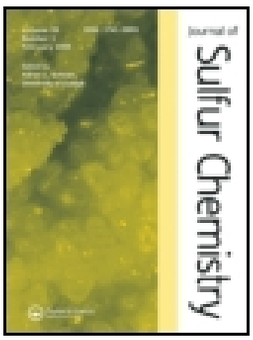

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SHORT COMMUNICATION

Expedient synthesis of 2-alkylthio-N^6-aryladenosines from guanosine

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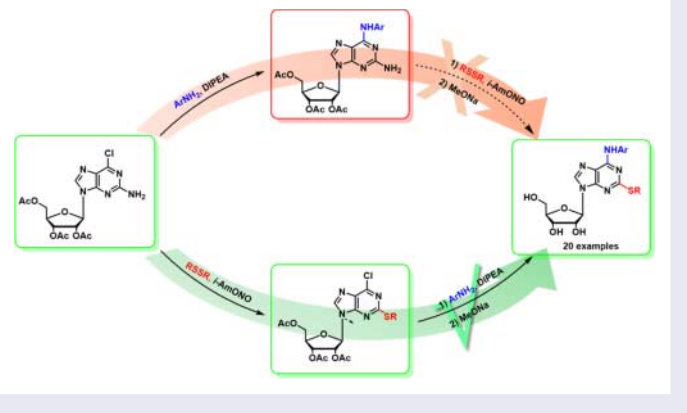
ABSTRACT

A general approach for the synthesis of 2-alkylthio-N^6-aryladenosine was developed from the commercially available guanosine through the acetyl protection, chlorination, diazotization-alkylthionation, aromatic nucleophilic substitution and deacetylation. Two approaches were designed for the transformation of 2-amino-6-chloroguanosine to 2-alkylthio-N^6-aryladenosines but only the one with diazotization-alkylthionation first could afford the target molecules. Both electron-rich and deficient anilines can afford the desired products in moderate to good yield. Finally, under the optimized condition, 20 2-alkylthio-N^6-aryladenosines were synthesized, 5 of which exhibit poor antiplatelet aggregation activities.



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Adenosine; guanosine; purine riboside; diazotization-alkylthionation; antiplatelet aggregation

1. Introduction

Adenosine derivatives, with various substituents at C^2, C^6, C^8, and N^9 positions, have attracted much attention due to their broad spectrum of biological activities [1–6]. In 1999, 2-alkylthio-6-aminopurine riboside derivatives were first reported as inhibitors for $P2Y_{12}$

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receptor [7]. Since then, great endeavors have been devoted to developing various outstanding antiplatelet inhibitors through the modification of the substituents on the purine moiety [8–11]. In particular, adenosine derivatives with various substituents on the purine motif, including the alkylthio group at the C^2 position, the alkyl substituent at the N^6 position and the triphosphate side chain at the 5′ position, possess unique biological effects, such as Cangrelor [7] (Figure 1, **I**) and Ticagrelor [12] (Figure 1, **II**). In view of the significant antiplatelet activities exhibited by purine derivatives, it is still highly desirable to search for more effective antiplatelet aggregation molecules from purine derivatives.

General methods to produce adenosine derivatives varied from guanosine or 6-halopurine riboside through alkylation, amination, and Buchwald–Hartwig amination [9,13–15]. In recent years, our research group synthesized a series of adenosine derivatives with alkoxy or alkylthio groups at position 2 and alkylamine at position 6 using guanosine as a raw material [16,17]. Meanwhile, we also studied the antiplatelet activities of these compounds and found that molecules BF061 and BF081 (Figure 1, **III** and **IV**) show excellent antiplatelet activities [16,18]. As the ongoing work, we planned to shorten the N^6-arylalkyl substituent to an aryl group in adenosine derivatives to investigate their bioactivities. Herein, we report our recent progress for the synthesis and the antiplatelet aggregation evaluation of various substituted 2-alkylthio-N^6-aryladenosines.

2. Results and discussion

Following our previous method [16], commercially available guanosine (**1**) was used as a starting material (Scheme 1). Initially, after acetylation with acetyl anhydride, **1** afforded the corresponding acetyl guanosine **2** with 85% yield and the following chlorination with $POCl_3$ provided key intermediates 6-chlordine purine nucleoside **3** in 78% yield (Scheme 1).

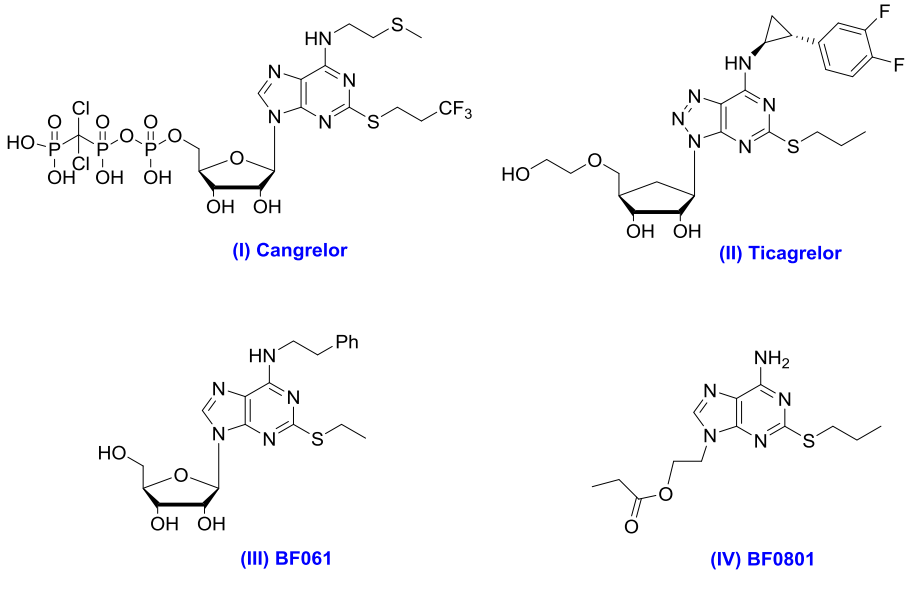
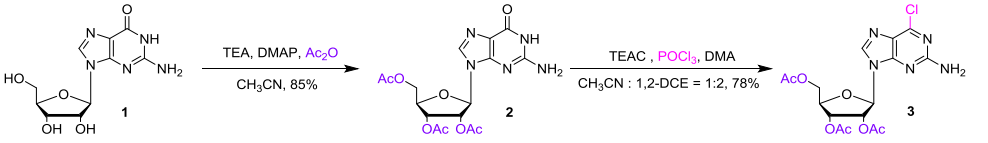
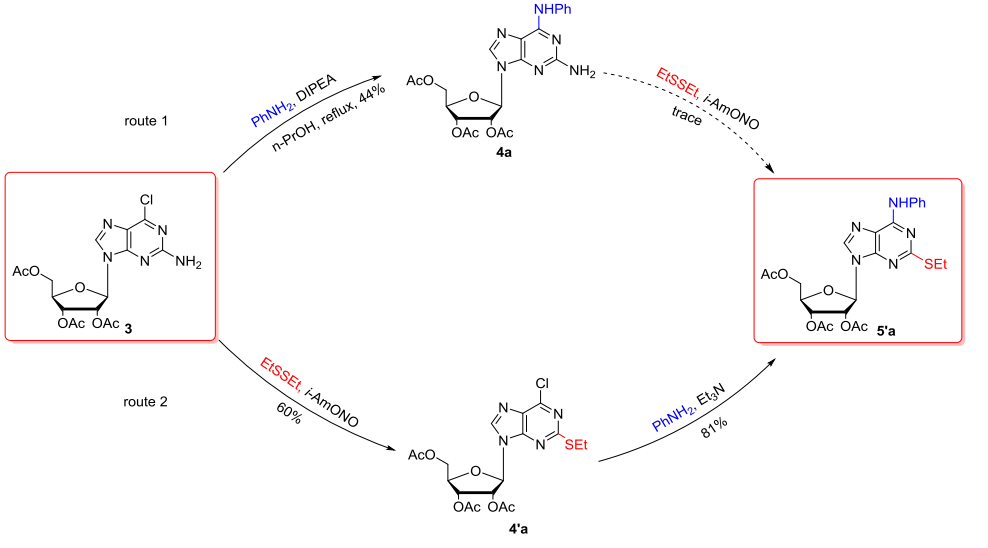


