SYNTHESIS OF ACYCLIC NUCLEOSIDE AND NUCLEOTIDE ANALOGS DERIVED FROM 6-AMINO-7*H*-PURINE-8(9*H*)-THIONE AND 8-(METHYLSULFANYL)ADENINE

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Reaction of 8-bromoadenine derivatives **1** with thiourea in ethanol or butanol was used for the synthesis of the corresponding N^9-substituted 6-amino-7*H*-purine-8(9*H*)-thiones **2**. 8-(Methylsulfanyl)adenine derivatives **3** were prepared by reaction of thiones **2** with iodomethane in 1 M sodium methoxide or in aqueous 1.5 M potassium hydroxide. Alkylation of 6-amino-7*H*-purine-8(9*H*)-thione (**2a**) proceeds preferentially on the sulfur atom. Under similar conditions, alkylation of 8-(methylsulfanyl)adenine (**3a**) with diverse alkylation agents afforded N^9-substituted adenine derivatives **3** and **6**, and N^3-substituted adenine derivatives **5** and **7**. 8,3′-*S*-Anhydro derivatives **9** were prepared in good yields by cyclization of 6-amino-7*H*-purine-8(9*H*)-thiones **2d** and **2f** under the Mitsunobu reaction conditions.

Key words: Purines; Acyclic nucleoside and nucleotide analogues; Nucleosides; Nucleotides; Alkylation; Mitsunobu reaction; Anhydro derivatives; Cyclization.

The importance of 8-substituted purine derivatives in nucleoside and nucleotide chemistry and their potency as biologically active compounds is obvious. This work is a continuation of the structure–biological activity relationship (SAR) studies in the series of *N*-(2,3-dihydroxypropyl) (DHP), *N*-[2-(phosphonomethoxy)ethyl] (PME) and (*S*)-*N*-[3-hydroxy-2-(phosphonomethoxy)propyl] (HPMP) derivatives of heterocyclic bases[1]. The synthesis of the DHP, PME and HPMP derivatives with various substituents in position 8 of adenine was undertaken in order to obtain information about the effect of substitution in this position on the biological activity in these series. A recent study[2] was dedicated to 8-hydroxyadenine (6-amino-7*H*-purine-8(9*H*)-one) derivatives. Analogous compounds derived from 6-amino-7*H*-purine-8(9*H*)-thione and 8-(methylsulfanyl)adenine are now of our special interest.

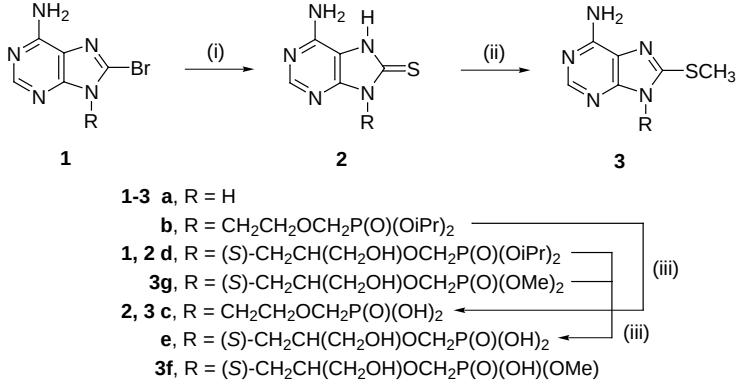
Some 8-sulfanyl or *S*-substituted 8-sulfanylpurine derivatives possess important biological activities. For instance, 8-(benzylsulfanyl)purines are known as irreversible inhibitors of xanthine oxidase[3], 8-thiocyanopurine derivatives as anticancer agents[4], and 8-[(phenoxyalkyl)sulfanyl]adenosines exhibit hypolipidemic activity[5]. Also the importance of 6-sulfanylpurine as a bacterial growth antagonist[6] and as an antitumor agent[7] is worth mentioning.

RESULTS AND DISCUSSION

The synthesis of 6-amino-7*H*-purine-8(9*H*)-thione (8-mercaptoadenine) derivatives was usually performed either by the purine ring formation from suitably substituted pyrimidines with thiourea or carbon disulfide[8], or by the reaction of the appropriate 8-bromopurine derivatives with thiourea[9], hydrogen sulfide[10], sodium hydrogen sulfide[11], or newly with 2-(trimethylsilyl)ethane-1-thiol followed by the deprotection of the thione function[12].

Similarly as in the 8-oxo (8-hydroxy) purine series[2], two principal approaches were used in this study for preparation of 8-substituted purine acyclic nucleoside and nucleotide analogues containing 6-amino-7*H*-purine-8(9*H*)-thione or 8-(methylsulfanyl)adenine as a base: (i) modification of the corresponding acyclic nucleoside or nucleotide derivative in position 8 of the purine moiety or, (ii) preparation of the 8-substituted purine base and its subsequent alkylation.

Synthesis of compounds containing sulfanyl group in position 8 of the purine moiety (Scheme 1) was performed by the reaction of appropriate



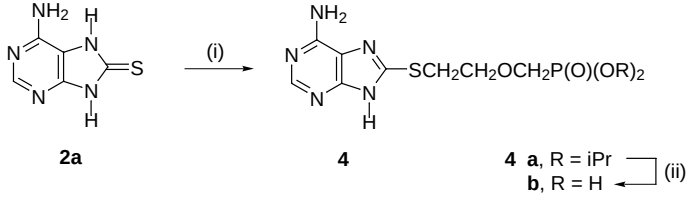
(ia) thiourea, BuOH, reflux, 24 h; (i) thiourea, EtOH, reflux, 15 h;
(iia) CH_3I, 2 M aq. KOH, (ii) CH_3I, 1 M MeONa; (iii) TMSBr, CH_3CN

SCHEME 1

8-bromo compounds **1** (ref.[2]) with thiourea in ethanol or butanol[9,13]. Thus, 6-amino-7*H*-purine-8(9*H*)-thione (**2a**), PME derivative **2b** and, HPMP derivative **2d** were synthesized from compounds **1**.

The transformation of compounds **2** to the 8-(methylsulfanyl)purine derivatives **3** was performed by the reaction of the corresponding 8-sulfanyl derivative **2** with one equivalent of iodomethane in 1 M sodium methoxide at room temperature. In the case of HPMP derivative a mixture of two products was detected by TLC and electrophoresis: dimethyl ester **3g** (according to MS spectrum) and monoester. It was proved by ^{1}H NMR and ^{13}C NMR spectra to be a monomethyl ester **3f**, which evidently arises by transesterification of the diisopropyl ester to dimethyl ester **3g** followed by partial cleavage of the protected phosphonate moiety. The crude reaction mixture was directly treated with TMSBr to afford phosphonate **3e**. 8-(Methylsulfanyl)purine derivatives can also be obtained directly by the reaction of the corresponding 8-bromopurine derivatives with sodium methanethiolate[14].

Alkylation of 6-amino-7*H*-purine-8(9*H*)-one (8-hydroxyadenine) with diverse alkylation agents afforded N^9-monosubstituted and N^7,N^9-disubstituted derivatives[2]. Compared to oxygen atom, the sulfur atom in 6-amino-7*H*-purine-8(9*H*)-thione (**2a**) is an easy target for alkylation[5,15]. Alkylations of compound **2a** with one equivalent of an alkylation agent gave the corresponding 8-(alkylsulfanyl) derivatives: 8-(methylsulfanyl)adenine (**3a**, Scheme 1) and PME derivative **4a** (Scheme 2). Similarly, the literature[5] describes alkylation of 6-amino-7*H*-purine-8(9*H*)-thione with ({[4-(ethoxycarbonyl)phenyl]oxy}methyl)oxirane catalyzed with 2,6-lutidine under the formation of the corresponding 8-(alkylsulfanyl)adenine derivative in 50% yield.

