, 84.8 (CH), 73.7 ($2\times$CH), 53.0 (CH_2), 52.2 (CH), 40.5 (CH), 38.3 (CH_2), 38.1 (CH_2), 36.8 (CH), 36.0 (CH_3), 29.9 (CH_2), 25.8 (CH_3), 25.7 (CH_3), 21.4 (CH_2), 18.0 (C), 17.8 (C), −4.5 (CH_3), −4.6 (CH_3), −4.7 (CH_3), −5.6 (CH_3). LRMS *m*/*z* (%): 603.5 ($M+H^+$, 100), 604.5 (48), 605.5 (18). HRMS: $C_{30}H_{54}N_6O_3Si_2$ requires $[M+H]^+$ 603.3869. Found 603.3850.

3.1.2. 2′,3′-Bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-N^6-(*endo*-norborn-2-yl)-5′-(2-fluorophenylthio)adenosine (11c).

To a solution containing NaH (133 mg, 3.325 mmol, 11.0 equiv) in dry THF (4 mL) held at 0 °C under an atmosphere of Ar was added 2-fluorothiphenol (0.351 mL, 421 mg, 10.9 equiv) in a dropwise fashion over 10 min, then allowed to warm to room temperature over 1 h. The reaction mixture was then cooled to 0 °C and **10a** (183.7 mg, 0.302 mmol) in THF (2 mL) was added in a dropwise manner over 5 min. The resultant mixture was stirred at rt for 52 h. before heating at reflux for a further 17 h. The resultant solution was taken up in sat. NH_4Cl (50 mL) and washed using EtOAc (2×50 mL). The combined organic phase was then washed using H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and reduced in vacuo. Purification via column chromatography using petroleum spirits/EtOAc (85:15) afforded **11c** (114 mg, 53.9%) as a clear oil. ^{1}H NMR δ 8.34 (s, 1H, H-2/8), 7.80, 7.79 (s, 1H, H-8/2), 7.44–7.40 (m, 1H, ArH), 7.21–7.20 (m, 1H, ArH), 7.08–7.02 (m, 2H, ArH), 5.83–5.80 (m, 2H, H-1′, NH), 5.31–5.21 (m, 1H, H-2′), 4.54 (br s, 1H, H-2″), 4.31–4.29 (m, 1H, H-3′), 4.21 (br s, 1H, H-4′), 3.62–3.54 (m, 1H, H-5a′/b′), 3.40–3.31 (m, 1H, H-5b′/a′), 2.64 (br s, 1H, H-1″), 2.29–2.21 (m, 2H, H-3x″, H-4″), 1.69–1.15 (m, 6H, H-5″, H-6″, H-7″), 0.91 (s, 10H, *t*-Bu, H-3n″), 0.76 (s, 9H, *t*-Bu), 0.10 (s, 3H, CH_3), 0.07 (s, 3H, CH_3), −0.11, −0.12 (s, 3H, CH_3), −0.33, −0.34 (s, 3H, CH_3). ^{13}C NMR δ 161.2 (d, $^1J_{CF}$ = 244.0 Hz, C), 154.9 (C), 152.9 (CH), 148.5 (C), 139.9, 139.7 (CH), 131.7 (CH), 128.5 (d, $^3J_{CF}$ = 7.7 Hz, CH), 124.4 (CH), 122.6 (d, $^2J_{CF}$ = 17.2 Hz, C), 120.7 (C), 115.7 (d, $^2J_{CF}$ = 22.3 Hz, CH), 89.8, 89.7 (CH), 84.6, 84.4 (CH), 74.5, 74.5 (CH), 73.3, 73.1 (CH), 52.2 (CH_2), 40.5 (CH), 38.2 (CH_2), 38.0 (CH_2), 36.7 (CH), 35.3 (CH_2), 29.9 (CH_2), 25.7 (CH_3), 25.6 (CH_3), 21.4 (CH_2), 17.9 (C), 17.8 (C), −4.6 (CH_3), −4.8 ($2\times CH_3$), −5.2 (CH_3). LRMS *m*/*z* (%): 700.6 ($M+H^+$, 100), 701.6 (55), 702.7 (25).

3.1.3. 5′-Acetylmercapto-2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-N^6-(*endo*-norborn-2-yl)adenosine (11d).

To a stirred solution of **10a** (601.4 mg, 0.989 mmol) in anhydrous DMF (6 mL) under a N_2 atmosphere was added KSAc (1.122 g, 9.820 mmol, 9.9 equiv) and the resultant solution was stirred for 50 h. The crude reaction mixture was taken up in EtOAc (100 mL), washed with H_2O (100 mL) which was then extracted with EtOAc (100 mL), the combined organic phase was washed using brine (2×100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subsequent column chromatography (EtOAc/hexane; 1:4) gave **11d** (476 mg, 74.3%) as a light tan oil. ^{1}H NMR δ 8.25 (s, 1H, H-2/8), 7.77 (s, 1H, H-8/2), 5.97 (d, J = 6.9 Hz,1H, NH), 5.76–5.74 (m, 1H, H-1′), 5.20–5.11 (m, 1H, H-2′), 4.44 (br s, 1H, H-2″), 4.12–4.04 (m, 2H, H-3′, H-4′), 3.49–3.42 (m, 1H, H-5a′/b′), 3.23–3.18 (m, 1H, H-5b′/a′), 2.55 (br s, 1H, H-1″), 2.24 (s, 3H, $C(O)CH_3$), 2.16–2.11 (m, 1H, H-3x″, H-4″), 1.60–1.22 (m, 6H, H-5″, H-6″, H-7″), 0.86 (s, 10H, *t*-Bu, H-3n″), 0.70 (s, 9H, *t*-Bu), 0.05 (s, 3H, CH_3), 0.04 (s, 3H, CH_3), −0.14, −0.14 (s, 3H, CH_3), −0.37, −0.38 (s, 3H, CH_3). ^{13}C NMR δ 194.3 (C=O), 154.8 (C), 152.7 (CH), 148.4 (C), 139.6, 139.4 (CH), 120.6 (C), 89.5, 89.4 (CH), 84.1, 84.0 (CH), 74.6, 74.5 (CH), 73.4, 73.1 (CH), 51.9 (CH), 40.3 (CH), 38.0 (CH_2), 37.9 (CH_2), 36.6 (CH), 31.1 (CH_2), 30.1 (CH_3), 29.7 (CH_2), 25.6 (CH_3), 25.4 (CH_3), 21.2 (CH_2), 17.8 (C), 17.6 (C), −4.7 (CH_3), −4.9 (CH_3), −5.0 (CH_3), −5.5 (CH_3). LRMS *m*/*z* (%): 615.4 (20), 648.4 ($M+H^+$, 100), 649.4 (62), 650.4 (27).

3.1.4. 2′,3′-Bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-N^6-(*endo*-norborn-2-yl)-5′-propylthioadenosine (11e).

To a stirred, degassed solution containing **11d** (153.4 mg, 0.237 mmol) in anhydrous MeOH (5 mL) was added *n*-PrBr (31.2 μL, 42.2 mg, 1.5 equiv) and the solution was cooled to −20 °C. Clean Na metal (14.5 mg, 0.631 mmol, 2.7 equiv) was added in one portion and the reaction mixture was allowed to slowly come up to rt and stirred overnight. The reaction mixture was taken up in H_2O (30 mL) and extracted using $CHCl_3$ (3×30 mL), the combined organic phase was dried ($MgSO_4$), filtered and reduced in vacuo. Purification via column chromatography (gradient elution; petroleum spirits/EtOAc (85:15) to EtOAc) gave **11e** (33.9 mg, 22.2%) as a clear oil. ^{1}H NMR δ 8.32 (s, 1H, H-2/8), 7.94 (s, 1H, H-8/2), 6.21 (br s, 1H, NH), 5.88–5.86 (m, 1H, H-1′), 5.09–5.02 (m, 1H, H-2′), 4.53 (br s, 1H, H-2″), 4.31 (app. t, J_{app} = 3.9 Hz, 1H, H-3′), 4.24–4.19 (m, 1H, H-4′), 3.10–3.02 (m, 1H, H-5a′/b′), 2.90–2.83 (m, 1H, H-5b′/a′), 2.63 (br s, 1H, H-1″), 2.54 (t, J = 7.5 Hz, 2H, SCH_2CH_2), 2.27 (s, 1H, H-4″), 2.21–2.17 (m, 1H, H-3x″), 1.75–1.22 (m, 8H, H-5″, H-6″, H-7″, SCH_2CH_2), 0.96–0.94 (m, 12H, H-3n″, CH_2CH_3, *t*-Bu), 0.80 (s, 9H, *t*-Bu), 0.15 (s, 3H, CH_3), 0.12 (s, 3H, CH_3), −0.056, −0.060 (s, 3H, CH_3), −0.24, −0.25 (s, 3H, CH_3). ^{13}C NMR δ 154.8 (C), 153.0 (CH), 148.7 (C), 139.6 (CH), 120.4 (C), 89.7, 89.6 (CH), 84.7, 84.6 (CH), 74.4 (CH), 74.0, 73.7 (CH), 52.2 (CH), 40.5 (CH), 38.3 (CH_2), 37.9 (CH_2), 36.8 (CH), 35.2 (CH_2), 34.3 (CH_2), 29.9 (CH_2), 25.8 (CH_3), 25.7 (CH_3), 22.9 (CH_2), 21.5 (CH_2), 18.0 (C),

17.9 (C), 13.4 (CH_3), −4.4 (CH_3), −4.6 (CH_3), −4.7 (CH_3), −5.1 (CH_3). LRMS *m*/*z* (%): 648.4 (100), 649.4 (50), 650.3 (25).