Figure 1. Structures of Cangrelor, Tricagrelor, BF061, and BF0801.



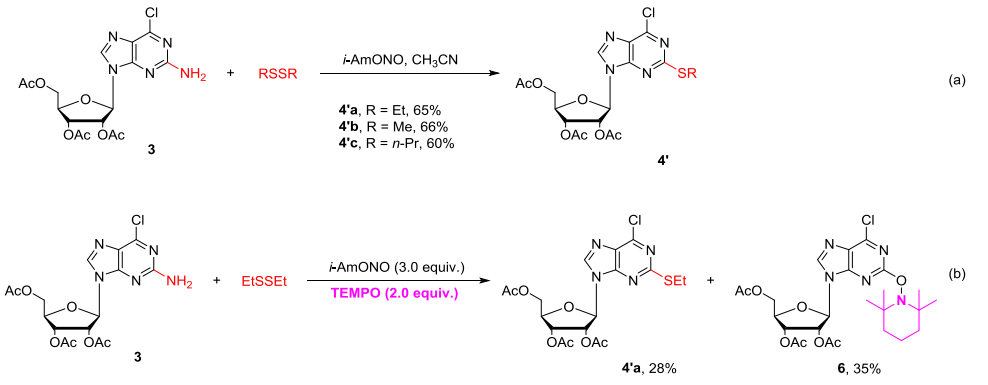
Scheme 1. The synthesis of 6-chloropurine nucleoside **3**.



Scheme 2. Two approaches for the synthesis of 6-arylamino-2-alkylthiopurines.

In order to afford 2-alkylthio-N^6-arylpurine riboside **5** (Scheme 2), two possible ways were designed: C6-amination first (route 1) or C2-arylthio-substitution first (route 2). Both approaches were examined, but only the latter one produced the target molecule. Take 2-ethylthio-N^6-phenylamino-purine acetyl nucleoside **5′a** as an example; in route 1, amination of **3a** from aniline gave corresponding 6-arylaminopurine riboside **4a** in 44% yield, but only trace yields of the target **5′a** was detected from thin-layer chromatography (TLC) in the followed diazotization-alkylthionation process with *iso*-amylnitrite and diethyl disulfide [17]. The result demonstrates that electron-donating group (alkylamino) on purine motif makes the purine too electron-rich to stabilize the followed aryl radical [19], thus inhibiting the further radical alkylthio coupling. We thus switched the sequences of the reactions. First, the diazotization-alkylthionation approach of **3** was carried out with 65% yield of isolated **4′a**, which further demonstrated that electron-withdrawing group C6-position facilitated the radical coupling. To our gratification, the subsequent amination of **4′a** with aniline in the presence of triethylamine afforded the substitution product **5′a** in 81% yield.

Having obtained the model molecule **5b′**, we next examined the application of this method. During the diazotization-alkylthionation process, we have exploited that ultrasound irradiation highly facilitated the radical coupling, which not only promoted the reaction efficiency but also avoid the use of inert gas [17]. Herein, beside the diethyl disulfide, dimethyl- and dipropyl disulfide could also convert the muriatic purine nucleoside



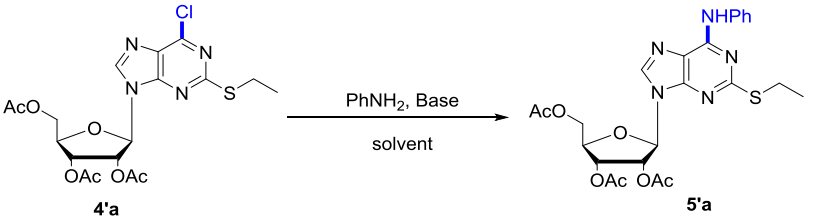
Scheme 3. The reaction of 6-chloropurine **3** and dialkyl disulfide, and the radical trapping experiment with TEMPO.

3 to the corresponding 2-alkylthiopurine derivatives in 66% (**4′a**) and 60% (**4′c**) isolated yield under ultrasound irradiation at 65°C in acetonitrile (Scheme 3, a). When TEMPO, a common radical scavenger, was added to the model reaction, both TEMPO-trapping product **6** (35%) and target product **4′b** (28%) were isolated (Scheme 3, b), revealing that the reaction was a radical process.

In our previous work, alkyl amine could directly react with 6-chloropurines to afford the corresponding substitution molecules in excellent yield under the catalysis of Et_3N in EtOH (b.p. 78°C) [16]. However, in the current system, only 61% yield of **5′a** was obtained (Table 1, entry 1). As is generally known, the nucleophicity of arylamine (aniline) is much lower than that of alkylamine. We thus changed the solvent to *n*-propanol (b.p. 97°C), and to our gratification the yield of **5′a** was promoted to 81% under refluxing. Further screening of the organic bases (Table 1, entries 2−8) indicated that trimethylamine, pyridine, and diisopropylethylamine (DIPEA) prompted the reaction with high efficiency, and DIPEA was the best one (Table 1, entry 6), while DMAP and DBU showed no catalytic activity. Moreover, focused on the DIPEA, ethanol and *n*-butanol were also investigated as solvents but the reaction yields were diminished (Table 1, entries 7 and 8).

Under the optimized conditions, a series of substituted anilines, including electron-donating (methyl and methoxy) and electron-withdrawing (fluoro-, cholro-, and nitro-) substituents, were investigated. Moreover, **4′a** could be easily deacetylation by adding 3.0 equiv. of sodium methoxide [17]. To simplify the reaction operation, we tried the one-pot strategy. Followed by the substitution, sodium methoxide was added to the reaction solution directly, and to our gratification, the target deacetylation 2-ethylthio-6-phenylaminopurine nucleoside **5a** was obtained in 66% yield (Table 2, **5a**). On the further scope for *para*-substituted anilines, we found that electron-rich anilines shows better reactivity than that of electron-withdrawing ones probably due to their nucleophilicity nature (**5b**, **5c** vs. **5d**, **5e**). However, all *meta*-substituted anilines provided moderate to good yield (**5f**–**5i**). It is noteworthy that *para*-nitroaniline shows no reactivity in the current condition even though we made every endeavor to develop it, but *meta*-nitroaniline could produce the target **5j** in 45% yield because of the great difference in electronic influence between the *para*- and *meta*-substituents. Furthermore, other purine substrates with 2-methylthio- (**4′b**) and

Table 1. Optimization of substitution of aniline and 6-purine **4′a.**



Entry	Base	Solvent	Yield[a] (%)
1	Et_3N	EtOH	61
2	Et_3N	*n*-PrOH	81
3	DMAP	*n*-PrOH	Trace
4	DBU	*n*-PrOH	Trace
5	Pyridine	*n*-PrOH	80
6	DIPEA	*n*-PrOH	85
7	DIPEA	EtOH	62
8	DIPEA	*n*-BuOH	59

[a]Reaction condition: **4′a** (0.2 mmol), $PhNH_2$ (0.4 mmol), base (0.4 mmol) solvent (4.0 mL), reflux 3 h; yields were determined by ^{1}H NMR obtained by using dimethyl maleate as an internal standard.