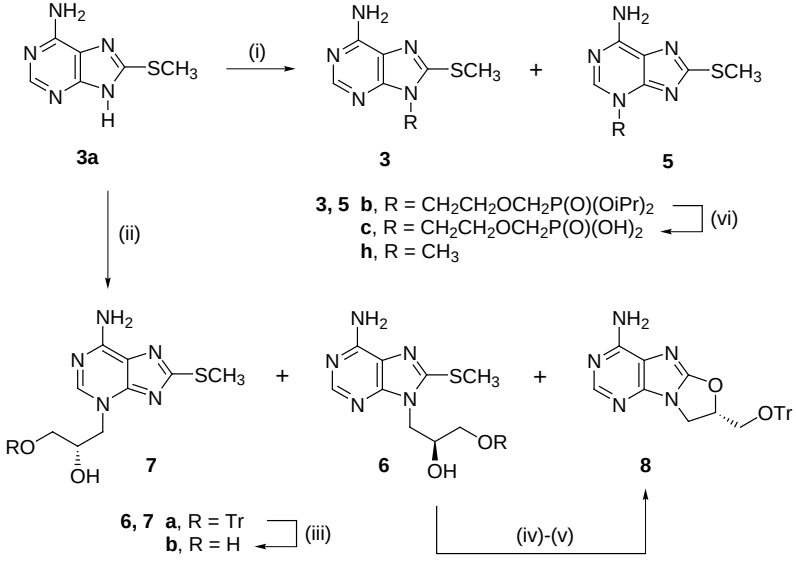


(i) $ClCH_2CH_2OCH_2P(O)(OiPr)_2$, NaH, DMF, reflux, 11 h; (ii) TMSBr, CH_3CN

SCHEME 2

To avoid the alkylation at the sulfur atom, we have performed analogous alkylations of 8-(methylsulfanyl)adenine (**3a**). The base **3a** was prepared by methylation of compound **2a** with iodomethane in aqueous 1.5 M potas-

sium hydroxide in 86% yield. Its alkylation gave rise to N^9-alkyl derivatives **3** and **6**, and N^3-alkyl derivatives **5** and **7** (Scheme 3, ratio *ca* 1 : 1). The N^9-substituted derivative **3b** is identical with an authentic compound prepared by the base modification of compound **2b** (Scheme 1). In the alkylation with (*S*)-[(trityloxy)methyl]oxirane ((*S*)-tritylglycidol), also the *O*-anhydro derivative **8** was isolated as a minor product arising from the intramolecular cyclization of the N^9-regioisomer **6a** under the Cs_2CO_3 catalysis. On acid treatment, the N^3-substituted derivative **7a** and N^9-substituted derivative **6a** were detritylated to give compounds **7b** and **6b**, respectively (Scheme 3).



(i) $ClCH_2CH_2OCH_2P(O)(OiPr)_2$, NaH, DMF; (ih) MeOTs, DMF, NaH, (ii) (*S*)-tritylglycidol, DMF, Cs_2CO_3; (iii) 80% aq. AcOH, reflux, 1 h; (iv) $Me_2NCH(OMe)_2$, DMF; (v) $TsOCH_2P(O)(OiPr)_2$, THF, NaH; (vi) TMSBr, CH_3CN

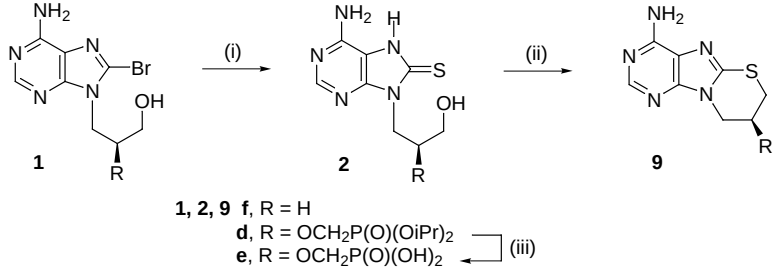
SCHEME 3

The attempts to prepare HPMP derivatives from N^6-[(dimethylamino)methylidene] derivatives of compounds **6a** and **7a** (which were prepared by their reaction with dimethylformamide dimethyl acetal) were unsuccessful. Under the standard synthetic procedure leading to the (*S*)-HPMP derivatives (treatment with NaH in THF followed by reaction with diisopropyl [(tosyloxy)methyl]phosphonate[16]), the protected N^3-derivative did not react; the unchanged starting compound **7a** was regenerated

(75%) from the reaction mixture after (dimethylamino)methylidene deprotection. Under the same conditions, the protected N^9-derivative underwent cyclization to the anhydro derivative **8**, identical with the compound prepared by another synthetic approach in the previous work[2]. This intramolecular nucleophilic substitution in the presence of Cs_2CO_3 or NaH confirms that the 8-SCH_3 group can serve as a leaving group.

Some acyclic analogs of 8-cyclonucleosides and 8-cyclonucleotides with the *O*-anhydro linkage were prepared[17]. Also a cyclic HPMPA analog was obtained[2]. We have attempted preparation of an analogous compound containing the *S*-anhydro linkage. There are several approaches available for the synthesis of purine *S*-cyclonucleosides[18]. Generally, the cyclization reactions using mesyl and tosyl leaving groups on the sugar moiety are accompanied by cyclization to the N^3,5′-cyclonucleosides[19]. Therefore, the use of the intramolecular Mitsunobu reaction[20] seemed to be the reaction of choice. It was successfully used for the *S*-cyclonucleoside synthesis[21].

Compound **2f** was prepared by the reaction of bromo derivative **1f** (ref.[22]) with thiourea in absolute ethanol (Scheme 4). Under the Mitsunobu reaction conditions, it cyclized to the anhydro derivative **9f** in 90% yield. Despite initial failure[21b], the acyclic analog of *S*-cyclonucleotide **9d** was synthesized from compound **2d** by analogous cyclization in 92% yield.



(i) thiourea, EtOH, reflux, 15 h; (ii) PPh_3, DEAD, DMF; (iii) TMSBr, CH_3CN

SCHEME 4

The *O*-anhydro linkage of purine cyclonucleoside is easily cleaved under mild conditions[23]. In contrast, purine *S*-cyclonucleosides in general are resistant to mild acid or alkaline hydrolysis, while hydrolysis with a strong acid or alkali leads to cleavage of the glycosidic and/or anhydro linkage or even to destruction of the purine ring[24]. Compound **9d** resisted the action of 1 M HCl, as well of 1 M NaOH at room temperature for 24 h. The altered character of the bond between N-9 and C-1′ atoms can be the cause of the enhanced stability to the hydrolysis.

Standard treatment with bromotrimethylsilane (TMSBr) in acetonitrile followed by hydrolysis was used for the ultimate cleavage of phosphonate diesters **2b**, **2d**, **3b**, mixture of **3g** and **3f**, **4a**, **5b**, and **9d**. Deionisation on Dowex 50 (H^+) followed by Dowex 1 (AcO^-) ion-exchange chromatography was used for isolation of the free phosphonates **2c**, **2e**, **3c**, **3e**, **4b**, **5c**, and **9e**. The purified compounds were crystallized from water.

