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Design and Synthesis of N^6-Substituted-4′-thioadenosine-5′-uronamides As Potent and Selective Human A_3 Adenosine Receptor Agonists

Won Jun Choi[1], **Hyuk Woo Lee**[1], **Hea Ok Kim**[1], **Moshe Chinn**[2], **Zhan-Guo Gao**[2], **Amit Patel**[2], **Kenneth A. Jacobson**[2], **Hyung Ryong Moon**[3], **Young Hoon Jung**[4], and **Lak Shin Jeong**[1,*]

[1]Department of Bioinspired Science and Division of Life and Pharmaceutical Sciences, College of Pharmacy, Ewha Womans University, Seoul 120–750, Korea

[2]Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes, and Digestive and Kidney Disease, National Institute of Health, Bethesda, Maryland 20892, USA

[3]College of Pharmacy and Research Institute for Drug Development, Pusan National University, Busan 609-735, Korea

[4]College of Pharmacy, Sungkyunkwan University, Suwon 440-746, Korea

Abstract

On the basis of a bioisosteric rationale, 4′-thionucleoside analogues of IB-MECA, which is a potent and selective A_3 adenosine receptor agonist (AR), were synthesized from D-gulonic acid γ-lactone. The 4′-thio analogue (**5h**) of IB-MECA showed extremely high binding affinity (K_i = 0.25 nM) at the human A_3AR and was more potent than IB-MECA (K_i = 1.4 nM). Bulky substituents at the 5′-uronamide position, such as cyclohexyl and 2- methylbenzyl, in this series of 2-H nucleoside derivatives were tolerated in A_3AR binding, although small alkyl analogues were more potent.

Keywords

A_3 adenosine receptor; 4'-thionucleosides; agonist; binding affinity

Introduction

The A_3 adenosine receptor (AR), which belongs to the family of G-protein-coupled receptors (GPCRs), is known to be involved in cell signaling by modulating the levels of cAMP, inositol triphosphate (IP_3), and diacylglycerol (DAG) through binding of the endogenous chemical messenger, adenosine.[1] Thus, the A_3AR has been regarded as good therapeutic target for the treatment of several diseases associated with cell signaling such as cancer, ischemia, inflammation, and glaucoma.[2]

To whom correspondence should be addressed: Lak Shin Jeong, Ph.D., Department of Bioinspired Science and Division of Life and Pharmaceutical Sciences, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea, Tel) 82-2-3277-3466, Fax) 82-2-3277-2851, lakjeong@ewha.ac.kr.

Adenosine has served as a good template for the development of A_3AR ligands. Extensive modification of adenosine resulted in the discovery of Cl-IB-MECA, **1** (K_i = 1.0 nM for human A_3AR)[3] and IB-MECA, **2** (K_i = 1.4 nM for human A_3AR) [4] as potent and selective A_3AR agonists and these are in clinical trials as anticancer agents[5] (Figure 1). Recently, probing the structure-activity relationship (SAR) of compound **1** on the basis of a bioisosteric rationale indicated that a 4′-thionucleoside could serve as an excellent template for the development of A_3AR agonists, among which compounds **3** and **4** were discovered as more potent A_3AR agonists (K_i = 0.38 and 0.28 nM, respectively) than Cl-IB-MECA **1**.[6] Compound **3** also showed potent in vitro as well as in vivo anticancer activity.[7] Because IB-MECA **2** is another representative of A_3AR agonists, it would be of great interest to synthesize its 4′-thio analogue and to compare their biological activities and substituent effects (H vs Cl) at the C2 position. It would be also interesting to study SAR surrounding the 5′-uronamide moiety of the 4′-thionucleosides. The A_3AR has displayed a moderate tolerance for sterically bulky substituents at this position, in contrast to the *N*-methylamides of the protypical agonists **1** and **2**.[6b] Herein, we report the synthesis and binding affinity of the series of compound **5** as potent and selective A_3AR agonists.

Results and discussion

The target nucleoside **5** was synthesized from D-gulonic acid γ-lactone, as shown in Scheme 1.

D-Gulonic acid γ-lactone was smoothly converted to the glycosyl donor **6** according to our previously published procedure.[6] Condensation of **6** with 6-chloropurine in the presence of TMSOTf afforded the 6-chloropurine derivative 7 (53%) and its α-anomer (5.4%).[8] The anomeric configuration of **7** was easily confirmed by an NOE effect between 1′-H and 4′-H. Irradiation on 1′-H of compound **6** gave NOE effect on its 4′-H, indicating β-anomer, but no NOE effect was observed on the same experiment in the case of its α-anomer.[8] Treatment of **7** with methyl amine and 3-iodobenzylamine gave the N^6-methyladenine derivative **8** and N^6-(3-iodobenzyl)adenine derivative **9**, respectively. For the conversion of 4′-hydroxymethyl group into various 5′-uronamides, the 2′,3′-isopropylidene group was first changed to the 2′, 3′-di-*O*-TBS group, because the removal of the 2′,3′-isopropylidene group at the final step resulted in the deglycosylation. Treatment of **8** and **9** with 80% acetic acid followed by protection of the resulting diol with the TBS group yielded **10** and **11**, respectively. Removal of the benzoyl group in **10** and **11** with sodium methoxide gave the 4′-hydroxymethyl derivatives **12** and **13**, respectively.

Treatment of **12** and **13** with PDC in DMF afforded the carboxylic acid derivatives **14** and **15**, respectively. Coupling of the acids **14** and **15** with various primary amines in the presence of EDC and HOBt yielded various 5′-uronamides **5a–w** after the removal of the TBS group.

Radioligand binding assay was performed using adherent CHO (Chinese hamster ovary) cells stably transfected with cDNA encoding the human ARs.[9] Bindings at the human ARs were carried out using [^{3}H]R-PIA for A_1AR, [^{3}H]CGS21680 for A_{2A}AR, and [^{125}I]I-AB-MECA for A_3AR as radioligands. In cases of weak binding, the percent inhibition of radioligand binding to the human ARs was determined at 1 μM. Percent activation (inhibition of adenylate cyclase in comparison to the full agonist Cl-IB-MECA, **1**) of the human A_3AR was determined at 1 μM.

Most of the synthesized compounds showed very high binding affinity at the human A_3AR with high selectivity in comparison to other subtypes (Table 1). When compared with the 4′-oxonucleoside, IB-MECA (**2**) (K_i = 1.4 nM), the corresponding 4′-thionucleoside, thio-IB-MECA (**5h**) exhibited higher binding affinity at the human A_3AR (K_i = 0.25 nM) as well as higher selectivity over other subtypes, indicating that thio-IB-MECA (**5h**) has the potential to

be developed as a clinical candidate as IB-MECA (**2**). A similar trend was observed between Cl-IB-MECA (**1**) (K_i = 1.0 nM) and thio-Cl-IB-MECA (**3**) (K_i = 0.38 nM). However, thio-IB-MECA (**5h**) was found to be less selective (81- vs 508-fold) for the human A_3AR in comparison to the human A_1AR than thio-Cl-IB-MECA (**3**). This result indicated that substitution of the 2-H atom with more hydrophobic 2-Cl substituent increased the A_3 AR selectivity.[10] It should be noted that thio-IB-MECA (**5h**) showed the best binding affinity at the human A_3AR among 4′-thionucleosides synthesized so far. This compound also showed very high binding affinity (K_i = 1.86 ± 0.36 nM) at the rat A_3AR. In the N^6-methyladenine series, the binding affinity at the human A_3AR of the synthesized 5′-uronamides was dependent on the 5′-N substitution in the following order: ethyl = cyclopentyl > cyclobutyl > cyclopropylmethyl > methyl > cyclopropyl > 3-iodobenzyl, indicating that alkyl and cycloalkyl derivatives **5a–f** showed better binding affinity (K_i = 0.97 ~ 2.16 nM) than arylalkyl derivative **5g** (K_i = 15.6 nM). A similar trend was observed in the N^6-(3-iodobenzyl)adenine series, except that the N^6-(3-iodobenzyl) adenine derivatives showed slightly better binding affinity at the human A_3AR and generally were more selective versus the human A_1AR than the N^6-methyladenine derivatives.

The most potent and selective compound **5h** was a full agonist in an assay of human A_3 adenosine receptor-mediated inhibition of cyclic AMP in transfected CHO cells, as previously observed for compounds **1–4**.

In summary, we have established SARs of bioisosteric 4′-thio analogues of potent and selective A_3AR agonist, IB-MECA (**2**). From this study, thio-IB-MECA (**5h**) was discovered as being among the most potent A_3 AR agonists and more potent than IB-MECA (**2**). It was also revealed that small alkyl or cycloalkyl substituents on the 5′-uronamide were essential for optimal binding affinity. We believe that compound **5h** has promise to be developed as a clinically useful agent.

Experimental Section

^{1}H NMR spectra ($CDCl_3$, CD_3OD, or DMSO-d_6) were recorded on Varian Unity Inova 400 MHz. Chemical shifts were reported in ppm units with TMS as the internal standard. ^{13}C NMR spectra ($CDCl_3$, CD_3OD, or DMSO-d_6) were recorded on Varian Unity Inova 100 MHz. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60F-254 glass plates. Optical rotations were determined on Jasco III in methanol. UV spectra were recorded on U-3000 made by Histachi in methanol. Elementary analyses were measured on EA1110. The crude products were purified using a silica gel 60 (230–400 mesh, Merck). Reagents were purchased from Aldrich Chemical Company. All the anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to the reaction.

Benzoic acid (3aS,4R,6R,6aR)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-thieno[3,4-d] [1,3]dioxol-4-ylmethyl ester (7)[8]

To a suspension of 6-chloropurine (3.36 g, 21.69 mmol) in a solution of dry CH_3CN (20 mL) and 1,2-dichloroethane (10 mL) were added Et_3N (2.19 g, 21.69 mmol) and TMSOTf (9.64 g, 43.38 mmol), and the mixture was stirred at room temperature until the solution was clear. A solution of sulfoxide **6** (3.36 g, 10.85 mmol) in dry 1,2-dichloroethane (10 mL) was added to the resulting solution in one shot at room temperature. An additional amount of Et_3N (2.19 g, 21.69 mmol) was added to the reaction mixture to initiate the Pummerer reaction. The reaction mixture was stirred under reflux at 80 °C for 4 d, during which time the initially formed N-3 isomer was converted to N-9 isomer. The reaction mixture was partitioned between EtOAc and aqueous saturated $NaHCO_3$ solution, and the organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash silica gel column chromatography (Hexane:EtOAc = 5:1) to give **7** (2.57 g, 53%), whose spectral data were identical with those of authentic sample[8].

General procedure for the preparation of the *N*^{6}-substituted nucleosides 8 and 9

To a solution of **7** in anhydrous EtOH (20 mL per mmol) were added triethylamine (3.0 equiv) and appropriate amine (1.2 equiv). After being stirred at room temperature for 24 h, the reaction mixture was evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1) to give the *N*^{6}-substituted nucleosides **8** and **9.**

6-Methylamino-9-[(5'-*O*-benzoyl-2',3'-*O*-isopropylidene)-4'-thio-β-D-ribofuranosyl]purine (8)

Compound **8** was prepared using methylamine·HCl: yield 74%; white foam; UV (MeOH) λ_{max} 271 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 3.10 (d, 3 H, *J* = 3.0 Hz, N-CH_3), 4.12 (td, 1 H, *J* = 2.7, 7.8 Hz, 4'-H), 4.60 (dd, 1 H, *J* = 6.7, 11.4 Hz, BzOC*H*H), 4.63 (dd, 1 H, J = 7.8, 11.5 Hz, BzOCH*H*), 4.99 (dd, 1 H, *J* = 2.9, 5.6 Hz, 3'-H), 5.03 (dd, 1 H, *J* = 1.9, 5.6 Hz, 2'-H), 6.01 (d, 1 H, *J* = 1.9 Hz, 1'-H), 6.31 (br s, 1 H, NH), 7.37–7.88 (m, 5 H, Ph), 8.46 (s, 1 H, H-8), 8.57 (s, 1H, H-2); FAB-MS *m/z* 442 (M^++1); Anal. Calcd for $C_{21}H_{23}N_5O_4S$: C, 57.13; H, 5.25; N, 15.86; S, 7.26. Found: C, 57.20; H, 5.28; N, 15.75; S, 7.32.