3.1.5. 2′,3′-Bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-5′-dimethylamino-N^6-(*endo*-norborn-2-yl)adenosine (14a). To a solution containing **13** (72.7 mg, 0.123 mmol) in MeCN (2 mL), stirred at ambient temperature, was added formalin (35% $CH_2O_{(aq)}$, 0.310 mL, 115 mg, 3.816 mmol, 30.9 equiv) in a single portion to give a cloudy solution. After 5 min. the solution had cleared and $NaBH_3CN$ (31.8 mg, 0.506 mmol, 4.1 equiv) was added to again give a cloudy solution which clears with stirring. After 15 min. AcOH (5 drops) was added to adjust pH to 7 and stirred for 24 h. The reaction mixture was reduced in vacuo, taken up in $CHCl_3$ (50 mL) and washed using 2.5 M NaOH (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subsequent column chromatography gave the title compound (27.4 mg, 36.0%) as a clear oil. ^{1}H NMR δ 8.33 (s, 1H, H-2/8), 7.84 (s, 1H, H-8/2), 5.83, 5.83 (d, J = 4.8 Hz, 1H, H-1′), 5.74, 5.71 (br s, 1H, NH), 5.02–4.96 (m, 1H, H-2′), 4.52 (br s, 1H, H-2″), 4.23–4.19 (m, 2H, H-3′, H-4′), 2.88 (br s, 1H, H-5a′/b′), 2.63 (br s, 2H, H-5b′/a′, H-1″), 2.34 (s, 6H, $N(CH_3)_2$), 2.28–2.18 (m, 2H, H-4″, H-3x″), 1.71–1.27 (m, 6H, H-5″, H-6″, H-7″), 0.94 (s, 10H, H-3n″, *t*-Bu), 0.82 (s, 9H, *t*-Bu), 0.13 (s, 3H, CH_3), 0.11 (s, 3H, CH_3), −0.03, −0.04 (s, 3H, CH_3), −0.20, −0.22 (s, 3H, CH_3). ^{13}C NMR δ 155.0 (C), 152.9 (CH), 148.5 (C), 139.6, 139.5 (CH), 120.8 (C), 90.0 (CH), 82.5, 82.4 (CH), 74.3 (CH), 74.0, 73.8 (CH), 61.4 (CH_2), 52.1 (CH), 45.9 (CH_3), 40.5 (CH), 38.2 (CH_2, CH_2), 36.8 (CH), 29.9 (CH_2), 25.8 (CH_3), 25.7 (CH_3), 21.4 (CH_2), 18.0 (C), 17.8 (C), −4.4 (CH_3), −4.7 (2 × CH_3), −5.0 (CH_3). LRMS *m*/*z* (%): 617.7 ($M+H^+$, 100), 618.6 (45), 619.6 (19).

3.1.6. 5′-Acetamido-2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-N^6-(*endo*-norborn-2-yl)adenosine (14b). To a stirred solution containing **13** (118 mg, 0.201 mmol) in anhydrous pyridine (1 mL) held at 0 °C, was added Ac_2O (19 μL, 21 mg, 0.201 mmol, 1 equiv). The reaction mixture was then stirred at rt for 1.5 h. after which time it was poured into EtOAc (20 mL) and washed with 0.5 M HCl (2 × 20 mL). The organic layer was then dried ($MgSO_4$), filtered and reduced in vacuo. Column chromatography was performed using $CHCl_3$/MeOH (95:5) as the eluent. Concentration of the appropriate fractions gave **14b** (118 mg, 93.3%) as an orange oil. ^{1}H NMR δ 9.06 (br s, 1H, NHAc), 8.33 (s, 1H, H-2/8), 7.77 (s, 1H, H-8/2), 6.00 (br s, 1H, N^6H), 5.71 (d, J = 7.8 Hz, 1H, H-1′), 4.91−4.84 (m, 1H, H-2′), 4.47 (br s, 1H, H-2″), 4.23−4.15 (m, 2H, H-5a′, H-5b′), 4.08 (d, J = 3.6 Hz, 1H, H-3′), 3.10−3.06 (m, 1H, H-4′), 2.62 (br s, 1H, H-1″), 2.27−2.17 (m, 2H, H-4″, H-3x″), 2.12 (s, 3H, CH_3), 1.68−1.25 (m, 6H, H-5″, H-6″, H-7″), 0.92 (s, 10H, *t*-Bu, H-3n″), 0.69 (s, 9H, *t*-Bu), 0.11 (s, 3H, CH_3), 0.09 (s, 3H, CH_3), −0.20 (s, 3H, CH_3), −0.53 (s, 3H, CH_3). ^{13}C NMR δ 170.3 (C=O), 155.2 (C), 152.4 (CH), 147.6 (C), 140.5 (CH), 121.4 (C), 90.1 (CH), 87.0 (CH), 73.4, 73.3 (CH), 52.1 (CH), 40.6 (CH_2), 40.4 (CH), 38.2 (CH_2), 37.8 (CH_2), 36.7 (CH), 29.8, 29.8 (CH_2), 25.7 (CH_3), 25.5 (CH_3), 24.2 (CH_3), 22.6 (CH_2), 17.9 (C), 17.7 (C), −4.6 (CH_3), −4.8 (CH_3), −4.9 (CH_3), −5.76, −5.83 (CH_3). LRMS *m*/*z* (%): 631.5 ($M+H^+$, 100), 632.5 (40), 633.5 (20), 654.5 (15, $M+Na^+$).

3.1.7. N^6-(*endo*-Norborn-2-yl)adenosine (17). A solution containing **16** (1.005 g, 3.504 mmol), N(*i*-Pr)$_2$Et (1.50 mL, 1.113 g, 8.611 mmol, 2.5 equiv), and (±)-*endo*-norborn-2-yl amine.HCl (0.618 g, 4.186 mmol, 1.2 equiv) in *t*-BuOH was heated at reflux for 14 h. The reaction mixture was reduced in vacuo and purified via column chromatography ($CHCl_3$/MeOH, 9:1) to give **17** (1.192 g, 94.1%) as a tan foam. ^{1}H NMR δ 8.17 (s, 1H, H-2/8), 7.88 (s, 1H, H-8/2), 6.26 (br s, 1H, NH), 5.83 (s, 1H, H-1′), 4.93 (s, 1H, H-2′), 4.45 (br s, 2H, H-2″, H-3′), 4.27 (s, 1H, H-4′), 3.89 (d, J = 11.9 Hz, 1H, H-5a′/b′), 3.71 (d, J = 11.9 Hz, 1H, H-5b′/a′), 2.55 (s, 1H, H-1″), 2.25–2.17 (m, 2H, H-3x″, H-4″), 1.57–1.21 (m, 6H, H-5″, H-6″, H-7″), 0.88 (br s, 1H, H-3n″). ^{13}C NMR δ 154.7 (C), 153.2 (CH), 146.9 (C), 139.8 (CH), 120.3 (C), 90.6 (CH), 86.4 (CH), 73.9 (CH), 72.0 (CH), 62.8 (CH_2), 52.2 (CH), 40.3 (CH), 38.1 (CH_2), 37.6 (CH_2), 36.7 (CH), 29.8 (CH_2), 21.4 (CH_2). LRMS *m*/*z* (%): 362.2 ($M+H^+$, 100).