All new compounds were fully characterized by ^{1}H NMR (and ^{13}C NMR), MS, and HRMS or microanalysis. The structures of the compounds prepared by alkylation of starting compound **3a** were determined on the basis of proton-coupled ^{13}C NMR spectra: N^9-alkyl derivatives of 8-(methylsulfanyl)adenine **3b**, **3h**, and **6b** are characterized by doublet of C-2 (^1J(C-2,H-2) = 199.2), by doublet of C-6 (^3J(C-6,H-2) = 11.7), and by triplet of C-5 (^3J(C-5,NH_2) = 3.9) disappearing after D_2O addition. The signal of C-4 was splitted by H-2 and H-1′ protons (^3J(C-4,H-2) = 12.7 and ^3J(C-4,H-1′) = 2.9) and that of C-8 by CH_3-group protons and H-1′ (J = 3.9). The alkylation in the N-3 position of compounds **5b**, **5c**, **5h**, and **7b** was confirmed by the observation of characteristic alkylation effects and an alteration of signal multiplicity of C-2 (upfield shift (–8 ppm), ^1J(C-2,H-2) = 209.0, ^3J(C-2,H-1′) = 3.9), C-8 (downfield shift (12 ppm), ^3J(C-8,CH_3) = 3.9, absence of ^3J(C-8,H-1′)), C-6 (upfield shift (–2 ppm), ^3J(C-6,H-2) = 11.7), and C-5 (downfield shift (2 ppm), ^3J(C-5,NH_2) = 3.9). The chemical shift of C-4 in N^3-alkyl derivatives was virtually the same, only the value of the coupling constants was changed (^3J(C-4,H-2) = 6.8 and ^3J(C-4,H-1′) = 3.9).

Compared with corresponding 8-(methylsulfanyl)adenine derivatives **3** and **6**, a considerable downfield shift of C-8 (δ 166 ppm) and splitting of C-4, C-5, and C-8 by NH proton (^3J(C-4,NH) = 5.9, ^2J(C-5,NH) = 4.9, ^2J(C-8,NH) = 5.9) were observed for N^9-alkyl derivatives of 6-amino-7*H*-purine-8(9*H*)-thione **2b** and **2d**.

The structure of modified purine bases is unambiguously reflected in their UV spectra. They are an additional evidence of the substituent type in position 8 of the purine moiety and of the corresponding alkyl regioisomers. Thus, it is possible to distinguish between (average values of λ_{max} and ε_{max} are given, respectively): N^9-alkyl derivatives of 8-sulfanyladenine **2** (pH 2: 308 nm, 25 000 and 241 nm, 15 000; pH 12: 300 nm, 24 000 and 228 nm, 22 000), their 8-(methylsulfanyl)adenine analogues **3** (pH 2: 284 nm, 20 000; pH 12: 222 nm, 20 000 and 280 nm, 20 000), and N^3-alkyl derivatives of 8-(methylsulfanyl)adenine **5** (pH 2: 301 nm, 12 000 and 235 nm, 10 000; pH 12: 305 nm, 18 000 and 235 nm, 14 000).

The CD spectra of enantiopure chiral acyclic nucleoside and nucleotide analogues **2e**, **3e**, **6b**, and **7b** do not exhibit considerable Cotton effect,

which reflects the flexible character of the side aliphatic chain bearing a chiral carbon atom. On the contrary, the CD spectrum of *S*-anhydro derivative **9e**, which shows a significant negative Cotton band around 223 nm, is another evidence of the rigid character of this tricyclic system. This spectrum agrees qualitatively with that of 8,5′-*S*-cycloadenosine[25].

In conclusion, two independent methods were used for preparation of acyclic nucleoside and nucleotide derivatives derived from 6-amino-7*H*-purine-8(9*H*)-thione (**2a**) and 8-(methylsulfanyl)adenine (**3a**): (i) modification of 8-bromoadenines in position 8, (ii) alkylation of the both 8-substituted adenine bases with diverse alkylation agents. The former method is direct and convenient, affords good yields of products, and is not accompanied by any side products except for the transesterification and partial formation of the monoester in the case of HPMP derivatives. The latter method, the base alkylation, is suitable for 8-(methylsulfanyl)adenine (**3a**) only. The yields are lower and two regioisomers are formed as main products in an approximately equimolar ratio: N^3-alkyl derivatives **5** and **7**, and N^9-alkyl derivatives **3** and **6**. The alkylation of 6-amino-7*H*-purine-8(9*H*)-thione (**2a**) is not convenient for the synthesis of acyclic nucleoside and nucleotide analogs, because the reaction occurs preferentially at the sulfur atom in position 8. N^9-substituted analog **3b** was prepared by two independent routes. Successful preparation of 8,3′-*S*-anhydro derivatives **9** was also performed. Biological activities of the final compounds will be examined.

EXPERIMENTAL

Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 2 kPa over P_2O_5. Melting points were determined on a Kofler block and are uncorrected. Analytical TLC were performed on Silufol UV 254 plates (Kavalier Votice, Czech Republic) in the systems chloroform–methanol (9 : 1) (S1), chloroform–methanol (85 : 15) (S2), chloroform–methanol (8 : 2) (S3), isopropyl alcohol–concentrated aqueous ammonia–water (7 : 1 : 2) (S4), and water–ethanol–aceton–ethyl acetate (1 : 1 : 1 : 4) (S5). Preparative TLC were carried out on 40 × 17 × 0.4 cm loose-layer plates of silica gel containing UV indicator (made in the Service Laboratory of the Institute). Paper electrophoresis was performed on a Whatman No. 3 MM paper at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogencarbonate (TEAB) at pH 7.5; the electrophoretical mobilities are referenced to uridine 3′-phosphate. NMR spectra were measured on a Varian Unity 500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C NMR) in hexadeuteriodimethyl sulfoxide (DMSO-d_6) referenced to the solvent signals (2.5 for ^{1}H and 39.7 for ^{13}C NMR), or in deuterium oxide containing sodium deuteroxide with sodium 3-(trimethylsilyl)propane-1-sulfonate as an internal standard for ^{1}H NMR and dioxane as an external standard for ^{13}C NMR (δ(dioxane) 66.86 ppm). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer

using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix). UV absorption spectra (λ in nm) were measured on a UV mini-1240 Shimadzu spectrometr, CD spectra on a Jobin Yvon Mark V instrument.

Starting Materials and Reagents

Bromotrimethylsilane and cesium carbonate were purchased from Fluka (Switzerland); DBU was purchased from Aldrich (Germany). Dimethylformamide was distilled from P_2O_5 and stored over molecular sieves (4 Å). Acetonitrile was refluxed with CaH_2 and distilled over molecular sieves (4.Å). Tetrahydrofuran was distilled before use from sodium metal.

6-Amino-7*H*-purine-8(9*H*)-thione (**2a**)

A mixture of 8-bromoadenine (**1a**; 6 g, 28.0 mmol), thiourea (17 g, 0.22 mol), and butan-1-ol (140 ml) was refluxed for 28 h, evaporated *in vacuo* and the residue was suspended in water (120 ml). The precipitate was filtered off and washed successively with water, acetone, ether, and dried over phosphorus pentoxide. Yellowish powder, m.p. >360 °C, yield 3.9 g (96%), R_F = 0.28 (S1). FAB MS, *m/z* (rel.%): 168 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 6.75 (brs, 2 H, NH_2); 8.06 (s, 1 H, H-2); 12.04 (brs, 1 H, NH); 13.04 (brs, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 108.22 (C-5); 147.55 (C-6); 150.06 (C-4); 152.84 (C-2); 166.73 (C-8). IR (KBr): 3 439, 3 323, 3 169, 3 092 (NH_2, NH); 2 587 (SH); 1 659 (NH_2); 1 613, 1 486, 1 466, 1 419, 1 329 (ring). Exact mass (FAB HRMS) found: 168.0354; calculated for $C_5H_6N_5S$ [M + H]: 168.0344.

