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Original article

Synthesis of N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines as antiplatelet agents

Guocheng Liu [a], Jiaxi Xu [a], Ning Chen [a], Si Zhang [b], Zhongren Ding [b], Hongguang Du [a,*]

[a] State Key Laboratory of Chemical Resource Engingeering, Department of Organic Chemistry, College of Science, Beijing University of Chemical Technology, Beijing 100029, China
[b] Key Laboratory of Molecular Medicine, Ministry of Education and Department of Biochemistry and Molecular Biology, Fudan University Shanghai Medical College, Shanghai 200032, China

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ABSTRACT

A series of novel N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines were synthesized, and their human antiplatelet aggregation activities were evaluated by the stimulation of adenosine 5′-diphosphate (ADP). Some of these compounds showed strong activity, among which compound **5b$_{11}$** displayed the highest activity with an IC_{50} value of 29 ± 3 μM. Furthermore, five compounds were tested against arachidonic acid (AA)-induced human platelet aggregation. The results showed that compound **5b$_{10}$** exhibited the highest activity with an IC_{50} value of 3 ± 2 μM. The adenosine derivatives substituted with a phenethyl group at the N^6 position and a methylthio or ethylthio group at the C-2 position displayed high antiplatelet aggregation activity.

1. Introduction

Platelets play a pivotal role in atherothrombosis [1]; their activation, adhesion and aggregation are important processes in the initiation of thrombus formation at sites showing high-grade stenosis, ruptured atheromatous plaque and endothelial damage within arteries [2,3]. Platelet-mediated thrombus formation in the coronary artery is a primary factor in the development of thrombotic disorders, such as acute coronary syndromes [4], including unstable angina, myocardial infarction and symptomatic peripheral artery disease [5–7]. Current antiplatelet agents include available drugs, such as aspirin, ticlopidine, clopidogrel and glycoprotein IIb/IIIa antagonists [8,9]. However, these current antiplatelet drugs are still not satisfactory in terms of efficacy and safety [10–12]. Therefore, intensive efforts are urgently desirable to develop novel antiplatelet agents.

Adenosine is a potent inhibitor of platelet aggregation [13], but it has intense effects on the cardiovascular system and is readily inactivated by contact with erythrocytes or platelets [14]. Therefore, a lot of adenosine derivatives have been prepared and evaluated for their ability to inhibit platelet aggregation, such as 2-chloroadenonsine [15], 2-(substituted thio) adenosines [16,17], 2-(substituted amino) adenosines [17] and N^6-substituted adenosines [18]. However, these adenosine derivatives still have various drawbacks, such as low activity and serious undesirable side effects [19]. In 1999, the AR-C compounds have been reported as the $P2Y_{12}$ receptor antagonists by Ingall and his co-workers [20]. The $P2Y_{12}$ receptor is a G protein-coupled receptor, primarily a specific platelet receptor, which is an attractive therapeutic target for selective modulation of ADP-induced platelet activation [21]. The AR-C compounds are also adenosine derivatives with the alkylthio group at C-2 position, the alkyl substituent at N^6 position and the triphosphate side chain at the 5′ position. Among these AR-C compounds, cangrelor (Fig. 1) is one of the most potent inhibitors of ADP-induced human platelet aggregation ($IC_{50} = 0.4$ nM, 30 μM ADP, human washed platelets) [20,22], which does not require conversion to an active metabolite, and is immediately active after intravenous infusion. However, the synthetic route of the AR-C compounds consists of a long multistep process. What is more, the unwieldy 5′-triphosphate group is not necessary to be recognized by the $P2Y_{12}$ receptor [23,24]. Ticagrelor (Fig. 1) is one of the examples with a high affinity for the $P2Y_{12}$ receptor and is currently under clinical trials [25]. Considering these findings, we modified the C-2 and N^6 substituents of the adenosine scaffold and obtained a series of N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines (Fig. 1). To date, a few of N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines have been reported [26–29], but their biological evaluations as antiplatelet agents have not been studied.

In our attempt to develop novel and potent antiplatelet agents, a series of new N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines were synthesized and evaluated as antiplatelet agents together with their primary structure–activity relationships.

* Corresponding author. College of Science, Beijing University of Chemical Technology, Beijing 100029, China. Tel./fax: +86 10 64439218.
E-mail address: dhg@mail.buct.edu.cn (H. Du).

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2. Results and discussion

2.1. Chemistry

The synthesis of N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines is outlined in Scheme 1.

2-Amino-6-chloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine (**3**) was synthesized from the starting material guanosine (**1**) via acetylation and chlorination by a well-established procedure [30,31]. Next, compound **3** was diazotized with isoamyl nitrite and then reacted with dialkyl(aryl) disulfides to afford 2-alkyl(aryl)thio-6-chloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purines (**4**). However, in the previous procedure for synthesis of **4**, abundant dialkyl(aryl) disulfide (10 equiv of **3**) was used in each of cases [20,32,33], and the reaction was kept for a long time (16 h). To improve the synthetic efficiency, we optimized the conditions of diazotization–alkylthionation with dibutyl disulfide. The results are summarized in Table 1. It can be found that the optimum molar ratio is 1:5 (**3**:dibutyl disulfide) and the reaction time can be shortened to 6 h (Table 1, entries 3 and 8). A series of 2-alkyl(aryl)thio-6-chloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purines (**4a**–**g**) were obtained in moderate yields (43–66%) under the modified reaction conditions.

Subsequently, the target compounds **5** were obtained in good yields via the reaction of compounds **4** and various amines in ethanol using triethylamine as an acid binding agent and sodium ethanoxide as a deacetylating agent. Comparing with the previously reported method [20], the current method shows advantages of short reaction time and complete deacetylation due to the better solubility in ethanol. Thirty-two N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines (Table 2, **5a$_1$**–**a$_8$** and **5b$_1$**–**b$_{24}$**) were obtained under our modified conditions.

2.2. Antiplatelet activity evaluation

All the synthesized compounds were evaluated for the ability to inhibit human platelet aggregation induced by ADP in vitro using the Born's method [34]. Furthermore, five promising compounds **5b$_{10}$**, **5b$_{11}$**, **5b$_{12}$**, **5b$_{13}$** and **5b$_{21}$** were tested against AA-induced platelet aggregation (Table 2).

As can be seen from Table 2, most of the synthesized compounds **5** exhibited high potencies in antiplatelet aggregation activities. Among them, 2-ethylthio-N^6-phenethyladenosine (**5b$_{11}$**) displayed the best activity against ADP-induced platelet aggregation with an IC_{50} value of 29 ± 3 μM and 2-methylthio-N^6-phenethyladenosine (**5b$_{10}$**) exhibited the highest potency against AA-induced platelet aggregation with an IC_{50} value of 3 ± 2 μM. However, the methoxy substituted N^6-phenethyladenosine derivatives showed low inhibition activity in comparison with N^6-phenethyladenosine derivatives (Table 2, entries 18, 19, 24, 25, 28 and 29), and a similar tendency was also obtained by the further examination of the activities of N^6-benzyladenosine derivatives (Table 2, entries 9–12, 15–17). This reveals that the phenethyl group at the N^6 position of adenosine is crucial to the antiplatelet activity, while the electron-donating groups on the benzene ring of the benzyl and phenethyl groups at the N^6 position decreases the activity. The results are consistent with previous conclusions that a hydrogen binding moiety and a lipophilic moiety are critical for $P2Y_{12}$ receptor antagonist activity [35]. Phenethyl substituent, a relatively larger hydrophobic group, can increase the ligand and receptor binding. Therefore, the N^6-phenethyladenosine derivatives show better activity than others. Furthermore, the N^6-phenethyladenosine derivatives showed a broad spectrum of antiplatelet action against both ADP and AA-induced aggregations (Table 2, entries 18–21).

Additionally, the weak antiplatelet activity of compound **5a$_8$** confirmed that dialkylation at N^6 position of adenosine decreased the activity [20], revealing that a hydrogen atom at N^6 position is important for the activity.

The results also indicated that a small thio-substituted group at C-2 was optimal for the antiplatelet activity, methylthio and ethylthio showing high antiplatelet activity (Table 2, entries 10, 18, 19, 25 and 29), while bulky phenylthio and benzylthio illustrating dramatically low inhibitory activity (Table 2, entries 22 and 23). It was assumed that there is a steric interference between the two substituents on N^6 and C-2 due to the partial overlap between the N^6 and C-2 aryl-binding pockets. The distal aryl groups at N^6 and C-2 would occupy their respective pockets when present alone, but could not occupy the overlapping portion of the two pockets when present in the same molecule [26]. In this case, one of the two aryl groups would be forced into an unfavorable position, resulting in the loss of activity.

3. Conclusions

In summary, we have prepared a series of novel N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines and evaluated for their ability to inhibit human platelet aggregation induced by ADP in vitro. The most promising compounds in this series are **5b$_{10}$**, **5b$_{11}$**, **5b$_{12}$**, **5b$_{13}$** and **5b$_{21}$**. Especially, compound **5b$_{11}$** showed the highest activity with an IC_{50} value of 29 ± 3 μM. Furthermore, the five compounds were tested for their antiplatelet aggregation activities induced by AA. It was found that compound **5b$_{10}$** displayed the best activity with an IC_{50} value of 3 ± 2 μM. Interestingly, the presence of a phenethyl group at the N^6 position and methylthio or ethylthio group at the C-2 position of adenosine is optimal to the antiplatelet activity, while the electron-donating groups substituted on the benzene ring at the N^6 position decrease the activity. Finally, the present study demonstrates that some N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines exhibit broad spectrum antiplatelet activity against both ADP and AA induced aggregations. The results might provide a basis for the development of new candidates with potent antiplatelet aggregation activities.