2-propylthio- (**4′c**) substituents also investigated and the results were in line with **4′a** (**5k**–**5t**).

Finally, the antiplatelet aggregation of all synthetic compounds was assayed by adenosine-5′-diphosphate (ADP) and arachidonic acid (AA) with Ticagrelor and Cangrelor as positive controls (see Supplemental Materials, Table S1, http://dx.doi.org/10.1080/17415993.2017.1391812) [20]. Generally, most of them show poor antiplatelet aggregation compared with Ticagrelor and Cangrelor.

3. Conclusion

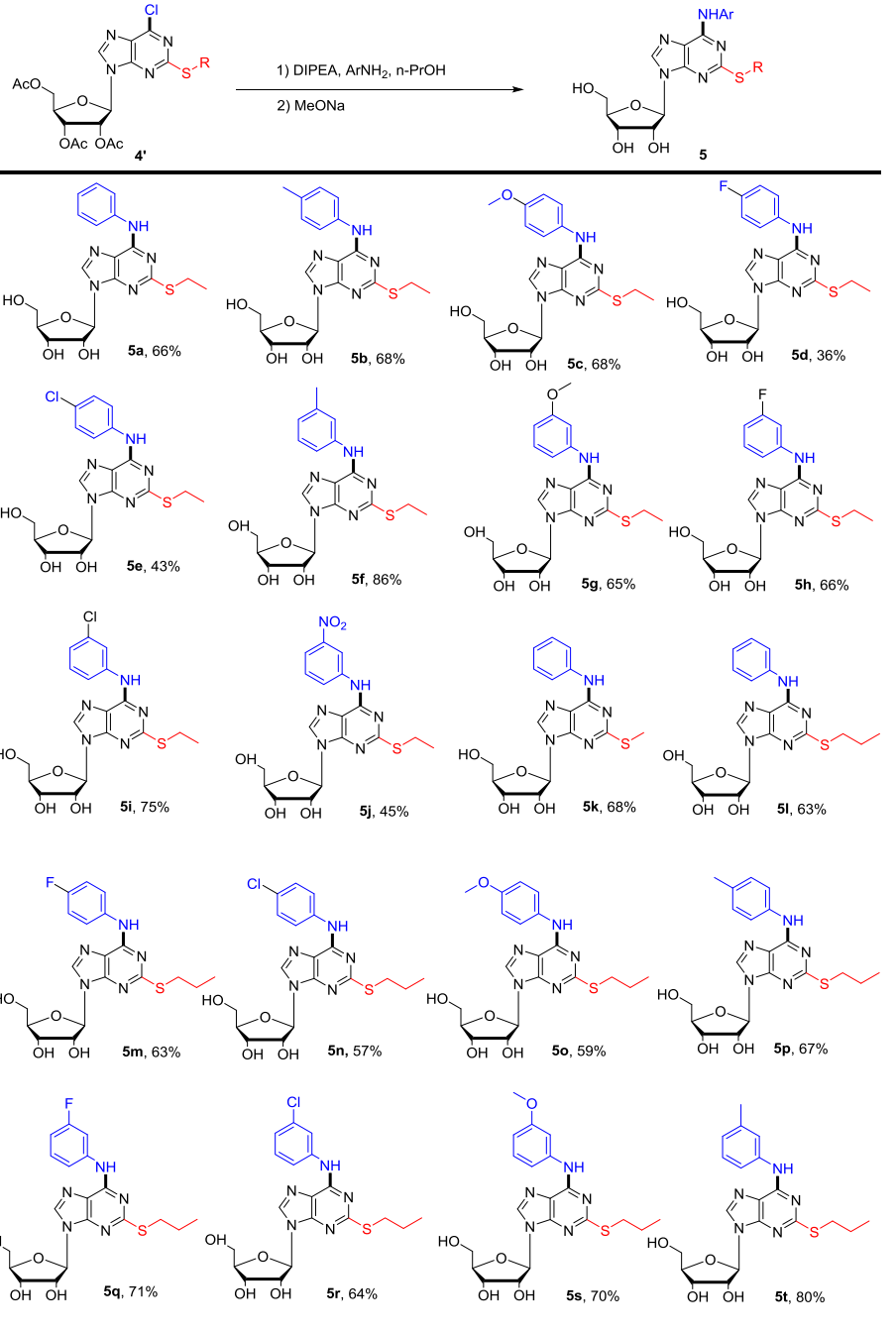
Herein, we have developed a general approach for the synthesis of 2-alkylthio-N^6-aryladenosine from the commercially available guanosine. After acetyl protection and chlorination, a key intermediate 2′,3′,5′-tri-*O*-acetyl-2-amino-6-chloropurine riboside **3** was obtained. Two approaches were designed for the transformation of **3** to 2-alkylthio-N^6-aryladenosines **5** but only the one with diazotization-alkylthionation first could afford the target molecules. The result demonstrates that electron-rich purine prohibits the diazotization-alkylthionation reaction. In the aromatic substitution, DIPEA can highly prompt the aromatic nucleophilic substitution of 6-chloropurine with arylamines and both electron-rich and deficient anilines afford the desired products in moderate to good yield. Moreover, a wide array of functional groups, such as halogens, ethers, esters, hydroxyl, and nitro, are also tolerated in this strategy.

4. Experimental section

4.1. General

Commercially available reagents were used without further purification. Melting points were determined on a hot-stage melting point apparatus (uncorrected). Nuclear magnetic resonance (NMR) spectra were recorded in the $CDCl_3$ or DMSO-d_6 with TMS as an internal standard (^{1}H: 400 MHz, ^{13}C: 100 MHz). The chemical shifts (δ) are reported

Table 2. Synthesis of target molecules 5.[a]



[a] yields of the isolated products are given.

in parts per million (ppm) and coupling constants *J* are in Hz. The signal multiplicities were distinguished with the common abbreviations with s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), br s (broad singlet), and m (multiplet). IR

spectra are recorded on an FT-IR instrument. HRMS measurements were carried out on an Liquid Chromatography/Mass Spectrometer Detector QTOF mass spectrometer. ADP, AA, and Aspirin were purchased from Sigma. Ticagrelor was purchased from Dalian Meilun Biotech Co., Ltd. 2′,3′,5′-Tri-*O*-acetyl-2-amino-6-chloropurine riboside **3** were synthesized according to the literature [21,22].