Reaction of 8-Bromopurine Derivatives **1** with Thiourea. General Procedure

A mixture of the corresponding 8-bromo derivative **1** (5 mmol) and thiourea (40 mmol) in ethanol (70 ml) was refluxed for 15 h and evaporated *in vacuo*. The residue was suspended in hot chloroform (100 ml), thiourea was filtered off and washed with hot chloroform (250 ml). The chloroform solution was taken down *in vacuo*. Chromatography of the residue on a column of silica gel (60 g) in chloroform–methanol gradient, followed by crystallization, afforded compounds **2**.

6-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}-7H-purine-8(9H)-thione (**2b**). White crystals, m.p. 191 °C (ethanol), yield 81%, R_F = 0.20 (S1). FAB MS, *m/z* (rel.%): 390 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 1.11 (d, 6 H, J(CH_3,CH) = 6.1, CH_3); 1.16 (d, 6 H, J(CH_3,CH) = 6.1, CH_3); 3.79 (d, 2 H, J(P,CH) = 8.5, PCH_2); 3.93 (t, 2 H, J(2′,1′) = 5.6, H-2′); 4.31 (t, 2 H, J(1′,2′) = 5.6, H-1′); 4.47 (m, 2 H, POCH); 6.85 (brs, 2 H, NH_2); 8.14 (s, 1 H, H-2); 12.35 (brs, 1 H, NH). For $C_{14}H_{24}N_5O_4PS$ (389.4) calculated: 43.18% C, 6.21% H, 17.98% N, 7.95% P, 8.23% S; found: 43.23% C, 6.26% H, 18.24% N, 8.13% P, 8.51% S.

6-Amino-9-{2-[(diisopropoxyphosphoryl)methoxy]-3-hydroxypropyl}-7H-purine-8(9H)-thione (**2d**). White crystals, m.p. 168 °C (ethanol–ether), yield 64%, R_F = 0.38 (S2), R_F = 0.70 (S5). FAB MS, *m/z* (rel.%): 420 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 1.09 (d, 3 H, J(CH_3,CH) = 6.1, CH_3); 1.12 (d, 6 H, J(CH_3,CH) = 6.1, CH_3); 1.16 (d, 3 H, J(CH_3,CH) = 6.1, CH_3); 3.50 (dt, 1 H, J(3′b,OH) = J(3′b,2′) = 4.8, J(gem) = 12.0, H-3′b); 3.60 (dt, 1 H, J(3′a,OH) = J(3′a,2′) = 5.0, J(gem) = 12.0, H-3′a); 3.71 (dd, 1 H, J(P,CHb) = 9.8, J(gem) = 13.4, PCHb); 3.89 (dd, 1 H, J(P,CHa) = 8.4, J(gem) = 13.4, PCHa); 4.06 (dd, 1 H, J(1′b,2′) = 4.6, J(gem) = 13.7, H-1′b); 4.13 (m, 1 H, H-2′); 4.35 (dd, 1 H, J(1′a,2′) = 7.6, J(gem) = 13.7, H-1′a); 4.45 (m, 2 H, POCH); 4.81 (t, 1 H, J(OH,3′) = 5.3, OH); 6.83 (brs, 2 H, NH_2); 8.13 (s, 1 H, H-2); 12.35 (brs, 1 H,

NH). ^{13}C NMR (125 MHz, DMSO-d_6): 23.68 (d, J(P,C) = 4.9, CH_3); 23.78 (d, J(P,C) = 4.9, CH_3); 23.85 (d, J(P,C) = 3.9, CH_3); 23.91 (d, J(P,C) = 3.9, CH_3); 43.33 (C-1′); 61.13 (C-3′); 63.77 (d, J(C,P) = 164.4, PC); 70.24 (d, J(C,P) = 6.4, POC); 70.40 (d, J(C,P) = 6.4, POC); 78.80 (d, J(C,P) = 11.9, C-2′); 107.06 (C-5); 147.78 (C-6); 149.73 (C-4); 152.58 (C-2); 166.89 (C-8). For $C_{15}H_{26}N_5O_5PS$ (419.4) calculated: 42.95% C, 6.25% H, 16.70% N, 7.38% P, 7.64% S; found: 42.92% C, 6.27% H, 16.68% N, 7.29% P, 7.98% S.

6-Amino-9-(3-hydroxypropyl)-7H-purine-8(9H)-thione (**2f**). Yellowish crystals, m.p. 266 °C (ethanol), yield 51%, R_F = 0.35 (S2). FAB MS, *m/z* (rel.%): 226 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 1.87 (br pent, 2 H, H-2′); 3.44 (dt, 2 H, J(3′,OH) = 5.2, J(3′,2′) = 6.3, H-3′); 4.16 (t, 2 H, J(1′,2′) = 7.3, H-1′); 4.55 (t, 1 H, J(OH,3′) = 5.2, OH); 6.84 (brs, 2 H, NH_2); 8.15 (s, 1 H, H-2); 12.30 (s, 1 H, NH). UV, λ_{max} (ε_{max}): (MeOH) 307 (23 900), 237 (14 400). For $C_8H_{11}N_5OS$ (225.3) calculated: 42.65% C, 4.92% H, 31.09% N, 14.23% S; found: 42.44% C, 4.88% H, 30.89% N, 13.84% S.

8-(Methylsulfanyl)adenine (**3a**)

A mixture of 6-amino-7*H*-purine-8(9*H*)-thione (**2a**; 1.5 g, 9 mmol), 1.5 M KOH (50 ml), and iodomethane (1.4 g, 10 mmol) was stirred at 15 °C for 0.5 h in a closed flask. The mixture was neutralized with acetic acid. The precipitated solid was filtered off and washed successively with water, acetone and ether to give 1.4 g (86%) of product **3a**. Yellowish powder, m.p. 274–275 °C, R_F = 0.31 (S1). FAB MS, *m/z* (rel.%): 182 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 2.67 (s, 3 H, SCH_3); 6.98 (brs, 2 H, NH_2); 8.03 (s, 1 H, H-2); 12.99 (brs, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 13.94 (SCH_3); 119.53 (C-5); 148.09 (C-8); 151.63 (C-2); 152.44 (C-4); 153.99 (C-6). Exact mass (FAB HRMS) found: 182.0497; calculated for $C_6H_8N_5S$ [M + H]: 182.0500.

8-(Methylsulfanyl)purine Derivatives **3**. General Procedure

A mixture of the corresponding derivative **2** (5 mmol), 1 M sodium methoxide (25 ml), and iodomethane (5.5 mmol, 0.78 g) was stirred at room temperature for 0.5 h. The mixture was neutralized with acetic acid, extracted with chloroform (3 × 25 ml), and the organic layer was dried with anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on a column (250 ml) of silica gel (chloroform–methanol gradient) and/or crystallized. In the case of HPMPA derivative, a mixture of dimethyl phosphonate **3g** (R_F = 0.48 (S2), E_{Up} = 0.05) and monomethyl phosphonate **3f** (R_F = 0.00 (S2), E_{Up} = 0.52) was detected by TLC, electrophoresis, and mass spectrum. This mixture was directly treated with TMSBr under standard conditions (see compound **3e**). Analytical sample of monoester **3f** was purified by standard technique using Dowex 1 (AcO^-).