6-(3-Iodo-benzylamino)-9-[(5'-*O*-benzoyl-2',3'-*O*-isopropylidene)-4'-thio-β-D-ribofuranosyl] purine (9)

Compound **9** was prepared using 3-iodo-benzylamine: yield 88%; white foam; UV (MeOH) λ_{max} 272 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 4.06 (td, 1 H, *J* = 2.4, 7.3 Hz, 4'-H), 4.46 (dd, 1 H, *J* = 6.8, 11.4 Hz, BzOC*H*H), 4.53 (dd, 1 H, *J* = 2.7, 11.4 Hz, BzOCH*H*), 4.73 (d, 2 H, *J* = 5.8 Hz, N-CH_2), 4.89 (dd, 1 H, *J* = 2.4, 5.6 Hz, 3'-H), 5.02 (dd, 1 H, *J* = 2.0, 5.6 Hz, 2'-H), 5.96 (s, 1H, 1'-H), 6.59 (br s, 1 H, NH), 7.11–7.84 (m, 9 H, aromatic H), 8.52 (s, 1 H, H-8), 8.58 (s, 1 H, H-2); FAB-MS *m/z* 644 (M^++1); Anal. Calcd for $C_{27}H_{26}IN_5O_4S$: C, 50.40; H, 4.07; N, 10.88; S, 4.98. Found: C, 50.33; H, 4.21; N, 10.90; S, 4.88.

General Procedure for the preparation of the 4'-hydroxymethyl analogues 12 and 13

A solution of per mmol of *N*^{6}-substituted nucleosides **(8** and **9)** in 80% aqueous AcOH solution (30 mL) was stirred at 70 °C for 12 h. The solvent was removed under reduced pressure and the mixture was neutralized with methanolic ammonia. After evaporation, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 10:1) to give diol as a white foam.

To a stirred solution of per mmol of diol in dry pyridine (20 mL) was added a solution of TBDMSOTf (5.0 equiv) dropwise and the reaction mixture was stirred at 50 °C for 5 h. The mixture was partitioned between CH_2Cl_2 and H_2O and the organic layer was washed with water, aqueous $NaHCO_3$ solution, water, brine, dried over anhydrous $MgSO_4$, and evaporated. The crude disilyl ether was used in the next step without further purification.

To a stirred solution of per mmol of disilyl ether in anhydrous methanol (30 mL) was added sodium methoxide (1.5 equiv) and the mixture was stirred at room temperature for 4 h. After being neutralized with glacial acetic acid, the mixture was evaporated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1) to gve 4'-hydroxymethyl analogues **12** and **13**, respectively.

9-[(2',3'-Bis-*tert*-butyl-dimethyl-silanyloxy-5'-hydroxymethyl)-6-methylamino-4'-thio-β-D-ribofuranosyl] purine (12)

yield 63%; white solid; UV (MeOH) λ_{max} 270 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 0.01 (m, 12 H, 4×Si-CH_3), 0.60 (s, 9 H, C(CH_3)$_3$), 0.85 (s, 9 H, C(CH_3)$_3$), 3.10 (br s, 3 H, N-CH_3), 3.20 (dd, 1 H, *J* = 5.6, 11.7 Hz, 4'-H), 4.20 (m, 1 H, 3'-H), 4.45 (dd, 1 H, *J* = 5.8, 11.7 Hz,

HOC*H*H), 4.75 (m, 1 H, 2'-H), 4.87 (dd, 1 H, *J* = 6.3, 11.7 Hz, HOCH*H*), 5.43 (d, 1 H, *J* = 4.6 Hz, 1'-H), 5.65 (br s, 1 H, OH), 8.00 (s, 1 H, H-2), 8.03 (br s, 1 H, NH), 8.23 (s, 1 H, H-8); FAB-MS *m/z* 526 (M^++1); Anal. Calcd for $C_{23}H_{43}N_5O_3SSi_2$: C, 52.53; H, 8.24; N, 13.32; S, 6.10. Found: C, 52.40; H, 8.35; N, 13.22; S, 6.14.

9-[(2',3'-Bis-*tert*-butyl-dimethyl-silanyloxy-5'-hydroxymethyl)-4'-thio-β-D-ribofuranosyl]-6-(3-iodobenzylamino)purine (13)

yield 82%; white solid; UV (MeOH) λ_{max} 270 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 0.01 (m, 12 H, 4×Si-CH_3), 0.62 (s, 9 H, C(CH_3)$_3$), 0.83 (s, 9 H, C(CH_3)$_3$), 3.27 (dd, 1 H, *J* = 5.6, 11.7 Hz, 2-H), 3.74 (m, 1 H, HOC*H*H), 3.86 (m, 1 H, HOCH*H*), 4.14 (dd, 1 H, *J* = 5.7, 11.5 Hz, 3'-H), 4.63 (br s, 2H, N-CH_2), 5.20 (dd, 1 H, *J* = 6.3, 11.9 Hz, 2'-H), 5.60 (d, 1 H, *J* = 4.6 Hz, 1'-H), 5.93 (br s, 1 H, OH), 6.93 (t, 1 H, *J* = 7.7 Hz, aromatic H), 7.13 (s, 1 H, NH), 7.58 (d, 1 H, *J* = 7.5 Hz, aromatic H), 7.60 (d, 1 H, *J* = 7.8 Hz, aromatic H), 7.67 (s, 1 H, aromatic H), 8.01 (s, 1 H, H-2), 8.28 (s, 1 H, H-8); FAB-MS *m/z* 728 (M^+); Anal. Calcd for $C_{29}H_{46}IN_5O_3SSi_2$: C, 47.86; H, 6.37; N, 9.62; S, 4.41. Found: C, 48.02; H, 6.43; N, 9.65; S, 4.39.

General Procedure for the preparation of the *N*^{6}-Substituted-4′-thioadenosine-5′-uronamides 5a–w

To a stirred solution of 4′-hydroxymethyl analogue (1 mmol, **12** and **13**) in dry DMF (10 mL) was added pyridinium dichromate (10.0 equiv) and the reaction mixture was stirred at room temperature for 20 h. Water (50 mL) was added to the reaction mixture, and stirred at room temperature for 1 h. The precipitate was filtered and the filter cake was washed with water many times and dried under high vacuum to give the acid (**14** and **15**) as a brownish solid, which was used in the next step without further purification.

To a solution of **14** and **15** (1 mmol) in CH_2Cl_2 (20 mL) were added EDC (1.5 equiv), HOBt (1.5 equiv), appropriate amine (1.5 equiv), and DIPEA (3.0 equiv) and the mixture was stirred at room temperature for 15 h. The reaction mixture was evaporated and the residue was purified by a silica gel column chromatography (hexane/EtOAc = 10:1-5:1) to give the corresponding silyl amide as a white foam. To a stirred solution of silyl amide (1 mmol) in THF (5 mL) was added TBAF (2.5 equiv) and the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated and the resulting residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 10:1) to give **5a–w** as white solids.

N^6-Methyl-9-(5'-methylaminocarbonyl-4'-thio-β-D-ribofuranosyl)adenine (5a)

Compound **5a** was prepared using methylamine·HCl: yield 70%; white solid; $[\alpha]^{25}_D$ −24.0° (c 0.13, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7); ^{1}H NMR (DMSO-d_6) δ 2.78 (d, 3 H, *J* = 4.0 Hz, N-CH_3), 2.90 (d, 3 H, *J* = 4.5 Hz, N-CH_3), 3.76 (d, 1 H, *J* = 4.2 Hz, 4'-H), 4.35 (dd, 1 H, *J* = 4.6, 8.0 Hz, 3'-H), 4.52 (dd, 1 H, *J* = 4.8, 8.5 Hz, 2'-H), 5.42 (d, 1 H, *J* = 5.4 Hz, exchangeable with D_2O, OH), 5.70 (d, 1 H, *J* = 5.1 Hz, exchangeable with D_2O, OH), 5.80 (d, 1 H, *J* = 5.4 Hz, 1'-H), 7.98 (s, 1 H, H-2), 8.32 (br q, 2 H, exchangeable with D_2O, NH, NH), 8.54 (s, 1 H, H-8); ^{13}C NMR (DMSO-d_6) δ 51.0, 55.3, 64.3, 70.2, 75.4, 78.2, 118.5, 139.9, 149.5, 150.3, 152.5, 174.4; FAB-MS *m/z* 325 (M^++1); Anal. Calcd for $C_{12}H_{16}N_6O_3S$: C, 44.44; H, 4.97; N, 25.91; S, 9.89. Found: C, 44.52; H, 5.03; N, 25.98; S, 9.86.

9-(5'-Ethylaminocarbonyl-4'-thio-β-D-ribofuranosyl)-*N*^{6}-methyladenine (5b)

Compound **5b** was prepared using ethylamine·HCl: yield 65%; white solid; $[\alpha]^{25}_D$ −48.2° (c 0.15, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7); ^{1}H NMR (DMSO-d_6) δ 1.07 (t, 3 H, *J* = 7.2 Hz, CH_2CH_3), 2.55 (d, 3 H, *J* = 4.5 Hz, N-CH_3), 3.11 (m, 2 H, N-CH_2), 3.76 (d, 1 H, *J* = 4.0 Hz, 4'-H), 4.04 (dd, 1 H, *J* = 4.0, 7.5 Hz, 3'-H), 4.48 (dd, 1 H, *J* = 5.5, 8.0Hz, 2'-H), 5.54 (d, 1 H, *J* = 5.0 Hz, exchangeable with D_2O, OH), 5.68 (d, 1 H, *J* = 5.2 Hz, exchangeable with

D_2O, OH), 5.80 (d, 1 H, *J* = 5.5 Hz, 1'-H), 8.05 (s, 1 H, H-2), 8.30 (br s, 2 H, exchangeable with D_2O, NH, NH), 8.53 (s, 1 H, H-8); ^{13}C NMR (DMSO-d_6) δ 24.3, 48.9, 50.2, 61.3, 73.2, 74.4, 78.5, 116.3, 140.5, 150.8, 151.5, 152.5, 173.4; FAB-MS *m/z* 339 (M^++1); Anal. Calcd for $C_{13}H_{18}N_6O_3S$: C, 46.14; H, 5.36; N, 24.84; S, 9.48. Found: C, 46.25; H, 5.30; N, 25.00; S, 9.56.

9-(5'-Cyclopropylaminocarbonyl-4'-thio-β-D-ribofuranosyl)-*N*^{6}-methyladenine (5c)

Compound **5c** was prepared using cyclopropyl amine: yield 61%; white solid; $[\alpha]^{25}_D$ −15.8° (c 0.15, MeOH); UV (MeOH) λ_{max} 269.0 nm (pH 7); ^1H NMR (DMSO-d_6) δ 0.04 (m, 2 H, cyclopropyl-CH_2), 0.27 (m, 2 H, cyclopropyl-CH_2), 2.65 (m, 1 H, NCH), 2.93 (d, 3 H, *J* = 4.5 Hz, N-CH_3), 3.65 (d, 1 H, *J* = 4.0 Hz, 4'-H), 4.45 (dd, 1 H, *J* = 4.5, 8.0 Hz, 3'-H), 4.52 (dd, 1 H, *J* = 5.0, 8.5 Hz, 2'-H), 5.40 (d, 1 H, *J* = 4.0 Hz, exchangeable with D_2O, OH), 5.59 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.85 (d, 1 H, *J* = 7.8 Hz, 1'-H), 8.05 (s, 1 H, H-2), 8.35 (br s, 1 H, exchangeable with D_2O, NH), 8.38 (br s, 1 H, exchangeable with D_2O, NH), 8.57 (s, 1 H, H-8); ^{13}C NMR (DMSO-d_6) δ 6.1, 6.8, 24.0, 48.5, 50.6, 58.4, 75.4, 78.3, 114.8, 148.3, 150.2, 152.5, 155.3, 174.5; FAB-MS *m/z* 351 (M^++1); Anal. Calcd for $C_{14}H_{18}N_6O_3S$: C, 47.99; H, 5.18; N, 23.98; S, 9.15. Found: C, 48.12; H, 5.25; N, 24.05; S, 9.23.