3.1.8. 2′,3′-*O*-Isopropylidene-N^6-(*endo*-norborn-2-yl)adenosine (18). To a magnetically stirred solution of **17** (1.125 g, 3.113 mmol) in dry acetone (40 mL) was added 2,2-dimethoxypropane (6.5 mL, 5.506 g, 52.861 mmol, 17.0 equiv) and *p*-TsOH (0.645 g, 3.745 mmol, 1.2 equiv). The resultant mixture was stirred at ambient temperature for 1.5 h. before being concentrated under reduced pressure, taken up in H_2O (30 mL) and extracted using $CHCl_3$ (2 × 50 mL). The combined organic phase was washed using sat. $NaHCO_3$ (30 mL), dried ($MgSO_4$), filtered and reduced in vacuo to give **18** (1.150 g, 92.0%) as a tan foam. ^{1}H NMR δ 8.28 (s, 1H, H-2/8), 7.76 (s, 1H, H-8/2), 6.68 (br s, 1H, OH), 6.01 (br s, 1H, NH), 5.82 (d, J = 4.5 Hz, 1H, H-1′), 5.20–5.07 (m, 1H, H-2′), 5.08 (d, J = 6.0 Hz, 1 H, H-3′), 4.49 (s, 2 H, H-4′, H-2″), 3.93 (d, J = 12.6 Hz, 1 H, H-5a′/b′), 3.75 (d, J = 12.6 Hz, 1H, H-5b′/a′), 2.59 (br s, 1H, H-1″), 2.24 (br s, 1H, H-4″), 2.18–2.14 (m, 1H, H-3x″), 1.60–1.23 (m, 6H, H-5″, H-6″, H-7″), 1.60 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 0.91–0.87 (m, 1H, H-3n″). ^{13}C NMR δ 155.0 (C), 152.5 (CH), 146.9 (C), 139.1 (CH), 121.0 (C), 113.6 (C), 93.9 (CH), 85.9 (CH), 82.8 (CH), 81.4 (CH), 63.1 (CH_2), 51.9 (CH), 40.2 (CH), 38.0 (CH_2), 37.7 (CH_2), 36.5 (CH), 29.7 (CH_2), 27.4 (CH_3), 25.0 (CH_3), 21.3 (CH_2). LRMS *m*/*z* (%): 402.4 ($M+H^+$, 100), 403.3 (20).

3.1.9. 2′,3′-*O*-Isopropylidene-5′-*O*-methylaminocarbamoyl-N^6-(*endo*-norborn-2-yl)adenosine (19a). To a solution containing**18** (15.2 mg, 0.038 mmol) in dry THF (1 mL) under N_2 was added CDI (22.3 mg, 0.138 mmol, 3.6 equiv). The reaction mixture was stirred for 1.5 h. after which time 2 drops of H_2O was added followed by 40% $MeNH_2$ in MeOH (0.5 mL), then the reaction vessel was sealed and left to stir overnight. The crude reaction mixture was reduced in vacuo and purified via column chromatography ($CHCl_3$/MeOH; 95:5) to give **19a** (15.7 mg, 90.4%) as a clear oil. ^{1}H NMR δ 8.34 (s, 1H, H-2/8), 7.82 (s, 1H, H-8/2), 6.07 (d, J = 1.8 Hz, 1H, H-1′), 5.87 (br s, 1H, N^6H), 5.49–5.47 (m, 1H, H-

2′), 5.02 (dd, J = 5.7 and 3.0 Hz, 1H, H-3′), 4.72 (br s, 1H, N*H*CH$_3$), 4.51–4.43 (m, 2H, H-4′, H-2″), 4.32 (dd, J = 11.7 and 3.9 Hz, 1H, H-5a′/b′), 4.20 (dd, J = 11.7 and 5.7 Hz, 1H, H-5b′/a′), 2.72 (d, J = 4.5 Hz, 3H, NHC*H*$_3$), 2.60 (br s, 1H, H-1″), 2.26–2.15 (m, 2H, H-3x″, H-4″), 1.68–1.24 (m, 12H, H-5″, H-6″, H-7″, C(CH$_3$)$_2$), 0.93–0.87 (m, 1H, H-3n″). ^{13}C NMR δ 156.3 (C═O), 155.0 (C), 153.3 (CH), 148.3 (C), 138.8 (CH), 120.4 (C), 114.4 (C), 91.1 (CH), 85.3 (CH), 84.0 (CH), 81.7 (CH), 64.4 (CH$_2$), 52.1 (CH), 42.4 (CH), 38.2 (CH$_2$), 38.1 (CH$_2$), 36.8 (CH), 29.9 (CH$_2$), 27.5 (CH), 27.1 (CH$_3$), 25.3 (CH$_3$), 21.4 (CH$_2$). LRMS m/z (%): 459.4 (M+H$^+$, 100), 460.5 (25).

3.1.10. 5′-*O*-Dimethylaminothiocarbamoyl-2′,3′-*O*-isopropylidene-*N*^{6}-(*endo*-norborn-2-yl)adenosine (19b). To a magnetically stirred solution of NaH (21.1 mg, 0.528 mmol, 1.1 equiv) in anhydrous THF (4 mL) held at 0 °C under an Ar atmosphere was added a solution of **18** (192.6 mg, 0.480 mmol) in dry THF (2 mL). After 30 min. NaI (4 mg, 0.027 mmol, 0.06 equiv) and DMTC-Cl (73.1 mg, 0.591 mmol, 1.2 equiv) were added successively and the resultant solution was allowed to warm to rt, then stirred overnight. The reaction mixture was quenched using sat. NH$_4$Cl (5 mL) and then extracted using Et$_2$O (3 × 10 mL). The combined organic phase was washed using H$_2$O (30 mL) and brine (30 mL), dried (Na$_2$SO$_4$), filtered and reduced in vacuo. Subsequent column chromatography gave the title compound (140 mg, 59.8%) as a white foam. ^{1}H NMR δ 8.32 (s, 1H, H-2/8), 7.80 (s, 1H, H-8/2), 6.04 (d, J = 1.8 Hz, 1H, H-1′), 5.88 (br s, 1H, NH), 5.48 (d, J = 6.3 Hz, 1H, H-2′), 5.08 (dd, J = 6.3 and 3.3 Hz, 1H, H-3′), 4.74 (dd, J = 11.3 and 3.9 Hz, 1H, H-5a′/b′), 4.60–4.44 (m, 3H, H-4′, H-5b′/a′, H-2″), 3.28 (s, 3H, NCH$_3$), 3.00 (d, J = 1.2 Hz, 3H, NCH$_3$), 2.59 (br s, 1H, H-1″), 2.24–2.15 (m, 2H, H-3x″, H-4″), 1.63–1.22 (m, 6H, H-5″, H-6″, H-7″), 1.58 (s, 3H, CCH$_3$), 1.36 (s, 3H, CCH$_3$), 0.92–0.85 (m, 1H, H-3n″). ^{13}C NMR δ 187.4 (C═S), 154.8 (C), 153.2 (CH), 148.1 (C), 138.7 (CH), 120.4 (C), 114.5 (C), 90.9 (CH), 84.9 (CH), 84.0 (CH), 81.5 (CH), 70.2 (CH$_2$), 52.0 (CH), 42.8 (CH$_3$), 40.4 (CH), 38.1 (CH$_2$), 38.0 (CH$_2$), 37.7 (CH$_3$), 36.7 (CH), 29.8 (CH$_2$), 27.0 (CH$_3$), 25.3 (CH$_3$), 21.4 (CH$_2$). LRMS m/z (%): 489.5 (M+H$^+$, 100), 490.4 (30).