4.2. General procedure for the synthesis of 2-alkythio-6-chloro-9-(2′,3′,5′-tri-O-acetyl-b-D-ribofuranosyl)-9H-purine (4′a–4′c)

2-Amino-6-chloropurine riboside **3** (3.0 g, 7.01 mmol) and dialkyl disulfides (21.04 mmol) were suspended in 15 mL anhydrous acetonitrile in a 50-mL vial. Then, isopentylnitrite (2.6 mL, 21.04 mmol) was then added to the mixture. The reaction was stirred at 65°C under the condition of ultrasound for 30 min. Upon completion of the reaction, solvent was evaporated in vacuo and the resulting residue was purified by silica gel column chromatography (EtOAc/PE = 2:3, *v*/*v*) to afford corresponding product **4** as yellow oil.

4.2.1. 6-Chloro-2-ethylthio-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (4′a) [16]

2.09 g, yield = 65%; a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (1H, s), 6.13 (1H, d, J = 4.8 Hz), 5.95 (1H, t, J = 4.8 Hz), 5.61 (1H, t, J = 5.2 Hz), 4.45–4.42 (2H, m), 4.35–4.31 (1H, m), 3.23 (2H, q, J = 7.2 Hz), 2.15 (3H, s), 2.11 (6H, app s), 1.43 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.5, 169.3, 166.9, 152.0, 151.3, 142.1, 129.1, 86.9, 80.1, 73.0, 70.1, 62.7, 26.0, 20.7, 20.5, 20.4, 14.1.

4.2.2. 6-Chloro-2-methylthio-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (4′b) [16]

2.18 g, yield = 66%; a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (1H, s), 6.12 (1H, d, J = 4.4 Hz), 6.00 (1H, t, J = 5.2 Hz), 5.65 (1H, t, J = 5.2 Hz), 4.46–4.40 (2H, m), 4.35–4.30 (1H, m), 2.65 (3H, s), 2.16 (3H, s), 2.11 (3H, s), 2.10 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.5, 169.3, 167.4, 151.9, 151.3, 142.2, 129.1, 87.1, 80.1, 73.0, 70.2, 62.7, 20.7, 20.5, 20.4, 14.9.

4.2.3. 6-Chloro-2-propyllthio-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (4′c) [16]

2.05 g, yield = 60%; a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (1H, s), 6.14 (1H, d, J = 4.8 Hz), 5.92 (1H, t, J = 5.2 Hz), 5.59 (1H, t, J = 5.2 Hz), 4.47–4.41 (2H, m), 4.36–4.32 (1H, m), 3.20 (2H, t, J = 7.2 Hz), 2.15 (3H, s), 2.11 (3H, s), 2.10 (3H, s), 1.80 (2H, sext, J = 7.2 Hz), 1.07 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.5, 169.3, 167.1, 152.0, 151.2, 141.9, 129.1, 86.8, 80.1, 73.1, 70.2, 62.8, 33.6, 22.3, 20.7, 20.5, 20.4, 13.4.

4.3. General procedure for the synthesis of 2-alkylthio-N^6-aryladenosines (5a–5t)

To a suspend solution of **4** (1.06 mmol) and 15 mL *n*-propanol, DIPEA (2.11 mmol) and anilines (2.11 mmol) were added to the mixture. The reaction was stirred under the refluxing condition till the disappearance of intermediate **4** (about 3−11 h). When the starting material disappeared as monitored by TLC (EtOAc/PE = 2:3, *v*/*v*), the system was cooled

to room temperature, and sodium methoxide (3.0 equiv.) was added into the mixture. The whole system was then heated to reflux for 1.5 h. The solvent was evaporated in vacuo. Then, the mixture was dissolved with 12 mL EtOAc and H_2O (1:1) and was neutralized with dilute hydrochloric acid to pH = 7. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over by anhydrous $MgSO_4$. After filtrating and evaporating the solvent, the resulting residue was purified by silica gel column chromatography (EtOAc/MeOH = 15:1, *v*/*v*) to afford corresponding product **5** as white crystals.

4.3.1. (2R,3S,4R,5R)-2-(hydroxymethyl)-5-(2-(ethylthio)-6-(phenylamino)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (5a)

282 mg, yield = 66%; white solid; m.p. = 171–172°C; R_f = 0.48 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (1H, s), 8.42 (1H, s), 7.91–7.89 (2H, m), 7.37–7.33 (2H, m), 7.08–7.05 (1H, m), 5.90 (1H, d, J = 5.6 Hz), 5.48 (1H, d, J = 6.0 Hz), 5.22 (1H, d, J = 5.2 Hz), 5.06 (1H, t, J = 5.6 Hz), 4.66–4.62 (1H, m), 4.19–4.16 (1H, m), 3.98–3.95 (1H, m), 3.71–3.66 (1H, m), 3.53.60–3.55(1H, m), 3.16–3.11 (2H, m), 1.35 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 151.5, 150.4, 139.6, 139.2, 128.3, 122.9, 120.9, 117.8, 87.4, 85.6, 73.4, 70.5, 61.5, 24.7, 14.9; FT-IR (film, cm^{-1}): 3348, 3291, 2966, 2924, 1616, 1578, 1498, 1444, 1334, 1191, 1078, 748, 691. ESI-HRMS $[M+H]^+$ calcd for $C_{18}H_{22}N_5O_4S^+$ *m*/*z* 404.1387, found 404.1388.

4.3.2. (2R,3R,4S,5R)-2-(2-(ethylthio)-6-(p-tolylamino)-9H-purin-9-yl)-5-(hydroxy methyl)tetrahydrofuran-3,4-diol (5b)

301 mg, yield = 68%; white solid; m.p. = 182–183°C; R_f = 0.50 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.90 (1H, s), 8.40 (1H, s), 7.76 (2H, d, J = 8.4 Hz), 7.15 (2H, d, J = 8.0 Hz), 5.89 (1H, d, J = 6.0 Hz), 5.48 (1H, br s), 5.22 (1H, br s), 5.07 (1H, br s), 4.64 (1H, br s), 4.18 (1H, br s), 3.96 (1H, dd, J = 4.0, 7.6 Hz), 3.70–3.66 (1H, m), 3.58–3.56 (1H, m), 3.14–3.10 (2H, m), 2.29 (3H, s), 1.35 (3H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 151.5, 150.3, 139.4, 136.6, 131.9, 128.7, 121.0, 117.7, 87.4, 85.5, 73.4, 70.5, 61.5, 24.7, 20.4, 14.9. FT-IR (film, cm^{-1}): 3333, 3232, 3104, 2921, 2863, 1625, 1580, 1511, 1454, 1334, 1234, 1083, 811. ESI-HRMS $[M+H]^+$ calcd for $C_{19}H_{24}N_5O_4S^+$ *m*/*z* 418.1544, found 418.1550.