9-(5'-Cyclopropylmethylaminocarbonyl-4'-thio-β-D-ribofuranosyl)-*N*^{6}-methyladenine (5d)

Compound **5d** was prepared using cyclopropyl methylamine·HCl: yield 68%; white solid; $[\alpha]^{25}_D$ −15.8° (c 0.15, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7); ^1H NMR (DMSO-d_6) δ 0.05 (m, 2 H, cyclopropyl-CH_2), 0.35 (m, 2 H, cyclopropyl-CH_2), 0.78 (m, 1 H, cyclopropyl-CH), 2.93 (d, 3 H, *J* = 4.0 Hz, N-CH_3), 3.03 (t, 2 H, *J* = 4.5, 7.8 Hz, N-CH_2), 3.77 (d, 1 H, *J* = 4.0 Hz, 4'-H), 4.27 (dd, 1 H, *J* = 4.5, 9.0 Hz, 3'-H), 4.45 (dd, 1 H, *J* = 4.6, 8.8 Hz, 2'-H), 5.46 (d, 1 H, *J* = 4.3 Hz, exchangeable with D_2O, OH), 5.68 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.77 (d, 1 H, *J* = 7.8 Hz, 1'-H), 8.12 (s, 1 H, H-2), 8.34 (br s, 1 H, exchangeable with D_2O, NH), 8.43 (br s, 1 H, exchangeable with D_2O, NH), 8.53 (s, 1 H, H-8); ^{13}C NMR (CD_3OD) δ 2.5, 2.7, 10.8, 43.2, 46.3, 58.3, 60.5, 72.3, 75.6, 120.5, 148.7, 150.1, 153.4, 156.5, 173.5; FAB-MS *m/z* 365 (M^++1); Anal. Calcd for $C_{15}H_{20}N_6O_3S$: C, 49.44; H, 5.53; N, 23.06; S, 8.80. Found: C, 49.40; H, 5.55; N, 22.98; S, 8.87.

9-(5'-Cyclobutylaminocarbonyl-4'-thio-β-D-ribofuranosyl)-*N*^{6}-methyladenine (5e)

Compound **5e** was prepared using cyclobutylamine: yield 59%; white solid; $[\alpha]^{25}_D$ −24.0° (c 0.10, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7); ^1H NMR (DMSO-d_6) δ 1.71 (m, 2 H, cyclobutyl-CH_2), 1.96 (m, 2 H, cyclobutyl-CH_2), 2.25 (m, 2 H, cyclobutyl-CH_2), 2.98 (d, 3 H, *J* = 4.5 Hz, N-CH_3), 3.84 (m, 1 H, cyclopropyl-CH), 4.01 (d, 1 H, *J* = 4.0 Hz, 4'-H), 4.47 (dd, 1 H, *J* = 4.7, 8.8 Hz, 3'-H), 4.54 (dd, 1 H, *J* = 4.5, 8.0 Hz, 2'-H), 5.63 (d, 1 H, *J* = 4.5 Hz, exchangeable with D_2O, OH), 5.83 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.90 (d, 1 H, *J* = 8.0 Hz, 1'-H), 8.21 (s, 1 H, H-2), 8.34 (br s, 1 H, exchangeable with D_2O, NH), 8.43 (br s, 1H, exchangeable with D_2O, NH), 8.53 (s, 1 H, H-8); ^{13}C NMR (CD_3OD) δ 16.3, 32.5, 33.2, 35.3, 40.3, 42.8, 65.4, 75.3, 76.5, 135.4, 145.3, 147.8, 153.4, 155.0, 175.4; FAB-MS *m/z* 365 (M^++1); Anal. Calcd for $C_{15}H_{20}N_6O_3S$: C, 49.44; H, 5.53; N, 23.06; S, 8.80. Found: C, 49.51; H, 5.49; N, 23.10; S, 8.78.

9-(5'-Cyclopentylaminocarbonyl-4'-thio-β-D-ribofuranosyl)-*N*^{6}-methyladenine (5f)

Compound **5f** was prepared using cyclopentylamine: yield 65%; white solid; $[\alpha]^{25}_D$ −13.8° (c 0.13, MeOH); UV (MeOH) λ_{max} 269 nm (pH 7); ^1H NMR (DMSO-d_6) δ 1.30 (m, 4 H, cyclopentyl-CH_2×2), 1.59 (m, 4 H, cyclopentyl-CH_2×2), 2.95 (d, 3 H, *J* = 4.0 Hz, N-CH_3), 3.53 (m, 1 H, NCH), 3.87 (d, 1 H, *J* = 4.0 Hz, 4'-H), 4.07 (dd, 1 H, *J* = 4.5, 8.0 Hz, 3'-H), 4.54 (dd, 1 H, *J* = 5.0, 8.8 Hz, 2'-H), 5.55 (d, 1 H, *J* = 4.0 Hz, exchangeable with D_2O, OH), 5.78 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.82 (d, 1 H, *J* = 7.8 Hz, 1'-H), 8.25 (s, 1

H, H-2), 8.33 (br s, 1H, exchangeable with D_2O, NH), 8.43 (br s, 1 H, *J* = 4.5 Hz, exchangeable with D_2O, NH), 8.53 (s, 1 H, H-8); ^{13}C NMR (CD_3OD) δ 23.4, 24.5, 31.7, 32.5, 38.3, 48.5, 48.6, 65.3, 74.5, 80.4, 129.3, 145.3, 148.5, 153.0, 155.4, 175.2; FAB-MS *m/z* 379(M^++1); Anal. Calcd for $C_{16}H_{22}N_6O_3S$: C, 50.78; H, 5.86; N, 22.21; S, 8.47. Found: C, 50.75; H, 5.53; N, 22.45; S, 8.68.

9-[(5'-(3-Iodo-benzylaminocarbonyl)-4'-thio-β-D-ribofuranosyl)]-*N*^{6}-methyladenine (5g)

Compound **5g** was prepared using 3-iodo-benzylamine: yield 54%; white solid; $[\alpha]^{25}_D$ −23.0° (c 0.10, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7); ^1H NMR (DMSO-d_6) δ 2.94 (d, 3 H, *J* = 4.5 Hz, N-CH_3), 3.87 (d, 1 H, *J* = 4.3 Hz, 4'-H), 4.25 (dd, 1 H, *J* = 4.4, 8.8 Hz, 3'-H), 4.56 (dd, 1 H, *J* = 4.9, 8.8 Hz, 2'-H), 4.68 (d, 2 H, *J* = 3.5 Hz, NH_2), 5.56 (d, 1 H, *J* = 4.0 Hz, exchangeable with D_2O, OH), 5.80 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.82 (d, 1 H, *J* = 7.8 Hz, 1'-H), 7.14–7.76 (m, 4 H, aromatic H), 7.98 (br s, 1H, exchangeable with D_2O, NH), 8.05 (br s, 1 H, *J* = 4.5 Hz, exchangeable with D_2O, NH), 8.25 (s, 1 H, H-2), 8.53 (s, 1 H, H-8); ^{13}C NMR (CD_3OD) δ 45.3, 50.1, 53.3, 65.4, 78.8, 85.4, 99.4, 125.3, 127.5, 128.4, 130.2, 135.0, 144.2, 145.3, 148.5, 152.3, 156.8, 173.5; FAB-MS *m/z* 527 (M^++1); Anal. Calcd for $C_{18}H_{19}IN_6O_3S$: C, 41.07; H, 3.64; N, 15.97; S, 6.09. Found: C, 41.35; H, 3.66; N, 16.12; S, 6.24.

N^6-(3-Iodo-benzyl)-9-(5'-methylaminocarbonyl-4'-thio-β-D-ribofuranosyl)adenine (5h)

Compound **5h** was prepared using methylamine·HCl: yield 53%; white solid; $[\alpha]^{25}_D$ −20.5° (c 0.15, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7); ^1H NMR (DMSO-d_6) δ 2.70 (d, 3 H, *J* = 4.0 Hz, N-CH_3), 3.82 (d, 1 H, *J* = 4.5 Hz, 4'-H), 4.37 (br dd, 1 H, *J* = 4.5, 8.4 Hz, 3'-H), 4.57 (m, 1 H, 2'-H), 4.65 (d, 2 H, *J* = 5.7 Hz, N-CH_2), 5.62 (d, 1 H, *J* = 5.5 Hz, exchangeable with D_2O, OH), 5.80 (d, 1 H, *J* = 5.1 Hz, exchangeable with D_2O, OH), 5.88 (d, 1 H, *J* = 5.4 Hz, 1'-H), 7.13 (t, 1 H, *J* = 7.8 Hz, aromatic H), 7.35 (d, 1 H, *J* = 7.6 Hz, aromatic H), 7.60 (d, 1 H, *J* = 7.8 Hz, aromatic H), 7.73 (s, 1 H, aromatic H), 8.26 (br s, 1 H, H-2), 8.54 (s, 1 H, H-8), 8.55 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (DMSO-d_6) δ 42.0, 51.5, 60.3, 64.5, 76.0, 78.2, 118.8, 126.4, 133.5, 135.3, 136.0, 140.3, 141.5, 149.9 , 150.4, 153.0, 154.7, 170.3; FAB-MS *m/z* 527 (M^++1); Anal. Calcd for $C_{18}H_{19}IN_6O_3S$: C, 41.07; H, 3.64; N, 15.97; S, 6.09. Found: C, 41.35; H, 3.66; N, 16.12; S, 6.24.

9-(5'-Ethylaminocarbonyl-4-thio-β-D-ribofuranosyl)-*N*^{6}-(3-iodo-benzyl)adenine (5i)

Compound **5i** was prepared using ethylamine·HCl: yield 66%; white solid; $[\alpha]^{20}_D$ −45.6° (c 0.15, MeOH); UV (MeOH) λ_{max} 273.0 nm (pH 7); ^1H NMR (DMSO-d_6) δ 1.09 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 3.19 (q, 2 H, *J* = 6.0 Hz, CH_2CH_3), 3.82 (d, 1 H, *J* = 4.0 Hz, 4'-H), 4.38 (d, 1 H, *J* = 4.5 Hz, 3'-H), 4.59 (d, 1 H, *J* = 3.6 Hz, 2'-H), 4.67 (d, 2 H, *J* = 4.5 Hz, N-CH_2), 5.60 (d, 1 H, *J* = 5.0 Hz, exchangeable with D_2O, OH), 5.77 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.88 (d, 1 H, *J* = 5.0 Hz, 1'-H), 7.12 (t, 1 H, *J* = 8.0 Hz, aromatic H), 7.38 (d, 1 H, *J* = 7.6 Hz, aromatic H), 7.60 (d, 1 H, *J* = 7.6 Hz, aromatic H), 7.73 (s, 1 H, aromatic H), 8.25 (s, 1H, H-2), 8.50 (br s, 1 H, exchangeable with D_2O, NH), 8.55 (s, 1 H, H-8); ^{13}C NMR (CD_3OD) δ 15.4, 35.3, 44.5, 54.4, 68.0, 79.1, 80.1, 94.5, 120.3, 125.8, 128.5, 130.5, 135.3, 140.4, 142.7, 151.4, 155.5, 172.3, 174.5; FAB-MS *m/z* 541 (M^++1); Anal. Calcd for $C_{19}H_{21}IN_6O_3S$: C, 42.23; H, 3.92; N, 15.55; S, 5.93. Found: C, 42.51; H, 3.95; N, 15.73; S, 5.95.

9-(5'-Cyclopropylaminocarbonyl-4'-thio-β-D-ribofuranosyl)-*N*^{6}-(3-iodo-benzyl)adenine (5j)

Compound **5j** was prepared using cyclopropyl amine: yield 62%; white solid; $[\alpha]^{20}_D$ −35.8° (c 0.15, MeOH); UV (MeOH) λ_{max} 272.0 nm (pH 7); ^1H NMR (DMSO-d_6) δ 0.48 (br s, 2 H, cyclopropyl-CH_2), 0.72 (m, 2 H, cyclopropyl-CH_2), 2.54 (m, 1 H, NH), 3.80 (d, 1 H, *J* = 4.3 Hz, 4'-H), 4.18 (dd, 1 H, *J* = 4.0, 8.5 Hz, 3'-H), 4.42 (m, 1 H, 2'-H), 4.70 (br s, 2 H, N-CH_2),

5.63 (d, 1 H, *J* = 5.5 Hz, exchangeable with D_2O, OH), 5.83 (d, 1 H, *J* = 5.0 Hz, exchangeable with D_2O, OH), 5.90 (d, 1 H, *J* = 5.4 Hz, 1'-H), 7.13 (t, 1 H, *J* = 7.8 Hz, aromatic H), 7.35 (d, 1 H, *J* = 7.6 Hz, aromatic H), 7.60 (d, 1 H, *J* = 7.8 Hz, aromatic H), 7.73 (s, 1 H, aromatic H), 8.27 (br s, 1 H, H-2), 8.58 (s, 1 H, H-8), 8.59 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (DMSO-d_6) δ 8.4, 10.5, 24.5, 50.5, 64.3, 66.8, 77.0, 80.4, 116.5, 127.4, 133.5, 135.4, 135.9, 140.3, 141.5, 148.5 , 150.3, 152.9, 153.5, 171.4; FAB-MS *m/z* 553 (M^++1); Anal. Calcd for $C_{20}H_{21}IN_6O_3S$: C, 43.49; H, 3.83; N, 15.21; S, 5.80. Found: C, 43.54; H, 3.92; N, 15.28; S, 5.85.