3.1.11. 5′-*O*-Methylaminocarbamoyl-*N*^{6}-(*endo*-norborn-2-yl)adenosine (20a). A solution of **19a** (49.9 mg, 0.109 mmol) in 80% AcOH (2 mL) was heated at 70–80 °C for 43 h. The reaction mixture was reduced in vacuo, co-evaporated using H$_2$O to give **20a** (35 mg, 76.1%) as a clear oil. ^{1}H NMR δ 8.27 (s, 1H, H-2/8), 7.95 (s, 1H, H-8/2), 6.05 (br s, 1H, N^{6}H), 5.96 (d, J = 5.1 Hz, 1H, H-1′), 4.93 (br s, 1H, N*H*CH$_3$), 4.51 (app. d, J_{app} = 4.2 Hz, 1H, H-2′), 4.41–4.30 (m, 4H, H-2′, H-3′, H-4′, H-5a′, H-5b′), 4.08 (br s, 1H, H-2″), 2.76, 2.74 (s, 3H, NHC*H*$_3$), 2.61 (br s, 1H, H-1″), 2.28–2.18 (m, 2H, H-3x″, H-4″), 1.65–1.21 (m, 6H, H-5″, H-6″, H-7″), 0.95–0.90 (m, 1H, H-3n″). ^{13}C NMR δ 156.7 (C═O), 154.7 (C), 152.6 (CH), 147.7 (C), 138.0 (CH), 119.8 (C), 89.9 (CH), 83.9 (CH), 75.6 (CH), 71.4 (CH), 64.0 (CH$_2$), 52.3 (CH), 40.6 (CH), 38.3 (CH$_2$), 37.9 (CH$_2$), 36.8 (CH), 29.9 (CH$_2$), 27.6 (CH), 21.5 (CH). LRMS m/z (%): 209.1 (55), 279.2 (100), 391.5 (50), 419.4 (M+H$^+$, 70). HRMS: C$_{19}$H$_{26}$N$_6$O$_5$ requires [M+H]$^+$ 419.2037. Found 419.2024.

3.1.12. 5′-*O*-Dimethylaminothiocarbamoyl-*N*^{6}-(*endo*-norborn-2-yl)adenosine (20b). A solution of **19b** (113.9 mg, 0.233 mmol) in 80% AcOH (4 mL) was heated at 80 °C for 17 h. The reaction mixture was reduced in vacuo and purified via column chromatography eluting with CHCl$_3$/MeOH (95:5) to give **20b** (83 mg, 79.0%) as a clear oil. ^{1}H NMR δ 8.24 (s, 1H, H-2/8), 7.92 (s, 1H, H-8/2), 6.19 (br s, 1H, NH), 5.96 (d, J = 4.5 Hz, 1H, H-1′), 4.76–4.69 (m, 2H, H-5a′, H-5b′), 4.62–4.58 (m, 1H, H-2′), 4.51–4.45 (m, 3H, H-2″, H-3′, H-4′), 3.31 (s, 3H, CH$_3$), 2.99 (d, J = 2.7 Hz, 3H, CH$_3$), 2.58 (br s, 1H, H-1″), 2.26–2.15 (m, 2H, H-3x″, H-4″), 1.67–1.24 (m, 6H, H-5″, H-6″, H-7″), 0.92 (m, 1H, H-3n″). ^{13}C NMR δ 187.7 (C═S), 154.7 (C), 152.8 (C), 147.6 (C), 137.9 (CH), 119.9 (C), 90.2 (CH), 83.4 (CH), 75.3 (CH), 71.1 (CH), 70.1 (CH$_2$), 52.2 (CH), 43.0 (CH$_3$), 40.4 (CH), 38.2 (CH$_2$), 38.0 (CH$_2$), 37.9 (CH$_3$), 36.8 (CH), 29.9 (CH$_2$), 21.5 (CH$_2$). LRMS m/z (%): 449.2 (M+H$^+$, 100). HRMS: C$_{20}$H$_{28}$N$_6$O$_4$S requires [M+H]$^+$ 449.1966. Found 449.1968.

3.1.13. 2′,3′-Bis-*O*-(*tert*-butyldimethylsilyl)-5′-chloro-5′-deoxy-*N*^{6}-(2*S*-*exo*-5,6-epithio-*endo*-norborn-2-yl)adenosine (23a). A mixture of **21** (255 mg, 0.48 mmol), **22** (132 mg, ~0.46 mmol) and N(*i*-Pr)$_2$Et (0.3 mL, 1.7 mmol) in *t*-BuOH (4 mL) was heated to reflux for 20 h. The reaction mixture was reduced in vacuo on SiO$_2$ and purification by column chromatography (petroleum ether/EtOAc, 10:1) afforded title compound **23a** (109 mg, 36%) as a transparent solid (mp 82–84 °C). ^{1}H NMR δ 8.35 (br s, 1H, H-2/8), 7.94 (br s, 1H, H-8/2), 6.07 (br s, 1H, NH), 5.86 (d, 1H, H-1′), 5.09 (t, 1H, H-2′), 4.72 (br s, 1H, H-2″), 4.37 (t, 1H, H-3′), 4.26–4.30 (m, 1H, H-4′), 4.08 (dd, 1H, H-5*a*′/H-5*b*′), 3.72 (dd, 1H, H-5*a*′/H-5*b*′), 3.03 (d, 1H, H-5″/H-6″), 2.96 (d, 1H, H-1″/H-4″), 2.93 (d, 1H, H-5″/H-6″), 2.51 (d, 1H, H-1″/H-4″), 2.41–2.32 (m, 1H, H-3x″), 1.66–1.63 (m, 1H, H-7s″), 1.20–1.10 (m, 1H, H-3n″), 0.98–0.92 (m, 1H, H-7a″), 0.92 (s, 9H, *t*-Bu), 0.79, (s, 9H, *t*-Bu), 0.13 (s, 3H, CH$_3$), 0.11 (s, 3H, CH$_3$), −0.05 (s, 3H, CH$_3$), −0.24 (s, 3H, CH$_3$). ^{13}C NMR δ 154.6, 154.6, 152.9, 139.6, 120.6, 89.8, 84.0, 73.5, 72.6, 53.0, 43.5, 41.2, 38.1, 37.3, 36.2, 33.2, 27.5, 25.7, 25.6, 17.9, 17.8, −4.5, −4.7, −4.8, −5.1.

3.1.14. 2′,3′-Bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-*N*^{6}-(2*S*-*exo*-5,6-epithio-*endo*-norborn-2-yl)-5′-methylselenoadenosine (24). To a suspension of KH (20 mg, in oil) in DMF (0.5 mL) was added a solution of Me$_2$Se$_2$ (15 mg, 0.11 mmol) in DMF (1 mL). The reaction was stirred at rt for 2 h, then a solution of **23a** (35 mg, 0.055 mmol) in DMF (1 mL) was added. After 4 h. the reaction was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic phase was reduced in vacuo and purification by column chromatography (CHCl$_3$/MeOH; 98:2) afforded the title compound **24** (6 mg, 23%) as a transparent solid (mp 47–49 °C). ^{1}H NMR δ 8.39 (s, 1 H, H-2/8), 7.91 (s, 1H, H-8/2), 5.89 (d, 1H, H-1′), 5.77 (br s, 1H, NH), 5.13 (t, 1H, H-2′),

4.75 (br s, 1H, H-2″), 4.35–4.24 (m, 2H, H-3′, H-4′), 3.10–2.89 (m, 5H, H-1″, H-5″, H-6″, H-5a′, H-5b′), 2.55 (s, 1H, H-4″), 2.46–2.37 (m, 1H, H-3x″), 2.04 (s, 3H, $SeCH_3$), 1.69 (m, 1H, H-7s″), 1.15–1.10 (m, 1H, H-3n″), 0.91–0.87 (m, 1H, H-7a″), 0.80 (s, 9H, *t*-Bu), 0.95 (s, 9H, *t*-Bu), 0.16 (s, 3H, CH_3), 0.13 (s, 3H, CH_3), −0.06 (s, 3H, CH_3), −0.27 (s, 3H, CH_3). ^{13}C NMR δ 154.7, 152.9, 140.0, 128.8, 120.8, 89.7, 85.0, 75.1, 73.7, 53.0, 41.2, 38.1, 37.3, 36.5, 33.1, 29.7, 27.6, 25.8, 25.7, 18.0, 17.9, 5.5, −4.4, −4.5, −4.7, −5.1.

3.1.15. 5′-Deoxy-N^6-(2*S*-*exo*-5,6-epithio-*endo*-norborn-2-yl)-5′-methylthioadenosine (25a). The thiirane **23a** (32 mg, 0.05 mmol) and $NaSCH_3$ (18 mg, 0.26 mmol) were dissolved in DMF (1 mL) and stirred at rt for 41 h. The reaction mixture was packed on SiO_2 and purification by column chromatography ($CHCl_3$ to $CHCl_3$/MeOH, 98:2) afforded the title compound **25a** (10 mg, 47%) as a transparent solid (mp 69–71 °C). ^1H NMR δ 8.33 (s, 1H, H-2/8), 8.01 (s, 1H, H-8/2), 6.27 (br s, 1H, NH), 5.93 (d, 1H, H-1′), 4.70 (br s, 1H, H-2″), 4.56 (t, 1H, H-2′), 4.47–4.43 (m, 1H, H-4″), 4.40–4.38 (m, 1H, H-3′), 3.05 (d, 1H, H-6n″), 2.98–2.97 (m, 2H, H-1″, H-5n″), 2.83 (d, 2H, H-5a′/b′), 2.55 (s, 1H, H-4″), 2.39–2.34 (m, 1H, H-3x″), 2.18 (s, 3H, SCH_3), 1.68 (d, 1H, H-7s″), 1.19–1.14 (m, 1H, H-3n″), 0.97 (d, 1H, H-7a″). ^{13}C NMR δ 154.7, 152.6, 147.8, 137.9, 119.9, 90.2, 84.9, 75.4, 73.4, 53.0, 41.2, 38.1, 37.3, 36.8, 36.1, 33.1, 27.5, 16.7. HRMS: $C_{18}H_{23}N_5O_3S_2$ requires $[M+H]^+$ 422.1315. Found 422.1316.