4.3.3. (2R,3R,4S,5R)-2-(2-(ethylthio)-6-((4-methoxyphenyl)amino)-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (5c)

312 mg, yield = 68%; white solid; m.p. = 158–160°C; R_f = 0.44 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.85 (1H, s), 8.37 (1H, s), 7.75 (2H, d, J = 9.2 Hz), 6.93 (2H, d, J = 8.8 Hz), 5.88 (1H, d, J = 6.0 Hz), 5.47 (1H, d, J = 6.0 Hz), 5.21 (1H, d, J = 4.8 Hz), 5.07 (1H, t, J = 5.6 Hz), 4.63 (1H, dd, J = 5.6, 11.2 Hz), 4.17 (1H, dd, J = 4.4, 8.4 Hz), 3.96–3.95 (1H, m), 3.76 (3H, s), 3.70–3.65 (1H, m), 3.60–3.55 (1H, m), 3.13–3.07 (2H, m), 1.33 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 155.2, 151.5, 150.1, 139.3, 132.2, 122.7, 117.6, 113.5, 87.4, 85.5, 73.4, 70.5, 61.5, 55.2, 24.7, 15.0. FT-IR (film, cm^{-1}): 3381, 3352, 3110, 2927, 1619, 1582, 1509, 1455, 1334, 1243, 1118, 1038, 828. ESI-HRMS $[M+H]^+$ calcd for $C_{19}H_{24}N_5O_5S^+$ *m*/*z* 434.1493, found 434.1495.

4.3.4. (2R,3R,4S,5R)-2-(2-(ethylthio)-6-((4-fluorophenyl)amino)-9H-purin-9-yl)-5-(hydroxymethyl)-tetrahydrofuran-3,4-diol (5d)

161 mg, yield = 36%; white solid; m.p. = 208–210°C; R_f = 0.46 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.05 (1H, s), 8.41 (1H, s), 7.88 (2H, dd, J = 4.8, 8.8 Hz), 7.19 (2H, t, J = 8.8 Hz), 5.89 (1H, d, J = 6.0 Hz), 5.48 (1H, d, J = 6.0 Hz), 5.22 (1H, d, J = 4.8 Hz), 5.06 (1H, t, J = 5.6 Hz), 4.65–4.61 (1H, m), 4.19–4.16 (1H, m), 3.97–3.94 (1H, m), 3.71–3.58 (1H, m), 3.57–3.54 (1H, m), 3.13–3.08 (2H, m), 1.33 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 158.0 (d, J = 238 Hz), 151.4, 150.4, 139.6, 135.6, 122.8, (d, J = 8 Hz), 117.7, 114.4 (d, J = 22 Hz), 87.4, 85.6, 73.4, 70.4, 61.5, 24.8, 14.9. ^{19}F NMR (376 MHz, DMSO-d_6): δ = −119.90. FT-IR (film, cm^{-1}): 3342, 3277, 3125, 2964, 2927, 1620, 1580, 1506, 1448, 1335, 1220, 1073, 838. ESI-HRMS $[M+H]^+$ calcd for $C_{18}H_{21}FN_5O_4S^+$ *m*/*z* 422.1293, found 422.1293.

4.3.5. (2R,3R,4S,5R)-2-(2-(ethylthio)-6-((4-chlorophenyl)amino)-9H-purin-9-yl)-5-(hydroxymethyl)-tetrahydrofuran-3,4-diol (5e)

200 mg, yield = 43%; white solid; m.p. = 188–190°C; R_f = 0.48 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.16 (1H, s), 8.43 (1H, s), 7.94 (2H, d, J = 9.2 Hz), 7.41 (2H, d, J = 8.8 Hz), 5.89 (1H, d, J = 6.0 Hz), 5.48 (1H, d, J = 6.0 Hz), 5.22 (1H, d, J = 4.8 Hz), 5.05 (1H, t, J = 5.6 Hz), 4.63 (1H, dd, J = 6.0, 11.2 Hz), 4.17 (1H, dd, J = 4.8, 8.4 Hz), 3.96 (1H, dd, J = 4.0, 8.0 Hz), 3.70–3.65 (1H, m), 3.59–3.54 (1H, m), 3.16–3.11 (2H, m), 1.35 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 151.2, 150.5, 139.8, 138.3, 128.2, 126.5, 122.3, 117.8, 87.4, 85.6, 73.4, 70.4, 61.5, 24.8, 14.8. FT-IR (film, cm^{-1}): 3342, 3288, 3122, 2961, 2928, 1614, 1573, 1491, 1443, 1334, 1192, 1069, 810. ESI-HRMS $[M+H]^+$ calcd for $C_{18}H_{21}ClN_5O_4S^+$ *m*/*z* 438.0997, found 438.1003.

4.3.6. (2R,3R,4S,5R)-2-(2-(ethylthio)-6-(m-tolylamino)-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (5f)

381 mg, yield = 86%; white solid; m.p. = 168–170°C; R_f = 0.41 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.90 (1H, s), 8.40 (1H, s), 7.80 (1H, app s), 7.62 (1H, d, J = 8.4 Hz), 7.21 (1H, t, J = 8.0 Hz), 6.88 (1H, d, J = 7.2 Hz), 5.88 (1H, d, J = 6.0 Hz), 5.47 (1H, d, J = 6.4 Hz), 5.20 (1H, d, J = 4.8 Hz), 5.06 (1H, t, J = 5.6 Hz), 4.61 (1H, dd, J = 6.0, 11.2 Hz), 4.16 (1H, dd, J = 4.8, 8.4 Hz), 3.95 (1H, dd, J = 4.0, 7.6 Hz), 3.70–3.64 (1H, m), 3.59–3.53 (1H, m), 3.16–3.11 (2H, m), 2.31 (3H, s), 1.35 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 151.5, 150.4, 139.5, 139.2, 137.4, 128.2, 123.6, 121.4, 118.1, 117.8, 87.4, 85.6, 73.4, 70.5, 61.5, 24.7, 21.2, 15.0. FT-IR (film, cm^{-1}): 3330, 3247, 3110, 2924, 2869, 1624, 1577, 1486, 1449, 1332, 1219, 1120, 1083, 779, 688. ESI-HRMS $[M+H]^+$ calcd for $C_{19}H_{24}N_5O_4S^+$ *m*/*z* 418.1544, found 418.1548.

4.3.7. (2R,3R,4S,5R)-2-(2-(ethylthio)-6-((3-methoxyphenyl)amino)-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (5g)

299 mg, yield = 65%; white solid; m.p. = 95–96°C; R_f = 0.47 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.95 (1H, s), 8.42 (1H, s), 7.65 (1H, t, J = 2.0 Hz), 7.52–7.50 (1H, m), 7.24 (1H, t, J = 8.0 Hz), 6.6–6.63 (1H, m), 5.90 (1H, d, J = 2.0 Hz), 5. 44–5.15 (3H, m), 4.64 (1H, t, J = 7.2 Hz), 4.19–4.17 (1H, m), 3.96–3.98 (1H, m), 3.77 (3H, s), 3.70–3.66 (1H, m), 3.59–3.55 (1H, m), 3.18–3.12 (2H, m), 1.36 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 159.4, 151.4, 150.3, 140.5, 139.6, 129.1, 117.9, 113.0,

108.1, 106.7, 87.4, 85.5, 73.4, 70.4, 61.5, 55.0, 24.7, 14.9. FT-IR (film, cm^{-1}): 3350, 3235, 3113, 2927, 1624, 1577, 1491, 1454, 1330, 1225, 1157, 1046, 768, 694. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{24}N_5O_5S^+$ m/z 434.1493, found 434.1497.