4. Experimental section

4.1. General

All reagents were purchased and used without further purification, and solvents used in reactions were dried prior to use by standard procedures. Melting points were measured on a Yanaco MP-500 melting point apparatus without correction. IR spectra

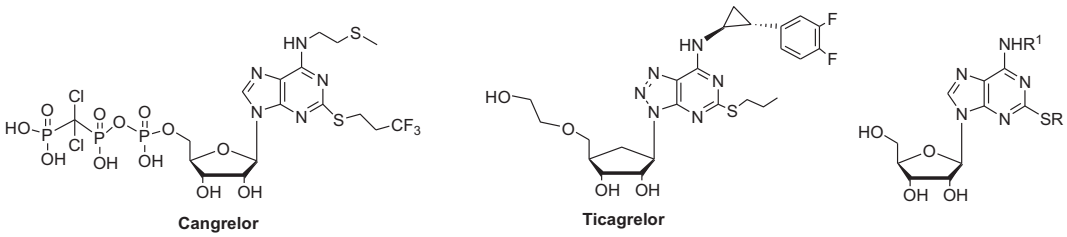
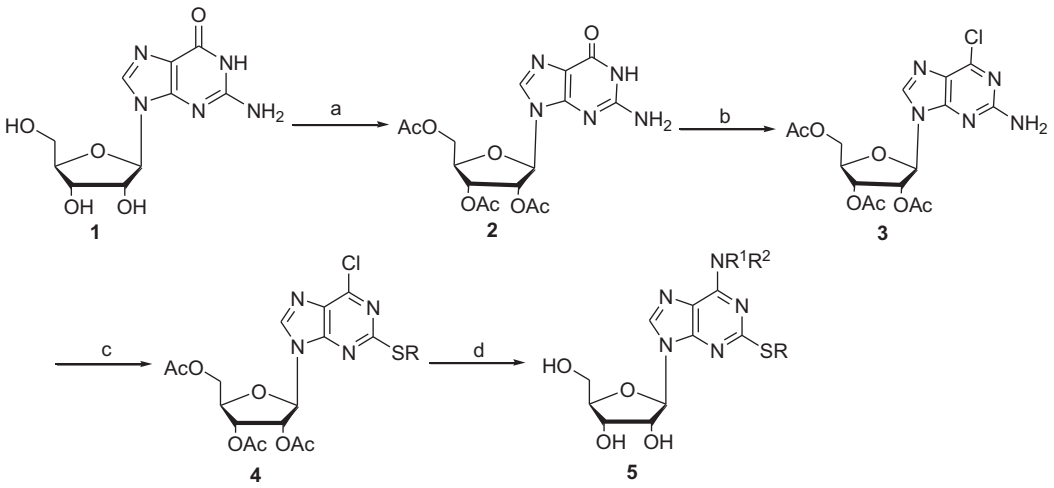


Fig. 1. Structures of cangrelor, ticagrelor and N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines.



Scheme 1. Synthesis of N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines. Reagents and conditions: (a) Ac_2O, DMAP, Et_3N, CH_3CN, r.t.; (b) $POCl_3$, Et_4NCl, *N*,*N*-dimethylaniline, CH_3CN, reflux; (c) isoamyl nitrite, MeCN, RSSR, 60 °C; (d) 1) HNR^1R^2, Et_3N, EtOH, reflux; 2) Na, reflux.

were recorded on PerkinElmer Spectrum 100 spectrophotometer and values were represented in cm^{-1}. The NMR spectra were recorded with Varian Mercury plus 200 (200 MHz), Varian Mercury plus 300 (300 MHz), Bruker 400 AMX (400 MHz) or Bruker 600 AMX (600 MHz) spectrometer. Chemical shifts were expressed in parts per million on δ scale relative to the internal TMS (^{1}H). High resolution mass spectra (HRMS-ESI) were obtained on an Agilent LC/TOF mass spectrometer. Cangrelor was obtained from AstraZeneca (Loughborough, UK). ADP was purchased from Chrono-Log (Havertown, PA, USA); Arachidonic acid and sodium citrate were purchased from Sigma (St Louis, MO).

4.2. General procedure for the synthesis of 2-alkyl(aryl)thio-6-chloro-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-9H-purines (**4a**–**g**)

A solution of compound **3** (2.5 g, 5.85 mmol) and a corresponding dialkyl disulfide (29.25 mmol) in dry acetonitrile (35 mL) was stirred at room temperature for 30 min under N_2 atmosphere. Then isoamyl nitrite (4.25 g, 36.3 mmol) was added dropwise into the mixture. After stirring for 10 min, the solution was heated at 60 °C for 6 h. The solvent was evaporated in vacuo, and the resulting residue was purified by silica gel column chromatography (EtOAc/petroleum ether, 2:3–1:1, v/v) to afford corresponding product **4** as yellow oil.

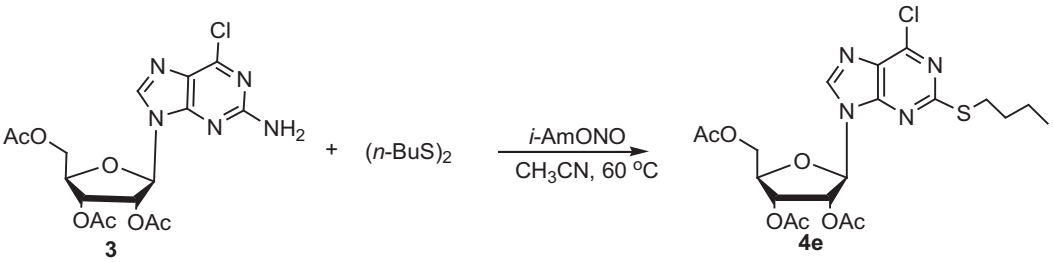
4.2.1. 6-Chloro-2-methylthio-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (**4a**) [33]

Compound **3** was allowed to react with dimethyl disulfide according to the general procedure. The product was purified by column chromatography to give **4a**. Yield: 66%.

4.2.2. 6-Chloro-2-ethylthio-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (**4b**) [20]

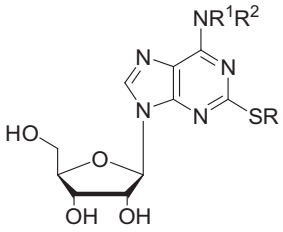
Compound **3** was allowed to react with diethyl disulfide according to the general procedure. The product was purified by column chromatography to give **4b**. Yield: 62%.

Table 1
Optimizing reaction conditions of the diazotization–alkylthionation reaction.



Entry	(n-BuS)$_2$ (equiv)	i-AmONO (equiv)	Time (h)	Product **4e** (Yield, %)
1	10	6.2	16	54
2	7	6.2	16	53
3	5	6.2	16	53
4	4	6.2	16	46
5	2	6.2	16	43
6	1	6.2	16	39
7	0.5	6.2	16	23
8	5	6.2	6	52
9	5	6.2	4	45
10	5	6.2	2	30

Table 2
The structures and antiplatelet activity evaluations of N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines (**5**).



5

Entry	Compound **5**	R	R^1	R^2	IC_{50} (μM)[a]	
					ADP	AA
1	**5a$_1$**	Et	$CH_2(CH_2)_4CH_3$	H	nc[b]	
2	**5a$_2$**	*n*-Pr	$CH_2(CH_2)_4CH_3$	H	102 ± 11	
3	**5a$_3$**	*n*-Bu	$CH_2(CH_2)_4CH_3$	H	nc	
4	**5a$_4$**	Et	*c*-C_6H_{11}	H	104 ± 7	
5	**5a$_5$**	*n*-Pr	*c*-C_6H_{11}	H	151 ± 9	
6	**5a$_6$**	*i*-Pr	*c*-C_6H_{11}	H	187 ± 15	
7	**5a$_7$**	*n*-Bu	*c*-C_6H_{11}	H	83 ± 4	
8	**5a$_8$**	Et	*n*-Bu	*n*-Bu	nc	
9	**5b$_1$**	Me	CH_2Ph	H	nc	
10	**5b$_2$**	Et	CH_2Ph	H	176 ± 16	
11	**5b$_3$**	*n*-Pr	CH_2Ph	H	216 ± 12	
12	**5b$_4$**	*n*-Bu	CH_2Ph	H	202 ± 20	
13	**5b$_5$**	Me	*p*-$MePhCH_2$	H	nc	
14	**5b$_6$**	Et	*p*-$MePhCH_2$	H	nc	
15	**5b$_7$**	Me	*p*-$MeOPhCH_2$	H	nc	
16	**5b$_8$**	Et	*p*-$MeOPhCH_2$	H	nc	
17	**5b$_9$**	*n*-Pr	*p*-$MeOPhCH_2$	H	181 ± 14	
18	**5b$_{10}$**	Me	$PhCH_2CH_2$	H	36 ± 5	3 ± 2
19	**5b$_{11}$**	Et	$PhCH_2CH_2$	H	29 ± 3	30 ± 9
20	**5b$_{12}$**	*n*-Pr	$PhCH_2CH_2$	H	52 ± 3	44 ± 7
21	**5b$_{13}$**	*n*-Bu	$PhCH_2CH_2$	H	59 ± 6	>300
22	**5b$_{14}$**	Ph	$PhCH_2CH_2$	H	nc	
23	**5b$_{15}$**	CH_2Ph	$PhCH_2CH_2$	H	nc	
24	**5b$_{16}$**	Me	*p*-$MeOPhCH_2CH_2$	H	153 ± 13	
25	**5b$_{17}$**	Et	*p*-$MeOPhCH_2CH_2$	H	89 ± 10	
26	**5b$_{18}$**	*n*-Pr	*p*-$MeOPhCH_2CH_2$	H	267 ± 18	
27	**5b$_{19}$**	*n*-Bu	*p*-$MeOPhCH_2CH_2$	H	93 ± 7	
28	**5b$_{20}$**	Me	*m*-$MeOPhCH_2CH_2$	H	nc	
29	**5b$_{21}$**	Et	*m*-$MeOPhCH_2CH_2$	H	38 ± 4	>300
30	**5b$_{22}$**	*n*-Pr	*m*-$MeOPhCH_2CH_2$	H	69 ± 5	
31	**5b$_{23}$**	*n*-Bu	*m*-$MeOPhCH_2CH_2$	H	nc	
32	**5b$_{24}$**	Et	$CH(CH_3)Ph$	H	197 ± 12	

[a] IC_{50} values were expressed as mean ± S.E.M. ($n = 3$) and calculated when platelet aggregation was below 50% of control (10 μM ADP or 0.5 mM AA was used as agonist).
[b] nc = not calculated, because maximal inhibition of aggregation was lower than 50% at final concentration of 300 μM (10 μM ADP as agonist).

*4.2.3. 6-Chloro-2-propylthio-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (**4c**) [20]*

Compound **3** was allowed to react with dipropyl disulfide according to the general procedure. The product was purified by column chromatography to give **4c**. Yield: 57%.

*4.2.4. 6-Chloro-2-isopropylthio-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (**4d**) [32]*

Compound **3** was allowed to react with diisopropyl disulfide according to the general procedure. The product was purified by column chromatography to give **4d**. Yield: 43%.

*4.2.5. 2-Butylthio-6-chloro-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (**4e**)*

Compound **3** was allowed to react with dibutyl disulfide according to the general procedure. The product was purified by column chromatography to give **4e**. Yield: 50%; IR (film): 3443, 3110, 2962, 1748, 1546, 1360, 1224 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.11 (1H, s, H-8), 6.14 (1H, d, $J = 4.8$ Hz, H-1′), 5.89 (1H, dd, $J = 5.2$, 5.3 Hz, H-2′), 5.58 (1H, dd, $J = 5.3$, 5.4 Hz, H-3′), 4.44 (1H, ddd, $J = 3.1$, 4.2, 5.4 Hz, H-4′), 4.41 (1H, dd, $J = 3.1$, 12.3 Hz, H-5′a), 4.33 (1H, dd, $J = 4.2$, 12.3 Hz, H-5′b), 3.20 (2H, t, $J = 7.3$ Hz, SCH_2), 2.13 (3H, s, CH_3CO), 2.10 (3H, s, CH_3CO), 2.08 (3H, s, CH_3CO), 1.74 (2H, quint, $J = 7.3$ Hz, $SCH_2\underline{CH_2}$), 1.48 (2H, sextet, $J = 7.3$ Hz, $SCH_2CH_2\underline{CH_2}$), 0.95 (3H, t, $J = 7.3$ Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.0, 169.2, 169.0, 166.7, 151.7, 150.9, 142.0, 128.7, 86.5, 79.7, 72.9, 69.8, 62.5, 31.04, 30.6, 21.7, 20.4, 20.2, 20.1, 13.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{26}ClN_4O_7S$: 501.1205; found: 501.1212.