9-(5'-Cyclopropylmethylaminocarbonyl-4'-thio-β-D-ribofuranosyl)-*N*^{6}-(3-iodobenzyl) adenine (5k)

Compound **5k** was prepared using cyclopropylmethyl amine·HCl: yield 61%; white solid; $[\alpha]^{20}_{D}$ −14.8° (c 0.15, MeOH); UV (MeOH) λ_{max} 274.0 nm (pH 7); ^1H NMR (DMSO-d_6) δ 0.18 (m, 2 H, cyclopropyl-CH_2), 0.23 (m, 2 H, cyclopropyl-CH_2), 0.75 (m, 1 H, cyclopropyl-CH), 2.54 (m, 1 H, NH), 2.87 (t, 2 H, *J* = 3.8 Hz, N-CH_2), 3.67 (d, 1 H, *J* = 4.2 Hz, 4'-H), 4.19 (dd, 1 H, *J* = 4.0, 8.7 Hz, 3'-H), 4.42 (m, 1 H, 2'-H), 4.47 (br s, 2 H, N-CH_2-cyclopropyl), 5.41 (d, 1 H, *J* = 5.0 Hz, exchangeable with D_2O, OH), 5.59 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.70 (d, 1 H, *J* = 5.3 Hz, 1'-H), 6.92 (t, 1 H, *J* = 7.6 Hz, aromatic H), 7.18 (d, 1 H, *J* = 7.6 Hz, aromatic H), 7.40 (d, 1 H, *J* = 7.8 Hz, aromatic H), 7.53 (s, 1 H, aromatic H), 8.05 (br s, 1 H, H-2), 8.33 (s, 1 H, H-8), 8.43 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (DMSO-d_6) δ 2.3, 3.2, 13.4, 23.8, 54.3, 63.5, 67.0, 77.4, 81.0, 116.4, 126.3, 132.1, 133.4, 135.2, 139.8, 140.2, 147.5 , 150.1, 151.9, 153.4, 171.8; FAB-MS *m/z* 567 (M^++1); Anal. Calcd for $C_{21}H_{23}IN_6O_3S$: C, 44.53; H, 4.09; N, 14.84; S, 5.66. Found: C, 44.60; H, 4.12; N, 14.95; S, 5.62.

9-(5'-Cyclobutylaminocarbonyl-4'-thio-β-D-ribofuranosyl)-*N*^{6}-(3-iodobenzyl)adenine (5l)

Compound **5l** was prepared using cyclobutyl amine: yield 53%; white solid; $[\alpha]^{20}_{D}$ −15.3° (c 0.10, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7); ^1H NMR (DMSO-d_6) δ 1.71 (m, 2 H, cyclobutyl-CH_2), 1.96 (m, 2 H, cyclobutyl-CH_2), 2.25 (m, 2 H, cyclobutyl-CH_2), 3.84 (d, 1 H, *J* = 4.0 Hz, 4'-H), 4.30 (m, 1 H, NCH), 4.41 (dd, 1 H, *J* = 4.5, 8.7 Hz, 3'-H), 4.61 (m, 1 H, 2'-H), 4.70 (br s, 2 H, N-CH_2), 5.63 (d, 1 H, *J* = 5.5 Hz, exchangeable with D_2O, OH), 5.83 (d, 1 H, *J* = 5.0 Hz, exchangeable with D_2O, OH), 5.90 (d, 1 H, *J* = 5.4 Hz, 1'-H), 7.15 (t, 1 H, *J* = 8.0 Hz, aromatic H), 7.41 (d, 1 H, *J* = 7.6 Hz, aromatic H), 7.62 (d, 1 H, *J* = 7.8 Hz, aromatic H), 7.76 (s, 1 H, aromatic H), 8.28 (br s, 1 H, H-2), 8.57 (s, 1 H, H-8), 8.72 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (DMSO-d_6) δ 20.4, 35.3, 37.2, 50.5, 54.8, 64.2, 66.5, 78.0, 79.5, 116.4, 126.5, 132.7, 135.3, 135.8, 141.7, 142.3, 148.4, 151.3, 153.0, 154.5, 172.0; FAB-MS *m/z* 567 (M^++1); Anal. Calcd for $C_{21}H_{23}IN_6O_3S$: C, 44.53; H, 4.09; N, 14.84; S, 5.66. Found: C, 44.55; H, 4.12; N, 14.96; S, 5.70.

9-(5'-Cyclohexylaminocarbonyl-4'-thio-β-D-ribofuranosyl)-*N*^{6}-(3-iodobenzyl)adenine (5m)

Compound **5m** was prepared using cyclohexyl amine: yield 68%; white solid; $[\alpha]^{20}_{D}$ −25.4° (c 0.13, MeOH); UV (MeOH) λ_{max} 272 nm (pH 7); ^1H NMR (DMSO-d_6) δ 1.41–1.82 (m, 10 H, cyclohexyl-CH_2), 3.65 (m, 1 H, cyclohexyl-CH), 3.83 (d, 1 H, *J* = 4.5 Hz, 4'-H), 4.45 (dd, 1 H, *J* = 4.4, 9.0 Hz, 3'-H), 4.75 (m, 1 H, 2'-H), 4.82 (br s, 2 H, N-CH_2), 5.65 (d, 1 H, *J* = 5.5 Hz, exchangeable with D_2O, OH), 5.85 (d, 1 H, *J* = 5.0 Hz, exchangeable with D_2O, OH), 5.95 (d, 1 H, *J* = 5.4 Hz, 1'-H), 7.25 (t, 1 H, *J* = 7.5 Hz, aromatic H), 7.43 (d, 1 H, *J* = 8.0 Hz, aromatic H), 7.65 (d, 1 H, *J* = 7.8 Hz, aromatic H), 7.79 (s, 1 H, aromatic H), 8.25 (br s, 1 H, H-2), 8.54 (s, 1 H, H-8), 8.56 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (DMSO-d_6) δ 20.5, 22.4, 30.5, 35.4, 36.8, 46.3, 55.6, 64.4, 66.9, 77.5, 79.4, 117.5, 128.4, 133.5, 134.0, 135.6, 141.6, 142.1, 148.5, 152.1, 153.5, 154.4, 172.8; FAB-MS *m/z* 595 (M^++1); Anal. Calcd

for $C_{23}H_{27}IN_6O_3S$: C, 46.47; H, 4.58; N, 14.14; S, 5.39. Found: C, 46.55; H, 4.46; N, 14.25; S, 5.50.

9-[5'-(3-Fluoro-benzylaminocarbonyl-4'-thio-β-D-ribofuranosyl)]-*N*^{6}-(3-iodobenzyl)adenine (5n)

Compound **5n** was prepared using 3-fluoro-benzylamine: yield 59%; white solid; $[\alpha]^{20}_{D}$ −40.1° (c 0.10, MeOH); UV (MeOH) λ_{max} 272 nm (pH 7); ^{1}H NMR (DMSO-d_6) δ 3.79 (d, 1 H, *J* = 4.0 Hz, 4'-H), 4.28 (m, 3 H, 3'-H, N-CH_2), 4.50 (d, 1 H, *J* = 4.0 Hz, 2'-H), 4.62 (d, 2 H, *J* = 4.4 Hz, N-CH_2), 5.54 (d, 1 H, *J* = 5.6 Hz, exchangeable with D_2O, OH), 5.67 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.78 (d, 1 H, *J* = 5.2 Hz, 1'-H), 6.92–7.58 (m, 8 H, aromatic H), 8.34 (s, 1 H, H-2), 8.53 (s, 1 H, H-8), 8.91 (br s, 1 H, exchangeable with D_2O, NH), 9.03 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (CD_3OD) δ 50.3, 52.4, 54.3, 60.4, 77.4, 78.5, 101.3, 114.3, 115.4, 116.8, 125.7, 125.9, 128.4, 130.5, 135.0, 140.3, 142.1, 145.8, 150.2, 155.31, 158.2, 160.5, 164.8, 173.5; FAB-MS *m/z* 621 (M^++1); Anal. Calcd for $C_{24}H_{22}FIN_6O_3S$: C, 46.46; H, 3.57; N, 13.55; S, 5.17. Found: C, 46.55; H, 3.46; N, 13.65; S, 5.26.

9-[5'-(3-Chloro-benzylaminocarbonyl-4'-thio-β-D-ribofuranosyl)]-*N*^{6}-(3-iodobenzyl)adenine (5o)

Compound **5o** was prepared using 3-chloro-benzylamine: yield 68%; white solid; $[\alpha]^{20}_{D}$ −25.4° (c 0.13, MeOH); UV (MeOH) λ_{max} 273 nm (pH 7); ^{1}H NMR (DMSO-d_6) δ 3.78 (d, 1 H, *J* = 3.8 Hz, 4'-H), 4.26 (m, 3 H, 3'-H, N-CH_2), 4.49 (m, 3 H, N-CH_2), 5.52 (d, 1 H, *J* = 5.0 Hz, exchangeable with D_2O, OH), 5.67 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.77 (d, 1 H, *J* = 5.2 Hz, 1'-H), 6.94–7.58 (m, 8 H, aromatic H), 8.03 (s, 1 H, H-2), 8.37 (s, 1 H, H-8), 8.38 (br s, 1 H, exchangeable with D_2O, NH), 9.02 (br s, 1H, exchangeable with D_2O, NH); ^{13}C NMR (CD_3OD) δ 51.4, 52.5, 54.0, 61.3, 78.1, 79.8, 102.3, 114.8, 115.6, 117.2, 125.9, 128.0, 136.3, 138.4, 140.0, 141.2, 142.0, 148.3, 149.5, 150.2, 153.4, 157.2, 158.4, 174.0; FAB-MS *m/z* 637 (M^++1); Anal. Calcd for $C_{24}H_{22}ClIN_6O_3S$: C, 45.26; H, 3.48; N, 13.20; S, 5.03. Found: C, 45.46; H, 3.46; N, 13.25; S, 5.26.

N^6-(3-Iodo-benzyl)-9-[5'-(2-methyl-benzylaminocarbonyl-4'-thio-β-D-ribofuranosyl)]adenine (5p)

Compound **5p** was prepared using 2-methyl-benzylamine: yield 60%; white solid; $[\alpha]^{20}_{D}$ −43.0° (c 0.10, MeOH); UV (MeOH) λ max 274 nm (pH 7); ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3 H, CH_3), 3.98 (d, 1 H, *J* = 2.7 Hz, 4'-H), 4.40 (m, 3 H, 3'-H, N-CH_2), 4.69 (m, 3 H, 2'-H, N-CH_2), 5.68 (d, 1 H, *J* = 5.0 Hz, exchangeable with D_2O, OH), 5.85 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.94 (d, 1 H, *J* = 5.0 Hz, 1'-H), 7.13–7.76 (m, 8 H, aromatic H), 8.11 (s, 1 H, H-2), 8.54 (s, 1 H, H-8), 8.96 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (CD_3OD) δ 24.8, 49.8, 50.3, 52.8, 56.3, 68.4, 78.0, 80.3, 98.6, 102.4, 115.8, 120.3, 125.6, 135.4, 137.6, 139.8, 140.4, 142.5, 146.4, 148.1, 151.3, 154.5, 156.7, 158.4, 173.8; FAB-MS *m/z* 617 (M^++1); Anal. Calcd for $C_{25}H_{25}IN_6O_3S$: C, 48.71; H, 4.09; N, 13.63; S, 5.20. Found: C, 48.88; H, 4.14; N, 13.82; S, 5.26.