4.3.8. (2R,3R,4S,5R)-2-(2-(ethylthio)-6-((3-fluorophenyl)amino)-9H-purin-9-yl)-5-(hydroxymethyl)-tetrahydrofuran-3,4-diol (5h)

295 mg, yield = 66%; white solid; m.p. = 176–178°C; R_f = 0.48 (EtOAc:MeOH = 15:1, v/v). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.24 (1H, s), 8.46 (1H, s), 7.98–7.94 (1H, m), 7.74–7.71 (1H, m), 7.40–7.34 (1H, m), 6.90–6.85 (1H, m), 5.91 (1H, d, J = 6.0 Hz), 5.50 (1H, d, J = 6.0 Hz), 5.23 (1H, d, J = 4.0 Hz), 5.06 (1H, br s), 4.64 (1H, dd, J = 5.6, 10.8 Hz), 4.18 (1H, m), 3.97 (1H, dd, J = 4.0, 7.6 Hz), 3.70–3.67 (1H, m), 3.59–3.56 (1H, m), 3.19–3.14 (2H, m), 1.38 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 162.0 (d, J = 239 Hz), 151.2, 150.6, 141.1, 139.9, 129.9, 117.9, 116.3, 109.0 (d, J = 21 Hz), 107.2 (d, J = 26 Hz), 87.4, 85.6, 73.4, 70.4, 61.5, 24.8, 14.9. ^{19}F NMR (376 MHz, DMSO-d_6): δ = −112.59. FT-IR (film, cm^{-1}): 3357, 3303, 3140, 2969, 2928, 1623, 1578, 1490, 1445, 1333, 1253, 1225, 1124, 1078, 810, 681. ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{21}FN_5O_4S^+$ m/z 422.1293, found 422.1295.

4.3.9. (2R,3R,4S,5R)-2-(6-((3-chlorophenyl)amino)-2-(ethylthio)-9H-purin-9-yl)-5-(hydroxymethyl)-tetrahydrofuran-3,4-diol (5i)

348 mg, yield = 75%; white solid; m.p. = 168–170°C; R_f = 0.47 (EtOAc:MeOH = 15:1, v/v). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (1H, s), 8.46 (1H, s), 8.24 (1H, t, J = 2.0 Hz), 7.82–7.80 (1H, m), 7.36 (1H, t, J = 8.0 Hz), 7.12–7.09 (1H, m), 5.91 (1H, d, J = 6.0 Hz), 5.50 (1H, d, J = 6.0 Hz), 5.23 (1H, d, J = 4.8 Hz), 5.07 (1H, t, J = 5.6 Hz), 4.63 (1H, dd, J = 5.6, 11.2 Hz), 4.18 (1H, dd, J = 4.4, 8.0 Hz), 3.97 (1H, dd, J = 4.0, 7.6 Hz), 3.71–3.66 (1H, m), 3.61–3.55 (1H, m), 3.19–3.14 (2H, m), 1.38 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 151.2, 150.6, 140.9, 139.9, 132.7, 130.0, 122.3, 120.0, 119.0, 117.9, 87.4, 85.6, 73.5, 70.4, 61.5, 24.8, 14.9. FT-IR (film, cm^{-1}): 3324, 3232, 3119, 2964, 2927, 1623, 1573, 1480, 1447, 1331, 1120, 1082, 777, 706. ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{21}ClN_5O_4S^+$ m/z 438.0997, found 438.0997.

4.3.10. (2R,3R,4S,5R)-2-(2-(ethylthio)-6-((3-nitrophenyl)amino)-9H-purin-9-yl)-5-(hydroxymethyl)-tetrahydrofuran-3,4-diol (5j)

214 mg, yield = 45%; white solid; m.p. = 115–116°C; R_f = 0.34 (EtOAc:MeOH = 15:1, v/v). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.56 (1H, s), 9.14 (1H, s), 8.49 (1H, app s), 8.25–8.23 (1H, m), 7.92–7.90 (1H, m), 7.66–7.62 (1H, m), 5.92 (1H, d, J = 6.0 Hz), 5.50 (1H, d, J = 6.0 Hz), 5.23 (1H, d, J = 4.8 Hz), 5.06 (1H, t, J = 5.6 Hz), 4.63 (1H, dd, J = 5.6, 11.2 Hz), 4.18 (1H, dd, J = 4.8, 8.4 Hz), 3.97 (1H, dd, J = 4.0, 7.6 Hz), 3.71–3.66 (1H, m), 3.60–3.55 (1H, m), 3.24–3.19 (2H, m), 1.36 (3H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 151.1, 150.7, 147.9, 140.7, 140.2, 129.7, 126.4, 118.0, 117.0, 114.4, 87.4, 85.6, 73.5, 70.4, 61.5, 24.9, 14.6. FT-IR (film, cm^{-1}): 3324, 3220, 3127, 2927, 1623, 1575, 1528, 1483, 1433, 1349, 1329, 1121, 1077, 789, 697. ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{21}N_6O_6S^+$ m/z 449.1238, found 449.1233.

4.3.11. (2R,3S,4R,5R)-2-(hydroxymethyl)-5-(2-(methylthio)-6-(phenylamino)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (5k)

281 mg, yield = 68%; white solid, m.p. = 185–186°C; R_f = 0.44 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (1H, s), 8.41 (1H, s), 7.91–7.89 (2H, m), 7.36–7.32 (2H, m), 7.07–7.04 (1H, m), 5.90 (1H, d, J = 6.0 Hz), 5.47 (1H, d, J = 6.4 Hz), 5.21 (1H, d, J = 4.8 Hz), 5.04 (1H, t, J = 6.0 Hz), 4.66–4.62 (1H, m), 4.19–4.16 (1H, m), 3.96–3.94 (1H, m), 3.70–3.33 (2H, m), 2.54 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 151.3, 150.4, 139.6, 139.2, 128.4, 122.8, 120.9, 117.7, 87.3, 85.6, 73.4, 70.5, 61.5, 14.0. FT-IR (film, cm^{-1}): 3327, 3286, 3095, 2907, 1618, 1578, 1498, 1444, 1339, 1298, 1076, 745, 691. ESI-HRMS $[M + H]^+$ calcd for $C_{17}H_{20}N_5O_4S^+$ *m*/*z* 390.1231, found 390.1239.

4.3.12. (2R,3S,4R,5R)-2-(hydroxymethyl)-5-(6-(phenylamino)-2-(propylthio)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (5l)

279 mg, yield = 63%; white solid; m.p. = 159–160°C; R_f = 0.42 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (1H, s), 8.42 (1H, s), 7.89 (2H, d, J = 8.0 Hz), 7.35 (2H, t, J = 8.0 Hz), 7.07 (1H, t, J = 7.2 Hz), 5.89 (1H, d, J = 6.0 Hz), 5.49 (1H, d, J = 6.0 Hz), 5.22 (1H, d, J = 4.8 Hz), 5.07 (1H, t, J = 5.2 Hz), 4.66–4.62 (1H, m), 4.18–4.17 (1H, m), 3.97–3.95 (1H, m), 3.71–3.67 (1H, m), 3.60–3.55 (1H, m), 3.13–3.08 (2H, m), 1.69 (2H, sext, J = 7.2 Hz), 0.98 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 151.4, 150.3, 139.6, 139.2, 128.3, 122.9, 120.9, 117.8, 87.4, 85.6, 73.4, 70.5, 61.5, 32.3, 22.8, 13.3. FT-IR (film, cm^{-1}): 3316, 3104, 2964, 2926, 1616, 1577, 1495, 1444, 1330, 1296, 1234, 1080, 750, 690. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{24}N_5O_4S^+$ *m*/*z* 418.1544, found 418.1552.