*4.2.6. 6-Chloro-2-phenylthio-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (**4f**) [27]*

Compound **3** was allowed to react with diphenyl disulfide according to the general procedure. The product was purified by column chromatography (petroleum ether to EtOAc/petroleum ether, 2:3, v/v) to give **4f**. Yield: 45%.

4.2.7. 2-Benzylthio-chloro-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (**4g**)

Compound **3** was allowed to react with dibenzyl disulfide according to the general procedure. The product was purified by column chromatography (petroleum ether to EtOAc/petroleum ether, 2:3, v/v) to give **4g**. Yield: 50%; IR (film): 3445, 3025, 2927, 1750, 1494, 1360, 1231, 822, 755, 700 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 8.57 (1H, s, H-8), 7.53 (2H, d, $J = 7.2$ Hz, ArH), 7.33 (2H, t, $J = 7.2$ Hz, ArH), 7.26 (1H, t, $J = 7.2$ Hz, ArH), 6.36 (1H, d, $J = 4.6$ Hz, H-1′), 6.08 (1H, dd, $J = 4.6$, 5.8 Hz, H-2′), 5.71 (1H, dd, $J = 5.8$, 5.8 Hz, H-3′), 4.55 (2H, s, SCH_2), 4.48 (1H, ddd, $J = 3.5$, 5.1, 5.8 Hz, H-4′), 4.42 (1H, dd, $J = 3.5$, 12.2 Hz, H-5′a), 4.32 (1H, dd, $J = 5.1$, 12.2 Hz, H-5′b), 2.10 (3H, s, CH_3CO), 2.08 (3H, s, CH_3CO), 2.06 (3H, s, CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 169.3, 169.2, 166.0, 151.8, 150.9, 142.0, 136.6, 129.0, 128.9, 128.3, 127.2, 86.4, 79.9, 72.9, 70.0, 62.6, 35.9, 20.6, 20.4, 20.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{24}ClN_4O_7S$: 535.1049; found: 535.1048.

4.3. General procedure for the synthesis of N^6-alkyl(aryl)-2-alkyl(aryl)thioadenosines (**5a₁–a₈** and **5b₁–b₂₄**)

A solution of compound **4** (0.7 mmol), a corresponding amine (3.5 mmol) and triethylamine (0.7 mmol) in ethanol (20 mL) was refluxed for the time reported below. When the starting material disappeared as monitored by TLC (MeOH/EtOAc, 1:15, v/v), sodium (0.05 equiv) was added into the resulting mixture. After the deacetylations were completed, the solvent was evaporated in vacuo. The resulting residue was purified by flash column chromatography (Et_3N-neutralized silica gel, gradient elution separation with MeOH/EtOAc, 1:30–1:15, v/v) and/or recrystallization, affording the product **5** as white crystals.

4.3.1. 2-Ethylthio-N^6-hexyladenosine (**5a₁**)

Compound **4b** was allowed to react with *n*-hexylamine for 7 h according to the general procedure. The product was recrystallized from MeOH to give **5a₁**. Yield: 83%, mp 180–182 °C; IR (KBr): 3446, 3343, 3151, 2927, 1622, 1396, 1120 cm^{-1}; ^1H NMR: (600 MHz, DMSO-d_6): δ 8.20 (1H, s, H-8), 7.92 (1H, br s, NH), 5.80 (1H, d, $J = 5.6$ Hz, H-1′), 5.38 (1H, d, $J = 6.0$ Hz, OH), 5.14 (1H, d, $J = 4.8$ Hz, OH), 5.04 (1H, br s, OH), 4.56 (1H, ddd, $J = 4.4$, 5.6, 6.0 Hz, H-2′), 4.13 (1H, ddd, $J = 3.6$, 4.4, 4.8 Hz, H-3′), 3.92 (1H, ddd, $J = 3.6$, 4.7, 5.7 Hz, H-4′), 3.64 (1H, ddd, $J = 4.2$, 4.7, 11.9 Hz, H-5′a), 3.53 (1H, ddd, $J = 4.4$, 5.7, 11.9 Hz, H-5′b), 3.43 (2H, br s, $N\underline{CH_2}$), 3.07 (2H, q, $J = 7.3$ Hz, SCH_2), 1.58 (2H, quint, $J = 6.9$ Hz, $NCH_2\underline{CH_2}$), 1.33 (3H, t, $J = 7.3$ Hz, CH_3), 1.30–1.24 (6H, m, $NCH_2CH_2\underline{CH_2CH_2CH_2}$), 0.86 (3H, t, $J = 6.4$ Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.6, 154.0, 149.3, 138.5, 117.3, 87.5, 85.6, 73.4, 70.6, 61.6, 39.7, 31.0, 29.0, 26.1, 24.7, 22.1, 15.0, 13.9; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{30}N_5O_4S$: 412.2013; found: 412.2021.

4.3.2. N^6-hexyl-2-propylthioadenosine (**5a₂**)

Compound **4c** was allowed to react with *n*-hexylamine for 8 h according to the general procedure. The product was recrystallized from MeOH to give **5a₂**. Yield: 84%, mp 186–188 °C; IR (KBr): 3436, 3346, 3154, 2920, 1617, 1399, 1120 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 8.19 (1H, s, H-8), 7.92 (1H, br s, NH), 5.80 (1H, d, $J = 5.8$ Hz, H-1′), 5.37 (1H, d, $J = 6.0$ Hz, OH), 5.13 (1H, d, $J = 4.8$ Hz, OH), 5.06 (1H, br s, OH), 4.58 (1H, ddd, $J = 5.6$, 5.8, 6.0 Hz, H-2′), 4.13 (1H, ddd, $J = 3.8$, 4.8, 5.6 Hz, H-3′), 3.92 (1H, ddd, $J = 3.8$, 4.4, 5.4 Hz, H-4′), 3.64 (1H, ddd, $J = 4.4$, 4.6, 11.9 Hz, H-5′a), 3.53 (1H, ddd, $J = 4.6$, 5.4, 11.9 Hz, H-5′b), 3.44 (2H, br s, $N\underline{CH_2}$), 3.07 (1H, dt, $J = 13.5$, 7.3 Hz, $SC\underline{H}H$), 3.05 (1H, dt, $J = 13.5$, 7.3 Hz, $SCH\underline{H}$), 1.70 (2H, sextet, $J = 7.3$ Hz, $SCH_2\underline{CH_2}$), 1.58 (2H, quint, $J = 6.9$ Hz, $NCH_2\underline{CH_2}$), 1.33–1.25 (6H, m, $NCH_2CH_2\underline{CH_2CH_2CH_2}$), 0.99 (3H, t, $J = 7.3$ Hz, CH_3), 0.86 (3H, t, $J = 6.6$ Hz, $\underline{CH_3}$); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.7, 153.9, 149.4, 138.5, 117.3, 87.5, 85.6, 73.4, 70.6, 61.6, 39.7, 32.4, 31.0, 29.0, 26.1, 22.9, 22.1, 13.9, 13.3; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{32}N_5O_4S$: 426.2170; found: 426.2178.

4.3.3. 2-Butylthio-N^6-hexyladenosine (**5a₃**)

Compound **4e** was allowed to react with *n*-hexylamine for 9 h according to the general procedure. The product was recrystallized from MeOH to give **5a₃**. Yield: 81%, mp 186–188 °C; IR (KBr): 3433, 3337, 3125, 1627, 1393, 1117 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 8.19 (1H, s, H-8), 7.90 (1H, br s, NH), 5.80 (1H, d, $J = 5.8$ Hz, H-1′), 5.37 (1H, d, $J = 5.4$ Hz, OH), 5.12 (1H, d, $J = 3.0$ Hz, OH), 5.04 (1H, br s, OH), 4.58 (1H, ddd, $J = 5.4$, 5.7, 5.8 Hz, H-2′), 4.12 (1H, ddd, $J = 3.0$, 3.4, 5.7 Hz, H-3′), 3.92 (1H, ddd, $J = 3.4$, 4.1, 5.6 Hz, H-4′), 3.64 (1H, ddd, $J = 4.1$, 4.7, 11.9 Hz, H-5′a), 3.53 (1H, ddd, $J = 4.7$, 5.6, 11.9 Hz, H-5′b), 3.44 (2H, br s, $N\underline{CH_2}$), 3.09 (1H, dt, $J = 13.5$, 7.3 Hz, $SC\underline{H}H$), 3.08 (1H, dt, $J = 13.5$, 7.3 Hz, $SCH\underline{H}$), 1.66 (2H, quint, $J = 7.3$ Hz, $SCH_2\underline{CH_2}$), 1.58 (2H, quint, $J = 6.9$ Hz, $NCH_2\underline{CH_2}$), 1.42 (2H, sextet, $J = 7.3$ Hz, $SCH_2CH_2\underline{CH_2}$), 1.33–1.25 (6H, m, $NCH_2CH_2\underline{CH_2CH_2CH_2}$), 0.91 (3H, t, $J = 7.3$ Hz, CH_3), 0.86 (3H, t, $J = 6.4$ Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.7, 153.9, 149.4, 138.5, 117.3, 87.5, 85.6, 73.4, 70.6, 61.6, 39.8, 31.7, 31.0, 30.1, 29.1, 26.1, 22.1, 21.6, 13.8, 13.5; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{34}N_5O_4S$: 440.2326; found: 440.2323.

4.3.4. N^6-cyclohexyl-2-ethylthioadenosine (**5a₄**)

Compound **4b** was allowed to react with cyclohexylamine for 10 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5a₄**. Yield: 80%, mp 166–168 °C; IR (KBr): 3423, 3128, 1612, 1337, 1088 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.21 (1H, s, H-8), 7.73 (1H, br s, NH), 5.81 (1H, d, $J = 5.8$ Hz, H-1′), 5.41 (1H, br s, OH), 5.18 (1H, br s, OH), 5.07 (1H, br s, OH), 4.58 (1H, dd, $J = 5.4$, 5.5 Hz, H-2′), 4.13 (1H, dd, $J = 3.6$, 3.6 Hz, H-3′), 3.92 (1H, ddd, $J = 3.4$, 3.6, 5.6 Hz, H-4′), 4.02 (1H, br s, $NC\underline{H}$), 3.64 (1H, d, $J = 11.8$ Hz, H-5′a), 3.53 (1H, d, $J = 11.8$ Hz, H-5′b), 3.07 (1H, dq, $J = 13.6$, 7.3 Hz, $SC\underline{H}H$), 3.06 (1H, dq, $J = 13.6$, 7.3 Hz, $SCH\underline{H}$), 1.94–1.57 (6H, m, cyclohexyl), 1.33 (3H, t, $J = 7.3$ Hz, CH_3), 1.31–1.07 (4H, m, cyclohexyl); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.6, 153.2, 149.6, 138.5, 117.1, 87.52, 85.6, 73.4, 70.6, 61.6, 49.1, 32.4, 32.2 (2C), 25.2, 25.0 (2C), 15.1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{28}N_5O_4S$: 410.1857; found: 410.1864.