N^6-(3-Iodo-benzyl)-9-[5'-(3-methyl-benzylaminocarbonyl-4'-thio-β-D-ribofuranosyl)]adenine (5q)

Compound **5q** was prepared using 3-methyl-benzylamine: yield 58%; white solid; $[\alpha]^{20}_{D}$ −33.5° (c 0.13, MeOH); UV (MeOH) λ_{max} 274 nm (pH 7); ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3 H, CH_3), 3.96 (d, 1 H, *J* = 2.0 Hz, 4'-H), 4.40 (d, 2 H, *J* = 8.0 Hz, N-CH_2), 4.45 (dd, 1 H, *J* = 5.2, 7.8 Hz, 3'-H), 4.68 (m, 3 H, 2'-H, N-CH_2), 5.69 (d, 1 H, *J* = 5.0 Hz, exchangeable with D_2O, OH), 5.84 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.94 (d, 1 H, *J* = 5.0 Hz, 1'-H), 7.09–7.76 (m, 8 H, aromatic H), 8.17 (s, 1 H, H-2), 8.53 (s, 1 H, H-8), 8.54 (br s, 1 H,

exchangeable with D_2O, NH), 8.96 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (CD_3OD) δ 23.5, 50.0, 50.4, 52.8, 56.4, 68.4, 78.1, 80.3, 98.6, 102.4, 115.9, 120.3, 125.6, 135.4, 136.5, 140.0, 140.5, 142.5, 146.5, 148.2, 151.3, 154.6, 156.7, 158.5, 174.0; FAB-MS *m/z* 617 (M^++1); Anal. Calcd for $C_{25}H_{25}IN_6O_3S$: C, 48.71; H, 4.09; N, 13.63; S, 5.20. Found: C, 48.85; H, 4.13; N, 13.62; S, 5.15.

N^6-(3-Iodo-benzyl)-9-[5'-(4-methyl-benzylaminocarbonyl-4'-thio-β-D-ribofuranosyl)]adenine (5r)

Compound **5r** was prepared using 4-methyl-benzylamine: yield 60%; white solid; $[\alpha]^{20}_D$ −38.1° (c 0.15, MeOH); UV (MeOH) λ_{max} 273 nm (pH 7); ^1H NMR (DMSO-d_6) δ 2.31 (s, 3 H, CH_3), 3.95 (d, 1 H, *J* = 2.5 Hz, 4'-H), 4.39 (d, 2 H, *J* = 8.0 Hz, N-CH_2), 4.44 (br s, 1 H, 3'-H), 4.68 (br s, 3 H, 2'-H, N-CH_2), 5.69 (br s, 1 H, exchangeable with D_2O, OH), 5.82 (br s, 1 H, exchangeable with D_2O, OH), 5.95 (d, 1 H, *J* = 4.8 Hz, 1'-H), 7.13–7.76 (m, 8 H, aromatic H), 8.16 (s, 1 H, H-2), 8.53 (s, 1 H, H-8), 8.54 (br s, 1 H, exchangeable with D_2O, NH), 9.13 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (CD_3OD) δ 20.9, 49.8, 50.5, 53.4, 56.5, 67.9, 78.4, 80.5, 98.9, 102.7, 116.3, 120.4, 125.6, 135.5, 136.7, 140.5, 140.9, 142.5, 146.4, 148.2, 151.4, 154.6, 156.8, 158.5, 173.9; FAB-MS *m/z* 617 (M^++1); Anal. Calcd for $C_{25}H_{25}IN_6O_3S$: C, 48.71; H, 4.09; N, 13.63; S, 5.20. Found: C, 48.79; H, 4.15; N, 13.55; S, 5.18.

N^6-(3-Iodo-benzyl)-9-[5'-(2-methoxy-benzylaminocarbonyl-4'-thio-β-D-ribofuranosyl)] adenine (5s)

Compound **5s** was prepared using 2-methoxy-benzylamine: yield 72%; white solid; $[\alpha]^{20}_D$ −30.2° (c 0.10, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7); ^1H NMR (DMSO-d_6) δ 3.83 (s, 3 H, OCH_3), 3.98 (d, 1 H, *J* = 2.5 Hz, 4'-H), 4.38 (m, 3 H, 3'-H, N-CH_2), 4.69 (m, 3 H, 2'-H, N-CH_2), 5.69 (d, 1 H, *J* = 5.5 Hz, exchangeable with D_2O, OH), 5.82 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.94 (d, 1 H, *J* = 5.0 Hz, 1'-H), 6.94–7.61 (m, 8 H, aromatic H), 8.15 (s, 1 H, H-2), 8.53 (br s, 1 H, exchangeable with D_2O, NH), 8.54 (s, 1 H, H-8), 8.97 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (CD_3OD) δ 49.8, 50.4, 52.8, 56.3, 57.8, 68.0, 78.4, 80.9, 98.5, 102.8, 115.8, 120.5, 125.6, 135.8, 137.6, 139.8, 140.5, 142.7, 146.4, 148.1, 151.8, 153.5, 156.9, 158.3, 173.9; FAB-MS *m/z* 633 (M^++1); Anal. Calcd for $C_{25}H_{25}IN_6O_4S$: C, 48.48; H, 3.98; N, 13.29; S, 5.07. Found: C, 48.65; H, 4.04; N, 13.42; S, 5.01.

9-[5'-(2-Ethoxy-benzylaminocarbonyl-4'-thio-β-D-ribofuranosyl)]-*N*^{6}-(3-iodobenzyl)adenine (5t)

Compound **5t** was prepared using 2-ethoxy-benzylamine: yield 63%; white solid; $[\alpha]^{20}_D$ −35.8° (c 0.10, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7); ^1H NMR (DMSO-d_6) δ 1.36 (t, 3 H, *J* = 4.2 Hz, OCH_2CH_3), 4.09 (m, 2 H, OCH_2CH_3), 3.98 (d, 1 H, *J* = 2.5 Hz, 4'-H), 4.38 (m, 3 H, 3'-H, N-CH_2), 4.70 (m, 3 H, 2'-H, N-CH_2), 5.69 (d, 1 H, *J* = 5.5 Hz, exchangeable with D_2O, OH), 5.83 (d, 1 H, *J* = 4.8 Hz, exchangeable with D_2O, OH), 5.95 (d, 1 H, *J* = 4.8 Hz, 1'-H), 6.93–7.76 (m, 8 H, aromatic H), 8.14 (s, 1 H, H-2), 8.53 (br s, 1 H, exchangeable with D_2O, NH), 8.54 (s, 1 H, H-8), 8.93 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (CD_3OD) δ 23.8, 48.2, 51.3, 52.8, 57.8, 65.2, 67.3, 78.4, 81.0, 98.6, 103.4, 116.4, 120.1, 124.5, 135.7, 137.8, 139.8, 141.3, 142.9, 146.5, 148.3, 152.1, 153.6, 155.4, 158.4, 170.1; FAB-MS *m/z* 647 (M^++1); Anal. Calcd for $C_{26}H_{27}IN_6O_4S$: C, 48.30; H, 4.21; N, 13.00; S, 4.96. Found: C, 48.35; H, 4.24; N, 13.13; S, 5.04.

N^6-(3-Iodo-benzyl)-9-[5'-(1-naphthylmethylaminocarbonyl-4'-thio-β-D-ribofuranosyl)] adenine (5u)

Compound **5u** was prepared using 1-naphthyl-methylamine: yield 57%; white solid; $[\alpha]^{20}_D$ −13.5° (c 0.15, MeOH); UV (MeOH) λ_{max} 273 nm (pH 7); ^1H NMR (DMSO-d_6) δ 3.97 (d, 1

H, *J* = 2.5 Hz, 4'-H), 4.47 (d, 2 H, *J* = 8.4 Hz, N-CH_2), 4.68 (br s, 1 H, 3'-H), 4.92 (br s, 3 H, 2'-H, N-CH_2), 5.66 (br s, 1 H, exchangeable with D_2O, OH), 5.82 (br s, 1 H, exchangeable with D_2O, OH), 5.93 (d, 1 H, *J* = 4.8Hz, 1'-H), 7.10–7.98 (m, 11 H, aromatic H), 8.10 (s, 1 H, H-2), 8.53 (s, 1 H, H-8), 8.54 (br s, 1 H, exchangeable with D_2O, NH), 9.09 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (CD_3OD) δ 45.3, 46.5, 55.3, 60.4, 73.8, 89.1, 98.4, 121.2, 122.4, 122.5, 124.1, 124.8, 126.3, 127.0, 127.8, 128.1, 129.2, 132.4, 133.5, 135.4, 136.0, 144.8, 145.5, 147.8, 152.0, 154.4, 156.8, 174.4; FAB-MS *m/z* 653 (M^++1); Anal. Calcd for $C_{28}H_{25}IN_6O_3S$: C, 51.54; H, 3.86; N, 12.88; S, 4.91. Found: C, 51.68; H, 3.92; N, 12.92; S, 4.90.

N^6-(3-Iodo-benzyl)-9-[5'-(2-phenetylaminocarbonyl-4'-thio-β-D-ribofuranosyl)]adenine (5v)

Compound **5v** was prepared using 2-phenylethylamine: yield 59%; white solid; $[\alpha]^{20}_D$ −45.0° (c 0.15, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7); ^1H NMR (DMSO-d_6) δ 2.65 (t, 2 H, *J* = 2.5 Hz, NCH_2CH_2), 3.54 (m, 2 H, NCH_2CH_2), 3.71 (d, 1 H, *J* = 4.0 Hz, 4'-H), 4.23 (br s, 1 H, 3'-H), 4.48 (br s, 1 H, 2'-H), 4.55 (d, 2 H, *J* = 8.0 Hz, N-CH_2), 5.51 (br s, 1 H, exchangeable with D_2O, OH), 5.65 (br s, 1 H, exchangeable with D_2O, OH), 5.77 (d, 1 H, *J* = 5.2 Hz, 1'-H), 6.98–7.61 (m, 9 H, aromatic H), 8.09 (s, 1 H, H-2), 8.38 (s, 1 H, H-8), 8.39 (br s, 1 H, exchangeable with D_2O, NH), 8.57 (br s, 1 H, exchangeable with D_2O, NH); ^{13}C NMR (CD_3OD) δ 37.3, 44.5, 45.3, 56.0, 60.3, 74.2, 79.8, 97.3, 123.1, 123.4, 124.5, 125.3, 126.4, 126.8, 127.1, 128.4, 129.4, 136.2, 137.1, 144.3, 145.2, 147.1, 147.8, 154.2, 174.5; FAB-MS *m/z* 617 (M^++1); Anal. Calcd for $C_{25}H_{25}IN_6O_3S$: C, 48.71; H, 4.09; N, 13.63; S, 5.20. Found: C, 48.79; H, 4.15; N, 13.55; S, 5.18.

9-[5'-(3,3-Diphenylpropylaminocarbonyl-4'-thio-β-D-ribofuranosyl)]-*N*^{6}-(3-iodobenzyl) adenine (5w)

Compound **5w** was prepared using 3,3-diphenylpropylamine: yield 72%; white solid; $[\alpha]^{20}_D$ −25.6° (c 0.32, MeOH); UV (MeOH) λ_{max} 274 nm (pH 7); ^1H NMR (DMSO-d_6) δ 2.27 (m, 2 H, NCH_2CH_2CH), 3.10 (m, 2 H, NCH_2CH_2CH), 3.87 (d, 1 H, *J* = 4.0 Hz, 4'-H), 4.07 (t, 1 H, *J* = 8.0 Hz, NCH_2CH_2CH), 4.41 (dd, 1 H, *J* = 3.6, 7.4 Hz, 3'-H), 4.64 (m, 1 H, 2'-H), 4.69 (d, 2 H, *J* = 5.7 Hz, N-CH_2), 5.64 (d, 1 H, *J* = 5.6 Hz, exchangeable with D_2O, OH), 5.83 (d, 1 H, *J* = 5.6 Hz, exchangeable with D_2O, OH), 5.93 (d, 2 H, *J* = 4.2 Hz, 1'-H), 7.13–7.76 (m, 14 H, aromatic H), 8.20 (s, 1 H, H-2), 8.54 (s, 1 H, H-8), 8.55 (br s, 1 H, exchangeable with D_2O, NH), 8.62 (br d, 1 H, *J* = 6.1 Hz, exchangeable with D_2O, NH); ^{13}C NMR (CD_3OD) δ 34.5, 35.3, 40.6, 45.5, 60.1, 73.4, 79.1, 80.4, 97.1, 112.3, 120.5, 126.0, 128.4, 129.3, 129.5, 129.7, 129.9, 132.7, 135.3, 141.5, 143.0, 144.3, 147.8, 152.4, 155.7, 174.8; FAB-MS *m/z* 707 (M^++1); Anal. Calcd for $C_{32}H_{31}IN_6O_3S$: C, 54.39; H, 4.42; N, 11.89; S, 4.54. Found: C, 54.48; H, 4.45; N, 11.75; S, 4.64.