4.3.13. (2R,3R,4S,5R)-2-(6-((4-fluorophenyl)amino)-2-(propylthio)-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (5m)

291 mg, yield = 63%; white solid; m.p. = 171–173°C; R_f = 0.41 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.05 (1H, s), 8.41 (1H, s), 7.89–7.86 (2H, m), 7.21–7.17 (2H, m), 5.88 (1H, d, J = 6.0 Hz), 5.48 (1H, d, J = 6.0 Hz), 5.21 (1H, d, J = 4.8 Hz), 5.06 (1H, t, J = 5.6 Hz), 4.65–4.61 (1H, m), 4.17 (1H, dd, J = 4.8, 8.4 Hz), 3.96 (1H, dd, J = 4.0, 7.6 Hz), 3.71–3.65 (1H, m), 3.59–3.54 (1H, m), 3.10–3.06 (2H, m), 1.69 (2H, sext, J = 7.2 Hz), 0.98 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 158.0 (d, J = 238 Hz), 151.4, 150.3, 139.6, 135.5, 122.9 (d, J = 8 Hz), 117.7, 114.9 (d, J = 22 Hz), 87.4, 85.6, 73.4, 70.4, 61.5, 32.3, 22.7, 13.3. ^{19}F NMR (376 MHz, DMSO-d_6): δ = −119.85. FT-IR (film, cm^{-1}): 3313, 3268, 3125, 2961, 2925, 1621, 1581, 1506, 1450, 1332, 1222, 1123, 1081, 835. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{23}FN_5O_4S^+$ *m*/*z* 436.1449, found 436.1451.

4.3.14. (2R,3R,4S,5R)-2-(6-((4-chlorophenyl)amino)-2-(propylthio)-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (5n)

273 mg, yield = 57%; white solid; m.p. = 175–177°C; R_f = 0.42 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.15 (1H, s), 8.42 (1H, s), 7.92 (2H, d, J = 8.8 Hz), 7.39 (2H, d, J = 8.8 Hz), 5.88 (1H, d, J = 6.0 Hz), 5.48 (1H, d, J = 6.0 Hz), 5.21 (1H, d, J = 5.2 Hz), 5.05 (1H, t, J = 5.6 Hz), 4.65–4.61 (1H, m), 4.16 (1H, dd, J = 4.8, 8.4 Hz), 3.95 (1H, dd, J = 4.0, 7.6 Hz), 3.69–3.64 (1H, m), 3.59–3.54 (1H, m), 3.12–3.06 (2H, m), 1.71 (2H, sext, J = 7.2 Hz), 0.97 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8,

151.2, 150.5, 139.8, 138.3, 128.2, 126.5, 122.4, 117.9, 87.4, 85.6, 73.4, 70.4, 61.5, 32.4, 22.6, 13.3. FT-IR (film, cm^{-1}): 3326, 3232, 3113, 2967, 2929, 2871, 1620, 1576, 1528, 1492, 1451, 1328, 1236, 1086, 825. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{23}ClN_5O_4S^+$ m/z 452.1154, found 452.1155.

4.3.15. (2R,3S,4R,5R)-2-(hydroxymethyl)-5-(6-((4-methoxyphenyl)amino)-2-(propyl thio)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (5o)

280 mg, yield = 59%; white solid; m.p. = 119–121°C; R_f = 0.38 (EtOAc:MeOH = 15:1, v/v). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.85 (1H, s), 8.37 (1H, s), 7.73 (2H, d, J = 9.2 Hz), 6.93 (2H, d, J = 9.2 Hz), 5.87 (1H, d, J = 6.0 Hz), 5.47 (1H, d, J = 6.4 Hz), 5.20 (1H, d, J = 4.8 Hz), 5.07 (1H, t, J = 5.6 Hz), 4.65–4.61 (1H, m), 4.16 (1H, dd, J = 4.8, 8.0 Hz), 3.95 (1H, dd, J = 4.0, 7.6 Hz), 3.69–3.65 (1H, m), 3.59–3.54 (1H, m), 3.11–3.03 (2H, m), 1.69 (2H, sext, J = 7.2 Hz), 0.98 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 155.3, 151.5, 150.1, 139.3, 132.1, 122.8, 117.6, 113.5, 87.4, 85.5, 73.3, 70.5, 61.5, 55.2, 32.3, 22.8, 13.3. FT-IR (film, cm^{-1}): 3388, 3315, 3125, 2930, 2869, 1621, 1583, 1509, 1455, 1331, 1244, 1119, 1080, 828. ESI-HRMS $[M + H]^+$ calcd for $C_{20}H_{26}N_5O_5S^+$ m/z 448.1649, found 448.1656.

4.3.16. (2R,3S,4R,5R)-2-(hydroxymethyl)-5-(2-(propylthio)-6-(p-tolylamino)-9H-purin-9-yl)tetra-hydrofuran-3,4-diol (5p)

306 mg, yield = 67%; white solid; m.p. = 179–181°C; R_f = 0.44 (EtOAc:MeOH = 15:1, v/v). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.89 (1H, s), 8.38 (1H, s), 7.74 (2H, d, J = 8.8 Hz), 7.14 (2H, d, J = 8.4 Hz), 5.87 (1H, d, J = 5.6 Hz), 5.47 (1H, d, J = 6.0 Hz), 5.20 (1H, d, J = 4.8 Hz), 5.06 (1H, t, J = 5.2 Hz), 4.64–4.60 (1H, m), 4.16–4.15 (1H, m), 3.95 (1H, dd, J = 4.0, 7.6 Hz), 3.69–3.66 (1H, m), 3.59–3.53 (1H, m), 3.10–3.06 (2H, m), 2.28 (3H, s), 1.70 (2H, sext, J = 7.2 Hz), 0.99 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 151.5, 150.2, 139.4, 136.6, 131.9, 128.7, 121.1, 117.7, 87.4, 85.6, 73.4, 70.5, 61.5, 32.3, 22.8, 20.4, 13.3. FT-IR (film, cm^{-1}): 3325, 3235, 3116, 2922, 2869, 1624, 1580, 1512, 1454, 1335, 1236, 1124, 1083, 812. ESI-HRMS $[M + H]^+$ calcd for $C_{20}H_{26}N_5O_4S^+$ m/z 432.1700, found 432.1705.