4.3.5. N^6-cyclohexyl-2-propylthioadenosine (**5a₅**)

Compound **4c** was allowed to react with cyclohexylamine for 9 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5a₅**. Yield: 82%, mp 162–164 °C; IR (KBr): 3423, 3128, 1611, 1399, 1089 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.21 (1H, s, H-8), 7.72 (1H, br s, NH), 5.81 (1H, d, $J = 5.9$ Hz, H-1′), 5.42 (1H, d, $J = 6.1$ Hz, OH), 5.18 (1H, d, $J = 4.8$ Hz, OH), 5.10 (1H, dd, $J = 4.2$, 4.6 Hz, OH), 4.59 (1H, ddd, $J = 5.0$, 5.9, 6.1 Hz, H-2′), 4.14 (1H, ddd, $J = 3.4$, 4.8, 5.0 Hz, H-3′), 4.05 (1H, br s, $NC\underline{H}$), 3.94 (1H, ddd, $J = 3.4$, 4.6, 6.0 Hz, H-4′), 3.65 (1H, ddd, $J = 4.6$, 4.6, 11.9 Hz, H-5′a), 3.54 (1H, ddd, $J = 4.2$, 6.0, 11.9 Hz, H-5′b), 3.04 (2H, t, $J = 7.3$ Hz, SCH_2), 1.90–1.87 (2H, m, cyclohexyl), 1.73 (2H, sextet, $J = 7.3$ Hz, $SCH_2\underline{CH_2}$), 1.69–1.10 (8H, m, cyclohexyl), 0.99 (3H, t, $J = 7.3$ Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.6, 153.1, 149.5, 138.4, 117.2, 87.52, 85.6, 73.3, 70.5, 61.6, 49.0, 32.4, 32.2 (2C), 25.2, 25.0 (2C), 23.0, 13.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{30}N_5O_4S$: 424.2013; found: 424.2021.

4.3.6. N^6-cyclohexyl-2-isopropylthioadenosine (**5a₆**)

Compound **4d** was allowed to react with cyclohexylamine for 9 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5a₆**. Yield: 77%, mp 136–138 °C; IR (KBr): 3429,

3127, 3125, 1604, 1399, 1088, 896, 784, 627 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.20 (1H, s, H-8), 7.72 (1H, br s, NH), 5.80 (1H, d, J = 5.8 Hz, H-1′), 5.39 (1H, d, J = 6.1 Hz, OH), 5.15 (1H, d, J = 4.7 Hz, OH), 5.07 (1H, dd, J = 4.5, 4.5 Hz, OH), 4.57 (1H, ddd, J = 5.6, 5.8, 6.1 Hz, H-2′), 4.00 (1H, ddd, J = 3.7, 4.7, 5.6 Hz, H-3′), 4.01 (1H, br s, NCH), 3.91 (1H, ddd, J = 3.5, 4.7, 6.1 Hz, H-4′), 3.84 (1H, heptet, J = 6.1 Hz, SCH), 3.63 (1H, ddd, J = 4.5, 4.7, 11.8 Hz, H-5′a), 3.52 (1H, J = 4.5, 6.1, 11.8 Hz, H-5′b), 1.88–1.60 (6H, m, cyclohexyl), 1.37 (6H, d, J = 6.1 Hz, SCH(CH_3)$_2$), 1.32–1.11 (4H, m, cyclohexyl); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.8, 153.2, 149.6, 138.5, 117.2, 87.5, 85.6, 73.4, 70.6, 61.7, 49.1, 35.4, 32.3 (2C), 25.2, 25.0 (2C), 23.0 (2C); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{30}N_5O_4S$: 424.2013; found: 424.2021.

4.3.7. 2-Butylthio-N^6-cyclohexyladenosine (**5a$_7$**)

Compound **4e** was allowed to react with cyclohexylamine for 9 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5a$_7$**. Yield: 88%, mp 138–140 °C; IR (KBr): 3317, 3205, 1610, 1400, 1092 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.20 (1H, s, H-8), 7.72 (1H, br s, NH), 5.80 (1H, d, J = 5.6 Hz, H-1′), 5.40 (1H, d, J = 5.8 Hz, OH), 5.15 (1H, d, J = 4.5 Hz, OH), 5.08 (1H, dd, J = 4.1, 4.3 Hz, OH), 4.57 (1H, ddd, J = 4.9, 5.6, 5.8 Hz, H-2′), 4.12 (1H, ddd, J = 3.2, 4.5, 4.9 Hz, H-3′), 4.03 (1H, br s, NCH), 3.91 (1H, ddd, J = 3.2, 4.6, 6.0 Hz, H-4′), 3.64 (1H, J = 4.3, 4.6, 11.9 Hz, H-5′a), 3.53 (1H, J = 4.1, 6.0, 11.9 Hz, H-5′b), 3.06 (2H, t, J = 7.3 Hz, SCH_2), 1.89–1.74 (4H, m, cyclohexyl), 1.65 (2H, quint, J = 7.3 Hz, SCH_2CH_2), 1.43 (2H, sextet, J = 7.3 Hz, $SCH_2CH_2CH_2$), 1.38–1.11 (6H, m, cyclohexyl), 0.92 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.7, 153.2, 149.5, 138.4, 117.2, 87.5, 85.6, 73.3, 70.5, 61.6, 49.0, 32.2, 31.9 (2C), 30.1, 25.2, 25.0 (2C), 21.7, 13.6; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{32}N_5O_4S$: 438.2170; found: 438.2177.

4.3.8. N^6,N^6-dibutyl-2-ethylthioadenosine (**5a$_8$**)

Compound **4b** was allowed to react with dibutylamine for 14 h according to the general procedure. The product was purified by flash column chromatography (gradient elution separation with EtOAc/petroleum ether, 1:10–1:1, v/v), and followed by recrystallization from hexane to give **5a$_8$**. Yield: 58%, mp 88–90 °C; IR (KBr): 3414, 3138, 1575, 1396, 1229 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.24 (1H, s, H-8), 5.82 (1H, d, J = 6.0 Hz, H-1′), 5.41 (1H, d, J = 6.2 Hz, OH), 5.17 (1H, d, J = 4.8 Hz, OH), 5.07 (1H, dd, J = 4.0, 4.6 Hz, OH), 4.55 (1H, ddd, J = 5.3, 6.0, 6.2 Hz, H-2′), 4.13 (1H, ddd, J = 3.4, 4.9, 5.3 Hz, H-3′), 4.11–4.01 (2H, m, 2NH), 3.92 (1H, ddd, J = 3.4, 4.6, 6.2 Hz, H-4′), 3.67 (1H, ddd, J = 4.6, 4.6, 11.8 Hz, H-5′a), 3.65–3.55 (2H, m, 2NHH), 3.54 (1H, ddd, J = 4.0, 6.2, 11.8 Hz, H-5′b), 3.10 (1H, dq, J = 13.5, 7.3 Hz, SCHH), 3.06 (1H, dq, J = 13.5, 7.3 Hz, SCHH), 1.62 (4H, quint, J = 7.4 Hz, $2NCH_2CH_2$), 1.34 (4H, sextet, J = 7.4 Hz, $2NCH_2CH_2CH_2$), 1.33 (3H, t, J = 7.3 Hz, SCH_2CH_3), 0.92 (6H, t, J = 7.4 Hz, $2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.4, 153.2, 150.1, 137.8, 118.8, 90.5, 86.8, 72.6, 72.5, 63.3, 49.3, 48.4, 31.1, 29.6, 25.4, 20.0 (2C), 14.7, 13.9 (2C); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{34}N_5O_5S$:440.2326; found: 440.2334.

4.3.9. N^6-benzyl-2-methylthioadenosine (**5b$_1$**) [28]

Compound **4a** was allowed to react with benzylamine for 8 h according to the general procedure. The product was purified by flash column chromatography (gradient elution separation with MeOH/EtOAc, 1:50–1:25, v/v), and followed by recrystallization from EtOAc to give **5b$_1$**. Yield: 83%, mp 180–182 °C; IR (KBr): 3442, 3138, 2986, 1653, 1140, 864, 787, 620 cm^{-1}; ^1H NMR: (300 MHz, DMSO-d_6): δ 8.55 (1H, br s, NH), 8.25 (1H, s, H-8), 7.33–7.27 (4H, m, ArH), 7.22 (1H, t, J = 7.0 Hz, ArH), 5.83 (1H, d, J = 6.0 Hz, H-1′), 5.44 (1H, d, J = 6.2 Hz, OH), 5.20 (1H, d, J = 4.9 Hz, OH), 5.06 (1H, dd, J = 4.5, 4.7 Hz, OH), 4.67 (2H, br s, NCH_2), 4.59 (1H, ddd, J = 5.2, 6.0, 6.2 Hz, H-2′), 4.14 (1H, ddd, J = 3.3, 4.9, 5.2 Hz, H-3′), 3.91 (1H, ddd, J = 3.3, 4.8, 5.3 Hz, H-4′), 3.65 (1H, ddd, J = 4.7, 5.3, 12.0 Hz, H-5′a), 3.53 (1H, ddd, J = 4.5, 4.8, 12.0 Hz, H-5′b), 2.43 (3H, s, SCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.2, 153.6, 149.6, 140.0, 138.9, 128.3, 127.3, 126.7, 117.2, 87.4, 85.6, 73.4, 70.6, 61.6, 43.1, 13.9.

4.3.10. N^6-benzyl-2-ethylthioadenosine (**5b$_2$**)

Compound **4b** was allowed to react with benzylamine for 8 h according to the general procedure. The product was purified by flash column chromatography (gradient elution separation with MeOH/EtOAc, 1:50–1:25, v/v), and followed by recrystallization from EtOAc to give **5b$_2$**. Yield: 82%, mp 172–174 °C; IR (KBr): 3414, 3132, 1614, 1396, 854, 784, 694 cm^{-1}, ^1H NMR: (600 MHz, DMSO-d_6): δ 8.51 (1H, br s, NH), 8.24 (1H, s, H-8), 7.33–7.28 (4H, m, ArH), 7.21 (1H, t, J = 7.0 Hz, ArH), 5.82 (1H, d, J = 5.9 Hz, H-1′), 5.39 (1H, d, J = 6.1 Hz, OH), 5.15 (1H, d, J = 4.7 Hz, OH), 5.04 (1H, dd, J = 4.2, 4.5 Hz, OH), 4.66 (2H, br s, NCH_2), 4.58 (1H, ddd, J = 5.6, 5.9, 6.1 Hz, H-2′), 4.12 (1H, ddd, J = 3.4, 4.7, 5.6 Hz, H-3′), 3.91 (1H, ddd, J = 3.4, 4.7, 5.7 Hz, H-4′), 3.63 (1H, ddd, J = 4.2, 4.7, 12.0 Hz, H-5′a), 3.53 (1H, ddd, J = 4.5, 5.7, 12.0 Hz, H-5′b), 3.00 (2H, q, J = 7.3 Hz, SCH_2), 1.28 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.7, 153.8, 149.7, 140.0, 138.8, 128.2, 127.1, 126.7, 117.3, 87.5, 85.6, 73.4, 70.6, 61.6, 43.1, 24.7, 15.0; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{24}N_5O_4S$: 418.1544; found: 418.1552.