Acknowledgments

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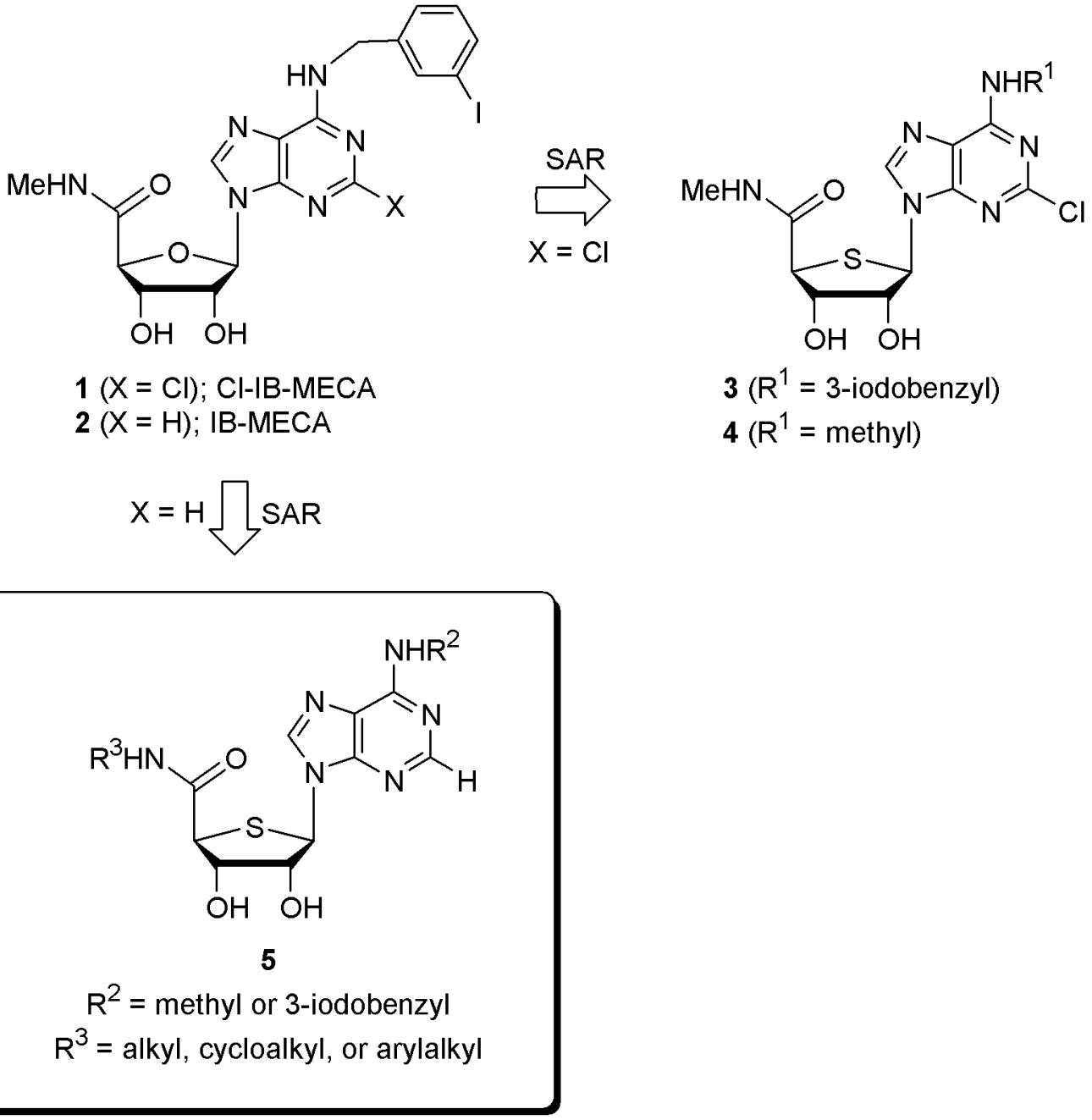
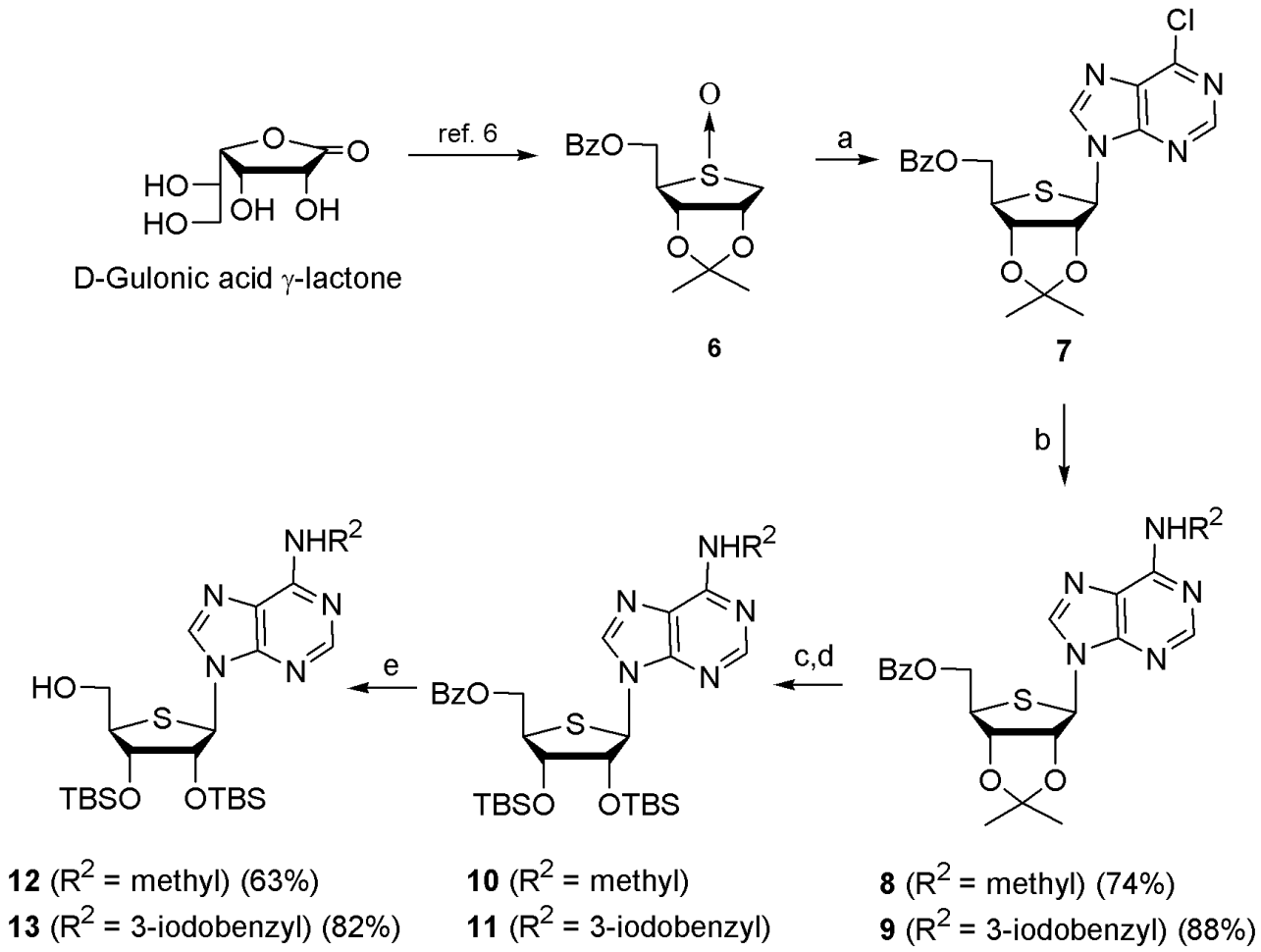
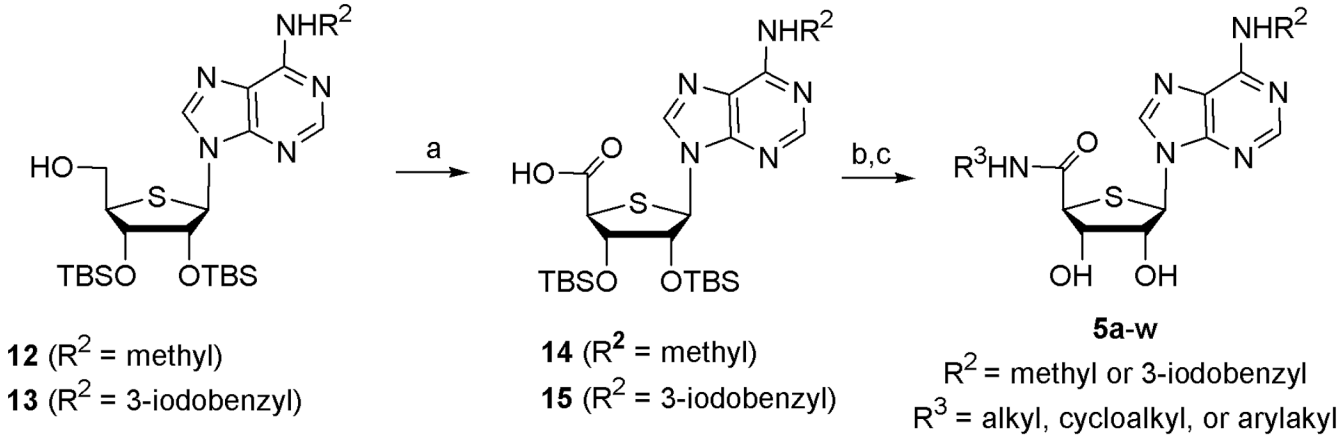


Figure 1.



Scheme 1a.

[a]**Reagents & conditions**: a) 6-chloropurine, TMSOTf, $ClCH_2CH_2Cl$, rt to 80 °C; b) R^2NH_2, Et_3N, EtOH, rt; c) 80% AcOH, 70 °C; d) TBSOTf, pyridine, 50 °C; e) NaOMe, MeOH