9-{2-[(Diisopropoxyphosphoryl)methoxy]ethyl}-8-(methylsulfanyl)adenine (**3b**). Yellow crystals, m.p. 106–108 °C (ethanol–ether), yield 92%, R_F = 0.35 (S1). FAB MS, *m/z* (rel.%): 404 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 1.09 (d, 6 H, J(CH_3,CH) = 6.1, CH_3); 1.14 (d, 6 H, J(CH_3,CH) = 6.1, CH_3); 2.70 (s, 3 H, SCH_3); 3.75 (d, 2 H, J(P,CH) = 8.3, PCH_2); 3.89 (t, 2 H, J(2′,1′) = 5.4, H-2′); 4.23 (t, 2 H, J(1′,2′) = 5.4, H-1′); 4.45 (m, 2 H, POCH); 7.07 (brs, 2 H, NH_2); 8.07 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 14.60 (SCH_3); 23.68 (d, 2 C, J(P,C) = 4.9, CH_3); 23.86 (d, 2 C, J(P,C) = 3.9, CH_3); 42.36 (C-1′); 64.90 (d, J(P,C) = 163.1, PC); 69.69 (d, J(P,C) = 11.2, C-2′); 70.32 (d, 2 C, J(P,C) = 6.3, POC); 119.04 (C-5); 149.16 (C-8); 151.73 (C-2); 151.85 (C-4); 154.20 (C-6). For $C_{15}H_{26}N_5O_4PS$ (403.4) calculated: 44.66% C, 6.50% H, 17.36% N, 7.68% P, 7.95% S; found: 44.80% C, 6.40% H, 17.38% N, 7.93% P, 8.29% S.

(S)-9-{2-[(Dimethoxyphosphoryl)methoxy]-3-hydroxypropyl}-8-(methylsulfanyl)adenine (**3g**). FAB MS, *m/z* (rel.%): 378 (100) [M + H].

(S)-9-[3-Hydroxy-2-{[hydroxy(methoxy)phosphoryl]methoxy}propyl)-8-(methylsulfanyl)adenine (**3f**). White crystals, m.p. 108–110 °C (ethanol–ether), E_{Up} = 0.52. FAB MS, *m/z* (rel.%): 364 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 2.70 (s, 3 H, SCH_3); 3.41 (d, 3 H, *J*(P,OCH) = 10.6, $POCH_3$); 3.48 (dd, 1 H, *J*(3′b,2′) = 4.9, *J*(gem) = 12.0, H-3′b); 3.52 (dd, 1 H, *J*(3′a,2′) = 4.5, *J*(gem) = 12.0, H-3′a); 3.59 (dd, 1 H, *J*(P,CHb) = 8.4, *J*(gem) = 13.9, PCHb); 3.66 (dd, 1 H, *J*(P,CHa) = 8.4, *J*(gem) = 13.9, PCHa); 3.90 (m, 1 H, H-2′); 4.15 (d, 2 H, *J*(1′,2′) = 6.2, H-1′); 4.90 (br, 1 H, OH); 7.44 (brs, 2 H, NH_2); 8.10 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 14.71 (SCH_3); 44.28 (C-1′); 51.87 (d, *J*(P,C) = 5.9, $POCH_3$); 60.80 (C-3′); 64.31 (d, *J*(P,C) = 160.2, PCH_2); 79.97 (d, *J*(P,C) = 8.8, C-2′); 118.88 (C-5); 150.11 (C-2); 150.48 (C-8); 151.68 (C-4); 153.13 (C-6). For $C_{11}H_{18}N_5O_5PS$ (363.3) calculated: 36.36% C, 4.99% H, 19.28% N, 8.53% P, 8.82% S; found: 36.15% C, 4.80% H, 17.23% N, 8.71% P, 9.03% S.

8-({2-[(Diisopropoxyphosphoryl)methoxy]ethyl}sulfanyl)adenine (**4a**)

A mixture of compound **2a** (0.8 g, 4.8 mmol) and sodium hydride (0.2 g of 60% dispersion, 5 mmol) in DMF (15 ml) was stirred at 110 °C for 0.5 h. Diisopropyl [(2-chloroethoxy)-methyl]phosphonate (1.2 ml, 5 mmol) was added and the mixture was stirred for another 4 h. The mixture was evaporated *in vacuo* and the residue was codistilled with toluene (2 × 10 ml). The crystallization from ethyl acetate afforded 1.25 g (67%) of white crystals, m.p. 93–95 °C, R_F = 0.41 (S1). FAB MS, *m/z* (rel.%): 390 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 1.22 (d, 6 H, *J*(CH_3,CH) = 6.3, CH_3); 1.23 (d, 6 H, *J*(CH_3,CH) = 6.3, CH_3); 3.45 (t, 2 H, *J*(1′,2′) = 5.3, H-1′); 3.80 (d, 2 H, *J*(P,CH) = 8.2, PCH_2); 3.81 (t, 2 H, *J*(2′,1′) = 5.3, H-2′); 4.58 (m, 2 H, POCH); 7.01 (brs, 2 H, NH_2); 8.04 (s, 1 H, H-2); 13.00 (br, 1 H, NH). ^{13}C NMR: 23.88 (d, 2 C, *J*(P,C) = 4.9, CH_3); 23.99 (d, 2 C, *J*(P,C) = 3.9, CH_3); 30.56 (C-1′); 64.83 (d, *J*(P,C) = 165.0, PC); 70.36 (d, 2 C, *J*(P,C) = 5.9, POC); 71.17 (d, *J*(P,C) = 11.7, C-2′); 119.23 (C-5); 148.79 (C-8); 151.57 (C-2); 153.11 (C-4); 155.26 (C-6). Exact mass (FAB HRMS) found: 390.1291; calculated for $C_{14}H_{25}N_5O_4PS$ [M + H]: 390.1364.

Alkylation of 8-(Methylsulfanyl)adenine (**3a**) with Methyl Tosylate

A mixture of compound **3a** (0.5 g, 2.8 mmol) and sodium hydride (0.12 g of 60% dispersion, 3 mmol) in DMF (15 ml) was stirred at 110 °C for 0.5 h. Methyl tosylate (0.5 ml, 3 mmol) was added and the mixture was stirred for another 8 h at this temperature. The solvent was evaporated and the preparative thin-layer chromatography on a silica gel in chloroform–methanol mixture (85 : 15) followed by crystallization from ethyl acetate afforded 233 mg (43%) of compound **3h** and 140 mg (26%) of compound **5h**.

9-Methyl-8-(methylsulfanyl)adenine (**3h**). Yellowish crystals, m.p. 215 °C, R_F = 0.52 (S2). FAB MS, *m/z* (rel.%): 196 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 2.71 (s, 3 H, SCH_3); 3.56 (s, 3 H, NCH_3); 7.07 (brs, 2 H, NH_2); 8.09 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 14.07 (SCH_3); 28.60 (NCH_3); 118.93 (C-5); 149.26 (C-8); 151.71 (C-2); 151.91 (C-4); 154.09 (C-6). UV, λ_{max} (ε_{max}) (MeOH): 278 (18 800), 221 (23 300). Exact mass (FAB HRMS) found: 196.0670; calculated for $C_7H_{10}N_5S$ [M + H]: 196.0657.

3-Methyl-8-(methylsulfanyl)adenine (**5h**): Yellowish crystals, m.p. 269 °C, R_F = 0.22 (S2). FAB MS, *m/z* (rel.%): 196 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 2.58 (s, 3 H, SCH_3); 3.84 (s, 3 H, NCH_3); 7.58 (brs, 2 H, NH_2); 8.19 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 14.13

(SCH_3); 35.88 (NCH_3); 121.67 (C-5); 142.60 (C-2); 151.84 (C-4); 152.12 (C-6); 161.65 (C-8). UV, λ_{max} (ε_{max}) (MeOH): 307 (16 100). Exact mass (FAB HRMS) found: 196.0632; calculated for $C_7H_{10}N_5S$ [M + H]: 196.0657.