4.3.11. N^6-benzyl-2-propylthioadenosine (**5b$_3$**)

Compound **4c** was allowed to react with benzylamine for 8 h according to the general procedure. The product was purified by flash column chromatography (gradient elution separation with MeOH/EtOAc, 1:50–1:25, v/v), and followed by recrystallization from EtOAc to give **5b$_3$**. Yield: 79%, mp 168–170 °C; IR (KBr): 3420, 3196, 1613, 1396, 851, 781, 640 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 8.52 (1H, br s, NH), 8.24 (1H, s, H-8), 7.28–7.31 (4H, m, ArH), 7.20–7.22 (1H, t, J = 7.0 Hz, ArH), 5.81 (1H, d, J = 5.7 Hz, H-1′), 5.40 (1H, d, J = 6.0 Hz, OH), 5.15 (1H, d, J = 4.5 Hz, OH), 5.04 (1H, dd, J = 4.3, 4.5 Hz, OH), 4.67 (2H, br s, NCH_2), 4.59 (1H, ddd, J = 5.4, 5.7, 6.0 Hz, H-2′), 4.13 (1H, ddd, J = 3.2, 4.5, 5.4 Hz, H-3′), 3.92 (1H, ddd, J = 3.2, 4.3, 5.8 Hz, H-4′), 3.64 (1H, ddd, J = 4.3, 4.3, 11.7 Hz, H-5′a), 3.53 (1H, ddd, J = 4.5, 5.8, 11.7 Hz, H-5′b), 2.98 (2H, t, J = 7.3 Hz, SCH_2), 1.59 (2H, sextet, J = 7.3 Hz, SCH_2CH_2), 0.89 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.7, 153.7, 149.6, 139.9, 138.8, 128.2, 127.0, 126.6, 117.3, 87.5, 85.5, 73.3, 70.5, 61.6, 43.0, 32.3, 22.7, 13.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{26}N_5O_4S$: 432.1700; found: 432.1708.

4.3.12. N^6-benzyl-2-butylthioadenosine (**5b$_4$**)

Compound **4e** was allowed to react with benzylamine for 8 h according to the general procedure. The product was purified by flash column chromatography (gradient elution separation with MeOH/EtOAc, 1:50–1:25, v/v), and followed by recrystallization from EtOAc to give **5b$_4$**. Yield: 80%, mp 170–172 °C; IR (KBr): 3372, 3308, 3141, 1752, 1614, 1396, 845, 748, 633 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 8.50 (1H, br s, NH), 8.24 (1H, s, H-8), 7.28–7.31 (4H, m, ArH), 7.21 (1H, t, J = 7.0 Hz, ArH), 5.81 (1H, d, J = 5.9 Hz, H-1′), 5.39 (1H, d, J = 6.0 Hz, OH), 5.14 (1H, d, J = 4.7 Hz, OH), 5.04 (1H, dd, J = 4.3, 4.5 Hz, OH), 4.67 (2H, br s, NCH_2), 4.59 (1H, ddd, J = 5.5, 5.9, 6.1 Hz, H-2′), 4.13 (1H, ddd, J = 3.6, 4.7, 5.5 Hz, H-3′), 3.92 (1H, ddd, J = 3.6, 4.6, 5.4 Hz, H-4′), 3.64 (1H, ddd, J = 4.3, 4.6, 11.8 Hz, H-5′a), 3.53 (1H, ddd, J = 4.5, 5.4, 11.8 Hz, H-5′b), 3.00 (2H, t, J = 7.3 Hz, SCH_2), 1.56 (2H, quint, J = 7.3 Hz, SCH_2CH_2), 1.32 (2H, sextet, J = 7.3 Hz, $SCH_2CH_2CH_2$), 0.89 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.8, 153.7, 149.6, 139.9, 138.8, 128.2, 127.0, 126.6, 117.3, 87.5, 85.6, 73.3, 70.5, 61.6, 42.9, 31.5, 30.1, 21.5, 13.5; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{28}N_5O_4S$: 446.1857; found: 446.1865.

*4.3.13. N^6-(4-methylbenzyl)-2-methylthioadenosine (**5b$_5$**) [29]*

Compound **4a** was allowed to react with 4-methylbenzylamine for 9 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_5$**. Yield: 83%, mp 188–190 °C; IR (KBr): 3445, 3333, 2986, 1616, 1392, 1126, 858, 787, 618 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.49 (1H, br s, NH), 8.24 (1H, s, H-8), 7.22 (2H, d, J = 8.0 Hz, ArH), 7.10 (2H, d, J = 8.0 Hz, ArH), 5.83 (1H, d, J = 5.9 Hz, H-1′), 5.43 (1H, d, J = 6.2 Hz, OH), 5.19 (1H, d, J = 4.8 Hz, OH), 5.05 (1H, dd, J = 5.4, 6.0 Hz, OH), 4.61 (2H, br s, NC$\underline{H}_2$), 4.58 (1H, ddd, J = 5.9, 6.1, 6.2 Hz, H-2′), 4.13 (1H, ddd, J = 3.4, 4.8, 6.1 Hz, H-3′), 3.91 (1H, ddd, J = 3.4, 4.4, 4.6 Hz, H-4′), 3.66 (1H, ddd, J = 4.6, 5.4, 11.9 Hz, H-5a′), 3.54 (1H, ddd, J = 4.4, 6.0, 11.9 Hz, H-5b′), 2.44 (3H, s, CH_3), 2.25 (3H, s, Ph$\underline{C}H_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.2, 153.7, 149.6, 138.8, 136.9, 135.7, 128.8, 127.3, 117.3, 87.4, 85.6, 73.4, 70.6, 61.6, 42.8, 20.7, 13.9.

*4.3.14. 2-Ethylthio-N^6-(4-Methylbenzyl)adenosine (**5b$_6$**)*

Compound **4b** was allowed to react with 4-methylbenzylamine for 9 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_6$**. Yield: 79%, mp 184–186 °C; IR (KBr): 3411, 3321, 3141, 1614, 1345, 854, 776, 627 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.48 (1H, br s, NH), 8.23 (1H, s, H-8), 7.21 (2H, d, J = 7.9 Hz, ArH), 7.10 (2H, d, J = 7.9 Hz, ArH), 5.81 (1H, d, J = 5.9 Hz, H-1′), 5.43 (1H, d, J = 6.1 Hz, OH), 5.18 (1H, d, J = 4.8 Hz, OH), 5.07 (1H, dd, J = 4.9, 5.2 Hz, OH), 4.61 (2H, br s, NC$\underline{H}_2$), 4.58 (1H, ddd, J = 5.6, 5.9, 6.1 Hz, H-2′), 4.13 (1H, ddd, J = 3.5, 4.8, 5.6 Hz, H-3′), 3.91 (1H, ddd, J = 3.2, 3.9, 5.6 Hz, H-4′), 3.63 (1H, ddd, J = 3.9, 4.9, 11.8 Hz, H-5a′), 3.52 (1H, ddd, J = 5.2, 5.6, 11.8 Hz, H-5b′), 3.01 (2H, q, J = 7.3 Hz, SCH_2), 2.25 (3H, s, Ph$\underline{C}H_3$), 1.24 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.8, 153.8, 149.7, 138.9, 136.9, 135.7, 128.8, 127.2, 117.3, 87.6, 85.6, 73.4, 70.6, 61.7, 42.9, 24.8, 20.7, 15.0; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{26}N_5O_4S$: 432.1700; found: 432.1708.

*4.3.15. N^6-(4-methoxybenzyl)-2-methylthioadenosine (**5b$_7$**) [29]*

Compound **4a** was allowed to react with 4-methoxybenzylamine for 11 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_7$**. Yield: 80%, mp 200–202 °C; IR (KBr): 3447, 3324, 2984, 1616, 1392, 1125, 859, 785, 618 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.48 (1H, br s, NH), 8.24 (1H, s, H-8), 7.27 (2H, d, J = 8.6 Hz, ArH), 6.86 (2H, d, J = 8.6 Hz, ArH), 5.82 (1H, d, J = 6.0 Hz, H-1′), 5.43 (1H, d, J = 6.0 Hz, OH), 5.19 (1H, d, J = 5.5 Hz, OH), 5.05 (1H, dd, J = 5.7, 5.8 Hz, OH), 4.60 (2H, br s, NC$\underline{H}_2$), 4.58 (1H, ddd, J = 5.9, 6.0, 6.0 Hz, H-2′), 4.14 (1H, ddd, J = 4.0, 5.5, 5.9 Hz, H-3′), 3.91 (1H, ddd, J = 3.8, 4.0, 4.5 Hz, H-4′), 3.70 (3H, s, OCH_3), 3.60 (1H, ddd, J = 4.5, 5.7, 11.8 Hz, H-5a′), 3.53 (1H, ddd, J = 4.0, 5.8, 11.8 Hz, H-5b′), 2.46 (3H, s, SCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.2, 158.2, 153.6, 149.6, 138.8, 131.9, 128.7, 117.3, 113.6, 87.4, 85.6, 73.4, 70.6, 61.6, 55.0, 42.5, 14.0.

*4.3.16. 2-Ethylthio-N^6-(4-methoxybenzyl)adenosine (**5b$_8$**)*

Compound **4b** was allowed to react with 4-methoxybenzylamine for 11 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_8$**. Yield: 80%, mp 164–166 °C; IR (KBr): 3433, 3324, 3135, 1617, 1402, 858, 778, 675 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.48 (1H, br s, NH), 8.23 (1H, s, H-8), 7.21 (2H, d, J = 7.9 Hz, ArH), 7.09 (2H, d, J = 7.9 Hz, ArH), 5.81 (1H, d, J = 5.9 Hz, H-1′), 5.40 (1H, d, J = 6.0 Hz, OH), 5.21 (1H, d, J = 4.7 Hz, OH), 5.10 (1H, dd, J = 5.3, 5.4 Hz, OH), 4.63 (2H, br s, NC$\underline{H}_2$), 4.60 (1H, ddd, J = 5.2, 5.9, 6.1 Hz, H-2′), 4.16 (1H, ddd, J = 3.4, 4.7, 5.2 Hz, H-3′), 3.94 (1H, ddd, J = 3.4, 4.4, 4.6 Hz, H-4′), 3.70 (3H, s, OCH_3), 3.64 (1H, ddd, J = 4.4, 5.3, 11.9 Hz, H-5a′), 3.55 (1H, ddd, J = 4.6, 5.4, 11.9 Hz, H-5b′), 3.04 (2H, q, J = 7.3 Hz, SCH_2), 1.26 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.7, 158.1, 153.8, 149.6, 138.7, 131.9, 128.5, 117.3, 113.6, 87.5, 85.6, 73.4, 70.6, 61.6, 55.0, 42.5, 24.7, 15.0; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{26}N_5O_5S$: 448.1649; found: 448.1648.