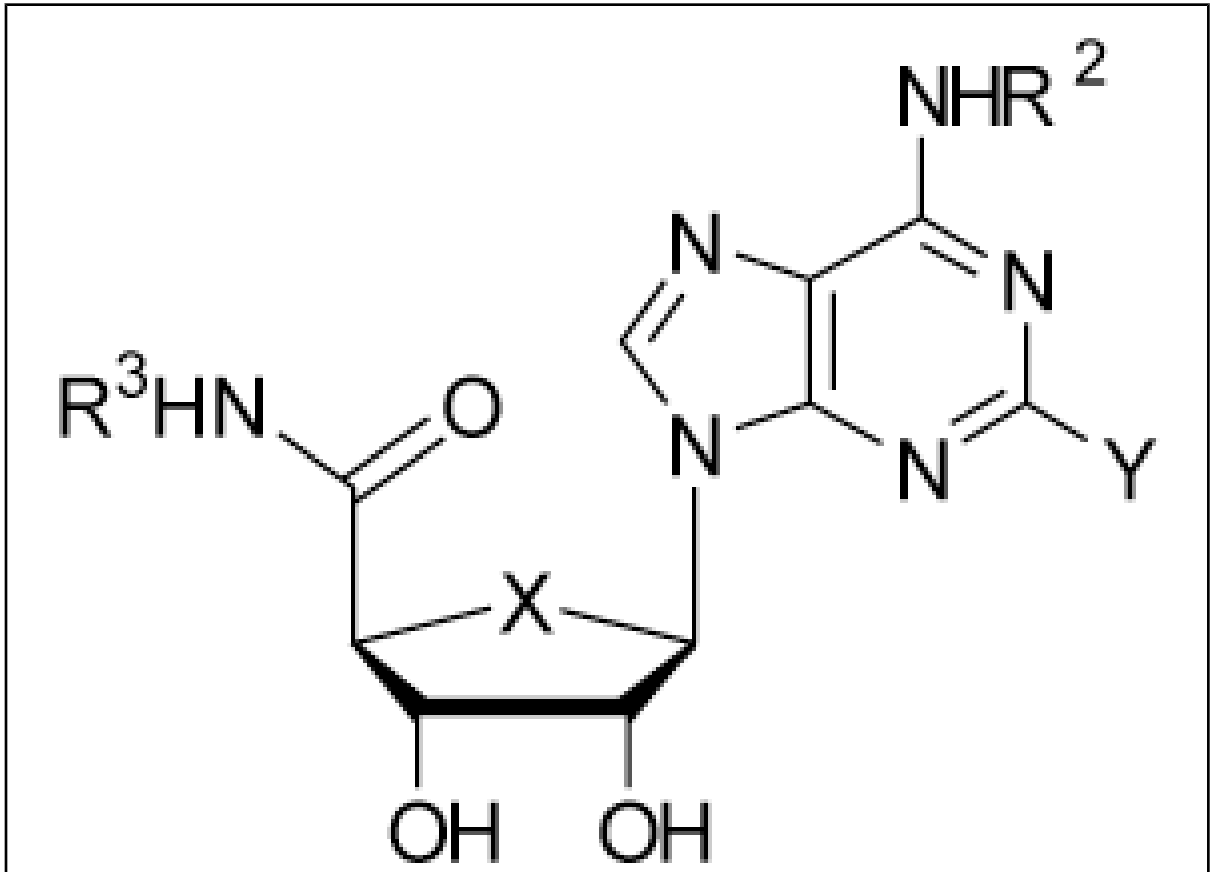


Scheme 2a.

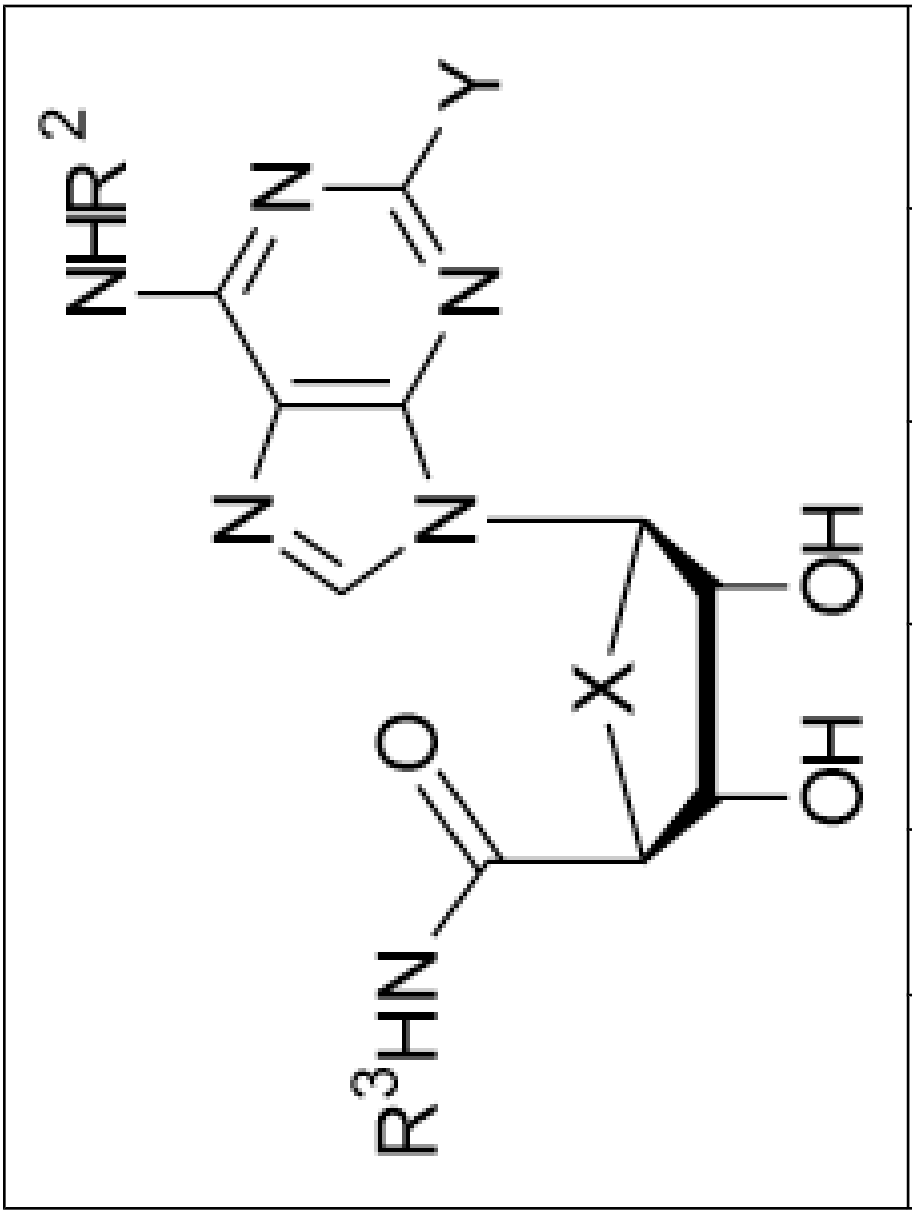
[a]**Reagents & conditions**: a) PDC, DMF; b) R^3NH_2, EDC, HOBt, DIPEA, CH_2Cl_2, c) TBAF, THF

Table 1

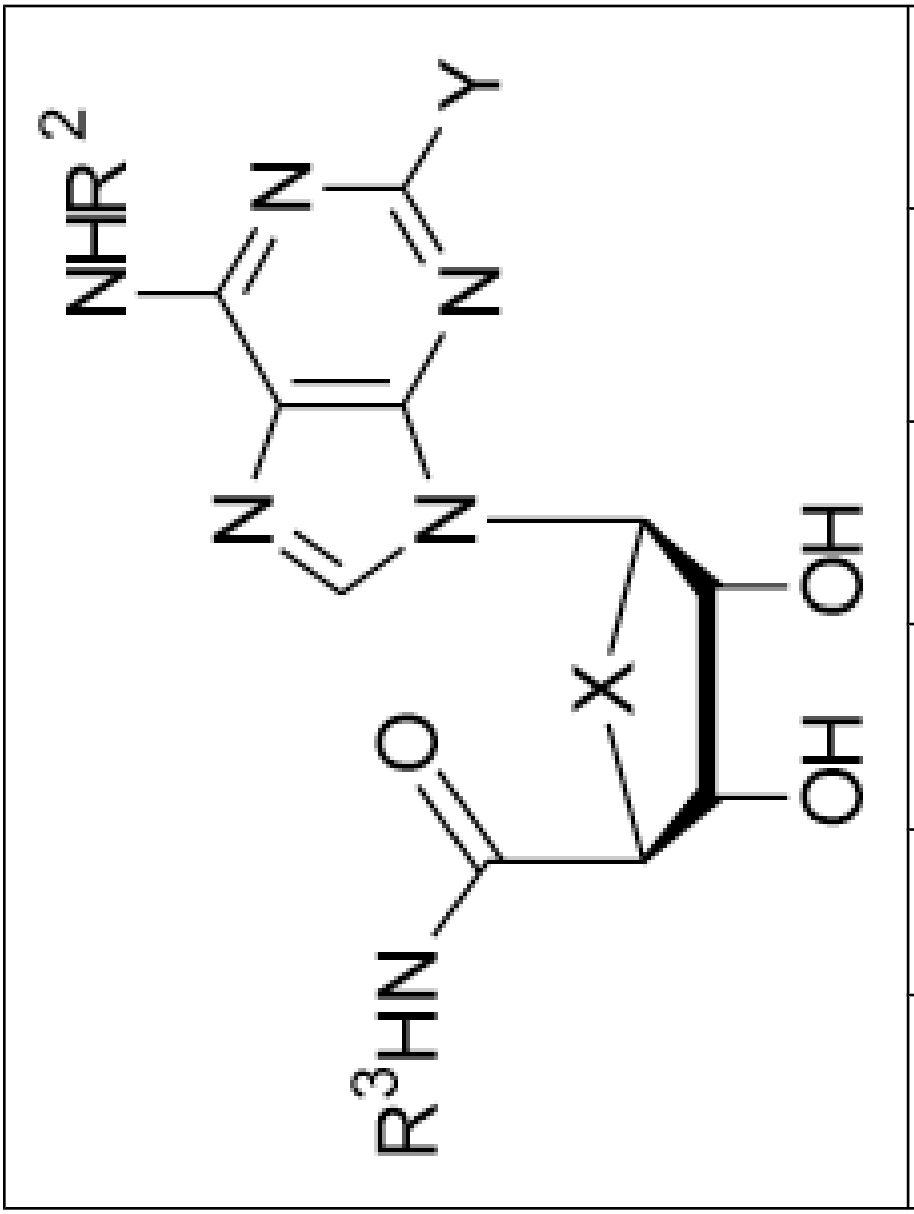
Potency of 4′-thioadenosine-5′-uronamide derivatives **5a–x** at human A_1, A_{2A}, and A_3ARs expressed in CHO cells.[a]



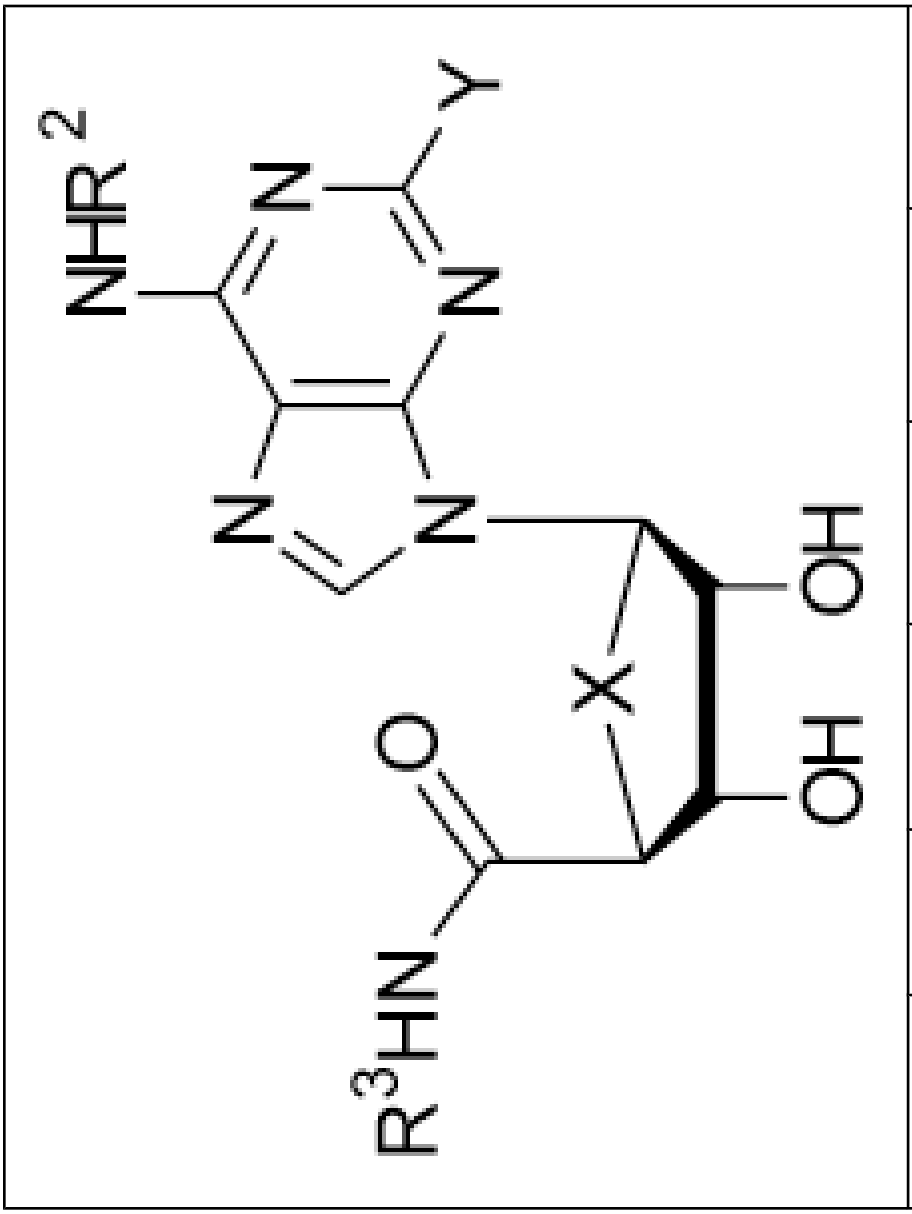
Compound No.	R^2	R^3	K_i (hA_1AR) nM[a] or % inhibition at 1 μM	K_i ($hA_{2A}AR$) nM[a] or % inhibition at 1 μM	K_i (hA_3AR) nM[a] or % inhibition at 1 μM
1 (X = O, Y = Cl)	3-iodobenzyl	methyl	222 ± 22	5360 ± 2470	1.4 ± 0.3
2 (X = O, Y = H)	3-iodobenzyl	methyl	51	2900	1.0
3 (X = S, Y = Cl)	3-iodobenzyl	methyl	193 ± 46	223 ± 36	0.38 ± 0.07