Alkylation of 8-(Methylsulfanyl)adenine (**3a**) with Diisopropyl [(2-Chloroethoxy)methyl]phosphonate

A mixture of compound **3a** (0.5 g, 2.8 mmol) and sodium hydride (0.12 g of 60% dispersion, 3.1 mmol) in DMF (15 ml) was stirred at 110 °C for 0.5 h. Diisopropyl [(2-chloroethoxy)methyl]phosphonate (0.7 ml, 3.1 mmol) was added and the mixture was stirred for another 15 h. The solvent was evaporated and the residue codistilled with toluene (2 × 15 ml). Preparative chromatography on a silica gel plate in chloroform–methanol mixture (9 : 1) followed by crystallization from ethanol afforded 0.20 g (18%) of compound **3b** and 0.20 g (18%) of compound **5b**.

9-{2-[(Diisopropoxyphosphoryl)methoxy]ethyl}-8-(methylsulfanyl)adenine (**3b**). The compound is identical with the authentic material (according to FAB MS, ^{1}H NMR, and ^{13}C NMR spectra) prepared by modification at the position 8. White crystals, m.p. 118 °C, R_F = 0.35 (S1).

3-{2-[(Diisopropoxyphosphoryl)methoxy]ethyl}-8-(methylsulfanyl)adenine (**5b**). White crystals, m.p. 156 °C, R_F = 0.31 (S1). FAB MS, *m/z* (rel.%): 404 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 1.11 (d, 6 H, J(CH_3,CH) = 6.1, CH_3); 1.15 (d, 6 H, J(CH_3,CH) = 6.1, CH_3); 2.58 (s, 3 H, SCH_3); 3.78 (d, 2 H, J(P,CH) = 8.5, PCH_2); 3.94 (t, 2 H, J(2′,1′) = 4.9, H-2′); 4.43 (t, 2 H, J(1′,2′) = 4.9, H-1′); 4.46 (m, 2 H, POCH); 7.64 (brs, 2 H, NH_2); 8.14 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 14.13 (SCH_3); 23.73 (d, 2 C, J(P,C) = 4.9, CH_3); 23.87 (d, 2 C, J(P,C) = 3.9, CH_3); 48.67 (C-1′); 64.69 (d, J(P,C) = 164.1, PCH_2); 69.31 (d, J(P,C) = 11.7, C-2′); 70.32 (d, 2 C, J(P,C) = 6.3, POC); 121.78 (C-5); 142.57 (C-2); 151.06 (C-4); 152.17 (C-6); 161.58 (C-8). For $C_{15}H_{26}N_5O_4PS$ (403.4) calculated: 44.66% C, 6.50% H, 17.36% N, 7.68% P, 7.95% S; found: 44.36% C, 6.34% H, 17.14% N, 7.66% P, 8.16% S.

Alkylation of 8-(Methylsulfanyl)adenine (**3a**) with (*S*)-[(Trityloxy)methyl]oxirane

A mixture of 8-(methylsulfanyl)adenine (**3a**; 1.5 g, 8.3 mmol), DMF (50 ml), (*S*)-[(trityloxy)-methyl]oxirane (2.9 g, 9.2 mmol), and cesium carbonate (0.54 g, 1.7 mmol) was stirred at 110 °C for 15 h. The white solid was filtered off, washed with DMF (10 ml), methanol (2 × 10 ml) and ether (2 × 10 ml), and dried to give 0.15 g (4%) of compound **8**. The filtrate after evaporation and codistillation with toluene (3 × 15 ml) afforded, by column chromatography on silica gel (chloroform–methanol), two products: **6a** (1.45 g, 35%) and **7a** (1.6 g, 39%). The compounds **6a** and **7a** were fully characterized after detritylation.

(S)-7-[(Trityloxy)methyl]-7,8-dihydro[1,3]oxazolo[3,2-e]purine-4-amine (**8**). White crystals, m.p. 281 °C, R_F = 0.66 (S2). FAB MS, ^{1}H NMR, and ^{13}C NMR spectra are identical with the previously described compound[2]. For $C_{27}H_{23}N_5O_2$ (449.5) calculated: 72.14% C, 5.16% H, 15.58% N; found: 71.84% C, 5.08% H, 15.41% N.

(S)-9-[2-Hydroxy-3-(trityloxy)propyl]-8-(methylsulfanyl)adenine (**6a**). Yellowish solid, R_F = 0.40 (S1). FAB MS, *m/z* (rel.%): 498 (30) [M + H], 243 (100) [trityl].

(S)-3-[2-Hydroxy-3-(trityloxy)propyl]-8-(methylsulfanyl)adenine (**7a**). White solid, R_F = 0.36 (S1). FAB MS, *m/z* (rel.%): 498 (35) [M + H], 243 (100) [trityl].

Deprotection of the Trityl Derivatives **6a** and **7a**. General Procedure

The corresponding trityl derivative (2 mmol) was refluxed in a mixture water–methanol (1 : 1, 50 ml) with Dowex 50 (H^+ form, 20 ml) and a trace of hydrochloric acid for 0.5 h. The resin was filtered off, washed with water (3 × 10 ml), ether (3 × 10 ml) and 5% ammonia in 50% aqueous methanol. The ammonia solution was evaporated and the residue crystallized from water–ethanol mixture.

(S)-9-(2,3-Dihydroxypropyl)-8-(methylsulfanyl)adenine (**6b**). White crystals, m.p. 175 °C, yield 62%, R_F = 0.20 (S1). FAB MS, *m/z* (rel.%): 256 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 2.68 (s, 3 H, SCH_3); 3.33 (brdt, 1 H, *J*(3′b,2′) = 5.5, *J*(3′b,OH) = 5.9, *J*(gem) = 11.2, H-3′b); 3.39 (ddd, 1 H, *J*(3′a,2′) = 5.2, *J*(3′a,OH) = 5.9, *J*(gem) = 11.2, H-3′a); 3.91 (m, 1 H, H-2′); 3.95 (dd, 1 H, *J*(1′b,2′) = 8.2, *J*(gem) = 13.8, H-1′b); 4.12 (dd, 1 H, *J*(1′a,2′) = 3.9, *J*(gem) = 13.8, H-1′a); 4.83 (t, 1 H, *J*(OH,3′) = 5.9, OH); 5.04 (d, 1 H, *J*(OH,2′) = 5.1, OH); 7.07 (brs, 2 H, NH_2); 8.07 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 14.70 (SCH_3); 46.61 (C-1′); 63.93 (C-3′); 69.59 (C-2′); 118.99 (C-5); 149.99 (C-8); 151.56 (C-2); 151.99 (C-4); 154.18 (C-6). UV, λ_{max} (ε_{max}) (MeOH): 279 (22 500), 223 (26 900). CD, λ (Δε) (MeOH): 279 (–0.60), 223 (1.16), 197 (–1.75). Exact mass (FAB HRMS) found: 256.0818; calculated for $C_7H_{10}N_5S$ [M + H]: 256.0868.