*4.3.17. N^6-(4-methoxybenzyl)-2-propylthioadenosine (**5b$_9$**)*

Compound **4c** was allowed to react with 4-methoxybenzylamine for 11 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_9$**. Yield: 81%, mp 152–154 °C; IR (KBr): 3436, 3333, 3119, 1610, 1399, 810, 781, 672 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.46 (1H, br s, NH), 8.25 (1H, s, H-8), 7.26 (2H, d, J = 8.6 Hz, ArH), 6.86 (2H, d, J = 8.6 Hz, ArH), 5.84 (1H, d, J = 6.0 Hz, H-1′), 5.47 (1H, d, J = 6.1 Hz, OH), 5.22 (1H, d, J = 4.8 Hz, OH), 5.14 (1H, dd, J = 5.2, 5.7 Hz, OH), 4.61 (2H, br s, NC$\underline{H}_2$), 4.58 (1H, ddd, J = 5.8, 6.0, 6.1 Hz, H-2′), 4.16 (1H, ddd, J = 3.4, 4.8, 5.8 Hz, H-3′), 3.95 (1H, ddd, J = 3.4, 3.9, 4.6 Hz, H-4′), 3.70 (3H, s, OCH_3), 3.65 (1H, ddd, J = 4.6, 5.2, 11.9 Hz, H-5a′), 3.57 (1H, ddd, J = 3.9, 5.7, 11.9 Hz, H-5b′), 3.02 (2H, t, J = 7.3 Hz, SCH_2), 1.63 (2H, sextet, J = 7.3 Hz, $SCH_2C\underline{H}_2$), 0.92 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.9, 158.2, 153.8, 149.7, 138.9, 131.9, 128.5, 117.4, 113.7, 87.6, 85.7, 73.4, 70.6, 61.7, 55.1, 42.5, 32.4, 22.8, 13.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{28}N_5O_5S$: 462.1806; found: 462.1812.

*4.3.18. 2-Methylthio-N^6-phenethyladenosine (**5b$_{10}$**)*

Compound **4a** was allowed to react with phenethylamine for 9 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{10}$**. Yield: 85%, mp 156–158 °C; IR (KBr): 3349, 3132, 2920, 1613, 1399, 858, 781, 634 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.22 (1H, s, H-8), 8.02 (1H, br s, NH), 7.30–7.25 (3H, m, ArH), 7.20–7.17 (2H, m, ArH), 5.83 (1H, d, J = 5.6 Hz, H-1′), 5.45 (1H, d, J = 5.5 Hz, OH), 5.20 (1H, d, J = 4.2 Hz, OH), 5.08 (1H, dd, J = 5.0, 5.4 Hz, OH), 4.60 (1H, ddd, J = 5.4, 5.5, 5.6 Hz, H-2′), 4.14 (1H, ddd, J = 3.4, 4.2, 4.6 Hz, H-3′), 3.92 (1H, ddd, J = 3.4, 4.5, 4.9 Hz, H-4′), 3.78–3.65 (2H, m, NC$\underline{H}_2$), 3.63 (1H, ddd, J = 4.6, 5.0, 11.9 Hz, H-5′a), 3.54 (1H, ddd, J = 4.2, 5.4, 11.9 Hz, H-5′b), 2.90 (2H, t, J = 7.6 Hz, $NCH_2C\underline{H}_2$), 2.50 (3H, s, SCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.2, 153.8, 149.5, 139.8, 138.6, 128.6, 128.3, 126.1, 117.2, 87.3, 85.5, 73.4, 70.5, 61.6, 41.4, 35.0, 13.9; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{24}N_5O_4S$: 418.1544; found: 418.1552.

*4.3.19. 2-Ethylthio-N^6-phenethyladenosine (**5b$_{11}$**)*

Compound **4b** was allowed to react with phenethylamine for 9 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{11}$**. Yield: 84%, mp 130–132 °C; IR (KBr): 3426, 3330, 3119, 1612, 1399, 864, 778, 701 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (1H, s, H-8), 8.02 (1H, br s, NH), 7.32–7.18 (5H, m, ArH), 5.81 (1H, d, J = 5.7 Hz, H-1′), 5.42 (1H, d, J = 6.1 Hz, OH), 5.17 (1H, d, J = 4.8 Hz, OH), 5.07 (1H, dd, J = 5.0, 5.4 Hz, OH), 4.58 (1H, ddd, J = 5.6, 5.7, 6.1 Hz, H-2′), 4.13 (1H, ddd, J = 3.5, 4.8, 5.6 Hz, H-3′), 3.92 (1H, ddd, J = 3.5, 4.3, 4.8 Hz, H-4′), 3.75–3.65 (2H, m, NC$\underline{H}_2$), 3.63 (1H, ddd, J = 4.8, 5.0, 11.9 Hz, H-5′a), 3.53 (1H, ddd, J = 4.3, 5.4, 11.9 Hz, H-5′b), 3.11 (2H, q, J = 7.3 Hz, SCH_2), 2.91 (2H, t, J = 7.0 Hz, $NCH_2C\underline{H}_2$), 1.34 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.7, 153.8, 149.6, 139.4, 138.6, 128.6, 128.3, 126.1, 117.3, 87.4, 85.6, 73.4, 70.5, 61.6, 41.4, 35.1, 24.7, 15.1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{26}N_5O_4S$: 432.1700; found: 432.1706.

*4.3.20. N^6-phenethyl-2-propylthioadenosine (**5b$_{12}$**)*

Compound **4c** was allowed to react with phenethylamine for 9 h according to the general procedure. The product was purified by

flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{12}$**. Yield: 80%, mp 110–112 °C; IR (KBr): 3430, 3330, 3129, 1612, 1391, 906, 738, 697 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.22 (1H, s, H-8), 8.03 (1H, br s, NH), 7.32–7.26 (3H, m, ArH), 7.24–7.17 (2H, m, ArH), 5.82 (1H, d, J = 5.9 Hz, H-1′), 5.44 (1H, d, J = 6.2 Hz, OH), 5.18 (1H, d, J = 4.8 Hz, OH), 5.10 (1H, dd, J = 5.2, 5.5 Hz, OH), 4.59 (1H, ddd, J = 5.4, 5.9, 6.2 Hz, H-2′), 4.14 (1H, ddd, J = 3.5, 4.2, 4.8 Hz, H-3′), 3.93 (1H, ddd, J = 3.5, 4.6, 5.2 Hz, H-4′), 3.76–3.65 (2H, m, NCH$_2$), 3.63 (1H, ddd, J = 4.6, 5.2, 11.9 Hz, H-5′a), 3.54 (1H, ddd, J = 4.2, 5.5, 11.9 Hz, H-5′b), 3.09 (2H, t, J = 7.3 Hz, SCH$_2$), 2.91 (2H, t, J = 7.0 Hz, NCH$_2$CH$_2$), 1.70 (2H, sextet, J = 7.3 Hz, SCH$_2$CH$_2$), 0.97 (3H, t, J = 7.3 Hz, CH$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.8, 153.8, 149.5, 139.4, 138.6, 128.6, 128.3, 126.1, 117.3, 87.4, 85.5, 73.3, 70.5, 61.6, 41.4, 35.0, 32.4, 22.8, 13.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{28}N_5O_4S$: 446.1857; found: 446.1865.

4.3.21. 2-Butylthio-N^6-phenethyladenosine (**5b$_{13}$**)

Compound **4e** was allowed to react with phenethylamine for 9 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{13}$**. Yield: 81%, mp 124–126 °C; IR (KBr): 3340, 3112, 2927, 1613, 1348, 784, 711, 632 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (1H, s, H-8), 8.01 (1H, br s, NH), 7.31–7.26 (3H, m, ArH), 7.25–7.18 (2H, m, ArH), 5.80 (1H, d, J = 5.6 Hz, H-1′), 5.41 (1H, d, J = 6.1 Hz, OH), 5.16 (1H, d, J = 4.7 Hz, OH), 5.07 (1H, dd, J = 5.7, 5.8 Hz, OH), 4.57 (1H, ddd, J = 5.6, 5.7, 6.1 Hz, H-2′), 4.12 (1H, ddd, J = 3.7, 4.7, 5.7 Hz, H-3′), 3.92 (1H, ddd, J = 3.7, 4.6, 5.8 Hz, H-4′), 3.76–3.65 (2H, m, NCH$_2$), 3.61 (1H, ddd, J = 4.6, 5.7, 11.4 Hz, H-5′a), 3.53 (1H, ddd, J = 5.0, 5.8, 11.4 Hz, H-5′b), 3.10 (2H, t, J = 7.3 Hz, SCH$_2$), 2.91 (2H, t, J = 7.5 Hz, NCH$_2$CH$_2$), 1.66 (2H, quint, J = 7.3 Hz, SCH$_2$CH$_2$), 1.41 (2H, sextet, J = 7.3 Hz, SCH$_2$CH$_2$CH$_2$), 0.89 (3H, t, J = 7.3 Hz, CH$_3$); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.8, 153.8, 149.5, 139.4, 138.6, 128.6, 128.3, 126.1, 117.3, 87.5, 85.6, 73.4, 70.6, 61.6, 41.4, 35.1, 31.6, 30.2, 21.6, 13.6; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{30}N_5O_4S$: 460.2013; found: 460.2021.