3.1.16. N^6-(2*S*-*exo*-5,6-epithio-*endo*-norborn-2-yl)-*N*-ethyladenosine-5′-uronamide (27). Compound **26** (74 mg, 0.200 mmol) was suspended in water (2 mL) with Dowex-50W (H^+) resin (148 mg) and stirred at rt for 45.5 h. The reaction was then filtered and reduced in vacuo to afford a viscous oil which was taken up in *t*-BuOH (4 mL). To this mixture was added **21** (43 mg, 0.15 mmol) and N(*i*-Pr)$_2$Et (0.1 mL, 0.600 mmol) and was then heated at reflux for 15.5 h. The reaction mixture was reduced in vacuo on SiO_2 and purification by column chromatography ($CHCl_3$/MeOH; 95:5) afforded **27** (25 mg, 40%) as a white solid (mp 206–207 °C). ^1H NMR δ 8.33 (s, 1H, H-2/8), 8.28 (s, 1H, H-8/2), 6.02 (d, 1H, H-1′), 4.76 (dd, 1H, H-2′), 4.72–4.65 (m, 1H, H-2″), 4.47 (d, 1H, H-4′), 4.32 (dd, 1H, H-3′), 3.37 (q, 2H, CH_2CH_3), 3.08 (d, 1H, H-6″), 3.04 (d, 1H, H-5″), 2.89 (d, 1H, H-1″), 2.51 (d, 1H, H-4″), 2.40–2.31 (m, 1H, H-3x″), 1.68 (d, 1H, H-7s″), 1.31–1.24 (m, 1H, H-3n″), 1.23 (t, 3H, CH_2CH_3), 0.97 (d, 1H, H-7a″). ^{13}C NMR δ 172.0, 156.2, 153.9, 149.5, 142.2, 121.5, 90.5, 86.4, 75.0, 73.4, 54.4, 42.5, 39.4, 38.0, 36.3, 35.1, 33.8, 28.2, 15.1. HRMS: $C_{19}H_{24}N_6O_4S$ requires $[M+H]^+$ 433.1653. Found 433.1649.

3.1.17. 2′,3′-Bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-5′-ethylthioinosine (29). To a solution of **28** (515 mg, 1.000 mmol) in anhydrous DMF (10 mL) under N_2 was added NaSEt (480 mg, 5.706 mmol, 5.7 equiv) and stirred vigorously at ambient temperature overnight. The resultant solution was taken up in EtOAc (50 mL) and washed using 4% $NaHCO_3$ (50 mL) and H_2O (50 mL), dried (Na_2SO_4), filtered and reduced. Crystallisation using MeOH gave **29** (240 mg, 0.444 mmol, 44.4%) as clear prisms. ^1H NMR δ 8.57 (s, 1H, H-2/8), 8.27 (s, 1H, H-8/2), 5.97 (d, J = 4.8 Hz, 1H, H-1′), 4.82 (br s, 1H, H-2′), 4.26 (br s, 2H, H-3′, H-4′), 3.02 (dd, J = 14.1 and 6.3 Hz, 1H, H-5a′/b′), 2.91 (dd, J = 14.1 and 3.9 Hz, 1H, H-5b′/a′), 2.61 (q, J = 7.4 Hz, 2H, CH_2), 1.27 (t, J = 7.4 Hz, 3H, CH_3), 0.95 (s, 9H, *t*-Bu), 0.81 (s, 9H, *t*-Bu), 0.16 (s, 3H, CH_3), 0.13 (s, 3H, CH_3), −0.02 (s, 3H, CH_3), −0.19 (s, 3H, CH_3). ^{13}C NMR δ 157.7 (C), 148.4 (C), 146.0 (CH), 139.9 (CH), 123.5 (C), 89.7 (CH), 84.9 (CH), 75.0 (CH), 74.2 (CH), 34.0 (CH_2), 27.1 (CH_2), 25.8 (CH_3), 25.7 (CH_3), 18.0 (C), 17.9 (C), 14.7 (CH_3), −4.4 (CH_3), −4.5 (CH_3), −4.6 (CH_3), −5.0 (CH_3). LRMS *m*/*z* (%): 541.3 ($M+H^+$, 100), 405.4 (40).

3.1.18. N^6-Cyclopentyl-2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-5′-ethylthioadenosine (30). To a magnetically stirred solution containing **29** (37.3 mg, 0.069 mmol) and PyBroP (66.3 mg, 0.142 mmol, 2.1 equiv) in DCE (1 mL) was added N(*i*-Pr)$_2$Et (48.6 μL, 36.1 mg, 0.279 mmol, 4.0 equiv). The reaction mixture was stirred at ambient temperature for 10 min. after which time *c*-PentNH$_2$ (13.6 μL, 11.7 mg, 0.138 mmol, 2.0 equiv) was added and the resultant solution was heated at reflux for 22 h. The reaction mixture was reduced in vacuo then purified via column chromatography, eluting using $CHCl_3$/MeOH (98:2) to give the title compound (38.4 mg, 91.6%) as a clear oil. ^1H NMR δ 8.32 (s, 1H, H-2/8), 7.91 (s, 1H, H-8/2), 5.86 (d, J = 5.4 Hz, 2H, H-1′, NH), 5.04 (br s, 1H, H-2′), 4.61 (br s, 1H, H-1″), 4.29 (br s, 1H, H-3′), 4.21 (br s, 1H, H-4′), 3.06 (dd, J = 14.1 and 6.6 Hz, 1H, H-5a′/b′), 2.87 (dd, J = 14.1 and 5.7 Hz, 1H, H-5b′/a′), 2.58 (q, J = 7.2 Hz, 2H, SCH_2CH_3), 2.14–2.10 (m, 2H, H-2a″, H-5a″), 1.77–1.57 (m, 6H, H-2b″, H-3a″, H-3b″, H-4a″, H-4b″, H-5b″), 1.24 (t, J = 7.2 Hz, 3H, SCH_2CH_3), 0.93 (s, 9H, *t*-Bu), 0.78 (s, 9H, *t*-Bu), 0.14 (s, 3H, CH_3), 0.11 (s, 3H, CH_3), −0.07 (s, 3H, CH_3), −0.28 (s, 3H, CH_3). ^{13}C NMR δ 154.2 (C), 152.7 (CH), 148.7 (C), 139.8 (CH), 120.5 (C), 89.5 (CH), 84.6 (CH), 74.3 (CH), 73.7 (CH), 52.4 (CH), 33.8 (CH_2), 33.4 (CH_2), 26.9 (CH_2), 25.8 (CH_3), 25.6 (CH_3), 23.7 (CH_2), 18.0 (C), 17.8 (C), 14.6 (CH_2), −4.4 (CH_3), −4.6 (CH_3), −4.7 (CH_3), −5.1 (CH_3). LRMS *m*/*z* (%): 608.4 ($M+H^+$, 100), 609.6 (45).

3.2. General procedure for TBS deprotection

5′-Modified compounds and NH_4Cl ($\geqslant$10 equiv) were heated to ~60 °C in dry methanol (1–4 mL) for 24–48 h. under a N_2 atmosphere. The reaction mixture was then packed onto SiO_2 and purified by column chromatography ($CHCl_3$:MeOH).