4.3.17. (2R,3R,4S,5R)-2-(6-((3-fluorophenyl)amino)-2-(propylthio)-9H-purin-9-yl)-5-(hydroxymethyl) tetrahydrofuran-3,4-diol (5q)

328 mg, yield = 71%; white solid; m.p. = 155–157°C; R_f = 0.44 (EtOAc:MeOH = 15:1, v/v). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (1H, s), 8.45 (1H, s), 7.96–7.91 (1H, m), 7.73–7.71 (1H, m), 7.40–7.34 (1H, m), 6.90–6.86 (1H, m), 5.90 (1H, d, J = 6.0 Hz), 5.49 (1H, d, J = 6.0 Hz), 5.22 (1H, d, J = 3.2 Hz), 5.06 (1H, br s), 4.65–4.61 (1H, m), 4.17 (1H, br s), 3.97–3.94 (1H, m), 3.70–3.67 (1H, m), 3.59–3.56 (1H, m), 3.17–3.11 (2H, m), 1.73 (2H, sext, J = 7.2 Hz), 1.01 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 162.0 (d, J = 239 Hz), 151.2, 150.5, 141.2 (d, J = 11 Hz), 139.9, 129.9 (d, J = 10 Hz), 117.9, 116.4, 109.0 (d, J = 21 Hz), 107.3 (d, J = 26 Hz), 87.4, 85.6, 73.4, 70.4, 61.5, 32.4, 22.7, 13.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ = −112.45. FT-IR (film, cm^{-1}): 3319, 3226, 3134, 2931, 2869, 1621, 1578, 1489, 1444, 1331, 1226, 1124, 1079, 770, 680. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{23}FN_5O_4S^+$ m/z 436.1449, found 436.1451.

4.3.18. (2R,3R,4S,5R)-2-(6-((3-chlorophenyl)amino)-2-(propylthio)-9H-purin-9-yl)-5-(hydroxymethyl) tetrahydrofuran-3,4-diol (5r)

307 mg, yield = 64%; white solid; m.p. = 137–139°C; R_f = 0.44 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (1H, s), 8.45 (1H, s), 8.19–8.18 (1H, m), 7.83–7.80 (1H, m), 7.38–7.34 (1H, m), 7.12–7.09 (1H, m), 5.89 (1H, d, J = 6.0 Hz), 5.48 (1H, d, J = 6.0 Hz), 5.22 (1H, d, J = 4.8 Hz), 5.06 (1H, t, J = 5.6 Hz), 4.65–4.61 (1H, m), 4.17 (1H, dd, J = 5.2, 8.8 Hz), 3.96 (1H, dd, J = 4.0, 7.6 Hz), 3.70–3.65 (1H, m), 3.60–3.57 (1H, m), 3.16–3.12 (2H, m), 1.73 (2H, sext, J = 7.2 Hz), 0.99 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 151.1, 150.6, 140.9, 139.9, 132.7, 130.0, 122.3, 120.1, 119.0, 117.9, 87.4, 85.6, 73.4, 70.4, 61.5, 32.4, 22.5, 13.2. FT-IR (film, cm^{-1}): 3321, 3225, 3155, 2962, 2929, 2872, 1624, 1573, 1479, 1447, 1331, 1237, 1120, 1079, 774,702. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{23}ClN_5O_4S^+$ m/z 452.1154, found 452.1157.

4.3.19. (2R,3S,4R,5R)-2-(hydroxymethyl)-5-(6-((3-methoxyphenyl)amino)-2-(propylthio)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (5s)

332 mg, yield = 70%; white solid; m.p. = 90–92°C; R_f = 0.40 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.94 (1H, s), 8.41 (1H, s), 7.61–7.60 (1H, m), 7.52–7.50 (1H, m), 7.25–7.21 (1H, m), 6.66–6.63(1H, m), 5.88 (1H, d, J = 6.0 Hz), 5.12 (3H, br s), 4.64–4.61 (1H, m), 4.17–4.15 (1H, m), 3.96–3.93 (1H, m), 3.76 (3H, s), 3.69–3.65 (1H, m), 3.58–3.54 (1H, m), 3.12 (2H, dt, J = 4.8, 7.2 Hz), 1.71 (2H, sext, J = 7.2 Hz), 0.99 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 159.3,151.4, 150.3, 140.4, 139.6, 129.1, 117.9, 113.1, 108.1, 106.9, 87.4, 85.5, 73.4, 70.4, 61.5, 55.0, 32.3, 22.7, 13.2. FT-IR (film, cm^{-1}): 3345, 3238, 3107, 2958, 2928, 2869, 1624, 1577, 1492, 1454, 1329, 1287, 1226, 1157, 1084, 776, 685. ESI-HRMS $[M + H]^+$ calcd for $C_{20}H_{26}N_5O_5S^+$ m/z 448.1649, found 448.1648.

4.3.20. (2R,3S,4R,5R)-2-(hydroxymethyl)-5-(2-(propylthio)-6-(m-tolylamino)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (5t)

366 mg, yield = 80%; white solid; m.p. = 182–184°C; R_f = 0.40 (EtOAc:MeOH = 15:1, *v*/*v*). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.89 (1H, s), 8.39 (1H, s), 7.75 (1H, br s), 7.66–7.64 (1H, m), 7.23–7.19 (1H, m), 6.90–6.88 (1H, m), 5.88 (1H, d, J = 6.0 Hz), 5.47 (1H, d, J = 6.0 Hz), 5.20 (1H, d, J = 4.8 Hz), 5.07 (1H, t, J = 5.6 Hz), 4.64–4.61 (1H, m), 4.16 (1H, dd, J = 4.4, 8.0 Hz), 3.95 (1H, dd, J = 4.0,7.6 Hz), 3.69–3.65 (1H, m), 3.59–3.55 (1H, m), 3.14–3.09 (2H, m), 2.31 (3H, s), 1.70 (2H, sext, J = 7.2 Hz), 0.98 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 151.5, 150.3, 139.5, 139.1, 137.4, 128.2, 123.6, 121.6, 118.2, 117.8, 87.4, 85.6, 73.4, 70.5, 61.5, 32.4, 22.6, 21.3, 13.3. FT-IR (film, cm^{-1}): 3331, 3235, 3113, 2958, 2925, 2869, 1625, 1575, 1486, 1450, 1330, 1224, 1084, 779, 687. ESI-HRMS $[M + H]^+$ calcd for $C_{20}H_{26}N_5O_4S^+$ m/z 432.1700, found 432.1705.

4.4. Radical trapping experiment procedure for 6-chloropurine 3a, diethyl disulfide, and TEMPO

4.4.1. (2R,3R,4R,5R)-2-(acetoxymethyl)-5-(6-chloro-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-9H-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (6)

211 mg, yield = 35%; colorless oil; R_f = 0.51 (EtOAc:PE = 1:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (1H, s), 6.12 (1H, t, J = 5.2 Hz), 6.06 (1H, d, J = 5.2 Hz), 5.63 (1H, t,

J = 4.8 Hz), 4.69–4.65 (1H, m), 4.52–4.43 (2H, m), 2.16 (3H, s), 2.11 (3H, s), 2.07 (3H, s), 1.66–1.51 (6H, m), 1.31 (3H, s), 1.30 (3H, s), 1.11 (3H, s), 1.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 169.4, 169.1, 165.2, 152.7, 152.3, 142.5, 128.2, 87.4, 80.4, 72.4, 70.8, 63.2, 61.0, 60.8, 39.4, 39.3, 32.1, 31.8, 20.8, 20.7, 20.5, 20.3, 17.1. FT-IR (film, cm^{-1}): 2975, 2936, 1751, 1608, 1565, 1506, 1436, 1381, 1225, 938. ESI-HRMS $[M+H]^+$ calcd for $C_{25}H_{35}ClN_5O_8^+$ m/z 568.2169, found 568.2299

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