4.3.22. N^6-phenethyl-2-phenylthioadenosine (**5b$_{14}$**)

Compound **4f** was allowed to react with phenethylamine for 15 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{14}$**. Yield: 75%, mp 134–136 °C; IR (KBr): 3444, 3112, 2991, 1635, 1392, 1137, 861, 790, 617 cm^{-1}; ^{1}H NMR(600 MHz, DMSO-d_6): δ 8.22 (1H, s, H-8), 8.02 (1H, br s, NH), 7.63–7.62 (2H, m, ArH), 7.42–7.41 (3H, m, ArH), 7.26 (2H, t, J = 7.3 Hz, ArH), 7.18 (1H, t, J = 7.2 Hz, ArH), 7.00 (2H, d, J = 7.2 Hz, ArH), 5.76 (1H, d, J = 5.8 Hz, H-1′), 5.39 (1H, d, J = 6.0 Hz, OH), 5.11 (1H, d, J = 4.3 Hz, OH), 5.01 (1H, dd, J = 4.9, 5.0 Hz, OH), 4.56 (1H, ddd, J = 5.7, 5.8, 6.0 Hz, H-2′), 4.03 (1H, br s, H-3′), 3.89 (1H, br s, H-4′), 3.55 (1H, ddd, J = 4.3, 4.9, 11.8 Hz, H-5′a), 3.45 (1H, ddd, J = 5.0, 5.5, 11.8 Hz, H-5′b), 3.42–3.37 (2H, m, NCH$_2$), 2.67 (2H, t, J = 7.2 Hz, NCH$_2$CH$_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.4, 153.9, 149.4, 139.3, 139.1, 135.0, 130.7, 128.9, 128.7, 128.2, 126.0, 117.8, 87.6, 85.7, 73.2, 70.5, 61.6, 41.1, 34.9; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{24}H_{26}N_5O_4S$: 480.1700; found: 480.1715.

4.3.23. 2-Benzylthio-N^6-phenethyladenosine (**5b$_{15}$**)

Compound **4g** was allowed to react with phenethylamine for 12 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{15}$**. Yield: 78%, mp 262–264 °C; IR (KBr): 3436, 3112, 2991, 1635, 1397, 1139, 858, 778, 619 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.25 (1H, s, H-8), 8.10 (1H, br s, NH), 7.43 (2H, d, J = 7.1 Hz, ArH), 7.32–7.18 (8H, m, ArH), 5.85 (1H, d, J = 5.8 Hz, H-1′), 5.45 (1H, d, J = 6.2 Hz, OH), 5.22 (1H, d, J = 4.9 Hz, OH), 5.10 (1H, dd, J = 5.3, 5.8 Hz, OH), 4.55 (1H, ddd, J = 5.3, 5.8, 6.2 Hz, H-2′), 4.43 (2H, s, SCH$_2$), 4.12 (1H, ddd, J = 3.5, 4.1, 4.9 Hz, H-3′), 3.93 (1H, ddd, J = 3.5, 4.1, 4.7 Hz, H-4′), 3.75–3.65 (2H, m, NCH$_2$), 3.63 (1H, ddd, J = 4.9, 5.3, 11.8 Hz, H-5′a), 3.54 (1H, ddd, J = 4.1, 5.8, 11.8 Hz, H-5′b), 2.89 (2H, t, J = 7.0 Hz, NCH$_2$CH$_2$); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.3, 153.8, 149.4, 139.4, 138.6, 128.8, 128.6, 128.3, 126.8, 126.1, 117.4, 87.3, 85.5, 73.6, 70.5, 61.5, 41.5, 35.0, 34.5; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{25}H_{28}N_5O_4S$: 494.1857; found: 494.1860.

4.3.24. N^6-(4-methoxyphenethyl)-2-methylthioadenosine (**5b$_{16}$**)

Compound **4a** was allowed to react with 4-methoxyphenethylamine for 12 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{16}$**. Yield: 82%, mp 152–154 °C; IR (KBr): 3433, 3327, 3129, 1611, 1400, 858, 784, 631 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (1H, s, H-8), 7.98 (1H, br s, NH), 7.16 (2H, d, J = 7.9 Hz, ArH), 6.85 (2H, d, J = 8.5 Hz, ArH), 5.83 (1H, d, J = 5.8 Hz, H-1′), 5.42 (1H, d, J = 6.2 Hz, OH), 5.18 (1H, d, J = 4.8 Hz, OH), 5.05 (1H, dd, J = 5.5, 6.0 Hz, OH), 4.60 (1H, ddd, J = 5.4, 5.8, 6.2 Hz, H-2′), 4.14 (1H, ddd, J = 3.5, 4.8, 5.4 Hz, H-3′), 3.92 (1H, ddd, J = 3.5, 4.3, 4.6 Hz, H-4′), 3.71 (3H, s, OCH$_3$), 3.65 (1H, ddd, J = 4.6, 5.5, 11.8 Hz, H-5′a), 3.64–3.58 (2H, m, NCH$_2$), 3.54 (1H, ddd, J = 4.3, 6.0, 11.8 Hz, H-5′b), 2.85 (2H, t, J = 7.4 Hz, NCH$_2$CH$_2$), 2.51 (3H, s, SCH$_3$); ^{13}C NMR (50 MHz, DMSO-d_6): δ 164.3, 157.7, 153.8, 149.5, 138.7, 131.4, 129.7, 117.3, 113.9, 87.5, 85.6, 73.5, 70.6, 61.7, 55.0, 41.8, 34.2, 14.0; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{26}N_5O_5S$: 448.1649; found: 448.1655.

4.3.25. 2-Ethylthio-N^6-(4-methoxyphenethyl)adenosine (**5b$_{17}$**)

Compound **4b** was allowed to react with 4-methoxyphenethylamine for 12 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{17}$**. Yield: 81%, mp 140–142 °C; IR (KBr): 3340, 3119, 2920, 1614, 1399, 793, 787, 627 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (1H, s, H-8), 7.99 (1H, br s, NH), 7.15 (2H, d, J = 8.0 Hz, ArH), 6.86 (2H, d, J = 8.6 Hz, ArH), 5.81 (1H, d, J = 5.9 Hz, H-1′), 5.42 (1H, d, J = 6.2 Hz, OH), 5.22 (1H, d, J = 4.8 Hz, OH), 5.18 (1H, dd, J = 5.5, 6.2 Hz, OH), 4.58 (1H, ddd, J = 5.4, 5.9, 6.2 Hz, H-2′), 4.13 (1H, ddd, J = 3.4, 4.8, 5.4 Hz, H-3′), 3.92 (1H, ddd, J = 3.4, 4.2, 4.6 Hz, H-4′), 3.70 (3H, s, OCH$_3$), 3.65 (1H, ddd, J = 4.6, 5.5, 11.9 Hz, H-5′a), 3.63–3.57 (2H, m, NHCH$_2$), 3.54 (1H, ddd, J = 4.2, 6.2, 11.9 Hz, H-5′b), 3.11 (2H, q, J = 7.3 Hz, SCH$_2$), 2.84 (2H, t, J = 7.1 Hz, NCH$_2$CH$_2$), 1.34 (3H, t, J = 7.3 Hz, CH$_3$); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.7, 157.7, 153.9, 149.5, 138.7, 131.3, 129.6, 117.4, 113.8, 87.6, 85.7, 73.5, 70.6, 61.7, 55.0, 41.8, 34.3, 24.8, 15.1; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{28}N_5O_5S$: 462.1806; found: 462.1810.

4.3.26. N^6-(4-methoxyphenethyl)-2-propylthioadenosine (**5b$_{18}$**)

Compound **4c** was allowed to react with 4-methoxyphenethylamine for 12 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{18}$**. Yield: 83%, mp 170–172 °C; IR (KBr): 3430, 3344, 3133, 1617, 1400, 781, 697, 633 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.21 (1H, s, H-8), 8.00 (1H, br s, NH), 7.15 (2H, d, J = 8.0 Hz, ArH), 6.85 (2H, d, J = 8.0 Hz, ArH), 5.81 (1H, d, J = 5.8 Hz, H-1′), 5.42 (1H, d, J = 5.8 Hz, OH), 5.17 (1H, d, J = 4.6 Hz, OH), 5.08 (1H, br s, OH), 4.59 (1H, ddd, J = 5.3, 5.8, 5.8 Hz, H-2′), 4.13 (1H, br s, H-3′), 3.92 (1H, ddd, J = 3.5, 4.6, 5.6 Hz, H-4′), 3.71 (3H, s, OCH$_3$), 3.64–3.48 (4H, m, NCH$_2$ + H-5′a + H-5′b), 3.09 (2H, t, J = 7.3 Hz, SCH$_2$), 2.84 (2H, t, J = 7.5 Hz, NCH$_2$CH$_2$), 1.70 (2H, sextet, J = 7.3 Hz, SCH$_2$CH$_2$), 0.98 (3H, t, J = 7.3 Hz, CH$_3$); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.8, 157.7, 153.7, 149.4, 138.6, 131.3, 129.5, 117.2, 113.8, 87.4, 85.6, 73.3, 70.5, 61.6, 54.9, 41.6, 34.1, 32.4, 22.7, 13.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{30}N_5O_5S$: 476.1962; found: 476.1960.

*4.3.27. 2-Butylthio-N^6-(4-methoxyphenethyl)adenosine (**5b$_{19}$**)*

Compound **4e** was allowed to react with 4-methoxyphenethylamine for 12 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{19}$**. Yield: 80%, mp 122–124 °C; IR (KBr): 3433, 3334, 3122, 1604, 1399, 822, 781, 701 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (1H, s, H-8), 7.98 (1H, br s, NH), 7.15 (2H, d, J = 8.0 Hz, ArH), 6.85 (2H, d, J = 8.2 Hz, ArH), 5.80 (1H, d, J = 5.8 Hz, H-1′), 5.41 (1H, d, J = 6.1 Hz, OH), 5.16 (1H, d, J = 4.8 Hz, OH), 5.07 (1H, dd, J = 4.8, 5.2 Hz, OH), 4.58 (1H, ddd, J = 5.2, 5.8, 6.1 Hz, H-2′), 4.13 (1H, ddd, J = 3.8, 4.8, 5.2 Hz, H-3′), 3.92 (1H, ddd, J = 3.8, 4.3, 4.6 Hz, H-4′), 3.71 (3H, s, OCH_3), 3.66 (1H, ddd, J = 4.3, 4.8, 11.1 Hz, H-5′a), 3.63–3.58 (2H, m, NCH_2), 3.53 (1H, ddd, J = 4.6, 5.2, 11.1 Hz, H-5′b), 3.10 (2H, t, J = 7.3 Hz, SCH_2), 2.84 (2H, t, J = 7.4 Hz, NCH_2CH_2), 1.67 (2H, quint, J = 7.3 Hz, SCH_2CH_2), 1.41 (2H, sextet, J = 7.3 Hz, $SCH_2CH_2CH_2$), 0.89 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.8, 157.7, 153.8, 149.5, 138.6, 131.3, 129.5, 117.2, 113.7, 87.4, 85.6, 73.3, 70.6, 61.6, 54.9, 41.6, 34.1, 31.5, 30.2, 21.5, 13.6; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{23}H_{32}N_5O_5S$: 490.2119; found: 4890.2125.