3.2.1. N^6-Cyclopentyl-5′-deoxy-5′-ethylthioadenosine (2). Compound **30** (43 mg, 0.071 mmol) was reacted with NH_4F (25 mg, 0.683 mmol, 9.6 equiv) to afford **2** as a clear oil (10 mg, 37%). $CHCl_3$/MeOH (85:15). ^1H NMR δ 8.28 (s, 1H, H-2/8), 8.06 (s, 1H, H-8/2), 5.97 (br s, 1H, H-1′), 4.59 (br s, 2H, H-2′, H-1″), 4.40 (s, 2H, H-3′, H-4′), 2.87 (br s, 2H, H-5a′, H-5b′), 2.60 (q, J = 7.2 Hz, 2H, SCH_2CH_3), 2.16–2.11 (m, 2H, H-2″, H-5″), 1.79–1.58 (m, 6H, H-2″, H-3″, H-4″, H-5″), 1.25

(t, J = 7.2 Hz, 3H, CH_3). Data obtained for **2** were in accordance with the literature.[7]

3.2.2. 5′-Chloro-5′-deoxy-N^6-(*endo*-norborn-2-yl)adenosine (10b). Compound **10a** (37.9 mg, 0.062 mmol) was reacted with NH_4F (24.0 mg, 0.648 mmol, 10.4 equiv) to give **10 b** (18.9 mg, 79.8%) as a clear oil. $CHCl_3$/MeOH (95:5). ^{1}H NMR δ 8.27 (s, 1H, H-2/8), 8.03 (s, 1H, H-8/2), 6.13 (br s, 1H, NH), 5.99 (d, J = 4.8 Hz, 1H, H-1′), 4.59 (app. t, J_{app} = 5.1 Hz, 1H, H-2′), 4.53–4.43 (m, 1H, H-3′, H-4′, H-2″), 3.84 (dd, J = 12.0 and 4.5 Hz, 1H, H-5a′/b′), 3.77 (dd, J = 12.0 and 3.9 Hz, 1H, H-b′/a′), 2.62 (br s, 1H, H-1″), 2.29 (br s, 1H, H-4″), 2.23–2.19 (m, 1H, H-3x″), 1.67–1.22 (6H, H-5″, H-6″, H-7″), 0.98–0.93 (m, 1H, H-3n″). ^{13}C NMR δ 154.6 (C), 152.7 (CH), 147.6 (C), 137.7 (CH), 119.6 (C), 89.6, 89.5 (CH), 84.2 (CH), 75.0, 74.9 (CH), 52.0 (CH), 44.1 (CH_2), 40.3 (CH), 38.1 (CH_2), 37.7 (CH_2), 36.6 (CH), 29.7 (CH_2), 21.3 (CH_2). LRMS m/z (%): 380.3 ($M+H^+$, ^{35}Cl, 100), 382.3 (^{37}Cl, 25). HRMS: $C_{17}H_{22}ClN_5O_3$ requires $[M+H]^+$ 380.1484. Found 380.1485.

3.2.3. 5′-Deoxy-N^6-(*endo*-norborn-2-yl)-5′-methylaminoadenosine (12a). Compound **11a** (42 mg, 0.070 mmol) was reacted with NH_4F (29 mg, 11.2 mmol) to afford the title compound (15 mg, 57.7%) as a clear oil. $CHCl_3$/MeOH (8:2). ^{1}H NMR δ 8.24 (s, 1H, H-2/8), 8.22 (s, 1H, H-8/2), 5.96 (d, J = 5.4 Hz, 1H, H-1′), ~4.8 (1H, H-2′), 4.27–4.19 (m, 2H, H-3′, H-4′), 3.04 (dd, J = 12.8 and 7.5 Hz, 1H, H-5a′/b′), 2.95 (dd, J = 12.8 and 3.6 Hz, 1H, H-5b′/a′), 2.59 (br s, 1H, H-1″), 2.46 (s, 3H, NHCH_3), 2.28 (br s, 1H, H-4″), 2.23–2.13 (m, 1H, H-3x″), 1.67–1.33 (m, 6H, H-5″, H-6″, H-7″), 1.09–1.02 (m, 1H, H-3n″). ^{13}C NMR δ 156.3 (C), 154.1 (CH), 149.8 (C), 141.4 (CH), 121.2 (C), 91.1 (CH), 84.5 (CH), 74.9 (CH), 73.5 (CH), 54.5 (CH_2), 53.7 (CH), 41.9 (CH), 39.3 (CH_3), 38.3 ($2\times CH_2$), 36.1 (CH), 30.9 (CH_2), 22.5 (CH_2). LRMS m/z (%): 375.3 ($M+H^+$, 100), 376.3 (20). HRMS: $C_{18}H_{26}N_6O_3$ requires $[M+H]^+$ 375.2139. Found 375.2111.

3.2.4. 5′-Deoxy-N^6-(*endo*-norborn-2-yl)-5′-ethylthioadenosine (12b). A solution of **10a** (108.6 mg, 0.178 mmol) and NaSEt (150.4 mg, 1.788 mmol, 10.0 equiv) in anhydrous DMF (2 mL) under an N_2 atmosphere was stirred at ambient temperature for 44 h. The resultant crude solution was taken up in sat. NH_4Cl (90 mL) and extracted using EtOAc (2×60 mL), the combined organic phase was washed using H_2O (3×90 mL), dried (Na_2SO_4), filtered and reduced in vacuo. The crude material was reacted with NH_4F (77.3 mg, 2.087 mmol, ~11.7 equiv) to afford **12b** (36.0 mg, 49.9%) as a clear oil. $CHCl_3$/MeOH (95:5). ^{1}H NMR δ 8.27 (s, 1H, H-2/8), 7.99 (s, 1H, H-8/2), 6.09 (br s, 1H, NH), 5.94 (d, J = 5.1 Hz, 1H, H-1′), 4.59 (app. t, J_{app} = 3.6 Hz, 1H, H-2′), 4.44–4.37 (m, 3H, H-2″, H-3′, H-4′), 2.87 (s, 1H, H-5a′/b′), 2.85 (s, 1H, H-5b′/a′), 2.63–2.56 (m, 3H, H-1″, SCH_2CH$_3$), 2.28 (s, 1H, H-4″), 2.22–2.18 (m, 1H, H-3x″), 1.66–1.30 (m, 6H, H-5″, H-6″, H-7″), 1.25 (t, J = 7.5 Hz, 3H, SCH$_2$CH_3), 0.97–0.90 (m, 1H, H-3n″). LRMS m/z (%): 406.4 ($M+H^+$, 30). HRMS: $C_{19}H_{27}N_5O_3S$ requires $[M+H]^+$ 406.1907. Found 406.1906.

3.2.5. 5′-Deoxy-N^6-(*endo*-norborn-2-yl)-5′-(2-fluorophenylthio)adenosine (12c). Compound **11c** (118.7 mg, 0.170 mmol) was reacted with NH_4F (64.9 mg, 1.752 mmol) to afford the title compound **12c** (39.1 mg, 48.9%) as a clear oil. ^{1}H NMR δ 8.25 (s, 1H, H-2/8), 7.78 (s, 1H, H-8/2), 7.41 (app. t, J_{app} = 7.5 Hz, 1H, ArH), 7.23–7.18 (m, 1H, ArH), 7.06–7.00 (m, 2H, ArH), 6.52 (br s, 1H, OH), 6.05, 6.03 (br s, 1H, NH), 5.87 (d, J = 5.7 Hz, 1H, H-1′), 4.63 −4.58 (m, 1H, H-2′), 4.42 (br s, 3H, H-2″, H-3′, H-4′), 3.96 (br s, 1H, OH), 3.29–3.17 (m, 2H, H-5a′, H-b′), 2.60 (br s, 1H, H-1″), 2.27–2.17 (m, 2H, H-3x″, H-4″), 1.65–1.16 (m, 6H, H-5″, H-6″, H-7″), 0.94–0.85 (m, 1H, H-3n″). ^{13}C NMR δ 161.7 (d, $^1J_{CF}$ = 244.3 Hz, C), 154.9 (C), 152.7 (CH), 147.7 (C), 137.8 (CH), 133.1 (CH), 129.3 (d, $^3J_{CF}$ = 7.8 Hz, CH), 124.6 (d, $^4J_{CF}$ = 3.2 Hz, CH), 121.9 (d, $^2J_{CF}$ = 17.3 Hz, C), 119.9 (C), 115.9 (d, $^2J_{CF}$ = 22.4 Hz, CH), 90.2, 90.1 (CH), 84.9 (CH), 75.3, 75.2 (CH), 73.3 (CH), 52.2 (CH_2), 40.5 (CH), 38.2 (CH_2), 37.9 (CH_2), 36.8 (CH), 36.4 (CH_2), 29.9 (CH_2), 21.5 (CH_2). LRMS m/z (%): 472.3 ($M+H^+$, 100), 473.2 (30). HRMS: $C_{19}H_{28}N_6O_3$ requires $[M+H]^+$ 472.1813. Found 472.1821.