(S)-3-(2,3-Dihydroxypropyl)-8-(methylsulfanyl)adenine (**7b**). White crystals, m.p. 189–190 °C, yield 55%, R_F = 0.20 (S1). FAB MS, *m/z* (rel.%): 256 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 2.58 (s, 3 H, SCH_3); 3.29 (dd, 1 H, *J*(3′b,2′) = 6.4, *J*(gem) = 11.2, H-3′b); 3.41 (dd, 1 H, *J*(3′a,2′) = 5.1, *J*(gem) = 11.2, H-3′a); 3.95 (m, 1 H, H-2′); 4.06 (dd, 1 H, *J*(1′b,2′) = 8.3, *J*(gem) = 13.6, H-1′b); 4.42 (dd, 1 H, *J*(1′a,2′) = 3.3, *J*(gem) = 13.6, H-1′a); 5.02 (brs, 1 H, OH); 5.20 (brs, 1 H, OH); 7.64 (brs, 2 H, NH_2); 8.09 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 14.13 (SCH_3); 52.58 (C-1′); 63.53 (C-3′); 68.67 (C-2′); 121.65 (C-5); 143.25 (C-2); 151.47 (C-4); 152.24 (C-6); 161.26 (C-8). UV, λ_{max} (ε_{max}) (MeOH): 306 (14 500). CD, λ (Δε) (MeOH): 312 (–0.35), 278 (–0.80), 254 (–0.36), 198 (–5.72). Exact mass (FAB HRMS) found: 256.0810; calculated for $C_7H_{10}N_5S$ [M + H]: 256.0868.

Synthesis of 8,3′-S-Anhydro Compounds **9** by Mitsunobu Reaction. General Procedure

A mixture of the corresponding 6-amino-7*H*-purine-8(9*H*)-thione derivative **2f** or **2d** (1 mmol), triphenylphosphine (1 mmol), and DMF (20 ml) was cooled to –10 °C and diethyl azodicarboxylate (DEAD; 1 mmol) was added. The mixture was stirred at room temperature overnight. Then another part of triphenylphosphine (1 mmol) was added, the mixture was cooled to –10 °C and DEAD (1 mmol) was added. The stirring was continued at room temperature overnight. The solvent was evaporated *in vacuo* and the residue was codistilled with toluene (3 × 10 ml) and ethanol (2 × 10 ml). The residue was purified by preparative TLC chromatography on silica gel and crystallized.

8,9-Dihydro-7H-[1,3]thiazino[3,2-e]purine-4-amine (**9f**). Yellowish crystals, m.p. 289 °C (ethanol), yield 90%, R_F = 0.54 (S2). FAB MS, *m/z* (rel.%): 208 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 2.29 (m, 2 H, H-2′); 3.29 (t, 2 H, *J*(3′,2′) = 5.6, H-3′); 4.14 (t, 2 H, *J*(1′,2′) = 6.0, H-1′); 7.06 (brs, 2 H, NH_2); 8.05 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 22.70 (C-2′); 25.42 (C-3′); 41.60 (C-1′); 118.33 (C-5); 143.82 (C-8); 150.92 (C-4); 151.22 (C-2); 154.02 (C-6). UV, λ_{max} (ε_{max}) (MeOH): 281 (18 500), 223 (18 400). For $C_8H_9N_5S$ (207.3) calculated: 46.36% C, 4.38% H, 33.79% N, 15.47% S; found: 46.38% C, 4.41% H, 33.51% N, 15.24% S.

Diisopropyl (S)-{[(4-amino-8,9-dihydro-7H-[1,3]thiazino[3,2-e]purin-8-yl)oxy]methyl}phosphonate (**9d**). Hygroscopic white solid (ether), yield 92%, R_F = 0.51 (S5). FAB MS, *m/z* (rel.%): 402

(100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 1.11 (d, 3 H, J(CH_3,CH) = 6.2, CH_3); 1.14 (d, 3 H, J(CH_3,CH) = 6.2, CH_3); 1.16 (d, 3 H, J(CH_3,CH) = 6.2, CH_3); 1.18 (d, 3 H, J(CH_3,CH) = 6.2, CH_3); 3.49 (ddd, 1 H, J(3′b,P) = 1.5, J(3′b,2′) = 5.3, J(gem) = 13.3, H-3′b); 3.55 (dd, 1 H, J(3′a,2′) = 2.0, J(gem) = 13.3, H-3′a); 3.88 (dd, 1 H, J(P,CHb) = 9.4, J(gem) = 13.7, PCHb); 3.99 (dd, 1 H, J(P,CHa) = 8.9, J(gem) = 13.7, PCHa); 4.12 (dd, 1 H, J(1′b,2′) = 2.8, J(gem) = 13.6, H-1′b); 4.34 (ddd, 1 H, J(1′a,P) = 1.2, J(1′a,2′) = 3.8, J(gem) = 13.6, H-1′a); 4.45 (m, 1 H, H-2′); 4.53 (m, 2 H, POCH); 7.10 (brs, 2 H, NH_2); 8.05 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 23.68 (d, J(P,C) = 4.9, CH_3); 23.76 (d, J(P,C) = 4.9, CH_3); 23.92 (d, 2 C, J(P,C) = 3.9, CH_3); 27.94 (C-3′); 45.04 (C-1′); 62.62 (d, J(P,C) = 164.1, PC); 68.92 (d, J(P,C) = 12.7, C-2′); 70.53 (d, 2 C, J(P,C) = 5.9 (POC); 118.13 (C-5); 143.44 (C-8); 151.02 (C-2); 151.13 (C-4); 153.84 (C-6). UV, λ_{max} (ε_{max}) (MeOH): 281 (19 500), 223 (19 300). Exact mass (FAB HRMS) found: 402.1287; calculated for $C_{15}H_{25}N_5O_4PS$ [M + H]: 402.1364.

Deprotection of Phosphonates with TMSBr. General Procedure

A mixture of a phosphonate diester (1 mmol), TMSBr (1 ml) and acetonitrile (5 ml) was stirred at ambient temperature overnight, then evaporated and codistilled with acetonitrile (10 ml). The residue was dissolved in water and alkalinized with aqueous ammonia. After evaporation, the residue was dissolved in water and applied to a column of Dowex 50X8 (H^+ form, 50 ml); the column was washed with water and eluted with 2.5% aqueous ammonia. After evaporation of the UV absorbing fraction, the product was purified on a Dowex 1X2 (acetate) column by elution with linear gradient of acetic acid (0–0.5 M, 1 l each). The UV absorbing fractions were evaporated *in vacuo* and the residue was crystallized from water.

6-Amino-9-[2-(phosphonomethoxy)ethyl]-7H-purine-8(9H)-thione (**2c**). Yellowish crystals, m.p. >250 °C, yield 52%, E_{Up} = 1.10, R_F = 0.24 (S4). FAB MS, *m/z* (rel.%): 306 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O): 3.52 (d, 2 H, J(P,CH) = 8.3, PCH_2); 3.93 (t, 2 H, J(2′,1′) = 6.2, H-2′); 4.42 (t, 2 H, J(1′,2′) = 6.2, H-1′); 8.00 (s, 1 H, H-2). ^{13}C NMR (125 MHz, D_2O): 42.27 (C-1′); 69.00 (d, J(P,C) = 149.9, PC); 69.47 (d, J(P,C) = 9.8, C-2′); 118.03 (C-5); 149.30 (C-2); 150.45 and 150.74 (C-4 and C-6); 164.79 (C-8). UV, λ_{max} (ε_{max}): (pH 2) 308 (21 200), 241 (12 600); (pH 12) 300 (20 000), 229 (19 600). Exact mass (FAB HRMS) found: 306.0387; calculated for $C_8H_{13}N_5O_4PS$ [M + H]: 306.0425.