*4.3.28. N^6-(3-methoxyphenethyl)-2-methylthioadenosine (**5b$_{20}$**)*

Compound **4a** was allowed to react with 3-methoxyphenethylamine for 11 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{20}$**. Yield: 82%, mp 164–166 °C; IR (KBr): 3425, 3336, 3124, 1619, 1400, 1253, 783, 752, 675 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.22 (1H, s, H-8), 8.02 (1H, br s, NH), 7.19 (1H, t, J = 8.0 Hz, ArH), 6.82–6.74 (3H, m, ArH), 5.82 (1H, d, J = 5.8 Hz, H-1′), 5.42 (1H, d, J = 6.2 Hz, OH), 5.18 (1H, d, J = 4.8 Hz, OH), 5.05 (1H, dd, J = 5.0, 5.2 Hz, OH), 4.58 (1H, ddd, J = 5.5, 5.8, 6.2 Hz, H-2′), 4.14 (1H, ddd, J = 3.5, 4.8, 5.5 Hz, H-3′), 3.91 (1H, ddd, J = 3.5, 4.2, 4.6 Hz, H-4′), 3.71 (3H, s, OCH_3), 3.68–3.64 (2H, m, NCH_2), 3.62 (1H, ddd, J = 4.2, 5.0, 11.6 Hz, H-5′a), 3.53 (1H, ddd, J = 4.6, 5.2, 11.6 Hz, H-5′b), 2.88 (2H, t, J = 7.2 Hz, NCH_2CH_2), 2.50 (3H, s, SCH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 164.2, 159.3, 153.7, 149.4, 141.0, 138.6, 129.3, 120.9, 117.2, 114.2, 111.6, 87.3, 85.6, 73.4, 70.5, 61.6, 54.8, 41.3, 35.0, 13.9; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{26}N_5O_5S$: 448.1649; found: 448.1648.

*4.3.29. 2-Ethylthio-N^6-(3-methoxyphenethyl)adenosine (**5b$_{21}$**)*

Compound **4b** was allowed to react with 3-methoxyphenethylamine for 11 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{21}$**. Yield: 84%, mp 110–112 °C; IR (KBr): 3318, 2915, 1617, 1577, 1397, 861, 785, 698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.22 (1H, s, H-8), 8.01 (1H, br s, NH), 7.20 (1H, t, J = 8.0 Hz, ArH), 6.81–6.75 (3H, m, ArH), 5.82 (1H, d, J = 5.7 Hz, H-1′), 5.43 (1H, d, J = 6.1 Hz, OH), 5.18 (1H, d, J = 4.8 Hz, OH), 5.08 (1H, dd, J = 5.0, 5.6 Hz, OH), 4.59 (1H, ddd, J = 5.4, 5.7, 6.1 Hz, H-2′), 4.14 (1H, ddd, J = 3.7, 4.8, 5.4 Hz, H-3′), 3.93 (1H, ddd, J = 3.7, 4.5, 4.6 Hz, H-4′), 3.72 (3H, s, OCH_3), 3.71–3.64 (2H, m, NCH_2), 3.63 (1H, ddd, J = 4.6, 5.0, 11.7 Hz, H-5′a), 3.54 (1H, ddd, J = 4.5, 5.6, 11.7 Hz, H-5′b), 3.11 (2H, q, J = 7.3 Hz, SCH_2), 2.89 (2H, t, J = 6.9 Hz, NCH_2CH_2), 1.34 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.7, 159.3, 153.9, 149.6, 141.0, 138.7, 129.4, 120.9, 117.3, 114.2, 111.6, 87.5, 85.6, 73.4, 70.6, 61.6, 54.9, 41.3, 35.1, 24.8, 15.1; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{28}N_5O_5S$: 462.1806; found: 462.1813.

*4.3.30. N^6-(3-methoxyphenethyl)-2-propylthioadenosine (**5b$_{22}$**)*

Compound **4c** was allowed to react with 3-methoxyphenethylamine for 11 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{22}$**. Yield: 76%, mp 120–122 °C; IR (KBr): 3459, 3132, 2920, 1614, 1578, 1399, 867, 781, 691 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.22 (1H, s, H-8), 8.01 (1H, br s, NH), 7.20 (1H, t, J = 8.0 Hz, ArH), 6.82–6.75 (3H, m, ArH), 5.81 (1H, d, J = 5.9 Hz, H-1′), 5.43 (1H, d, J = 6.1 Hz, OH), 5.18 (1H, d, J = 4.8 Hz, OH), 5.09 (1H, dd, J = 4.8, 4.9 Hz, OH), 4.60 (1H, ddd, J = 5.7, 5.9, 6.1 Hz, H-2′), 4.13 (1H, ddd, J = 3.4, 4.8, 5.7 Hz, H-3′), 3.92 (1H, ddd, J = 3.3, 4.0, 4.5 Hz, H-4′), 3.72 (3H, s, OCH_3), 3.69–3.64 (2H, m, NCH_2), 3.62 (1H, ddd, J = 4.5, 4.8, 11.5 Hz, H-5′a), 3.51 (1H, ddd, J = 4.0, 4.9, 11.5 Hz, H-5′b), 3.09 (2H, t, J = 7.3 Hz, SCH_2), 2.89 (2H, t, J = 7.0 Hz, NCH_2CH_2), 1.68 (2H, sextet, J = 7.3 Hz, SCH_2CH_2), 0.98 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.8, 159.3, 153.8, 149.5, 141.0, 138.6, 129.3, 120.9, 117.4, 114.3, 111.6, 87.5, 85.6, 73.4, 70.6, 61.6, 54.9, 41.3, 35.1, 32.4, 22.8, 13.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{30}N_5O_5S$: 476.1962; found: 476.1968.

*4.3.31. 2-Butylthio-N^6-(3-methoxyphenethyl)adenosine (**5b$_{23}$**)*

Compound **4e** was allowed to react with 3-methoxyphenethylamine for 11 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from EtOAc to give **5b$_{23}$**. Yield: 81%, mp 124–126 °C; IR (KBr): 3429, 3330, 3129, 1611, 1396, 1338, 781, 700, 637 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (1H, s, H-8), 8.00 (1H, br s, NH), 7.21 (1H, t, J = 8.0 Hz, ArH), 6.80–6.75 (3H, m, ArH), 5.81 (1H, d, J = 5.7 Hz, H-1′), 5.41 (1H, d, J = 6.1 Hz, OH), 5.15 (1H, d, J = 4.8 Hz, OH), 5.06 (1H, dd, J = 4.6, 4.7 Hz, OH), 4.37 (1H, ddd, J = 5.6, 5.7, 6.1 Hz, H-2′), 4.12 (1H, ddd, J = 3.7, 4.8, 5.6 Hz, H-3′), 3.92 (1H, ddd, J = 3.7, 4.2, 5.1 Hz, H-4′), 3.72 (3H, s, OCH_3), 3.71–3.64 (2H, m, NCH_2), 3.63 (1H, ddd, J = 4.2, 4.6, 11.2 Hz, H-5′a), 3.53 (1H, ddd, J = 4.7, 5.5, 11.2 Hz, H-5′b), 3.11 (2H, t, J = 7.3 Hz, SCH_2), 2.89 (2H, t, J = 7.1 Hz, NCH_2CH_2), 1.66 (2H, quint, J = 7.3 Hz, SCH_2CH_2), 1.41 (2H, sextet, J = 7.3 Hz, $SCH_2CH_2CH_2$), 0.89 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.8, 159.3, 153.8, 149.4, 141.0, 138.6, 129.3, 120.8, 117.3, 114.2, 111.5, 87.4, 85.5, 73.3, 70.5, 61.6, 54.8, 41.2, 35.0, 31.5, 30.1, 21.5, 13.6; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{23}H_{32}N_5O_5S$: 490.2119; found: 490.2128.

*4.3.32. 2-Ethylthio-N^6-(1-phenylethyl)adenosine (**5b$_{24}$**)*

Compound **4b** was allowed to react with 1-phenylethylamine for 8 h according to the general procedure. The product was purified by flash column chromatography, and followed by recrystallization from cyclohexane to give **5b$_{24}$**. Yield: 72%, mp 84–86 °C; IR (KBr): 3423, 3324, 3125, 1604, 1393, 781, 710, 637 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.40 (1H, br s, NH), 8.24 (1H, s, 8-H), 7.40 (2H, d, J = 7.1 Hz, ArH), 7.30 (2H, t, J = 7.5 Hz, ArH), 7.18 (1H, t, J = 7.3 Hz, ArH), 5.80 (1H, d, J = 5.9 Hz, H-1′), 5.41 (1H, br s, NCH), 5.38 (1H, d, J = 6.1 Hz, OH), 5.13 (1H, d, J = 4.8 Hz, OH), 5.05 (1H, dd, J = 4.6, 4.9 Hz, OH), 4.58 (1H, ddd, J = 5.7, 5.9, 6.1 Hz, H-2′), 4.12 (1H, ddd, J = 3.7, 4.8, 5.7 Hz, H-3′), 3.92 (1H, ddd, J = 3.6, 4.2, 4.3 Hz, H-4′), 3.63 (1H, ddd, J = 4.2, 4.6, 11.9 Hz, H-5′a), 3.53 (1H, ddd, J = 4.3, 4.9, 11.9 Hz, H-5′b), 2.98 (2H, q, J = 7.3 Hz, SCH_2), 1.53 (3H, d, J = 6.8 Hz, $CHCH_3$), 1.21 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.5, 153.1, 149.7, 145.3, 138.6, 128.1, 126.5, 126.0, 117.2, 87.4, 85.5, 73.4, 70.5, 61.5, 49.3, 24.6, 22.5, 15.0; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{26}N_5O_4S$: 432.1700; found: 432.1709.

4.4. In vitro antiplatelet aggregation activity

All experiments using human subjects were performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board Fudan University. Blood was sampled from the cubital vein of healthy volunteers without taking aspirin or other nonsteroidal anti-inflammatory drugs for at least 14 days and the informed consent was obtained before blood collection. The blood sample was collected in 50 mL plastic tubes containing

3.8% sodium citrate (1:9, v/v) and centrifuged at 300 rpm for 20 min to generate platelet-rich plasma (PRP). The residual blood was centrifuged at 900 rpm for 10 min. The supernatant fraction was called platelet-poor plasma (PPP). Aliquots of 500 μL of PRP were distributed in test cuvettes and inserted into the incubation chamber of an aggregometer (Model 400VS, Chrono-Log, Haverston, PA) at 37 °C. Platelet aggregation was measured on the aggregometer using the PRP fractions after activation by ADP (final concentration 10 μM) or AA (final concentration 0.5 mM) according to the Born's method [34]. The test compounds were dissolved in DMSO (below at 0.5% final concentration) and added to the PRP for 1 min before platelet activation with agonists, the extent of aggregation was quantified by determining the maximum height of the aggregation tracing. Each sample was allowed to aggregate for at least 3 min. The chart recorder (Model 707, Chrono-Log, Haverston, PA, USA) was set for 1 cm min^{-1}. The baseline was set using the PPP as blank. The platelet aggregation inhibitory activity was expressed as percent inhibition by comparison with that measured in the presence of an equivalent amount of vehicle (DMSO) alone.

Data are presented as mean ± S.E.M. from 3 separate experiments. Concentration–response curves were analyzed by nonlinear regression using GraphPad Prism 5.0 and the IC_{50} values were derived from this analysis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2012.03.047. These data include MOL files and InChiKeys of the most important compounds described in this article.

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