3.2.6. 5′-Deoxy-N^6-(*endo*-norborn-2-yl)-5′-mercaptoadenosine (12d). Compound **11d** (50.6 mg, 0.078 mmol) was reacted with NH_4F (33.3 mg, 0.899 mmol) to afford the title compound **12d** (24.1 mg, 81.8%) as a clear oil. $CHCl_3$/MeOH (9:1). ^{1}H NMR (CD_3OD) δ 8.24 (s, 1H, H-2/8), 8.22 (s, 1H, H-8/2), 6.00 (d, J = 5.4 Hz, 1H, H-1′), ~4.85 (coincides with DOH, H-2′) 4.43 (br s, 1H, H-2″), 4.34–4.27 (m, 2H, H-3′, H-4′), 3.27–3.11 (m, 2H, H-5a′. H-5b′), 2.61 (br s, 1H, H-1′), 2.29 (br s, 1H, H-4′), 2.24–2.14 (m, 1H, H-3x″), 1.79–1.36 (m, 6H, H-5″, H-6″, H-7″), 1.09–1.02 (m, 1H, H-3n″). ^{13}C NMR (CD_3OD) δ 156.7 (C), 154.6 (CH), 149.6 (C), 141.4 (CH), 121.4 (C), 90.8 (CH), 85.2 (CH), 75.4 (CH), 74.8 (CH), 54.1 (CH), 43.7 (CH_2), 42.3 (CH), 39.7 (CH_2), 38.8 (CH), 38.7 (CH_2), 31.3 (CH_2), 23.0 (CH_2).

3.2.7. 5′-Deoxy-N^6-(*endo*-norborn-2-yl)-5′-propylthioadenosine (12e). Compound **11e** (34 mg, 0.052 mmol) was reacted with NH_4F (21 mg, 0.562 mmol, 10.9 equiv) to afford the title compound **12e** (15 mg, 69.1%) as a clear oil. ^{1}H NMR δ 8.28 (s, 1H, H-2/8), 7.99 (s, 1H, H-8/2), 6.07 (br s, 1H, NH), 5.93 (d, J = 5.1 Hz, 1H, H-1′), 4.57–4.38 (m, 4H, H-2′, H-2″, H-3′, H-4′), 2.84 (app. d, J_{app} = 5.7 Hz, 2H, H-5a′, H-b′), 2.62 (br s, 1H, H-1″), 2.55 (t, J = 7.2 Hz, 2H, SCH_2CH$_2$), 2.28–2.19 (m, 2H, H-3x″, H-4″), 1.67–1.26 (m, 8H, H-5″, H-6″, H-7″, SCH$_2$CH_2), 0.97 (t, J = 7.2 Hz, 4H, H-3n″, CH$_2$CH_3). ^{13}C NMR δ 155.0 (C), 152.7 (CH), 147.8 (C), 137.8 (CH), 120.0 (C), 90.2 (CH), 85.2 (CH), 75.5 (CH), 73.4 (CH), 52.2 (CH), 40.5 (CH), 38.3 (CH_2), 38.0 (CH_2), 36.8 (CH), 35.2 (CH_2), 34.7 (CH_2), 29.9 (CH_2), 22.9(CH_2), 21.5 (CH_2), 13.3 (CH_3). HRMS: $C_{20}H_{29}N_5O_3S$ requires $[M+H]^+$ 420.2064. Found 420.2074.

3.2.8. 5′-Deoxy-5′-dimethylamino-N^6-(*endo*-norborn-2-yl)-adenosine (15a). Compound **14a** (52.4 mg, 0.085 mmol) was reacted with NH_4F (37 mg, 1.004 mmol, 11.8 equiv) to afford **15a** as a clear oil (26 mg, 78.2%). ^{1}H NMR δ 8.30 (s, 1H, H-2/8), 7.95 (s, 1H, H-8/2), 6.06 (br s, 1H, NH), 5.92 (d, J = 4.5 Hz, 1H, H-1′), 4.53 (br s, 1H, H-2′),

4.46 (br s, 1H, H-2″), 4.30 (br s, 2H, H-3′, H-4′), 2.63–2.61 (m, 3H, H-1″, H-5a′, H-5b′), 2.32 (s, 6H, $N(CH_3)_2$), 2.28–2.18 (m, 2H, H-3x″, H-4″), 1.66–1.22 (m, 6H, H-5″, H-6″, H-7″), 0.95–0.91 (m, 1H, H-3n″). ^{13}C NMR δ 154.9 (C), 152.8 (CH), 147.7 (C), 138.0 (CH), 120.1 (C), 90.3 (CH), 83.0 (CH), 75.0 (CH), 73.1 (CH), 61.8 (CH_2), 52.1 (CH), 46.2 (CH_3), 40.4 (CH), 38.2 (CH_2), 37.9 (CH_2), 36.7 (CH), 29.9 (CH_2), 21.5 (CH_2). LRMS *m/z* (%): 389.3 ($M+H^+$, 100), 390.3 (25). HRMS: $C_{19}H_{28}N_6O_3$ requires $[M+H]^+$ 389.2296. Found 389.2292.

3.2.9. 5′-Acetamido-5′-deoxy-*N*^{6}-(*endo*-norborn-2-yl)adenosine (15b). Compound **14b** (118 mg, 0.187 mmol) was reacted with NH_4F (70 mg, 1.895 mmol, 10.1 equiv) to afford **15b** (39 mg, 51.3%) as an opaque oil. $CHCl_3$/MeOH (97:3). ^{1}H NMR δ 8.79 (br s, 1H, $N^{5'}H$), 8.26 (s, 1H, H-2/8), 7.85 (s, 1H, H-8/2), 6.19 (s, 1H, N^6H), 5.78 (d, J = 6.6 Hz, 1H, H-1′), 4.80–4.75 (m, 1H, H-2′), 4.42 (br s, 1H, H-2″), 4.32 (br s, 1H, H-5a′/b′), 4.22 (app. d, J_{app} = 6.0 Hz, 1H, H-5a′/b′), 4.08–4.00 (m, 1H, H-3′), 3.17 (app. d, J_{app} = 13.5 Hz, 1H, H-4′), 2.57 (br s, 1H, H-1″), 2.25 (br s, 1H, H-4″), 2.19–2.16 (m, 1H, H-3x″), 2.03 (s, 3H, CH_3), 1.62–1.18 (m, 6H, H-5″, H-6″, H-7″), 0.91–0.87 (m, 1H, H-3n″). ^{13}C NMR δ 171.6 (C=O), 155.1 (C), 152.5 (CH), 147.7 (C), 140.2 (CH), 121.0 (C), 90.9 (CH), 85.0 (CH), 73.1 (CH), 71.4 (CH), 52.2 (CH), 41.1 (CH_2), 40.4 (CH), 38.2 (CH_2), 37.9 (CH_2), 36.8 (CH), 29.9 (CH_2), 22.8 (CH_3), 21.4 (CH_2). LRMS *m/z* (%): 403.2 (100), 404.3 (25). HRMS: $C_{19}H_{26}N_6O_4$ requires $[M+H]^+$ 403.2088. Found 403.2102.

3.2.10. 5′-Chloro-5′-deoxy-*N*^{6}-(2*S*-*exo*-5,6-epithio-*endo*-norborn-2-yl)adenosine (23b). Compound **23a** (34 mg, 0.053 mmol) and NH_4F (53 mg, 1.431 mmol, 27.0 equiv) were heated to ~60 °C in MeOH (4 mL) for 14 h. The reaction mixture was then packed on SiO_2 and purified by column chromatography ($CHCl_3$/MeOH; 98:2) to yield **23b** (21 mg, 97%) as a white solid (mp 122–124 °C). ^{1}H NMR (CD_3OD) δ 8.29 (s, 1H, H-2/8), 8.27 (s, 1H, H-2/8), 6.04 (d, 1H, H-1′), 4.77 (t, 1H, H-2′), 4.71 (br s, 1H, H-2″), 4.39 (s, 1H, H-3′), 4.28 (d, 1H, H-4′), 3.95 (dd, 1H, H-5a′/b′), 3.85 (dd, 1H, H-5b′/a′), 3.07 (s, 1H, H-6″), 3.04 (s, 1H, H-5″), 2.87 (s, 1H, H-1″), 2.50 (s, 1H, H-4″), 2.41–2.32 (m, 1H, H-3x″), 1.66 (d, 1H, H-7s″), 1.34–1.24 (m, 1H, H-3n″), 0.96 (d, 1H, H-7a″). ^{13}C NMR (CD_3OD) δ 156.0, 154.0, 149.7, 140.6, 120.8, 89.9, 85.2, 75.0, 72.6, 54.3, 45.2, 42.4, 39.4, 38.0, 36.3, 33.8, 28.1. HRMS: $C_{17}H_{20}ClN_5O_3S$ requires $[M+H]^+$ 410.1048. Found 410.1054.