6-Amino-9-[(S)-3-hydroxy-2-(phosphonomethoxy)propyl]-7H-purine-8(9H)-thione (**2e**)**.** Yellowish crystals, m.p. 319–320 °C, yield 45%, E_{Up} = 1.07. FAB MS, *m/z* (rel.%): 336 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O): 3.50 (dd, 1 H, J(P,CHb) = 9.6, J(gem) = 12.3, PCHb); 3.54 (dd, 1 H, J(3′b,2′) = 5.6, J(gem) = 12.8, H-3′b); 3.66 (dd, 1 H, J(P,CHa) = 8.5, J(gem) = 12.3, PCHa); 3.70 (dd, 1 H, J(3′a,2′) = 2.7, J(gem) = 12.8, H-3′a); 4.01 (m, 1 H, H-2′); 4.25 (dd, 1 H, J(1′b,2′) = 7.8, J(gem) = 14.0, H-1′b); 4.41 (dd, 1 H, J(1′a,2′) = 6.2, J(gem) = 14.0, H-1′a); 8.01 (s, 1 H, H-2). ^{13}C NMR (125 MHz, D_2O): 43.63 (C-1′); 61.51 (C-3′); 69.03 (d, J(P,C) = 149.4, PC); 80.45 (d, J(P,C) = 9.8, C-2′); 118.94 (C-5); 150.28 (C-2); 151.36 (C-4); 151.75 (C-6); 165.87 (C-8). UV, λ_{max} (ε_{max}): (pH 2) 308 (26 900), 241 (15 900); (pH 12) 300 (25 600), 229 (24 700). CD, λ (Δε) (H_2O): 298 (–0.45), 256 (0.25), 225 (–1.99), 214 (–0.22). Exact mass (FAB HRMS) found: 336.0583; calculated for $C_9H_{15}N_5O_5PS$ [M + H]: 336.0532.

8-(Methylsulfanyl)-9-[2-(phosphonomethoxy)ethyl]adenine (**3c**). White crystals, m.p. 270 °C, yield 73%, E_{Up} = 0.73. FAB MS, *m/z* (rel.%): 320 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O): 2.53 (s, 3 H, SCH_3); 3.34 (d, 2 H, J(P,CH) = 8.2, PCH_2); 3.70 (t, 2 H, J(2′,1′) = 6.0, H-2′); 4.00 (t, 2 H, J(1′,2′) = 6.0, H-1′); 7.81 (s, 1 H, H-2). ^{13}C NMR (125 MHz, D_2O): 14.62 (SCH_3); 43.19 (C-1′); 69.79 (d, J(P,C) = 8.8, C-2′); 69.83 (d, J(P,C) = 149.4, PC); 118.85 (C-5); 151.05 (C-8);

151.77 (C-2); 153.05 and 153.44 (C-4 and C-6). UV, λ_{max} (ε_{max}): (pH 2) 284 (20 600); (pH 12) 279 (20 000), 221 (21 800). Exact mass (FAB HRMS) found: 320.0556; calculated for $C_9H_{15}N_5O_4PS$ [M + H]: 320.0582.

(S)-9-[3-Hydroxy-2-(phosphonomethoxy)propyl]-8-(methylsulfanyl)adenine (**3e**). White crystals, m.p. 146–148 °C, yield 69%, E_{Up} = 0.80. FAB MS, *m/z* (rel.%): 350 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 2.73 (s, 3 H, S-CH_3); 3.37 (dd, 1 H, *J*(P,CHb) = 9.5, *J*(gem) = 12.2, PCHb); 3.53 (dd, 1 H, *J*(3′b,2′) = 5.6, *J*(gem) = 12.4, H-3′b); 3.60 (dd, 1 H, *J*(P,CHa) = 8.2, *J*(gem) = 12.2, PCHa); 3.68 (dd, 1 H, *J*(3′a,2′) = 2.7, *J*(gem) = 12.4, H-3′a); 3.85 (m, 1 H, H-2′); 4.09 (dd, 1 H, *J*(1′b,2′) = 6.4, *J*(gem) = 14.8, H-1′b); 4.17 (dd, 1 H, *J*(1′a,2′) = 6.1, *J*(gem) = 14.8, H-1′a); 8.06 (s, 1 H, H-2). UV, λ_{max} (ε_{max}): (pH 2) 284 (17 200); (pH 12) 280 (16 600), 222 (17 500). CD, λ (Δε) (H_2O): 303 (0.18), 258 (–0.22), 226 (0.64), 207 (–4.62).

8-{[2-(Phosphonomethoxy)ethyl]sulfanyl}adenine (**4b**). White crystals, m.p. 310 °C, yield 71%, E_{Up} = 0.79. FAB MS, *m/z* (rel.%): 306 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O): 3.47 (t, 2 H, *J*(1′,2′) = 5.5, H-1′); 3.59 (d, 2 H, *J*(P,CH) = 8.5, PCH_2); 3.89 (t, 2 H, *J*(2′,1′) = 5.5, H-2′); 8.08 (s, 1 H, H-2). UV, λ_{max} (ε_{max}): (pH 2) 290 (17 400); (pH 12) 285 (17 800). For $C_8H_{12}N_5O_4PS$ (305.3) calculated: 31.48% C, 3.96% H, 22.94% N, 10.15% P, 10.50% S; found: 31.27% C, 3.87% H, 22.69% N, 10.22% P, 10.69% S.

8-(Methylsulfanyl)-3-[2-(phosphonomethoxy)ethyl]adenine (**5c**). White crystals, m.p. 279–280 °C, yield 73%, E_{Up} = 0.70. FAB MS, *m/z* (rel.%): 320 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O): 2.63 (s, 3 H, SCH_3); 3.47 (d, 2 H, *J*(P,CH) = 8.5, PCH_2); 3.95 (t, 2 H, *J*(2′,1′) = 5.1, H-2′); 4.46 (t, 2 H, *J*(1′,2′) = 5.1, H-1′); 8.26 (s, 1 H, H-2). ^{13}C NMR (125 MHz, D_2O): 14.625 (SCH_3); 50.505 (C-1′); 69.88 (d, *J*(P,C) = 10.7, C-2′); 69.89 (d, *J*(P,C) = 150.4, PC); 121.79 (C-5); 145.05 (C-2); 151.29 (C-4); 152.50 (C-6); 164.11 (C-8). UV, λ_{max} (ε_{max}): (pH 2) 301 (12 100), 236 (7 900); (pH 12) 305 (18 400). Exact mass (FAB HRMS) found: 320.0508; calculated for $C_9H_{15}N_5O_4PS$ [M + H]: 320.0582.

(S)-{[(4-Amino-8,9-dihydro-7H-[1,3]thiazino[3,2-e]purin-8-yl)oxy]methyl}phosphonic acid (**9e**). White crystals, m.p. 323–324 °C, yield 67%, E_{Up} = 0.73. FAB MS, *m/z* (rel.%): 318 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O): 3.52 (brdd, 1 H, *J*(3′b,2′) = 5.8, *J*(gem) = 13.4, H-3′b); 3.56 (dd, 1 H, *J*(3′a,2′) = 3.0, *J*(gem) = 13.4, H-3′a); 3.59 (dd, 1 H, *J*(P,CHb) = 9.0, *J*(gem) = 12.6, PCHb); 3.71 (dd, 1 H, *J*(P,CHa) = 8.9, *J*(gem) = 12.6, PCHa); 4.06 (dd, 1 H, *J*(1′b,2′) = 3.0, *J*(gem) = 13.3, H-1′b); 4.25 (brdd, 1 H, *J*(1′a,2′) = 4.7, *J*(gem) = 13.3, H-1′a); 4.55 (m, 1 H, H-2′); 7.92 (s, 1 H, H-2). UV, λ_{max} (ε_{max}): (pH 2) 284 (20 900); (pH 12) 282 (20 700), 222 (19 400). CD, λ (Δε) (H_2O): 300 (–0.4), 280 (2.0), 239 (2.9), 223 (–11.4), 209 (2.3). For $C_9H_{12}N_5O_4PS$ (317.3) calculated: 34.07% C, 3.81% H, 22.07% N, 9.76% P, 10.11% S; found: 34.18% C, 4.00% H, 21.73% N, 9.52% P, 10.21% S.

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