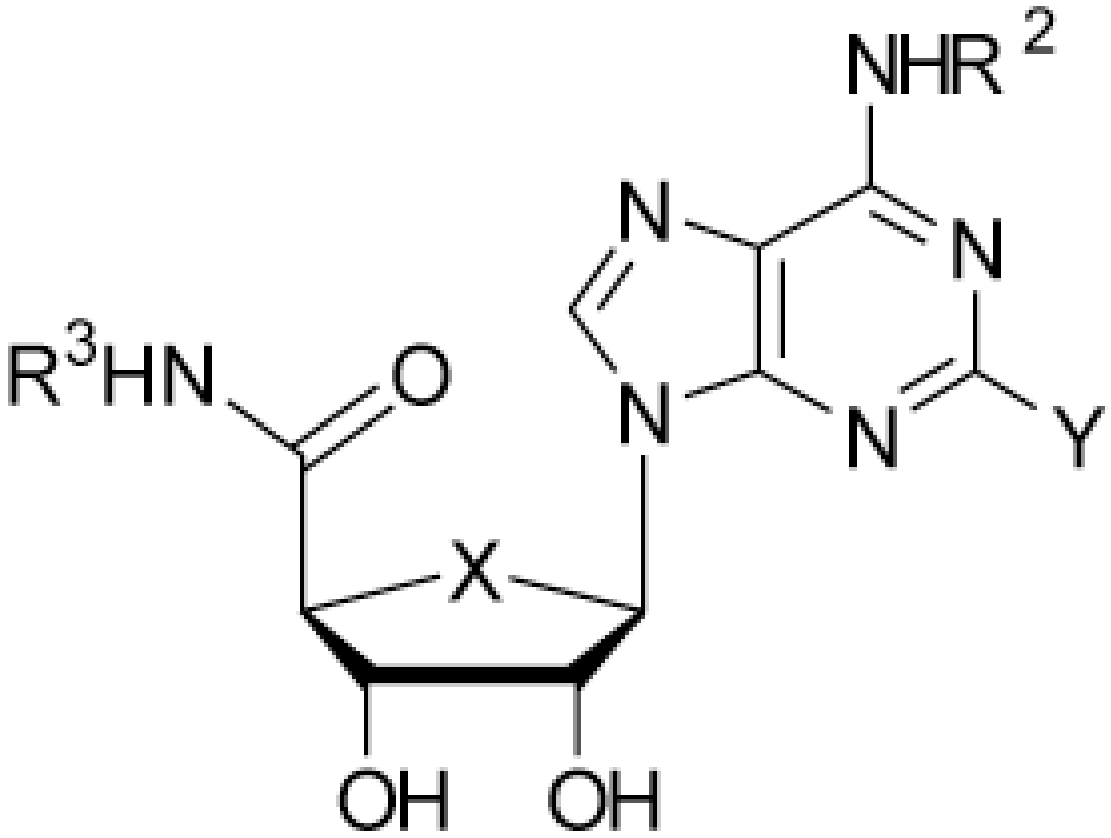
Compound No.	R^2	R^3	K_i (hA_1AR) nM[a] or % inhibition at 1 μM	K_i ($hA_{2A}AR$) nM[a] or % inhibition at 1 μM	K_i (hA_3AR) nM[a] or % inhibition at 1 μM
4 (X = S, Y = Cl)	methyl	methyl	1330 ± 240	20%	0.28 ± 0.09
5a (X = S, Y = H)	methyl	methyl	69.5±5.2	35±8%	1.19±0.23
5b (X = S, Y = H)	methyl	ethyl	4.83±0.20	20%	0.97±0.23
5c (X = S, Y = H)	methyl	cyclopropyl	6.58±0.60	161±16	2.16±0.24
5d (X = S, Y = H)	methyl	cyclopropylmethyl	33.1±1.6	38±5%	1.35±0.08



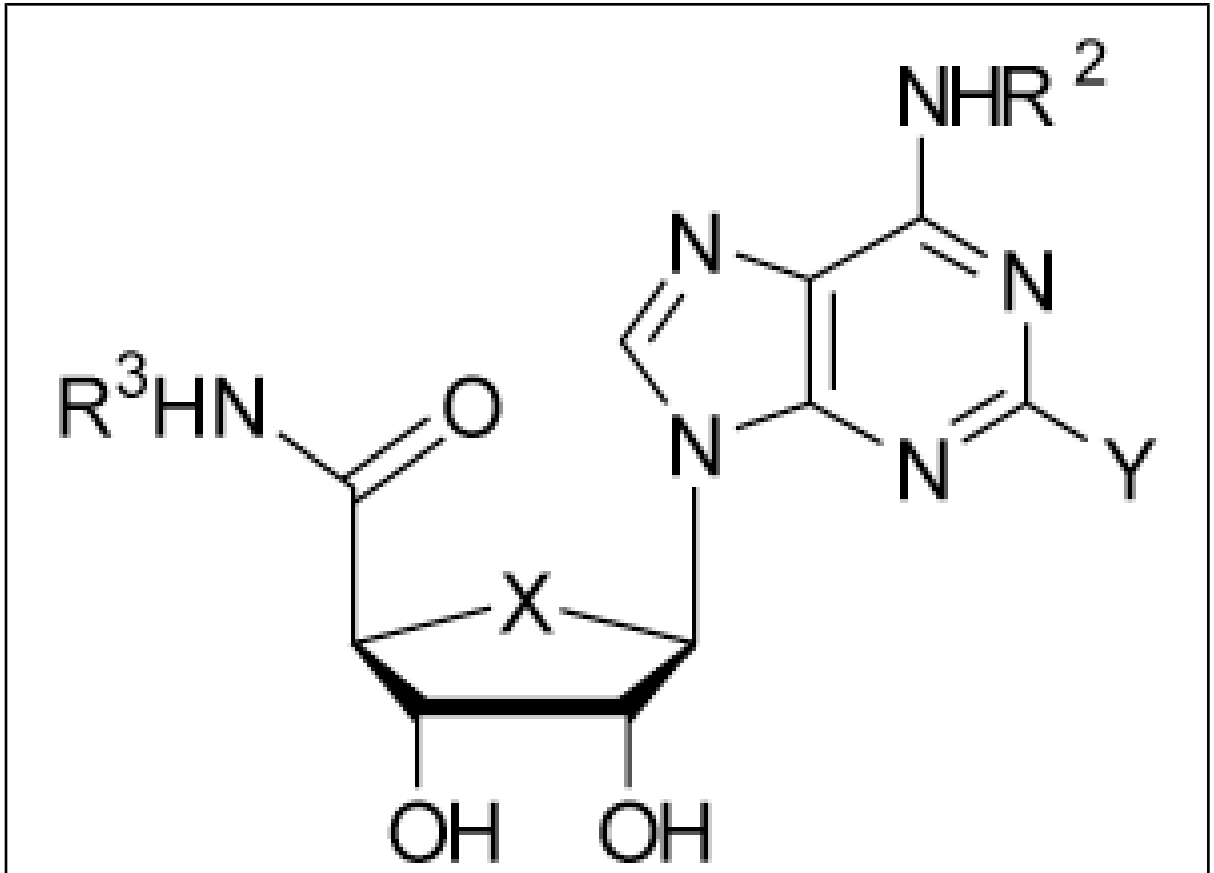
Compound No.	R^2	R^3	K_i (hA_1AR) nM[a] or % inhibition at 1 μM	K_i ($hA_{2A}AR$) nM[a] or % inhibition at 1 μM	K_i (hA_3AR) nM[a] or % inhibition at 1 μM
5e (X = S, Y = H)	methyl	cyclobutyl	6.27±0.50	108±18	1.04±0.05
5f (X = S, Y = H)	methyl	cyclopentyl	48.6±14.2	45±1%	0.97±0.07
5g (X = S, Y = H)	methyl	3-iodobenzyl	24±1%	27±10%	15.6±5.6
5h (X = S, Y = H)	3-iodobenzyl	methyl	20.2±2.9	475±144	0.25±0.06
5i (X = S, Y = H)	3-iodobenzyl	ethyl	5.4±0.3	57.6±6.9	0.42±0.22
5j (X = S, Y = H)	3-iodobenzyl	cyclopropyl	9.27±0.83	15.2±2.6	3.03±0.23



Compound No.	R^2	R^3	K_i (hA_1AR) nM[a] or % inhibition at 1 μM	K_i ($hA_{2A}AR$) nM[a] or % inhibition at 1 μM	K_i (hA_3AR) nM[a] or % inhibition at 1 μM
5k (X = S, Y = H)	3-iodobenzyl	cyclopropylmethyl	159±40	1600±80	2.16±0.29
5l (X = S, Y = H)	3-iodobenzyl	cyclobutyl	23.6±4.2	122±62	1.17±0.16
5m (X = S, Y = H)	3-iodobenzyl	cyclohexyl	28±14%	24±7%	35.4±10.5
5n (X = S, Y = H)	3-iodobenzyl	3-fluorobenzyl	25±4%	35±8%	61.1±17.6
5o (X = S, Y = H)	3-iodobenzyl	3-chlorobenzyl	25±3%	44±1%	144±33



Compound No.	R^2	R^3	K_i (hA_1AR) nM[a] or % inhibition at 1 μM	K_i ($hA_{2A}AR$) nM[a] or % inhibition at 1 μM	K_i (hA_3AR) nM[a] or % inhibition at 1 μM
5p (X = S, Y = H)	3-iodobenzyl	2-methylbenzyl	18±5%	26±10%	31.0±7.1
5q (X = S, Y = H)	3-iodobenzyl	3-methylbenzyl	4070±560	31±1%	94.9±37.3
5r (X = S, Y = H)	3-iodobenzyl	4-methylbenzyl	15±3%	37±0%	135±55
5s (X = S, Y = H)	3-iodobenzyl	2-methoxybenzyl	34±1%	28±9%	97.0±51.2
5t (X = S, Y = H)	3-iodobenzyl	2-ethoxybenzyl	12±7%	23±8%	113±2å
5u (X = S, Y = H)	3-iodobenzyl	α-naphthylmethyl	20±6%	20±8%	1208



Compound No.	R^2	R^3	K_i (hA_1AR) nM[a] or % inhibition at 1 μM	K_i ($hA_{2A}AR$) nM[a] or % inhibition at 1 μM	K_i (hA_3AR) nM[a] or % inhibition at 1 μM
5v (X = S, Y = H)	3-iodobenzyl	2-phenylethyl	20%	11%	433±141
5w (X = S, Y = H)	3-iodobenzyl	1,1-diphenylethyl	17±0%	38±8%	116±48

[a] All AR experiments were performed using adherent CHO cells stably transfected with cDNA encoding the human or rat ARs. Percent activation of the human A_3AR was determined at 1 μM. Binding was carried out as described in Methods using as radioligand [^{3}H]R-PIA or [^{3}H]NECA at the human A_1AR and [^{3}H]CGS 21680 at the human A_{2A}AR. Values from the present study are expressed as mean ± s.e.m., n = 3–5.