3.2.11. 5′-Deoxy-*N*^{6}-(2*S*-*exo*-5,6-epithio-*endo*-norborn-2-yl)-5′-methylselenoadenosine (25b). Compound **24b** (7 mg, 0.010 mmol) and NH_4F (81 mg, 2.187 mmol, 21.9 equiv) were heated to ~60 °C in MeOH (2 mL) for 40 h. The reaction mixture was then packed on SiO_2 and purified by column chromatography ($CHCl_3$/MeOH; 98:2) to yield the title compound **25b** (5 mg, 100%) as a white solid (mp 82–84 °C). ^{1}H NMR δ 8.36 (s, 1H, H-2/8), 8.00 (s, 1H, H-8/2), 5.90 (d, 1H, H-1′), 4.74 (br s, 1H, H-2″), 4.58 (t, 1H, H-2′), 4.54–4.49 (m, 1H, H-4′), 4.40–4.38 (m, 1H, H-3′), 3.05 (d, 1H, H-6″), 2.98–2.97 (m, 2H, H-1″, H-5″), 2.83 (dd, 2H, H-5a′, H-5b′), 2.56 (s, 1H, H-4″), 2.53–2.37 (m, 1H, H-3x″), 2.08 (s, 3H, CH_3), 1.69 (d, 1H, H-7s″), 1.27–1.24 (m, 1H, H-3n″), 0.98 (d, 1H, H-7a″). ^{13}C NMR (400 MHz) δ 154.9, 152.7, 148.2, 138.2, 120.2, 90.6, 85.9, 75.9, 74.2, 53.2, 41.4, 38.3, 37.4, 36.5, 33.1, 29.8, 27.7, 5.6. HRMS: $C_{18}H_{23}N_5O_3SSe$ requires $[M+H]^+$ 470.0760. Found 470.0770.

3.3. Cell culture and cAMP assay

DDT_1MF-2 cells were grown in 48-well culture plates using Dulbecco's modified Eagle's medium containing 2.5 μg/mL amphotericin B, 100 U/ml penicillin G, 0.1 mg/mL streptomycin sulfate and 5% foetal bovine serum in a humidified atmosphere of 95% air and 5% CO_2. Cells were routinely used at one day preconfluence. To begin an experiment, the culture medium was removed from each well, and warm Hank's Balanced Salt solution (HBSS) was added. This wash solution was removed after 6 min at 37 °C and replaced with HBSS containing adenosine deaminase (0.5 U/mL), 20 μM rolipram, with or without 1 μM (−)-isoproterenol and varying concentrations of the test compounds in the presence of (−)-isoproterenol. After a 6-min incubation at 37 °C, the incubation solution was aspirated, and HCl (0.5 mL, 50 mM) was added to terminate drug action.

The cAMP content in each well was determined by radioimmunoassay. Briefly, a standard was prepared in duplicate with tubes containing 100 μL cAMP (0.001–10 pmol) in 50 mM HCl. The well plates containing the samples were gently agitated and a 5-μL aliquot was transferred to tubes containing 100 μL of 50 mM HCl. Each sample was then acetylated by the addition of 4.5 μL of a 3.5:1 mixture of triethylamine and acetic anhydride and immediately vortexed. A 10-μL aliquot of [^{125}I]-ScAMP-TME containing 20,000 cpm was added followed by 100 μL cAMP antibody in a solution of 50 mM sodium–acetate buffer, pH 4.75, containing 0.125% BSA. After incubation at room temperature, 50 μL hydroxyapatite in a 1:1 suspension with water was added and incubated for 10 min at room temperature. Using a Brandell cell harvester, the samples were then aspirated through Whatman GF/B glass fibre filters under reduced pressure, and the filters rinsed with an additional 6 mL of ice-cold 10 mM Tris buffer at pH 7.0. The radioactivity retained by the filters was determined using a Beckman gamma counter.

Acknowledgements

The authors thank Mr. Stuart Thompson, Dr. Simon Egan and Dr. Martin Scanlon for assistance with the acquisition of NMR and mass spectra. We also thank the ARC Centre for Free Radical Chemistry and Biotechnology for funding this research, in part.

References and notes

1. Yan, L.; Burbiel, J. C.; Maaß, A.; Müller, C. E. *Expert Opin. Emerg. Drugs* **2003**, *8*, 537–576.
2. Lerman, B. B.; Belardinelli, L. *Circulation* **1991**, *83*, 1499–1509.

3. Hutchinson, S. A.; Scammells, P. J. *Curr. Pharm. Design* **2004**, *10*, 2021–2039.
4. Dhalla, A. K.; Shryock, J. C.; Shreeniwas, R.; Belardinelli, L. *Curr. Top. Med. Chem.* **2003**, *3*, 369–385.
5. Palle, V. P.; Varkhedkar, V.; Ibrahim, P.; Ahmed, H.; Li, Z.; Gao, Z.; Ozcek, M.; Wu, Y.; Zeng, D.; Wu, L.; Leung, K.; Chu, N.; Zablocki, J. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 535–539.
6. Song, Y.; Wu, L.; Shryock, J. C.; Belardinelli, L. *Circulation* **2002**, *105*, 118–123.
7. van der Wenden, E. M.; Carnielli, M.; Roelen, H. C. P. F.; Lorenzen, A.; von Frijtag Drabbe Künzel, J. K.; IJzerman, A. P. *J. Med. Chem.* **1998**, *41*, 102–108.
8. Fatholahi, M.; Xiang, Y.; Wu, Y.; Li, Y.; Wu, L.; Dhalla, A. K.; Berlardinelli, L.; Shryock, J. C. *J. Pharmacol. Exp. Ther.* **2006**, *317*, 676–684.
9. Roelen, H.; Veldman, N.; Spek, A. L.; von Frijtag Drabbe Künzel, J.; Mathôt, R. A. A.; IJzerman, A. P. *J. Med. Chem.* **1996**, *39*, 1463–1471.
10. Elzein, E.; Kalla, R.; Li, X.; Perry, T.; Marquart, T.; Micklatcher, M.; Li, Y.; Wu, Y.; Zeng, D.; Zablocki, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 161–166.
11. Hutchinson, S. A.; Baker, S. P.; Scammells, P. J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 933–936.
12. Hutchinson, S. A.; Baker, S. P.; Scammells, P. J. *Bioorg. Med. Chem.* **2002**, *10*, 1115–1122.
13. Trivedi, B. K.; Bridges, A. J.; Patt, W. C.; Priebe, S. R.; Bruns, R. F. *J. Med. Chem.* **1989**, *32*, 8–11.
14. Ashton, T. D.; Scammells, P. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3361–3363.
15. Ashton, T. D.; Scammells, P. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4564–4566.
16. Pignot, M.; Pljevaljcic, G.; Weinhold, E. *Eur. J. Org. Chem.* **2000**, *3*, 549–555.
17. Barma, D. K.; Bandyopadhyay, A.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4755–4757.
18. Hutchinson, S. A.; Baker, S. P.; Linden, J.; Scammells, P. J. *Bioorg. Med. Chem.* **2004**, *12*, 4877–4884.
19. Krief, A.; Trabelsi, M.; Dumont, W. *Synthesis* **1992**, *10*, 933–935.
20. Olsson, R. A.; Kusachi, S.; Thompson, R. D.; Ukena, D.; Padgett, W.; Daly, J. W. *J. Med. Chem.* **1986**, *29*, 1683–1689.
21. Wan, Z.-K.; Binnun, E.; Wilson, D. P.; Lee, J. *Org. Lett.* **2005**, *7*, 5877–5880.
22. Morrison, C. F.; Elzein, E.; Jiang, B.; Ibrahim, P. N.; Marquart, T.; Palle, V.; Shenk, K. D.; Varkhedkar, V.; Maa, T.; Wu, L.; Wu, Y.; Zeng, D.; Fong, I.; Lustig, D.; Leung, K.; Zablocki, J. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3793–3797.
23. de Ligt, R. A. F.; IJzerman, A. P. *Curr. Pharm. Design* **2002**, *8*, 2333–2344.